CLINICAL TRIALS WITH SILASTIC SUBDERMAL IMPLANTS OF PROGESTATIONAL STEROIDS IN REGULATING FERTILITY†

by

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Introduction

Hormonal contraceptives have been widely used as a means of family planning in the last two decades but the ideal contraceptive has yet to be discovered and the search is still on for a safe, effective, reversible and inexpensive method. Though the cyclic administration of tablets containing combination of oestrogen and progestogens have proved an inestimable boon to countless women in West, it is difficult to inculcate the habit of regular pill taking in poorly motivated subjects, and that led to the initiation of clinical trials by the I.C.M.R. with alternate methods of delivering the steroids such as subdermal implants and long acting injections. Clinical trials with subdermal silastic implants containing various contraceptive steroids such as Megestrol Acetate, Norgestrienone, Norethindrone and Norethindrone Acetate have been reported by various workers. (Croxatte *et al* 1969, Tatum *et al* 1969, Tejuja 1970, Coutinho *et al* 1970, Laumas *et al* in 1973, Tejuja *et al* 1974 and Takkar *et al* 1978). The present study has been carried out in the Contraceptive Testing Unit of I.C.M.R. in the Department of Obstetrics and Gynaecology of King Georg's Medical College, Lucknow (U.P.) and its aim was to evaluate the acceptability, antifertility efficacy and side effects of two types of silastic implants containing Norethindrone and Norethindrone Acetate in dosage of 65 and 99 mg. respectively.

Material and Methods

The implants used were supplied by the Population Council of New York through the courtesy of I.C.M.R. A total of 70 fertile women with ages varying from 18 to 38 years and parities ranging between 1 to 10 were enrolled for the investigation. Fifty received implants of 65 mg. Norethindrone rods (group I) and 20 received implants of capsules containing 99 mg. Norethindrone Acetate (group II). The implants were inserted subdermally under local anaestesia on anterolateral aspect of thigh through an 11 gauge trocar cannula. Norethindrone 65 mg. was incorporated in two rods, one of 40 mg. and the other of 25 mg while 99 mg. Norethindrone Acetate was incorporated in three capsules of 33 mg. each. In all cases after careful history taking, general and pelvic examination were

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carried out. Haemoglobin estimation, weight recording, urine analysis and vaginal cytological examination were done in every case before insertion of the implants and were subsequently repeated at six monthly intervals.

Observation and Results

Total period of observation was 1023 women months. All the implants were retained for a period of 1 year after which they were removed. A second implant was possible in 10 women (5 in each group) and 60 women had one insertion only.

Side Effects

The commonest side effects were menstrual abnormality (82.8%) and weight gain (35.7%) but only in 2 cases was the menstrual abnormality severe enough to necessitate removal of the implants. The average weight gain was 1 to 2 kg. but in 3 cases (2 with 65 mg. and 1 with 99 mg. implants), it was as high as 6 to 8 kg. Other side effects listed in Table I were minor in nature and none of these cases required removal because of side effcts.

Menstrual Abnormality

Break through bleeding (B.T.B.), irregular cycles, scanty menstruation and amenorrhoea were the commonest menstrual abnormalities found in this study, but only 2 cases (2.8%) required removal on this account in each group after 3 and 6 months respectively. Cycles of normal length were noted in 57.9% of women with 65 mg. implants and 63.4% of women with 99 mg. implants. Incidence of B.T.B. was higher in 99 mg. group (17.3%) than in 65 mg. group (13.5%). Alteration in cycle length and heavy or continuous bleeding were more frequently encountered with 65 mg. implants than with 99 mg. ones, but the differences were statistically insignificant. The incidence of amenorrhoea ranging from 46 to 90 days was also higher in 65

TABLE I
Side Effects in Implant Users

Side Effects	IMPLANTS		Total Number of cases (70)	Percentage
	65 mg. rods (50 cases)	99 mg. capsules (20 cases)		
Menstrual abnormality	43	15	58	82.8
Weight gain (1-8 kg.)	20	5	25	35.7
Weakness	10	4	14	20.0
Abdominal pain	5	1	6	8.5
Headache	5	1	6	8.5
Leg pain	3	1	4	5.7
Dizziness	3	—	3	4.2
Vaginal discharge	2	—	2	2.8
Breast secretion	2	—	2	2.8
Backache	2	1	3	4.2
Tingling sensation in lower extremity	1	1	2	2.8
Allergic rash	1	—	1	1.4
Loss of appetite	1	1	2	2.8
Depression	1	—	1	1.4

mg. group (11.9% as against 6.6% in 99 mg. group). In most cases the amenorrhoea was due to lactational irregularities. Nine cases with 65 mg. implants and 7 with 99 mg. implants were found lactating throughout the period of amenorrhoea but only 2 cases in 65 mg. group continued to have lactational amenorrhoea throughout the treatment cycles. There was no adverse effect on lactation and no women were given implants within three months of delivery.

Occurrence of Pregnancy

A total of 11 pregnancies occurred in the study group, 8 in 65 mg. and 3 in 99 mg. group. Two pregnancies occurred in first month in each group as they did not use conventional methods of contraception as advised. One pregnancy occurred

TABLE II

Menstrual Pattern in Implant Users Total Cycles—778

Menstrual Pattern	65 mg. Rods (565 cycles)			99 mg. capsule (213 cycles)		
	Cycles	Percentage		Cycles	Percentage	
Normal Cycles	327	57.9		135	63.4	
Cycles with B.T.B.	77	13.5		37	17.3	
Short Cycles	32	5.7	7.8	9	4.2	4.7
Long Cycles	12	2.1		1	0.5	
Scanty menstruation	26	4.6		14	6.6	
Heavy menstruation	15	2.7	4.3	1	0.5	1.4
Continuous bleeding	9	1.6		2	0.9	
Amenorrhoea	67	11.9		14	6.6	
Total	565	100		213	100	

TABLE III

Occurrence of Pregnancies and Outcome in Implant Users Accordng to Months of Use

Months	65 mg. Rods (50)	Outcome of pregnancy	99 mg. capsule (20)	Outcome of pregnancy	Total Number
1st	1	M.T.P. + Ligation	1	Pregnancy S.B. (APH) (Premature)	2
6th	1	M.R. + I.U.C.D.	—	—	1
9th	—	—	1	M.R. + I.U.C.D	1
10th	1	M.T.P. + Ligation	—	—	1
11th	1	F.T.N.D. + Ligation	—	—	1
12th	3	1 LSCS + Ligation 1 F.T.N.D. + Ligation 1 M.T.P. + I.U.C.D.	1	M.R. + I.U.C.D	4
19th (7 months after 2nd implant)	1	M.T.P. + I.U.C.D.	—	—	1
Total	8		3		11

in the 6th, 9th, 10th and 11th months, and 4 in the 12th month. In reimplant group only 1 pregnancy occurred after 7 months. Pregnancy rate was 15.2 in first year and 5.1 in second year as per Pearl Index formula and overall incidence was 12.7/100 women years of exposure. No congenital abnormalities were seen in babies born. (Table III).

Acceptability

At the end of 12 months 57 women had the implants in situ. Thirteen implants had been removed earlier because of undesirable side effects in 2 and occurrence of pregnancy in 11. Only 35 out of 57 (61.4%) opted for a second implant which was, however possible only in 10 cases because of the non-availability of fresh implants. Twenty-two cases (38.6%) refused the insertion of second implant for the following reasons.

(1) Opted for IUCD insertion — 12
(2) Sterilization — 5
(3) Pregnancy desired — 2
(4) Transferred elsewhere — 2
(5) Death of husband — 1

Difficulty was encountered in removing the implant in 10 cases (8 with 65 mg. and 2 with 99 mg.) because of fibrosis and in 2 because of migration from the site of insertion.

Release Rate

An assessment of release rate of the steroid in the implants carried out in 5 cases in group II. The average release rate varied from 60.16 μg to 326.26 μg/24 hours. The lowest release rate (60.16 μg/24 hours) was seen in case 1. In this patient conception occurred in first month after insertion of the implants which however were not removed as she failed to report about the occurrence of pregnancy. This patient went out of station retaining the implants and returned one year later after having delivered a premature still born baby associated with antepartum haemorrhage. The implants were removed at this stage and the release rate was calculated but of course this does not give any idea of the release rate when conception occurred. This is the only case in this series where the implants were retained throughout pregnancy. Since the infant was not available for examination it is not possible to state whether it had any congenital abnormalities or not. Case number 5 had irregular periods and the implants had to be removed after 3 months, showed higher release rate (326.26 μg/24 hours). Two cases of 65 mg. group returned for removal of implants 577 and 818 days after their insertion. Since these cases had not conceived it is indicative that the antifertility efficacy of the implant had persisted even after 1 year of insertion (Table IV).

Vaginal Cytology

Vaginal cytological examination was possible in 44 implants users. (36 with 65 mg. rods and 8 with 99 mg. capsule). Two cases of dysplasia (mild and moderate) were encountered in the follow-up smears after one year of insertion, 1 in each group. In both cases cervical cytology after 6 to 12 months of removal of implants revealed regression of lesion to normal.

Discussion

The incidence of pregnancy with Megestrol Acetate implants was reported as varying from 8-27/100 women years of exposure by various investigators (Croxatto *et al* 1969; Tatum *et al* 1969; Tejuja, 1970 and Coutinho *et al* 1970 and 1972). In an effort to overcome the shortcomings of Megestrol acetate im-

TABLE IV

Average Rate of Release of Norethindrone Acetate Capsule

S. No.	Name of Subjects	Removal Days	Treatment Capsules (35 mg. each)	Rate of release (μg/24 hr)	Total release (μg/24 hr)	Average release rate (μg/24 hr)	Remarks
1.	R.N.	385	capsules 1	34.40			
			2	75.60	180.50	60.16	conceived (first month Pre. M.S.B. (APH)
			3	70.50			
2.	V.K.	384	capsules 1	71.19			
			2	48.06	204.47	68.1	—
			3	85.20			
3.	U.K.	353	capsules 1	82.50			
			2	83.59	262.08	87.33	—
			3	95.99			
4.	S.S	365	capsules 1	67.22			
			2	104.60	271.72	90.57	—
			3	99.90			
5.	S.D.	93	capsules 1	306.93			
			2	377.20	978.83	326.26	removed earlier for irregular periods
			3	294.70			

plants, newer steroids such as Norethindrone and Norethindrone Acetate have been tried by Tejuja *et al* (1974) and Takkar *et al* (1978). In Tejuja *et al*'s (1974) series 3-4 implants of Norethindrone to provide a dosage of 60-80 mg. were used. 43 pregnancies were reported in 129 women. A single 40 mg. implant of Norethindrone Acetate was devised by Laumas *et al* (1973) and the results with this single implant have been reported upon by Takkar *et al* (1978) from different centres at Delhi and Bombay. Pregnancy rates of 2.3 and 3.9 were reported by these workers at the end of 7 and 8 months respectively (life table method). In the present study 11 pregnancies occurred, 8 with 65 mg. rods and 3 with 99 mg. Norethindrone acetate capsules. Pregnancy rate was 15.2 in first year and 5.1 in second year and over all incidence was 12.7 per 100 women years of exposures.

Forty two (60%) women complained of bleeding problems during the course of the study but removal on this account was only necessary in 2. Coutinho *et al* (1972) and Tejuja (1970) have reported 20-30% abnormal cycles in implant users. Tejuja *et al* (1974) have reported no change in menstrual pattern in 50.0% of cases. In the present series cycles of nor-

mal length were found in 57.9% of women with 65 mg. rods and 63.4% of women with 99 mg. capsules. 4.8 per 100 women required removal for bleeding at the end of 8 months in Takkar *et al's* series (1978) with a single implant of 40 mg. Norethindrone acetate. In the present series only 2.8% of cases required early removal on account of bleeding between 3-6 months.

Tejuja *et al* (1974) reported continuation rate of 59.7% and 66.3% at the end of one year with three to four capsules and rods respectively. Takkar *et al*, (1978) reported a continuation rate of 86.4 per 100 women at the end of 8 months with single implant of 40 mg. Norethindrone acetate. In the present series the acceptability at the end of 1 year was 61.4%.

Marked variation in release rate (from 23.4-151.2 μg/24 hours) was reported by Moore *et al* (1978) for 33.9 mg. D-Norgestrol capsule in vivo. In their series the release rates did not co-relate with the bleeding pattern and there was wide individual variation. Similarly, in the present study there was marked variation found in release rate. Only 1 case who had irregular menstrual pattern showed high release rate.

Conclusion

Silastic implants of long acting steroids constitute a promising method of contraception which obviates the need of daily pill taking. Several dosage schedules have been tried by different groups of workers, but so far the dose which will yield maximum contraceptive effectiveness with minimum menstrual abnormality does not appear to have been fully worked out. Of the two dosages used in this study the 99 mg. implants though associated with higher incidence of B.T.B., showed higher contraceptive effectiveness than the 65 mg. ones. The overall acceptability in our study was found to be 61.4%. The drawback of the method is that the implants have to be removed once they have lost their potency and most of the women objected to this minor operative procedure. A single biodegradable implant which does not require removal may prove to be more acceptable but this again might pose difficulty in removal in the event of undesirable side effects.

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