DOSAGE OF OESTROGEN AND INHIBITION OF OVULATION

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Today oral steroidal contraceptives enjoy a unique place in the field of temporary birth control measures. It seems to be most effective in controlling fertility, since its theoretical effectiveness is almost 100 per cent.

Most of the oral contraceptives available to-day are combinations of both oestrogen and progestogen. One of the major factors which may make this useful weapon in the armamentarium of reproductive bioogy unpopular, is its undesirable side effects. Starting from minor side effects like nausea or headache to more serious complications like metabolic disorders to thromboembolic manifestations, have all been alleged to be associated with oral contraceptive therapy. In this respect, oestrogen component of the pill is mainly blamed to be responsible for such complications. It has been observed that some of the complications (e.g. thromboembolic and metabolic, etc.) are dose related.

Naturally after substantiating such claims by prospective and retrospective studies, in 1969 Dunlop Committee in U.K. came out with the conclusion, not to use oestrogens in the dosage of more than 0.05 mgm. ethinyl oestradiol in any oral contraceptive formulation. While, to date this exists as general consensus throughout the world, attempts are still being made to further lower the dosage of oestrogen component of pills. But since, such oral contraceptives mainly act by inhibition of ovulation by the action of its oestrogen component, lowering the dosage of oestrogen may run the risk of less effectiveness as a contraceptive.

In this context, it was thought, it would be worthwhile to find out the incidence of ovulation with different dosage of oestrogen. Since ethinyl oestradiol is the commonly used oestrogen in pills, this was selected for the present study in the standard dosage of 0.05 mgm. and two still lower dosages of 0.04 mgm. and 0.03 mgm.

Material and Methods

Patients attending gynaecology O.P.D. of Nehru Hospital attached to the Postgraduate Institute of Medical Education and Research, Chandigarh were selected for this study. The subjects were of age group between 20-32 years. Each patient was well motivated to follow the advice before she was booked for the study.

Patients presenting with events in personal or family history or features on

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clinical examination contraindicating oestrogen administration were not selected for the study. None of the patients received any hormone therapy for atleast four months prior to enrolment to the present study. Only cases with normal menstrual history were selected. In each patient ovulation was confirmed by carrying out a premenstrual endometrial biopsy before starting the trial.

Altogether 4 groups (viz. A, B, C and D) were formed as follows: Group A received Placebo (prepared from sodium bicarbonate) served as control group. Group B received 0.03 mgm. of ethinyl oestradiol (E.E). Group C received 0.04 mgm. of E.E. Group D received 0.05 mgm. of E.E. There were 15 patients belonging to each group, making a total of 60 subjects. Patients for different groups were selected at random.

Each patient was instructed to ingest the prescribed tablet (either E.E. or placebo) every day at a fixed time after dinner starting from 5th day of cycle for 20 days for two consecutive cycles.

Follow up

The patients attended O.P.D. every week on appointed dates for verifying whether they were following advices rigidly or not. Each patient was called between 22nd to 24th day of second cycle on an appointed date and time. Any subject giving history of break-through bleeding or failure to ingest tablet even on single occasion was excluded from the study. In all but 2 patients (they became pregnant while on study) endometrial biopsy was carried out in the O.P.D.

Results and Discussion

The results of 60 patients who went through the fixed criteria of the study were compiled. The 4 groups of subjects were comparable for age, height and weight. The type of endometrium (i.e. secretory and proliferative) was taken to be indirect evidence of ovulation or inhibition of ovulation. As shown in Table I all patients belonging to the control group (Group A) ovulated (including the patient who became pregnant directly proving ovulation). In the groups tried with different dosages of ethinyl oestradiol it was observed that degree of inhibition of ovulation was directly proportional to the dosage of oestrogen used. With 0.03 mgm. of E.E. ovulation was inhibited in 3 (i.e. 20%). In Group C, i.e. in patients receiving 0.04 mgm. of E.E., taking one pregnancy into account incidence of an ovulation was 53.3% (8 out of 15). With 0.05 mgm. of E.E. an ovulation was achieved in 11 patients (i.e. 73.3%).

Since the control group showed 100% ovulation the results in other groups with

TABLE I

Group	Drug Used	Number of Patients	Pregnancy	Proliferative Endometrium	Secretory Endometrium	Incidence of Ovulation inhibition
A	Placebo	15	1	Nil	14	0%
B	0.03 mgm. E.O.	15	Nil	3	12	20%
C	0.04 mgm. E.O.	15	1	8	6	53.3%
D	0.05 mgm. E.O.	15	Nil	11	4	73.3%

oestrogen fairly represent a true incidence of ovulation. This study can be compared with earlier studies by different workers who tried to find out the minimum anti-ovulatory dosage of oestrogens. It can be noted that incidence of ovulation inhibition had been different with different workers using different parameter to detect ovulation and even while using the same parameter. But, it is evident from these studies that degree of ovulation inhibition is directly proportional to the dosage of oestrogen, by any particular parameter to detect ovulation. (Vorys *et al.*, 1965; Gueal *et al.*, 1967; Jackson *et al.*, 1968; Glodzieher *et al.*, 1975).

In the present study, this feature was reflected in the fact that incidence of ovulatory cycles have gradually decreased from 80% with 0.03 mgm. of E.E. through 46.7% with 0.04 mgm. to 26.7% while 0.05 mgm. of E.E. was used. In other studies the incidence of ovulation using 0.05 mgm. of E.E. varied from 3.4% (Gual *et al.*, 1967) to 15.4% (Goldzieher *et al.*, 1975). The present as well as other studies show that the minimum consistent antiovulatory dose of oestrogen is higher than 0.05 mgm. and as suggested by some workers, may be as high as 0.01 mgm. (Mc Bride, 1965; Jackson *et al.*, 1968).

But from 1968 onwards, in combination oral contraceptives, oestrogen dose was not more than 0.05 mgm. Afterwards even lesser dosage of oestrogen to the extent of 0.03 mgm. or 0.02 mgm., alongwith suitable progestogen have been marketted with almost equal effectiveness (pregnancy rate being extremely low) and good cycle control (Bye and Elstein, 1973; Schneider *et al.*, 1973; Foss and Fotherby, 1975).

When oestrogens at a higher dose fail to inhibit evulation completely, why combination pills containing much lower dose of oestrogen than minimum antiovulatory dose gives almost complete protection against pregnancy has been matter of further studies. Two factors seem to play role to cause such effectiveness.

Firstly, in the combination, the progestogens may have additional effects that ensure their efficacy. Certain indirect measure for detection of ovulation suggest that ovulation occurs in significant proportion of women taking combination products, yet pregnancy rarely takes place. (Goldzieher *et al.*, 1962; Laurie and Lewis, 1968). This holds true also for newer low dose ostrogen/progestogen combination pills (Molina *et al.*, 1973). Most data suggest that a significant number of cycles are ovulatory, but since no contraceptive failure rate approximating such levels has ever been reported, ancilliary mechanisms must be involved. These probably include changes in cervical mucus and alternations in the timing of endometrial development, which preclude nidation (Edgreen, 1969).

Secondly, from various studies using small doses of oestrogen/progestogen combination it is clear that very small amount of ethinyl derivatives of oestrogens, in combination with relatively small amounts of progestins, have as much antiovulatory activity as far higher dosages of ethinyl oestrogens by themselves (Goldzieher *et al.*, 1975). It is well known that micro dosages of progestogens even if given continuously have relatively little antiovulatory activity (Moghissi, 1972). Therefore, a synergism between the two types of steroid must exist at the hypothalamo-pituitary level. This was observed in castrated women by Wallach *et al.*, (1970).

So although the incidence of inhibition of ovulation is directly related to the dose of oestrogen, in a combination pill—the dose of oestrogen may be lowered even below the dose which when used alone fails to inhibit ovulation consistently. This is because, the efficacy of combination pills depends on the combined effects of oestrogen and progestogen. And rightly the present day combination oral contraceptives are containing much lower dosages (viz. 0.02 mgm. or 0.03 mgm.) than the previously known standard dose (i.e. 0.05 mgm.).

Summary

An attempt was made to find out the incidence of inhibition of ovulation with varying dose of oestrogen (Ethinyl Oestradiol). Ovulation was indirectly detected by histopathological examination of endometrium premenstrually. With 0.03 mgm., 0.04 mgm. and 0.05 mgm. of E.E. the ovulation was inhibited in 20%, 53.3% and 73.3% cycles respectively. With such low incidence of ovulation inhibition with oestrogen alone, the probable reasons for efficacy of combnation oral contraceptives where same dosage of oestrogens are used along with suitable progestogens have been discussed in detail.

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