Contraception with Long-Acting Subdermal Implants. A Five-Year Clinical Trial With Silastic Covered Rod Implants Containing Levonorgestrel

The International Committee for Contraception Research (ICCR) of the Population Council

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Abstract

A total of 189 women volunteered to accept subdermal implants for contraception. The implants were "covered rods", consisting of a core rod containing equal parts by weight of levonorgestrel and polydimethylsiloxane and sealed inside a thin-walled tube of Silastic tubing with medical adhesive. In one study 78 women used 4 3cm rods (study 07) and in the other 111 women used 6 3cm rods. In 5 years of use there were no pregnancies in either group. Terminations because of menstrual problems were twice as frequent among the 4-rod users than among users of the 6 rods. Menstrual pattern analysis is presented for the two rod regimens and compared with the previously reported patterns for the 6-capsule regimen (NORPLANT®). Long-term *in vivo* release rates are also presented.

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CONTRACEPTION

Introduction

During the development of subdermal implant systems releasing progestins, implants delivering levonorgestrel were found to provide extremely effective protection against pregnancy in comparative trials with another progestin implant system and the Copper T IUD (TCu 200) (1). This levonorgestrel system consists of six Silastic capsules which deliver an average of about 30 µg per day. It is currently being introduced for distribution under the tradename NORPLANT®, the Population Council's registered trademark for contraceptive subdermal implants (2).

In common with other low-dose progestin-only dosage forms, the NORPLANT® implant system is associated with disruption of the menstrual cycle in many women (1), which resulted in a termination rate of 12.3 per 100 women at 12 months. Although this disruption has been reported to improve in 6 to 9 months (3) it was felt that continuation rates would improve if this problem could be alleviated. Previous work with "homogenous rods" containing 25% by weight of levonorgestrel dispersed in polydimethylsiloxane had shown that they exhibited higher release rates than capsules (4), resulting in higher blood levels of drug and a reduction in the number of bleeding days per "cycle" (5,6,7). Amenorrhea was common among women using these implants. The rods were of low physical strength and fragmented easily when they were being removed.

To improve the physical strength of the implants and to increase the release rate per implant, the "covered rod" was designed in which a core rod of equal weights of levonorgestrel and polydimethylsiloxane was sealed inside Silastic medical grade tubing of one-half the wall thickness used for fabricating the NORPLANT® capsules.

Four 3 cm covered rods delivering a total of about 70 µg per day were used in the first trial (Study 07). The observed bleeding patterns among women in this study were not as good as desired so the number of implants was increased to six, delivering a total of about 105 µg per day (Study 12).

We now report the results of these two trials.

Materials and Methods

Admission Criteria

The study protocol required subjects to meet the criteria in Table I. To preclude enrollment of pregnant women, admission was within seven days of the onset of menses.

Table I. Criteria for Subject Selection

General	Medical
Age 18-35	No Cardiovascular Problems
Not currently pregnant	No Jaundice
Not currently breast-feeding	No Diabetes
At least one menses postpartum or post-abortion	No Pelvic Inflammatory Disease
	No Pathological Galactorrhea
Used non-steroid contraception continuously since last menses	No Mental Illness or Depression
Regularly exposed to risk of pregnancy	No Severe Varicosities
Willing to rely solely on implants for contraception	No Frequent and Severe Headaches
Accessible for regular follow-up	No Ectopic Pregnancy
	No Depo-Provera since Last Pregnancy
Gravidity 1+	No Steroid Contraception within 45 days
	Hemoglobin More than 10 g/100 ml

Characteristics of Subjects

Table II lists the mean values of several characteristics of the two groups of women. For each characteristic, mean values were slightly higher among Study 12 women than among women in Study 07.

Table II. Characteristics of Subjects
Mean values

	Study 07, 4 Rods	Study 12, 6 Rods
Age	24.6	27.0
School Years	7.6	8.6
No. Live Births	2.2	2.3
Height (cm)	156	158
Weight (Kg)	52.7	57.6
Systolic B.P.	112.9	116.9
Diastolic B.P.	70.1	70.9
Hemoglobin	13.2	13.4
No. of Women	78	111

Characteristics of Implants

Implants used in these studies were manufactured for the Population Council by Leiras Pharmaceuticals, Turku, Finland. The core rod containing equal parts by weight of micronized levonorgestrel and polydimethylsiloxane without filler was 3 cm in length and each rod was sealed inside a thin-walled medical grade Silastic Tube. The tube was sealed at each end with 1 or 2 mm of medical adhesive. Sets of either 4 or 6 implants were weighed to the nearest milligram, placed in serially numbered Tyvek pouches and the weight of each set was recorded on the label. The loss in weight while *in situ* could thus be determined by re-weighing each set on removal (8). All packages were sterilized with ethylene oxide in the pharmaceutical plant's commercial sterilizer.

Levonorgestrel was a gift from Wyeth International, Philadelphia, Pennsylvania. Each implant used in study 07 contained 53.9 $\pm$ 0.5 mg

(mean ± S.D.) of steroid and in Study 12, 51.6 ± 1.2 mg (mean ± S.D.).

Protocol of the Study

All women underwent a general physical and gynecological examination prior to placement of implants to exclude those who did not meet the admission criteria. Implants were placed under local anesthesia in either the palmar aspect of the forearm or the inner aspect of the upper arm (Finland) within 7 days of the onset of menses. Menstrual calendars were distributed and women were instructed to record all days of bleeding or spotting. Women were instructed to return to the clinic at 1 and 3 months after placement and every 3 months thereafter for the first 2 years. Subsequent visits were made every 6 months. Women were encouraged to return to the clinic any time they had problems with the method or if they suspected they were pregnant. Implants could be removed at any time at the discretion of the doctor or on request by the subject.

Originals of all Check Lists, Admissions, Follow-Up and Bleeding Record forms were mailed to New York. Life-Table analysis of event rates was performed as previously described (9).

Results

Net cumulative termination rates are presented in Table III for both regimens. There were no pregnancies during the 170 woman-years of use in Study 07 and the 300 woman-years of use in Study 12.

Menstrual problems led to termination at more than twice the rate in Study 07 as in Study 12. Terminations for "Other Medical" in Study 12 were almost double those in Study 07. Terminations that could be attributed to effects of the steroid, such as headache, nervousness, nausea, acne and hypertricosis were essentially the same, 12% in Study 07 and 14% in Study 12. The rest of the Other Medical was a miscellaneous list of minor complaints. The sum of terminations for menstrual problems and other medical problems was very similar in both studies.

The reasons for the differences in termination rates between the two regimens appears to be related to major differences in the kind of menstrual changes that occur. In Tables IV and V aspects of the bleeding patterns with the 4-and 6-covered rod regimens are compared with those reported for the 6-capsule system (1,10). It is seen in Table IV that most indicators of increased bleeding declined as the daily dose of steroid was increased. The only exception was numerous bleeding and spotting days (more than 31 days per interval) which was experienced by more women at the intermediate dose level than by those at either the higher or lower dose levels. The 6-rod regimen was associated with less bleeding than either of the other regimens.

Table III Net Cumulative Termination Rates Per 100 Women By Reason and Year

Study 07, 4 Covered Rods

	Years 1	2	3	4	5
Pregnancy	0	0	0	0	0
Menstrual Problems	8	17	20	24	24
Other Medical	5	10	13	13	13
Personal	9	17	25	33	34
Total	22	44	58	70	72
Continuation	78	56*	42	30	28
No. Completing Year	59	30*	22	16	14

N=78 Acceptors
Women-Years of Use 170

Study 12, 6 Covered Rods

	Years 1	2	3	4	5
Pregnancy	0	0	0	0	0
Menstrual	4	8	8	11	13
Other Medical	13	18	21	22	22
Personal	4	8	17	20	22
Total	21	34	46	53	57
Continuation	79	66*	54	47	43
No. Completing Year	87	62*	43	35	34

N=111 Acceptors
Woman-Years of Use 300

*One clinic terminated the study early in the second year which reduced the number of subjects by 16 in Study 07 and by 14 in Study 12.

Table V presents data on three measures of reduced bleeding for the three regimens, infrequent bleeding, amenorrhea and few bleeding days. As the dose was increased from 6 capsules to 4 rods to 6 rods, there was a progressive increase in the percentage of women experiencing these parameters of decreased bleeding.

Table IV. Manifestations of Increased Bleeding
Percent of women experiencing four indicators of increased bleeding during successive 90-day intervals

		Levonorgestrel Implants		
	Days	6 Capsules (18cm)	4 rods (12 cm)	6 Rods (18 cm)
Frequent	1-90	21	6 (70)*	2 (95)*
Bleeding	91-180	12	2 (62)	3 (74)
(5+ runs)	181-270	11	2 (59)	2 (49)
	271-360	9	4 (52)	0 (24)
Prolonged	1-90	35	10	7
Bleeding	91-180	27	5	4
(8+ days in	181-270	25	14	4
a run)	271-360	18	6	8
Numerous	1-90	27	19	6
Bleeding	91-180	23	6	3
Days	181-270	18	12	0
(21 days)	271-360	16	8	0
Numerous	1-90	36	39	25
Bleeding and	91-180	21	45	8
Spotting	181-270	15	25	2
Days	271-360	12	23	0
(31+ days)				

*Number of valid cases in interval.

Table V. Manifestations of Reduced Bleeding
Percent of women experiencing three indicators of reduced bleeding

		Levonorgestrel Implant		
	Days	6 capsules (18 cm)	4 rods (12 cm)	6 rods (18 cm)
Infrequent	1-90	14	21	58
Bleeding	91-180	19	37	84
(<2 runs)	181-270	15	39	80
	271-360	10	44	92
Amenorrhea	1-90	32	39	66
(60+ days	91-180	33	42	82
without	181-270	26	42	88
bleeding)	271-360	24	42	92
Few Bleeding	1-90	16	23	61
Days	91-180	14	31	79
(<5 days)	181-270	13	39	76
	271-360	8	29	79

Dose Rates

As implants were removed they were sent to the New York laboratories of the Population Council for analysis by methods previously described (8). Fig. 1 is a plot of milligrams of levonorgestrel lost from a single 3 cm covered rod vs. time. The points were calculated by dividing the total loss in weight from a set by either 4 or 6, the number of implants in a particular set. Table VI compares release rate estimates for the rod regimens with the rate for the six-capsule system reported by Diaz et al. (3)

Table VI. Daily Dose of Levonorgestrel

Regimen	Dose, µg per day
6-capsule	30
4-rod	70
6-rod	105

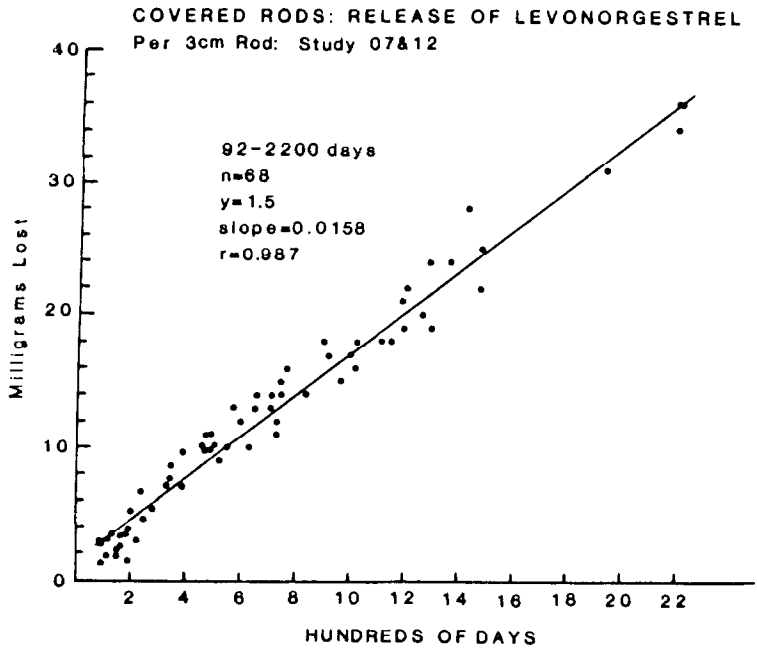

Fig. 1: Release of levonorgestrel from a single 3 cm covered rod, in milligrams vs time.

Discussion

The objective of reducing the termination rates for menstrual problems of 12.3 per 100 women in the first year of use among NORPLANT® capsule users by increasing the dose was moderately successful. First year termination rates for the 4-covered rod and 6-covered rod regimens were 8 and 4 per 100 women, respectively. For the second through fourth years of use, menstrual problem termination rates were over twice as high for the 4-rod users as for the 6-rod users. This appears to be associated with a higher percentage of women who experienced more than 31 days of bleeding and spotting while using the 4 rods than while using the 6 rods because all other parameters showed reduction in bleeding.

These data indicate that women tolerate reduced bleeding and even frank amenorrhea better than increased bleeding and particularly a high number of bleeding plus spotting days. The 4-year cumulative termination rate for menstrual problems with the 4-covered rod regimen is 10 points higher than that reported by Sivin et al. for a 4-year capsule study where 3 of the clinics were the same ones as in this study (2).

The reduction in termination rates for menstrual problems in users of the 6-rod regimens was offset by terminations for other medical reasons and the net result was about the same. First year continuation rates for both regimens were about the same as previously reported for NORPLANT® capsules (1).

At the end of 6 years (2200 days) there is still 33% of the initial steroid content in the rods and there is no evidence for a decline in the rate of disappearance of drug from the rods. One could then select the desired dose of levonorgestrel, adjust the number of centimeters of covered rod to deliver that dose and have considerable confidence that it will be delivered for at least 5 years.

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