CLINICAL TRIALS WITH INJECTABLE CONTRACEPTIVES

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Injectable contraceptive may provide the answer to the problem posed by women requiring temporary contraception who cannot tolerate IUD and at the same time are not able to use contraceptive pill regimen. Ideally, injectable contraceptive should be safe, inert locally, have minimum side effects, produce acceptably regular menstrual cycles, provide reasonable pregnancy protection and permit resumption of normal menstruation and fertility after discontinuation.

Once a cycle injection of long acting estrogen-estradiol enanthate (EE) and long acting progestrone-dyhydro progestrone acetophenide (DHPA) in various doses have been extensively tried in the Western countries. Felton *et al* (1961) summarised their results on various doses of inj. DHPA and EE given on 8th day of cycles and reported that 150 + 5 mg combination was the best among the lot.

Material and Method

Healthy women of proven fertility between 20 and 40 years of age who opted for injectable contraceptives in the Peripheral Contraceptive Testing Unit of ICMR at Madurai Medical College were taken up for study. South Indian women are 3″-5″ shorter and weigh 10-15 kg less than their occidental counterparts. Hence the dosage of progestogen was reduced to 100 mg and clinical trials were started. Initially injection was given on 8th day of each cycle. These women were closely monitored for occurrence of side effects, menstrual disorders, weight gain and blood pressure changes. Endometrial biopsies were done periodically both in the first and second half of menstrual cycle to study the effect of the injected steroids.

Observations

One hundred and seven women had injection DHPA 100 mg and EE 5 mg given on 8th day of each cycle for 940 cycles. Maximum period of use was 25 months. There were 8 pregnancies due to method failure (Pearl pregnancy rate was 10.2/100 women years) (Table I).

Table II shows the alteration of cycle length under the effect of the injectable contraceptive. Cycle length was normal (i.e. between 25-35 days)—in 64.2%; it was short (between 16-24 days) in 29.3% and long (over 35 days) in 6.5% of all cycles. Intermenstrual bleeding occurred in 2.1% of cycles and in 0.9%

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TABLE I
Clinical Trials with Inj. DHPA 100 mg and EE 5 mg

	8th day of cycle regimen	Once a month regimen
Total No. of women	107	34
Total No. of cycles	940	164
Pregnancy due to method failure	8	1

TABLE II
Effect on Menstrual Cycle Length

	8th day of cycle regimen		Once a month regimen	
	No.	%	No.	%
Normal	604	64.2	133	78.1
Short cycle	276	29.3	31	18.1
Long cycle	60	6.5	5	2.8

of cycles bleeding was profuse and/or prolonged.

Endometrial biopsy was done in 30 women. Biopsy was taken in the second half of the cycle in 23 cases. One of these showed proliferative and secretory glands lying side by side. In all others glands were non-secretory but stroma showed varying degree of progestational changes i.e. stromal edema and predecidual reaction. Some of the biopsies taken during a long cycle or in a cycle where there had been intermenstrual bleeding revealed secretory exhaution atrophy. In one patient during a 70 day cycle biopsy was done twice. The first biopsy done on the 42nd day of period showed non-secretory glands, the second one done on the 62nd day showed typical secretory change—illustrating the fact that the effect of injected steroid may wear off during long cycle, allowing breakthrough ovulation to occur. Nine biopsies were done within 14 days after last menstrual period; 8 of them showed non-secretory endometrium in a stroma showing progestational changes. One biopsy done on 10th day of what was later proved to be a short cycle of 20 days showed secretory glands.

From our study we found that once a cycle injection has the following disadvantages:

1. Due to variation in cycle length in almost 1/3rd of the women injections were not evenly distributed. The interval varied between 20-70 days depending upon the cycle length.

2. In short cycles ovulation might occur earlier than 8 days after L.M.P. and hence injection given on the 8th day may not prevent pregnancy.

3. In a long cycle the effect of steroid may wane and break-through ovulation may occur. This in turn may lead to pregnancy due to method failure.

To overcome these difficulties we commenced giving the injection once a month on the same calender date irrespective of cycle length. Thirty-four women were given inj DHPA 100 mg and EE 5 mg once a month for 169 months. Maximum period of use was 8 months. There was only one pregnancy due to method failure. (Pearl pregnancy rate 7.1/100 women years) (Table I).

Comparison of menstrual data of this regimen with the 8th day of cycle regi-

men showed that once a month schedule achieved a better cycle control (Table II).

Endometrial biopsies were taken in 8 women—6 were premenstrual and 2 within 14 days after L.M.P. All biopsies showed non-secretory glands in a stroma showing varying degree of progestational changes.

Comparison between the 8th day of cycle schedule with once a month schedule showed that once a month schedule was easier to administer, was more effective and achieved a better cycle control.

In view of the reported adverse effects of estrogens given for contraceptive purposes over a long time the estrogen dosage was halved to 2.5 mg and clinical trials were undertaken with inj DHPA 100 mg and EE 2.5 mg given one a month to find out whether estrogen dosage could be lowered without adversely affecting contraceptive efficacy.

Injection DHPA 100 mg and EE 2.5 mg was given once a month to 90 women for 325 cycles. Maximum period of use was 8 months. There were 11 pregnancies due to method failure (Pearl pregnancy rate 41.5/hundred women years). Thus there was almost 6 fold increase in pregnancies due to method failure when estrogen dosage was lowered (Table III). Table IV shows that the percentage of divergent cycles were similar in both the regimen. Decreasing estrogen dosage resulted in loss of contraceptive efficacy but did not have any beneficial effect on cycle control.

Endometrial biopsy was done in 45 women during the second half of the menstrual cycle. Twenty biopsies showed secretory glands and 6 deficient secretory or mixed pattern. In 19 cases glands were non-secretory. Four biopsies were taken after 40 days after IMP during long cycles. Of these 2 showed non-secretory glands, 1 mixed proliferative and secretory pattern and the last secretory exhaution artrophy. Biopsies were done within 14 days after menstrual cycle in 17 women. Fourteen biopsies showed non-secretory glands; one secretory change and two secretory exhaution atrophy. Stroma in all biopsies showed varying degree of progestational

TABLE III

Inj. DHPA and EE Once a Month Schedule

	DHPA 100 mg + EE 5 mg	DHPA 100 mg + EE 2.5 mg
Total No. of women	34	90
Total No. of Cycles	164	325
Pregnancies due to method failure	1	11

TABLE IV

Inj. DHPA and EE Once a Month Schedule—Effect on Menstrual Cycle Length

	DHPA 100 mg + EE 5 mg		DHPA 100 + EE 2.5 mg	
	No.	%	No.	%
Normal	133	78.1	249	76.6
Short	31	18.1	57	17.5
Long	5	2.8	19	5.9

changes. Endometrial study confirmed that Inj DHPA 100 mg and EE 2.5 mg given monthly does not prevent ovulation in majority of cases.

Summary and Conclusion

1. Clinical trials were conducted with injectable contraceptive containing 100 mg of DHPA and 5 mg of E.E.

2. Injection was administered either on 8th day of each cycle or one in a month irrespective of menstrual cycle.

3. Comparison between the two regimens showed that once a month injection is easier to administer, achieves better cycle control and contraceptive efficacy.

4. Clinical trials with injection containing 100 mg of DHPA and 2.5 mg of EE given once a month showed that decreasing the estrogen content did not cause a decrease in menstrual side effects but lowered the contraceptive efficacy to unacceptable levels.

Acknowledgement

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References

1. Felton, et al: Advances in planned parenthood Vol. II. PP. 101. Excerpta Medica Foundation (1961).