CONTRACEPTIVE EFFICACY OF NORETHINDRONE ACETATE (ENTA) IMPLANT: ITS RELEASE RATE AND FERTILITY POTENTIAL

by

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Introduction

Earlier reports on the metabolic and clinical evaluation with this contraceptive implant have shown its high acceptability (Shahani *et al*, 1979), inspite of relatively low cycle control.

The purpose of this study was:

(i) To relate the menstrual pattern to the average release rate of the hormone per day.

(ii) To assess the concentration of NET in peripheral blood in cases of accidental pregnancies and to ascertain the risk to the offspring in such cases.

(iii) To evaluate the fertility potential and menstrual pattern following implant removal over one year period.

Material and Methods

Seventy-nine healthy women in the age group 19 to 30 years volunteered for implant contraceptive. The subdermal implant D containing 40 mg ENTA was supplied by Dr. K. R. Laumas, Reproductive Biology Department, A.I.I.M.Sc., New Delhi. It was inserted subcutaneously under asepsis on the lateral aspect of the thigh as described earlier (Shahani *et al*, 1979).

The average release rate (μg/day) of the hormone was determined by recovering the implants after known periods of time and calculating the amount of steroid lost.

NET was measured by radioimmunoassay (RIA) in peripheral blood samples collected at the time of a suspected pregnancy. RIA of NET on those blood samples was carried out at the Reproductive Biology Department of A.I.I.M.Sc., New Delhi (Hillier *et al*, 1977).

Table I shows the average time of im-

TABLE I

Time of Removal of Implant

Time of removal of implant in Months	No. of cases
< 5	5
5-6	27
7-8	32
>10	11
Total	75*

* 4 patients did not come for removal.

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plant removal in 75 out of total 79 women. In most subjects it was removed between 5th-8th month. In 5 it was removed before 5 months due to either a pregnancy or bleeding problems. Eleven subjects had to be persuaded to get it removed after 10 months.

Following implant removal most of the subjects were followed up over a period of one year for assessment of menstrual function. Menstrual pattern was considered regular if the cycle interval varied between 25-32 days with an average blood flow of 3-4 days. Any variation from this pattern was considered irregular.

Results

Table II shows the average release rate to be 163.5 μg/day in subjects with regular menstrual cycles as against 190.9 μg/day in those with abnormal menstrual pattern. The difference was statistically significant at $P < 0.05$. In cases of accidental pregnancies the release rate was 143.3 μg/day which was lower than that with regular periods, but the difference was not significant. There were in all 19 pregnancies during this trial.

The release rate also appeared to go down significantly with time in terms of duration of implant in situ as seen in Table III. The failure rate in terms of conception seemed to increase with decreasing release rate of the steroid. There were 2 failures before the fourth month, but in 1 the implant was inserted during an undiagnosed conception cycle in which there had been bleeding around the time of menstruation. Two subjects conceived beyond 8 months because they neither came for removal in time nor did they protect themselves against a pregnancy.

Once the pregnancy was diagnosed, all the women were advised to undergo a medical termination (M.T.P.). Only 10 complied with this suggestion. The remaining 9 subjects insisted on continuing

TABLE II

Release Rate of ENTA Related to Menstrual Pattern

Menstrual Pattern	No. of subjects	Release Rate in μg/day		
		Range	Mean ± S.E.	'P'
Regular	18	65.94-213.9	163.53 ± 10.7	
Irregular	30	134.40-271.5	190.99 ± 6.32	<.05
Pregnancy	17	22.04-209.5	143.35 ± 13.25	N.S.

TABLE III

Release Rate of ENTA

No. of months implant was in situ	'n'	Release Rate μg/day		Pregnancies 'n'
		Range	Mean ± S.E.	
< 4	3	260.38 375.40	312.28 ± 33.67	2*
4 to 6	15	23.62 276.70	219.41 ± 15.25	8
6 to 8	33	22.04 216.60	183.31 ± 5.68	7
8 to 10	11	134.40 160.90	148.49 ± 2.89	1
> 10	9	65.86 126.27	106.51 ± 8.10	1

* In one subject implant was inserted during an undiagnosed conception cycle.

with the pregnancy despite adverse medical opinion. There were no spontaneous abortions.

The range and mean concentration of NET levels in peripheral blood at the time of pregnancy diagnosis was estimated in 13 women. The implants in such cases had been in situ from 22 to 330 days at the time of blood sampling. There seems to be wide variation in concentration of this steroid ranging from 48 to 203 pg/ml, the mean levels being 122.53 ± 14.3 S.E. The blood levels of norethindrone did not have any correlation to the duration of implant in the body.

It was important to evaluate the actual days of exposure of the conceptus to this steroidal implant. Table IV shows the sex of the offspring in relation to the duration of exposure of the conceptus to the implant.

TABLE IV

Days of Exposure of Conceptus to Contraceptive Steroid in Subjects Who had F.T.N.D.

Exposure in days*	No. of cases	Pregnancy Outcome	
		Male	Female
15 to 45	5	1	4
46 to 90	2	1	1
> 90	1**	—	1
Throughout Pregnancy	1	1	—
Total	9	3	6

* Approximate days of follicular phase are deducted from exposure duration.

** Implant was inserted during undiagnosed conception cycle.

There were 9 subjects who went to full term and delivered 6 females and 3 males. The babies appeared clinically quite normal at birth eventhough 4 out of 9 had been exposed to the steroid for over 6 weeks.

An attempt was made to follow up these women who had participated in this trial for a period of 1 year after removal of the implant. This was possible in only 52 subjects. Most of the women seemed to be menstruating regularly during this follow up period. Eight women had opted for other contraceptive measures like surgical sterilization, intrauterine device or oral contraceptive pills. Fertility was evaluated among the remaining 44 unprotected women. Twelve conceived soon after removal within 3 months, 10 conceived between 4th to 8th month following removal and 3 between 9th to 12th month. In all 25/44 women i.e. 56.8% became pregnant during the first year after the implant removal.

Discussion

Alteration in bleeding pattern is probably the major side effect of contraceptive implant containing progestin only (Coutinho, 1978). That the menstrual irregularities were more frequent during the earlier months due to increased release of the steroid has been reported by Croxatto *et al* (1971). The results of this study also show that the average release rate per day of the steroid ENTA was 190.9 μg in women having disturbed menstruation as against 163.5 μg/day in regularly menstruating group. The difference was statistically significant. In women who became pregnant, the average release rate was still lower 143.3 μg/day but not significant. However, the range of release rate in such cases of implant failure was quite wide and varied from 22 to 209 μg/day indicating that in some cases for reasons not known very low amount of the steroid had been released which could probably explain its failure as a contraceptive. According to Nash *et al* (1978), it is important to note that the release rates cal-

culated by averaging release over the duration of implant use may not give the actual release rate on any selected day.

In order to assess the actual circulating levels of NET nearer the time of conception in cases of implant failure blood collected for pregnancy diagnosis was assayed for NET concentration by RIA in 13 cases. It was found that the average levels were 122.5 pg/ml the range varying from 48-203 pg/ml. According to Laumas's group the effective level of NET for contraception was around 800 pg/ml (Hillier *et al*, 1977). Since these blood samples were assayed for NET by the same group, it is evident that the circulating levels of NET in those cases of implant failure were much below the effective levels.

A multicentered clinical trial on this implant D (Takkar *et al*, 1978) showed adequate contraceptive effectiveness for 7-8 months and the average release rate was about 150 μg/day. In this study 15 out of 19 pregnancies occurred between 4-8th month indicating that the contraceptive efficacy of this implant was satisfactory only for about 4 months. This disparity may be due to certain unknown production factors or differences in release rates amongst subjects using the same drug as suggested by Nash *et al* (1978) for levonorgestrel.

Out of 19 pregnancies which occurred during this trial 10 agreed to undergo a medical termination. Nine women inspite of adverse medical opinion preferred to continue with the pregnancy. The embryo in such cases (Table IV) was exposed to the progestin during the critical period of differentiation. These women were closely followed up during pregnancy and after. All had full term normal deliveries and offspring. There were 3 males and 6 female babies. There were no congenital birth defects. The external genitalia were carefully examined and found normal in all cases.

Follow-up for 2-3 years to date, of these children has not indicated any adverse changes in growth and development. Based on these results and those of others, (I.C.C.R., 1978) the reports asso ciating teratogenicity and progestin in early pregnancy are probably exaggerated.

It is important to evaluate the effect of any contraceptive drug on the future reproductive potential. Follow up of 52 out of 79 women in this study showed that almost all of them were getting regular menstrual cycles. 27.3% became pregnant within 3 months of implant removal and another 29.5% became pregnant within one year. Thus, one may safely conclude that the ENTA implant does not affect the future fertility potential of such contraceptive users.

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Summary

A single silastic Implant D containing 40 mg ENTA was inserted in 79 women for evaluating its contraceptive efficacy. The release rate of the steroid appeared to be higher in women complaining of menstrual disturbances than in those with regular cycles. The release rate was lower in women who became pregnant though the difference was not significant. There were 19 pregnancies during this trial and 15 of them occurred between 4-8 months

indicating that the contraceptive efficacy of this implant was not more than 4-5 months. Mean NET concentration in the sera of these women at the time of pregnancy diagnosis was 122.5 pg/ml which is much lower than the effective levels of 800 pg/ml obtained by Laumas's group. Nine subjects despite adverse medical opinion insisted on continuing with the pregnancy. The offspring in all cases were normal healthy babies who on follow up of 2-3 years have not shown any abnormal features. Following implant removal the menstrual pattern and fertility potential appeared to be quite normal.

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