

CONTRACEPTIVE EFFECTIVENESS OF SILASTIC*
IMPLANTS CONTAINING THE PROGESTIN R-2323

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ABSTRACT

Silastic capsules containing a synthetic progestin, R-2323, were inserted in 531 women of reproductive age who desired long-lasting contraception. Ninety-eight women received two capsules (Group A), 180 women received three capsules (Group B), 181 women had four capsules (Group C), and 68 subjects received five capsules (Group D). Group A had 5 pregnancies during 610 months of use; Group B had 3 pregnancies during 2,124 months; Group C had 4 pregnancies in 2,128 months of use; and Group D had 3 pregnancies in 732 months of use. Most pregnancies occurred more than 8 months after insertion. Amenorrhea was the most conspicuous side effect involving at least 30% of the subjects at any time during the study. Spotting and breakthrough bleeding were infrequent.

* Silastic is a registered trademark of Dow Corning Corporation, Midland, Michigan, U.S.A.

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INTRODUCTION

The use of subcutaneous capsules made of Silastic^R rubber containing a progestin has been proposed as a practical method to achieve long-term contraception in women (1,2,3). Early clinical trials were carried out with megestrol acetate (M.A.) (2,3,4) and we have continued to explore this contraceptive delivery method with other steroids. We reported recently on the contraceptive effect of capsules containing norgestrienone (5), which appeared to have an advantage over M.A. implants in that they had a significantly longer effective lifetime. On the basis of clinical experience and *in vitro* diffusion rates, it was calculated that 4-6 capsules containing norgestrienone can provide contraceptive protection for one and a half year.

Pilot studies with R-2323 indicated that a high degree of contraceptive effectiveness could be achieved with a small number of implants. The present report describes clinical trials of subdermal implants containing R-2323 (13-ethyl-17 α ethinyl-17 hydroxy-gona-4,9,11-trien-3-one) which is a 19-norsteroid into which three conjugated double bonds were introduced through total synthesis (6) (Figure 1).

Based on the affinity of R-2323 for progesterone receptors, Raynaud *et al.* (7) have characterized this compound as an anti-progesterone. R-2323 also binds to androgen and aldosterone receptors but without exerting any marked anti-androgenic or anti-aldosterone effect. On the other hand, the compound is slightly androgenic, an effect which may be accentuated by a marked anti-estrogenic action. The anti-estrogenic effect of R-2323, however, is not well understood since it counteracts the uterotrophic effects of estrogen without binding to estrogen receptors. R-2323 has been used experimentally to suppress spermatogenesis in men (8). The compound has also been used as a weekly and midcycle oral contraceptive pill for women (9,10).

MATERIAL AND METHODS

The implants were made of Silastic rubber tubing (Dow Corning Corp., Midland, Michigan, No. 602-235) having a 2.4 mm outside diameter and 1.6 mm inside diameter. Three centimeter segments were filled with 30-40 mg of R-2323 and sterilized by steam or irradiation. Following local infiltration anesthesia with 2% xylocaine, the capsules were inserted subcutaneously in the upper gluteal region of the patients through an 11-gauge trocar as previously described (3). Local anesthesia was also used for implant removal at the end of the study.

The clinical trials reported here include 531 women who used 2 to 5 implants containing R-2323. Ninety-eight women (Group A) received 2 capsules, 180 women (Group B) received 3 capsules, 181 women (Group C) were implanted with 4 capsules and 68 women received 5 implants (Group D). Implants used in Groups A, B, and C were derived from two sources; implants made in our laboratory and treated with steam for sterilization and implants supplied by The Population Council and sterilized by irradiation. Group D had irradiated implants only.

Implants removed from subjects at various times after insertion were returned to

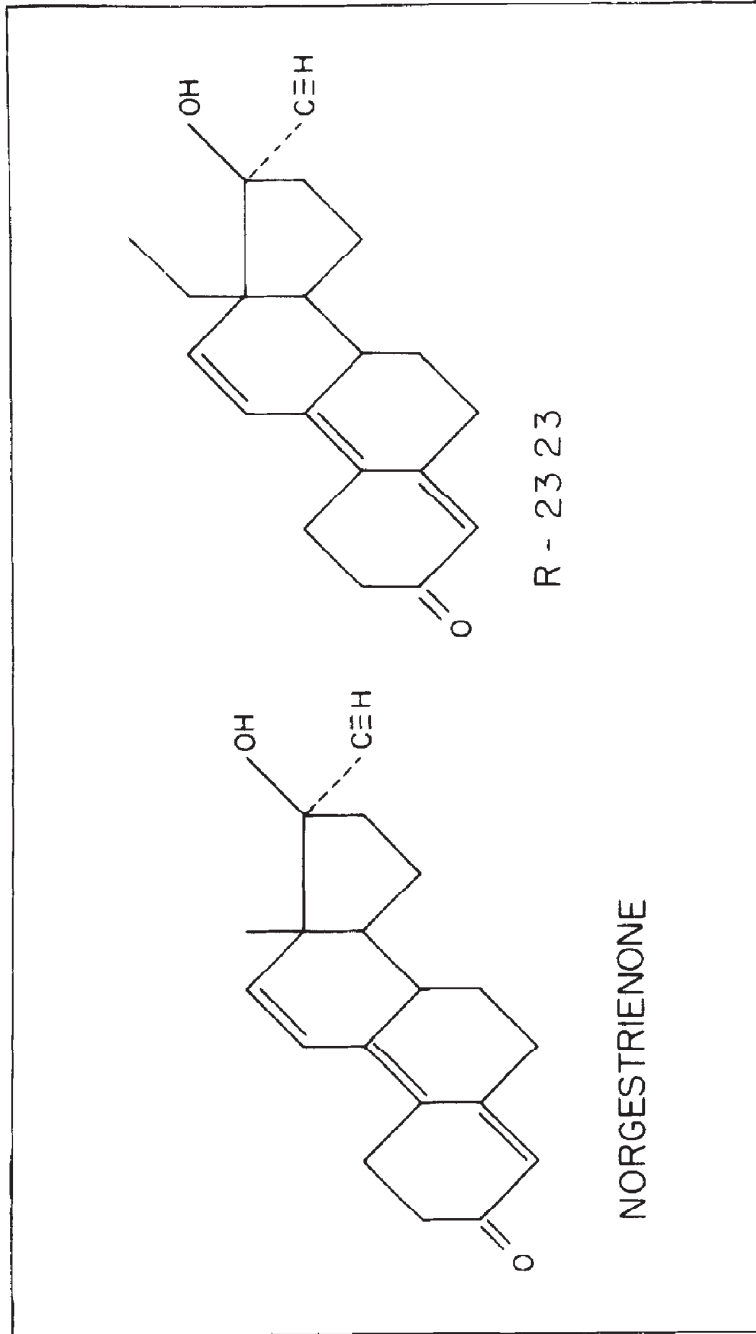


Fig. 1 Structural formulae of Norgestrienone and R-2323.

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The Population Council for analysis of the remaining steroid. The R-2323 was exhaustively extracted from the implant with methylene dichloride and quantitatively analyzed by UV spectrophotometry at 339 nm.

RESULTS

The age and parity characteristics of each study group is summarized in Table I. The distribution of women in each of the study groups is similar and indicates that the studies were composed of reproductive age women of proven fertility.

The accumulated experience and efficacy of R-2323 administered by subdermal implants are summarized by Table II. The 5 pregnancies in Group A occurred during the first (1), second (2), third (1) and fourth (1) months of use. Pregnancies in Group B were conceived in the fourth, sixth and twelfth month of treatment. Group C had one accidental pregnancy in the sixth and ninth and 2 in the eleventh month of use. The 3 pregnancies in Group D occurred in the ninth and tenth month of use. None of the 15 pregnancies was ectopic. Groups A and D, with the smallest experience, yielded a Pearl Index of 9.8 and 4.9, respectively. The larger experience of Groups B and C produced similar rates of 1.7 and 2.3 pregnancies per 100 woman years.

Since pregnancies in Group A occurred during the first few months of treatment, these women were advised that contraceptive efficacy was unsatisfactory. Many women chose to have the implants removed at the time they received this information. This is reflected in the low continuation rate of 54% at 7 months and 8% at 11 months. In the other groups, continuation was good. Eighty per cent of the subjects in Group B and 83% of those in Group C completed 11 months of use while for Group D, the continuation rate at 11 months was 73%.

The R-2323 contained in a group of capsules removed from women at various times after insertion was measured (Figure 2). The line drawn represents a visual average of the remaining steroid as a function of time. At about 12 months, less than 10 mg of R-2323 was left. In some cases, marked variation in steroid content occurred in sets of capsules removed from the same individual. This variation may be due to differences in the initial amount of steroid or to diffusion rate differences of individual capsules.

Amenorrhea was the most conspicuous side effect of the treatment. For purposes of analysis, each 45 days of non-bleeding was defined as a segment of amenorrhea; 90 days of no bleeding is 2 segments. One hundred six segments of amenorrhea were observed in Group A and in Group B, 662 segments during 2000 women months of observation were recorded. Amenorrhea was found 750 times during approximately 2000 women months of Group C's experience. A 45-day segment of non-bleeding was reported 275 times in about 700 women months in Group D. The distribution of amenorrhea during the study of Groups B, C and D is shown in Figure 3. Amenorrhea occurred more frequently during the first 5 months of use in all groups. The highest incidence of amenorrhea for Groups B and C was recorded during the 3rd month of use when 44% and 46% of all subjects were amenorrhetic. Approximately 50% of Group D women were without menstruation in the 2nd and 4th months of use.

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TABLE I
DISTRIBUTION OF WOMEN BY AGE AND PARITY

<u>STUDY</u>	<u>AGE</u>	<u>N</u>	<u>%</u>	<u>PARITY</u>	<u>N</u>	<u>%</u>
Group A 2-R2323 Implants	< 20	4	4.1	0	3	3.1
	20-24	25	25.5	1-2	31	31.6
	25-29	29	29.5	3-4	31	31.6
	30-34	20	20.4	5+	26	26.5
	35-39	10	10.2	N.A.	7	7.1
	40+	4	4.1			
	N.A.*	6	6.1			
Total		98	99.9		98	99.9
Group B 3-R2323 Implants	< 20	6	3.3	0	8	4.4
	20-24	42	23.3	1-2	52	28.9
	25-29	50	27.8	3-4	54	30.0
	30-34	42	23.3	5+	57	31.7
	40+	15	8.3	N.A.	9	5.0
	N.A.	5	2.8			
Total		180	99.9		180	100
Group C 4-R2323 Implants	< 20	5	2.8	0	7	3.9
	20-24	29	16.0	1-2	56	30.9
	25-29	51	28.2	3-4	45	24.9
	30-34	43	23.8	5+	60	33.1
	35-39	25	13.8	N.A.	9	7.2
	40+	11	6.0			
N.A.	17	9.4				
Total		181	100		181	100
Group D 5-R2323	< 20	1	1.5	0	6	8.8
	20-24	17	25.0	1-2	25	36.7
	25-29	23	33.8	3-4	18	26.5
	30-34	15	22.1	5+	17	25.0
	35-39	7	10.2	N.A.	2	3.0
	40+	3	4.4			
N.A.	2	3.0				
Total		68	100		68	100

*N.A. = not available
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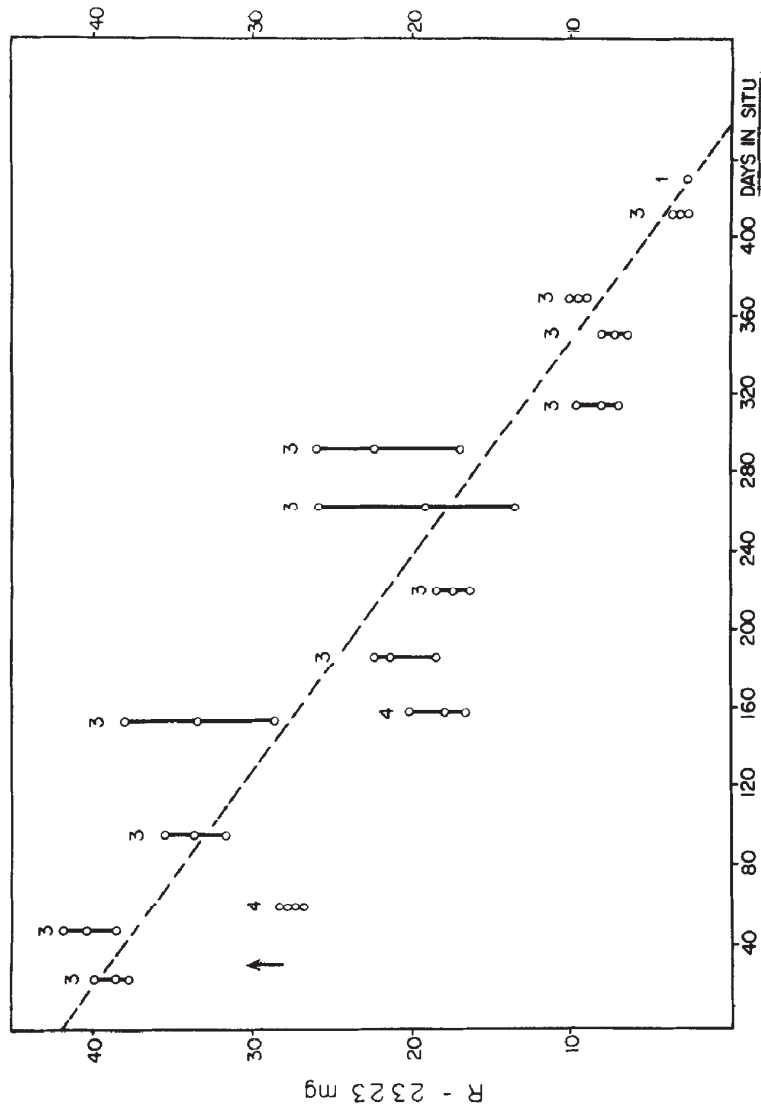


Fig. 2 Milligrams of R-2323 remaining in capsules implanted in women for various time intervals. The number of capsules originally inserted in the patient is indicated on the top of each set. Each capsule analyzed for steroid content is represented by one circle.

AMENORRHEA

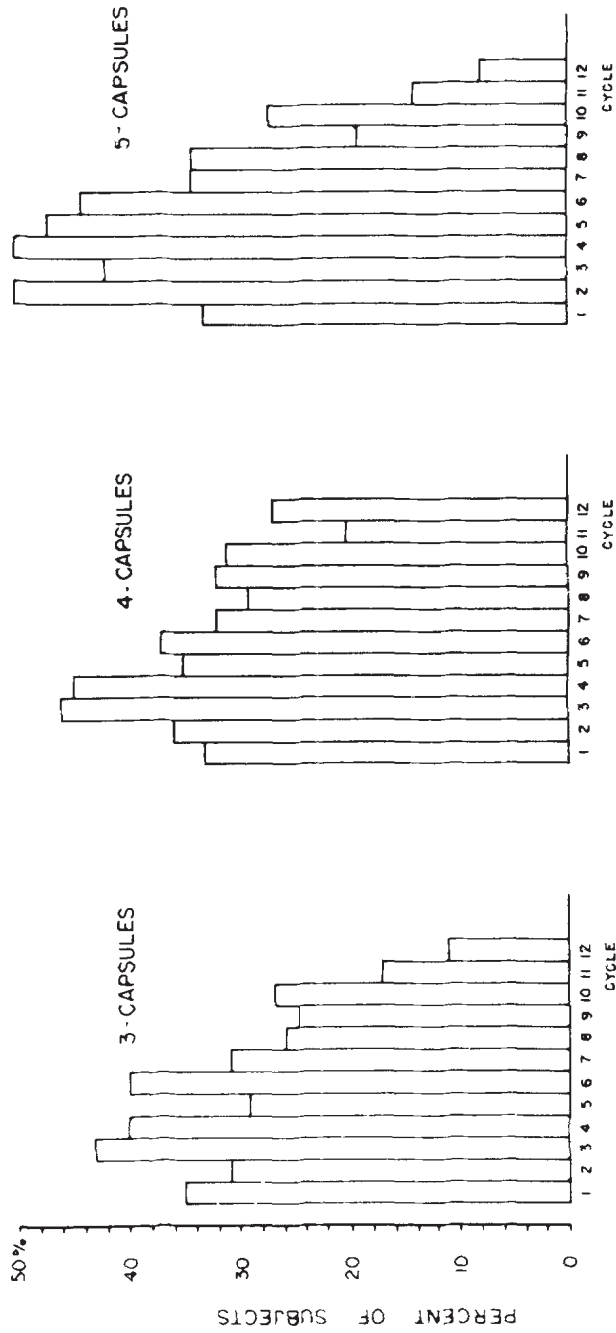


Fig. 3 Incidence of amenorrhea in women using R-2323 implants. Amenorrhea was considered a non-bleeding interval of 45 days or longer. Women included in the first month group were those who failed to bleed at the end of the first 45-day period following the insertion of capsules.

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TABLE II

EFFECTIVENESS OF SUBDERMAL IMPLANTS CONTAINING R-2323

Group	Number of Implants (total centimeters)	Number of Insertions	Women- Months	Pregnancies	Pearl Index
A	2 (6)	98	610	5	9.8
B	3 (9)	180	2124	3	1.7
C	4 (12)	181	2128	4	2.3
D	5 (15)	68	732	3	4.9

In this study, the pregnancy rate increased from 1.7 with 3 implants to 2.3 with 4 implants and 4.9 with 5 implants. This finding is in contrast to our early experience with megestrol acetate (3) and norgestrienone implants (4) which gave greater protection with an increased number of implants and may simply reflect the kind of variation obtained when a small number of subjects is studied. One factor in this discrepancy may be that the daily dosage of R-2323 did not differ greatly because of effective differences in two types of implants that were utilized in the study. During the course of these clinical trials, it was discovered from *in vitro* and *in vivo* (rat) diffusion studies carried out at The Population Council that Silastic capsules which had been sterilized by irradiation released less R-2323 than implants which were untreated or treated with steam or ethylene oxide. The *in vitro* diffusion rate of steroid from non-irradiated capsules was about $23 \mu\text{g}/\text{cm}/24 \text{ hrs}$ and that of irradiated capsules was about $17 \mu\text{g}/\text{cm}/24 \text{ hrs}$. The cause of this reduction is as yet undetermined but studies suggest an effect on the steroid rather than the Silastic tubing containing the steroid. The estimated daily dose administered by implants in Groups A, B and C which utilized both irradiated and non-irradiated capsules was 102-138 μg , 153-207 μg and 207-276 μg , respectively. Group D, which had irradiated capsules only, received about 255 μg of R-2323.

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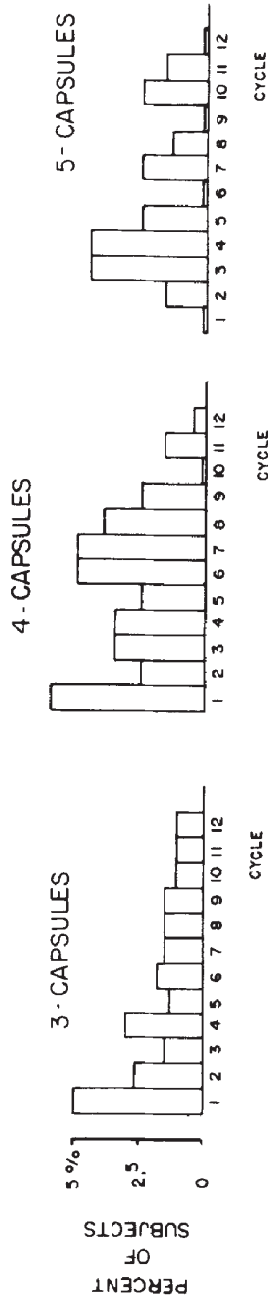


Fig. 4 Incidence of spotting during the treatment.

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Bleeding, whenever it occurred, was usually of 3 to 7 days duration. Intervals between these bleeding episodes varied from 24 to 40 days. Breakthrough bleeding occurred in 5% of all cycles of Group A, 3% in Groups B and C and in Group D, it was recorded in only 2.5% of cycles. Spotting was reported in 3.2% of cycles in Group A and 1.8% in Group B. In Groups C and D, spotting was reported in 2% of all cycles. The occurrence of spotting was highest during the first month of treatment as shown in Figure 4. Endometrial biopsies obtained from either menstruating or amenorrheic women revealed varying degrees of endometrial atrophy. Other side effects observed were acne in 3 cases, hirsutism in 3 cases and hoarseness in one case. One woman reported a decrease in breast size which returned to normal six months after the end of treatment. Subjective increases of breast size were reported by 4 women. The side effects did not have any correlation with number of capsules used, but were scattered throughout all treatment groups.

DISCUSSION

The clinical trials described in this report indicate that 3 or more capsules are required to provide contraceptive protection for about 9 months of use. Three pregnancies were reported in the first 8 months of use and 7 occurred during the ninth-twelfth months of use which suggested that contraceptive effectiveness is decreasing rapidly during that later period. The reasons for the declining protection are not clear since the capsule reservoir of steroid is estimated at about 10 mg or more at 9 months *in situ* (see Figure 2). However, preliminary measurements of blood levels of R-2323 in our laboratory and others (11) have shown that the release rate of this steroid may not be constant during the several months of treatment. Concentrations of R-2323 in the peripheral circulation ranged from 1-2 ng/ml the first few weeks after insertions and variably decreased to less than 1 ng/ml by 6-9 months when 3 to 4 implants were used. At present, the minimum level of steroid necessary to maintain an antifertility effect is not known.

The frequency of amenorrhea was much greater with R-2323 implants than in similar studies using other steroids (3,4). Ovulation inhibition, in addition to the weak progestimimetic activity of R-2323, may be the cause of the high incidence of amenorrhea during the first four months of use when R-2323 blood levels are apparently at their maximum. More prolonged amenorrhea or amenorrhea occurring at the end of treatment may result from endometrial atrophy. Some patients remained amenorrheic after discontinuation of therapy, and in some of these cases, uterine bleeding was induced by injection of 5 mg estradiol benzoate followed by 100 mg of progesterone injected daily for 5 days.

On the whole, the suppression of menses was well tolerated by this clinic population. However, the increasing numbers of pregnancies after 8 or 9 months of use and the appearance of androgenic side effects make this implant regimen less favorable than some others we have studied.

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