

LONG ACTING SYSTEMIC STEROIDS IN CONTRACEPTIVE PRACTICE

by

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Introduction

Long acting preparations for contraception are being developed to obviate the need of sustained motivation, as for oral contraceptives. Of the steroidal compounds used for contraceptive purpose, 19 nor-steroids have made the widest impact. The current mode of delivering the drug have been either subcutaneous implant (silastic or biodegradable) for 6 months, or 2-3 monthly injectables. As these procedures have given rise to menstrual irregularities, attempts have been made to develop monthly injectables, of suitable oestrogen-progestogen combination for better cycle control. This paper presents two of our studies—one with a 6 monthly silastic implant of Norethindrone acetate, and another with a monthly injection of Norethisterone Oenanthate and Oestradiol Valerate.

Material and Methods

In *Trial A*, a single silastic implant containing 40 mg of Norethindrone acetate was inserted subcutaneously on the late-

ral aspect of the thigh in healthy women under local anaesthesia, who were either regularly menstruating or had undergone an induced abortion recently. The implants were 22 mm long and 0.59 mm thick. The follow up visits were planned on the 8th post-insertional day and then at 1st, 3rd, 5th and 7th month. Both systemic and vaginal examination including vaginal cytology were carried out at each visit. Through a small incision under local anaesthesia, the implant was removed at the end of 6 months and the incision was sutured. A fresh implant was inserted in cases who opted continuation of the same method.

In *Trial B*, a combination of Norethisterone Oenanthate (50 mgm) and Oestradiol Valerate (5 mgm) in 1 ml oil, was injected intramuscularly once a month for 3 injections in 15 women between 15 to 40 years, with normal menstrual cycle. Each patient was given the first injection between 20-24 day of the cycle and two further injections at 28 days interval. The idea was to develop an injectable which would induce a withdrawal bleeding as a result of the fall in the short acting oestrogen while the progestogen will ensure contraceptive protection throughout the month. The study was carried out.

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only to study the bleeding pattern with this injectable, which explains the inclusion of only sterilized women for the trial. Levels of Norethisterone and Oestradiol were estimated at weekly intervals in 5 cases by R.I.A. (carried out by Prof. Fotherby at Hammersmith Hospital). After completion of 3 months' treatment period, the patients were followed up for

Reinsertions were done in 45 women (17.6%), 33 had first reinsertion, 10 had second reinsertion and 2 women had the third.

Characteristics of implant acceptors: Majority of the acceptors were less than 30 years of age (79.6%), mean being 25-29 years. They had an average family size of 1.93 living children (Table I).

TABLE I

Age	Per cent	Time of Acceptance	Per cent
Less than 20 years	3.1	Post-abortion	57.7
20-24 years	50.2	Interval	34.5
25-29 years	26.3	Post-partum	7.8
30 years or more	20.4		
MEANS	25.09		

No. of Living Children	Per cent	Prior use of Contraception	Per cent
0	2.8	Nil	68.3
1	32.6	I.U.C.D.	6.4
2	43.9	Oral	17.0
3	12.9	Injectable	0.4
4	6.3	Oral + I.U.C.D.	2.8
5 or more	1.5	Others (Nirodh etc.)	5.1
MEAN	1.93		

Wife's Education	Per cent
None	17.4
Read and write	1.6
(1-5) years of schooling	25.4
(6-8) " "	23.8
(9-11) " "	29.0
College	2.8

further 3 months to note the pattern of subsequent cycles.

Results (Table A)

A total number of 255 women were observed for a total period of 1,196 cycles.

First insertions were done immediate post-abortion in 147 women, 88 in interval cases and 20 women in 0.4 weeks post-partum.

Women with middle level of educational attainment preferred the implants. It is necessary to mention that the majority of the women coming to our hospital are from the lower and middle socioeconomic and educational level.

A total of 68.3% of the women had never used contraceptives during the last 2 years.

There was no cytological abnormality

detected in any of these patients and K.P.I. was less than 20%.

Event rates (Table II): The cumulative accidental pregnancy at 6 months was 2.2%. Where the patients failed to turn up for removal, due to declining efficacy of the implant, the pregnancy rate increased to 8% at the 7th month and 11% at the 8th month.

monthly injectable. When on treatment, 14 out of 15 women had a regular pattern. But 33% developed continuous and profuse bleeding in the 5th and 6th cycle subsequently. There seems to be no correlation between the circulating levels of Norethisterone and Oestradiol and the bleeding pattern. Probably it may be because of the imbalance at the endometrial

TABLE II

Net Cumulative Termination Rates per 100 Women Users or Implant-D by Type of Termination and Months of Use in a Bombay Hospital, India

Type of Termination	MONTHS OF USE					
	1	2	3	4	5	6
Pregnancy	—	—	0.5	1.0	1.6	2.2
Removals:						
Bleeding	0.4	0.9	2.4	3.5	5.8	7.7
Personal	—	—	0.5	0.5	0.5	0.5
Due to Sterilisation	—	—	0.5	0.5	0.5	0.5
Expulsion	0.4	1.4	1.4	1.4	1.4	1.4
Total Termination	0.8	2.3	5.3	6.9	9.8	12.9
Continuation	99.2	97.7	94.7	93.1	90.2	87.1
Woman months of use	227.0	209.5	193.0	177.0	158.5	140.0
Women exposed	235	219	200	186	168	149

The major reasons for discontinuation at the end of 6 months were bleeding 7.7%, personal 0.5% and due to sterilization 0.5%.

Menstrual Pattern: Menstrual abnormalities decrease with time. The percentage of abnormal cycles were 2.3, 51.1, 39.7 and 29.6 at the scheduled visits on the 8th day, 1st, 3rd, 5th and 7th month. Out of 29.6% abnormal cycles, 9% were menorrhagia, 15% were amenorrhoea and 4% were polymenorrhoea. A similar analysis was done for interval and M.T.P. group which also showed a trend towards lesser disturbance with time.

Results (Trial B)

The graph shows bleeding pattern with

tissue level.

Discussion

This implant with an average release of 150 $\mu\text{gm}/\text{day}$ (Hilher *et al.*, 1977) has been shown to result in a high level of Norethisterone initially, which decline gradually to maintaining dose of 80 $\text{ngm}/100$ ml of blood by the end of 2 months. Majority of the bleeding irregularities may be explained by this high level of the circulating of steroids in the earlier months after the insertion of the implant. It is worth noting, that during these months of treatment, a normal ovulatory pattern of serum FSH, LH, progesterone and oestradiol has been demonstrated, which tend to be disturbed in the latter

period (Rahman *et al*, 1977) when in fact the bleeding pattern tends to settle down. It however brings to light the fact that inhibition of ovulation is not the main mechanism of its contraceptive action in the first few months of treatment.

We have subsequently supplemented orally 20 μ gm of ethinyl oestradiol daily for the first three weeks, starting of the day of implant insertion, in 20 cases, with a view to achieve a better cycle control. However, this failed to improve the bleeding pattern.

The same compound Norethisterone has been used as oenanthate in doses of 200 mgm intramuscularly every 3 months yielding a cumulative 12 month gross pregnancy rate per 100 women years as 3.6 ± 0.7 (S.E.) (Benaglano, 1977) which is higher than that of implant at our centre. Majority of the pregnancies were seen to occur in the last 4 weeks of first injection. No such correlations were noted in cases of the implants. Further the injectable failures were more common with a low mean body weight indicating some influence of body fat on its contraceptive effect (Benagiano, 1977). A similar effect between body weight and clinical effects has been noted for the implants, where women in the higher weight group had lesser bleeding problems than their counterpart (Takkar *et al*, 1978). Recent studies (Fotherby *et al*, 1966) have shown the injectables to suppress FSH and LH which is maximal by 20th day, tending to return to its initial value by around 50 days suggesting the need to repeat the injections rather every 2 months.

On theoretical grounds the combination monthly injectable of our study was thought to control ovulation. It was interesting to note that none of the patients had any menstrual problems during the

treatment cycle. The serum level of 1500-1700 pgm/ml of Norethisterone seems to be adequate. But oestradiol levels were quite erratic. Body weight is unlikely to affect it since the patients were from rather uniform group. However, the menstrual irregularities which set in after discontinuing the injectable require further investigation.

In the net analysis one is thus confronted with several problems yet unsolved, indicating the rather primitive stage of development of depot injectables; though such preparations have been marketed in several countries over a decade.

As it stands today, regularly administered oral contraceptives of combination type are the most effective, simple contraceptives with good cycle control. In a large series of 3,500 cases studied in our centre, over the last 6 years we had only one pregnancy, regular cycles in 94.8%, but a drop out rate of nearly 50%. Hence, considering the drop out rate and the need for day to day motivation, a search for a depot hormonal preparation is very essential.

Summary

Long acting preparations for contraception are being developed to obviate the need of sustained motivation, as for oral contraceptives. The clinical data and problems related to two such long acting preparations—implants and injectables are presented. The first group was treated with a six monthly single silastic implant of 40 mg of Norethisterone acetate with an average release rate of 150 μ g per day. A total of 255 women were studied for a period of 1,196 cycles. Women with middle level of educational attainment and low socio-economic group preferred the implants.

The cumulative accidental pregnancy

at 6 months was 2.2%, 8% at 7th month and 11% at 8th month. The unpredictable bleeding pattern initiated in the early months of treatment often led to drop out. 7.7% patients were dropped for bleeding at the end of 6 months. The percentage of abnormal cycles decreased with time. 0.02 mgm ethynyl estradiol supplemented orally in the first 20 days following insertion of implant did not improve the bleeding patterns.

The other study was a monthly combination injection of 50 mgm Net-Oen and 5 mg estradiol valerate every 28 days to study the bleeding pattern. These women had a good cycle control during the treatment following which 33% developed some irregularities in the next 3 months. Levels of the exogenous hormones are presented. Though the oestradiol levels were erratic in both normal and abnormal cycles, Norethisterone values were quite consistent in both.

Review of three monthly injectables shows that the same compound Norethisterone as oenanthate in doses of 200 mg gives a gross pregnancy rate of 3.6 ± 0.7 (S.E.) per 100 women years as against that of 0.7 with Depot-provera.

However, though Depot-provera appears to be an effective contraceptive, it often gives rise to a higher incidence of amenorrhoea.

As it stands today, regularly administered oral contraceptives of combination type are the most effective, simple con-

traceptives with good cycle control. In a large series of 3,500 cases studied in our Centre over last 6 years we had only one pregnancy, regular cycles in 94.8% but a drop out rate of nearly 50%. Hence, considering the drop out rate and to reduce the need of day to day motivation, search for a depot hormonal preparation is very essential.

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References

1. Benagiano, G., Diczfalusy, E., Goldzieher, J. W. and Gray, R.: *Contraception*. 15: 513, 1977.
2. Fotherby, K., Howard, G., Shrimankar, K., Elder, M. and Bye, P. G.: *Contraception*. 16: 591, 1966.
3. Hilher, S. G., Jha, P., Giriffiths, K. and Laumas, K. R.: *Contraception*. 15: 473, 1977.
4. Rahman, S. A., Jha, P., Laumas, V., Jani, A. K., Dileepkumar, Takkar, D., Hingorani, V. and Laumas, K. R.: *Contraception*. 16: 487, 1977.
5. Takkar, D., Anantlaxmi, P. N., Chandra, V. L., Bhatnagar, S., Yadara, H. S., Laumas, K. R., Hingorani, V., Krishna, U. R., Mandekar, A., Purandare, V. N., Goel, V., Adatia, A. and Virkar, K. D.: *Contraception*. April, 1978.