CLINICAL TRIAL WITH ORAL CONTRACEPTIVES

(SEQUENTIAL REGIME)

by

GITA P. GIDWANI, M.D.. D.G.O.,

and

B. N. PURANDARE,* M.D., F.R.C.S.. F.I.C.S., F.C.P.S., F.R.C.O.G.

The practising gynaecologist is perplexed at the wide spectrum of oral contraceptives that is offered to him today. In this paper, we are presenting our experience of over 2 years of 354 Indian women who took the sequential type of therapy of oral contraceptive. These trials were conducted at the Dr. N. A. Purandare Research Centre.

Material & Methods

Two regimes of cyclic administration of hormones, viz. oestrogen and progestogen are used all over the world as oral contraceptives. In combination type of therapy, a fixed dose of oestrogen and progestogen is administered for 21 days. The sequential therapy consists of twenty to twenty-one days of oestrogen administration with a progestogen given concurrently during the last five to ten days of oestrogen treatment.

Table 1 indicates the composition of the pills used in this trial on 354 women, duration of trial, the number of cycles and the number of subjects given these pills. The difference in the two types of pills administered lies only in the dosage of Megestrol Acetate—each of the preparations A & B, contain 28 tablets, in which the first 16 tablets are pink in colour, each tablet containing 0.1 mg. of ethinyl oestradiol, next 5 tablets are

TABLE I

Composition	Code name	No. of women on trial	No. of cycles	Maximum No. of cycles
16 tabs. of 0.1 mg. E.E. + 5 tabs. of 0.1 mg. E.E. & 1 mg. M.A. + 7 tabs. of lactose.	A	179	1574	22
16 tabs. of 0.1 mg. E.E. + 5 tabs. of 0.1 mg. E.E. & 5 mg. of M.A. + 7 tabs. of lactose.	B	175	1406	24

E.E. Ethinyl oestrotdiol.
Duration of trial with A Pills — 22 monhts.
Duration of trial with B Pills — 26 months.

*Hon. Obst. & Gynec. K. E. Memorial Hospital and Hon. Principal Medical Officer, Nowrosjee Wadia Maternity Hostal, Bombay 7.

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white in colour, each containing 5 mg. (B) or 1 mg. (A) of Megestrol Acetate with 0.1 mg. of ethinyl oestradiol and the last 7 tablets are blue in colour, containing inert lactose base. The subjects start the first course of pills on 5th day of her menstrual cycle and continues to take tablets—one daily—in the order in which they are packed. She restarts the next packet immediately after the 1st course of 28 pills is finished. This schedule is meant to minimize patient error.

The age, parity, literacy status, income and religion, etc. of these 354 women are the same as reported in earlier trials. These women belong to the low socio-economic status, are illiterate and poorly educated and come for spacing or limitation of families. Most of them have used no other contraceptives before.

In our clinic the subject comes back every month for her supply of tablets and any side-effects volunteered by her and details regarding her menstrual cycle and weight are recorded.

Results

In a trial extending over a total of 2980 cycles and 48 months, there occurred one pregnancy in a woman on B type of tablets after she had taken this type of tablets for 5 cycles. Four other volunteers who had missed or taken the tablets wrongly also became pregnant. This gives a pregnancy rate of 2 per 100 women years in a field trial with women of low socio-economic strata.

Out of 354 women put on these preparations, 61 (17%) were lost to follow-up. Most of them came only for a first visit and then failed to turn up again. Out of the remaining 293 women, 119 continued the sequential regime to date—nearly a period of 3 years. The reasons for drop-out of the remaining 174 women over the period of 3 years are detailed in Table 2. About a year ago, since B type of tablets showed no particular advantage over A group of pills, we closed the trial, and 47 women who were taking B group of pills were switched over to the lower dose progestogen A type tablets. The notable feature of this group is that 45 of these women continue to date and of the two women who discontinued, one wished to become pregnant and the other one was sterilised.

The frequency of side-effects observed is given in Table 3. The

TABLE II

Acceptability of pills

Volunteers on trial	— 354
Lost to follow-up	— 61 (17%)
Continued on the same pills at the end of 3 years.	— 119

Reasons for discontinuation of pills :

Related Reasons

1. Side-effects—42
*2. Changed to other oral pills (doctor's advice)—18.
3. Irregular in taking pills—5.
4. Medically advised to discontinue—1

Unrelated Reasons

1. Out of Bombay—45
2. Inconvenient to visit centre—15
3. Sickness of subject or in the family—12
4. Desired pregnancy—17
5. Contraception not needed—10
6. Subject indifferent—2
7. Opposition in family—2
8. Pregnancy resulting because volunteer missed pills cr did not miss pills—5

10 of these women are continuing on the other oral pills.

TABLE III
Side-effects

Symptoms	No. of women disconted.
1. Nausea & vomiting	16
2. Menorrhagia or repeated BTB	13
3. Giddiness	12
4. White discharge	8
5. Cramps in legs	7
6. Weakness & loss of weight	6
7. Pain in abdomen	7

Note : The total number of women in tnis table exceeds the number of women who discontinued because of side-effects, because some subjects gave up medication since they had two or three symptoms at the same time.

women who either discontinued this regime because of side-effects or who were changed to some other regime on doctor's advice gave the symptoms detailed in Table 4.

cured by treatment of the cervical lesions.

This type of therapy produces remarkably regular cycles. We found that 80% of cycles after taking these tablets were 27-29 days in length and in 83. 5% cycles, the blood flow lasted for 3-5 days. The very welcome feature of these pills is that the amount of blood flow experienced by the woman is not reduced. This is in marked contrast to that seen after use of the conventional contraceptives. Also, the woman on sequential therapy does not experience further reduction in amount of menstrual loss as she continues medication for a long time. This is of particular importance

TABLE IV
Side-effects (Cycles%)

Side-effects	A		B	
	1st Cycle % (179)	Other cyc. % (1395)	1st cyc. % (175)	Other cyc. % (1231)
Nausea	2.3	0.9	3.9	0.3
Vomiting	1.7	0.3	1.7	0.3
Headache	1.7	0.8	2.2	0.3
Giddiness	5.6	0.6	5.0	0.8
Pain in abdomen	3.4	0.3	1.1	0.5
Break through bleeding	0	1.0	0.6	0.5
Spotting	0	0.1	0	0
Breast discomfort	0	0	0	0
Amenorrhoea	0	0.3	0	0

Most of the women who discontinue, do so at the first couple of cycles, though 4 women were switched to combination tablets after 15-25 cycles because they developed menorrhagia.

We would like to stress the importance of the symptom 'white discharge' with this type of therapy. About 8 women discontinued the pills or were changed to other pills because of this symptom. There were many more who complained of this but who were

to our Indian women, who are otherwise very upset by the reduction in the amount of menstrual flow. We have done endometrial biopsies on women who have been taking these preparations for as long as 16-20 cycles and there is no progressive endometrial involution which is seen with long term use of combination regimens. Probably, this histologic normalcy accounts for the normal character of ensuing withdrawal bleeding: this well-developed endo-

metrium does not show the tendency to diminished bleeding, so characteristic of the atrophic endometrium of combination therapy.

TABLE V
Weight gain

	A	B
No change in weight	55.3	52.8
Increase in weight (over 2 kg.)	20.9	17.6
Decrease in weight (more than 2 k.g).	23.8	29.6

Table 5 shows the weight changes of these volunteers. Most subjects, viz. 55.3%, show no change in weight. Of 354 volunteers, 41 have become pregnant—5 due to patient failure or drug failure and 36 women because they desired pregnancy or because they failed to collect the tablets from the centre. These women had taken these tablets for 1-15 cycles. Twelve women (33.0%) conceived in the first month following discontinuation of pills and 28 (77.0%) became pregnant at the end of 4 months following discontinuation of pills.

None of these women developed thrombophlebitis during the course of these trials. Twenty-five women with varicose veins of the lower extremities were also put on these pills and in only two the pills had to be discontinued as they complained of vague discomfort in the legs.

Liver function tests have been reported by the co-author on subjects taking these preparations and these showed no significant changes in the control and treated group. An interesting case was that of a woman, who after 12 cycles developed jaundice—diagnosed as infective hepatitis. She missed about 22 tablets when she was ill with jaundice, and insisted on taking the pills against our advice. She has completed 33 cycles to date and is absolutely normal and her liver function shows no deviation from the control group.

Discussion

The chief advantages offered by the sequential regime is that the sequential administration of oestrogen and progestogen imitates closely the physiological sequence of ovarian function. How is the gynaecologist to decide which particular woman is especially suited for the use of sequential therapy, when she chooses oral contraceptives? The effectiveness of sequential therapy, as reported by various authors, is definitely less than that in similar trials with combination therapy. Goldheizer reported a tablet failure rate of 0.66 per 100 women years and a total failure rate of 1.28. Mears tried several sequential formulae and gave a failure rate of 5 per 100 women years mostly due to tablet failure, but there occurred pregnancies in her series when volunteers took tablets regularly—one in 2nd cycle and others in later cycles (average 11). We had a pregnancy rate of 2 per 100 women years, but one pregnancy did occur in a woman who was vehement in stating that she never missed tablets in the 5th cycle. That patient subsequently delivered a normal baby and was sterilised. Mears explains these tablet failures in sequential therapy on the hypothesis that oestrogens inhibit ovulation in most cycles but break through ovulation occurs in occasional later cycles and that the normal endometrium formed with sequential therapy makes implanta-

tion and pregnancy possible. On the other hand, Rice-wray in trial with 13,000 cycles, Mead Johnson in a trial with 2056 cycles and McBride in a clinical trial with 3462 cycles have reported no tablet failures in their series. Theoretically, the patient on this regime has, however, more chances of becoming pregnant if medication were skipped for 1 or more days, because of greater endometrial development, less pituitary inhibition and earlier ovulation return.

When we study the side-effects reported, we find that the troublesome side-effects of combined oestrogen and progestogen therapy are still present in this type of therapy except that the progestogenic effects, like breast discomfort and weight gain, are virtually absent. The other big advantage would be the reduced cost, especially when A type of tablets which contain only a total of 1 mg. Progestogen per pack are marketed. The use of placebo tablets, thougl supposed to simplify this schedule, creates some new situations when the woman takes her tablets in the reverse order or if her child tears the foil packing and she mixes up the different coloured tablets or if she borrows tablets from the neighbour etc. We have had an occasional pregnancy occurring because of the volunteer taking placebo tablets on day 1-15 of the cycle.

The greatest advantage of the sequential therapy, in our experience, lies in its effect on the amount and duration of menstrual flow. Therefore, this type of therapy is especially indicated in women who have a normally scanty menstrual flow or who develop amenorrhoea or scanty menses on combined therapy of oral contraceptives. Goldheizer, Mears and other authors are all agreed about the normal character of the ensuing withdrawal bleeding. Mears found an increased amount of menstrual loss in 25% of her volunteers on sequential therapy and we had occasional patients who had to be put on combination type of therapy because they complained of excessive flow. The incidence of break-through bleeding and spotting is very low, 1.3% in our series. This excellent cycle control is another big advantage of this type of therapy. In case of break-through bleeding, because of the peculiar serialised packing of tablets, it is not possible to double the dose and hence the woman is asked to restart an entirely new pack from 5th day of her break-through bleeding.

TABLE VI
Volidan Sequential (B)

	Chinattamby		Present series	
	1st cycle (141)	Other cycles% (129)	1st cycle (179)	Other cycles % (1227)
Nausea & vomiting	12%	3.9%	5.6%	0.6%
Headache	11%	8.6%	2.2%	0.3%
Giddiness	10.0%	4.6%	5.0%	0.8%
Break through bleeding	0.7%	0.8%	0.6%	0.5%
Spotting	1.4%	0	0	0
Amenorrhoea	0	0	0	0

TABLE VII
Volidan Serial (A)

	McBride (450 subjects) %	Present series (179 (subjects) %
Nausea	14	2.8
Vomiting	19	1.7
Giddiness	Not mentioned	7.8
Headache	7.7	6.1
Pain in abdomen	Not mentioned	6.1
Breast discomfort	..	..
Break through bleeding	2.6	6.6

Tables 6 and 7 show the comparative results of side-effects obtained by other authors, viz. Chinattamby in Ceylon and McBride in Australia. This type of therapy is obviously suited for women who wish to use oral contraceptives but have scanty menses, are overweight or complain of scanty menses or amenorrhoea following the use of combined oral contraceptives. Sequentral therapy would be useful in mass programmes, but considering the lower efficacy (as compared to combined therapy), it forms a more suitable tool in the hands of the gynaecologist who can offer to his clinic patients a different type of oral contraceptive.

Conclusions

1. Three hundred and fifty-four women were given Megestrol Acetate and Ethinyloestradiol, in differing doses, as oral contraceptives.

2. The effect on menstrual cycles and the side-effects encountered are discussed.

3. Acceptability and efficacy in a mass programme over a period of 3 years with sequential oral contraceptives in Indian women are discussed.

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