Acceptability of long-term contraceptive steroid administration in humans by subcutaneous Silastic capsules

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Capsules of silicone rubber each containing approximately 18 mg. of megestrol acetate (MA) were implanted subcutaneously in 24 women. During the first portion of this study the patients were wearing IUCD's. Four different dosage groups were studied. Pregnancies occurred in patients who received one or two implants but not in those bearing either four or six capsules. Clinical, histologic, and cytologic data suggested that ovulation was not suppressed by four or fewer implants. The data suggested that there was frequent inhibition of ovulation in the patients bearing six implants. The patients' subjective reaction to this new technique was favorable. There were no local or systemic complications attributable to the implants. It is suggested that fewer than six implants of this size may provide acceptable long-term contraception without the inhibition of ovulation.

THE CONCEPT of using a subcutaneously placed inert capsule containing a contraceptive for long-term control of fertility evolved from two major discoveries. The first was the disclosure by Folkman and Long[1] that certain physiologically active materials could diffuse through the walls of a silicone rubber capsule into an aqueous phase at a slow sustained rate. Subsequently Dziuk and Cook[2] reported that silicone rubber implants in ewes allow "sustained passage of constant amounts of steroids over long periods of time." They also concluded that the rate of diffusion of the steroid through the capsule was governed largely by the thickness of the capsule wall and by its surface area. The second major discovery was made by Rudel, Martinez-Manautou and Maqueo-Topete[3] who demonstrated that conception could be prevented by small doses of a progestogen without suppressing ovulation. This latter observation initiated the new era of microdose progestogen contraceptive technology. Segal and Croxatto[4] combined Rudel and Martinez-Manautou's principle of slightly altering the hormonal control of the endometrium by daily microdoses of a hormone with the sustained release silicone rubber capsule of Folkman and Long and of Dziuk and Cook. They confirmed the earlier observations related to the sustained release of steroids through Silastic capsules and corroborated the reports that the rate of diffusion was determined to some extent by the surface area and by the wall thickness of the Silastic membrane. Addi-

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Table I. Classification of patients into different groups, according to number of implants and duration of therapy

Group	*No. of patients*	*No. of capsules (per patient)*	*Duration of therapy (months) Total for group*	*Exposure without IUCD (months)*	*Pregnancies*
A	6	1	70	10	2*
B	6	2	95	0	1
C	7	4	84	10	0
D	5	6	57	33	0
Total	24	—	306	53	3

*One of these occurred after the IUCD was removed.

tional refinements in knowledge of the physicochemical diffusion characteristics of Silastic capsules with particular reference to the biologic effectiveness of megestrol acetate were reported by Chang and Kincl.[5] With this background information two clinical pilot studies were begun in humans; one, by Croxatto and collaborators in Santiago, Chile[6] (see this JOURNAL, pp. 1135-1138), and the other by us in Salvador, Bahia, Brazil. This present report describes our Brazilian study which was carried out at the Maternity Hospital of the Federal University of Bahia. The principal objectives of this study were to determine the local effects of the implants and if possible the *maximum* number of implants which would permit the hypophyseal-ovarian-uterine axis to function normally. It was presumed that this dosage of MA would permit normal cycling while at the same time could provide effective contraception according to the continuous oral microdose progestogen concept of Rudel and associates.

Material and methods

The capsules or impants were hand made from medical grade dimethylpolysiloxane (DPS) tubing, No. 602-265, manufactured by Dow-Corning, Midland, Michigan. Each capsule was 20 mm. in length and 2.4 mm. in diameter. Approximately 18 mg. of crystalline MA* was placed in each capsule. Each end of the capsule was sealed with a 5 mm. plug of Silastic medical adhesive type A. Thus each capsule had a filled length of 10 mm. The in vitro diffusion from each capsule of this dimension into a distilled water system was approximately 18 μg MA per 24 hours. The capsules were steam sterilized and then introduced subcutaneously in the ventral aspect of the forearm through an 11 gauge trocar. Intracutaneous local anesthesia was used for the procedure. Four groups of women were studied (Table I). Depending upon the group to which they were assigned, each patient received either one (Group A), two (Group B), four (Group C), or six implants (Group D). A total of 24 women of proved fertility were admitted to the program. The duration of exposure to the implants varied from 10 to 18 months for individual patients. Initially, all patients were wearing intrauterine contraceptive devices.

Each patient was seen at monthly intervals at which time her uterine bleeding pattern for the preceding month was charted. Endometrial biopsies were obtained from all except 2 of the patients on day 17-24 of their cycles. This was done during several cycles for each patient during the course of the study. Spinnbarkheit tests were performed on cycle day 14-15 during one or more cycles on the majority of patients at random intervals during the study. Basal body temperature curves throughout the cycles were obtained from approximately one half of the patients. All patients had vaginal cytologic studies at the beginning of the study and at various intervals thereafter. In some patients the IUCD's were removed during the course

*17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione, The British Drug Houses, Ltd., London, England.

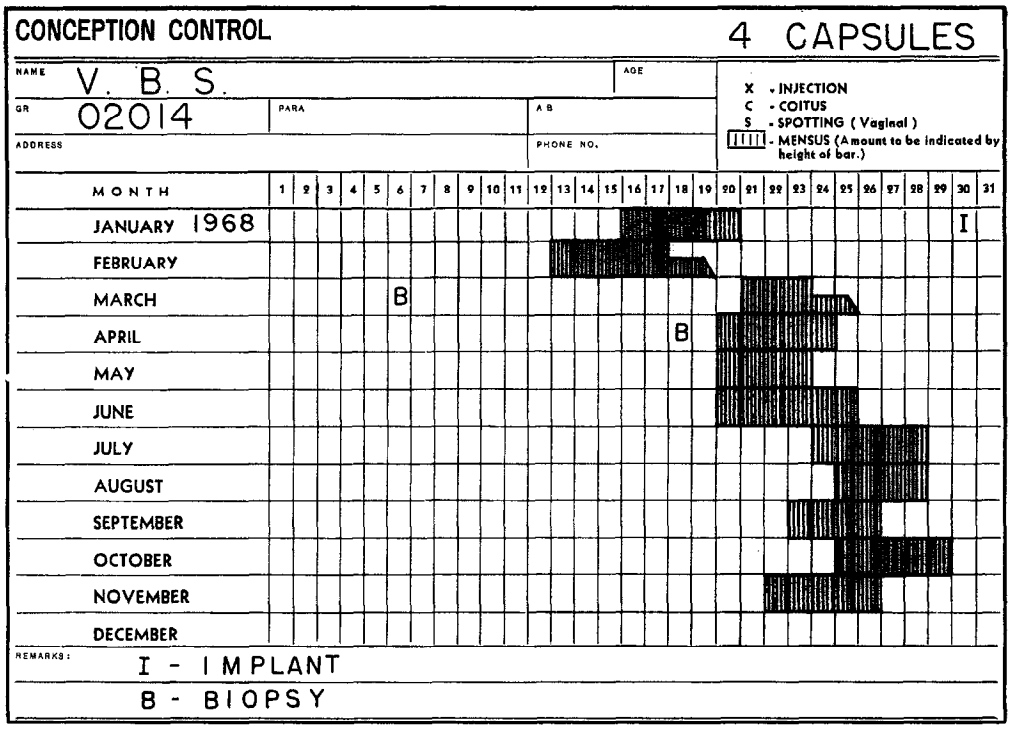

Fig. 1. Menstrual bleeding pattern of representative patient bearing four MA implants.

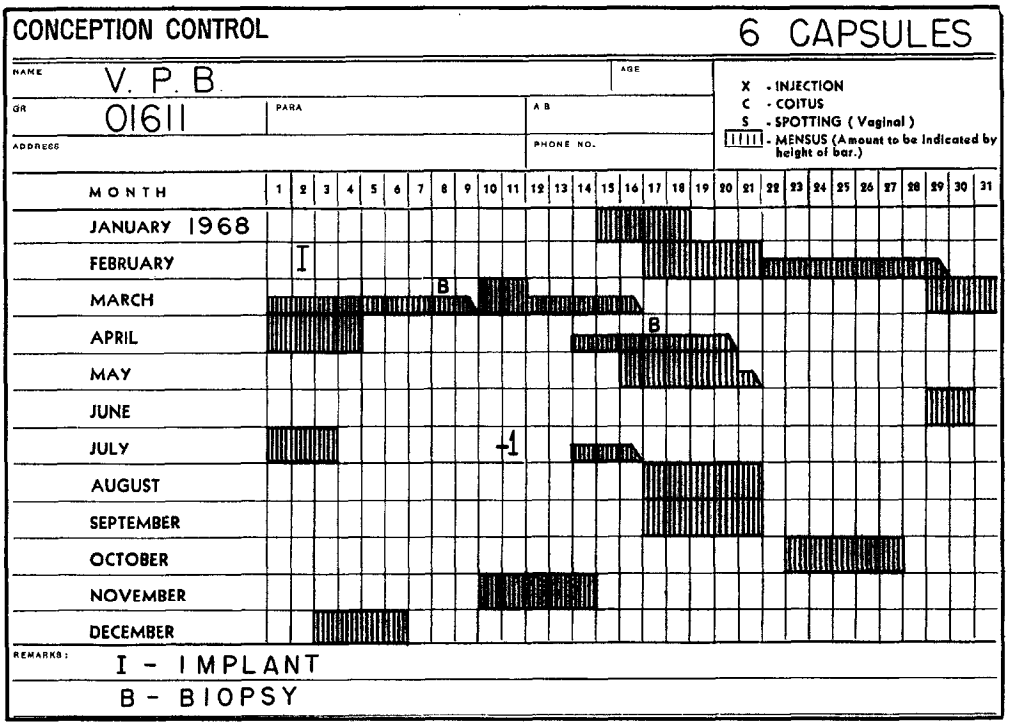

Fig. 2. Menstrual bleeding pattern of representative patient bearing six MA implants.

of study to permit better interpretation of the bleeding pattern and to make a preliminary assessment of the contraceptive effectiveness of the implants.

Results

Except for some local tenderness for a few days following the implantation, no local reactions occurred. Throughout the study the implants remained in their original location.

There were 3 pregnancies in this study. Two of these appeared in Group A around the fourth month. One of these occurred while the IUCD was in situ. The third pregnancy occurred in the fourth month in a patient in Group B. This patient also was wearing an IUCD (see Table I).

There were no changes in uterine bleeding patterns in patients of Groups A, B, and C. Fig. 1 shows a representative bleeding pattern of patients in these groups.

In Group D episodes of intermenstrual bleeding, hypermenorrhea, and spotting were frequent. These alterations were greater during the first two months after insertion of the implants (see Fig. 2). In no instance in any group was there amenorrhea except when pregnancy ensued.

The endometrial biopsies from patients in Groups A, B, and C during days 17-24 revealed consistently a secretory endometrium. In Group D, however, a mixed pattern of endometrium was found which did not allow a precise diagnosis. Cyclic changes in the vaginal cells were present in all patients of Groups A, B, and C, but were inconsistent in patients of Group D. No pathologic changes were observed in the vaginal smears.

Typical biphasic temperature curves and normal spinnbarkheit tests were recorded in patients in Groups A, B, and C. In Group D, the BBT curves were irregular and the spinnbarkheit tests could not be performed properly because of the intermenstrual bleeding.

In one patient from Group D one implant was removed after 4 months because of the abnormal bleeding pattern. A comparison of the bleeding patterns before and after this one implant was removed is shown in Fig. 2.

Comment

The present study supports the concept that a subcutaneously implanted capsule for long-term contraception is both practical and acceptable. Although the implant could have been introduced at many other sites, the ventral aspect of the forearm has proved to be very satisfactory. The capsules are readily available for visual and tactile inspection and yet are sufficiently obscured esthetically. They are also relatively well protected from direct external trauma. The patients reacted favorably to the idea of long-lasting protection afforded by this relatively simple method.

The occurrence of pregnancies in Groups A and B indicates clearly that the amount of MA released by two implants is not sufficient to interfere with ovulation and/or to prevent conception. In Group C the indirect evidence provided by the clinical, cytologic, and histologic data suggests that the amount of MA liberated from four implants does not interfere with ovulation. However, the antifertility effect of the four implants could not be adequately evaluated, since the patients of this group were exposed for a total of only 10 woman-months without the simultaneous protection of IUCD's.

Although the endometrial pattern of the patients in Group D did not provide a clear picture of anovulatory cycles, the abnormalities of the bleeding pattern and temperature curves suggested that this was the case. It should be noted that the IUCD's were responsible at least in part for the bleeding abnormalities in this group. A considerable improvement in the bleeding pattern was noted in all patients following removal of the IUCD's. The antifertility effect of the six implants was suggested by the absence of pregnancies during the 33 woman-months of exposure after the IUCD's were removed. No serious local or systemic complications attributable to the implants occurred.

The data derived from the patients in Groups C and D suggest that the minimum

daily dose which will afford contraception without suppression of ovulation is provided by the amount of MA liberated by four to six capsules of the dimensions used here (72-108 μg per 24 hours' in vitro liberation). The contraceptive effectiveness of this method is presently being studied in a larger series of patients and will be presented in a subsequent report.

REFERENCES

1. Folkman, J., and Long, D. M.: J. S. Res. **4:** 139, 1964.
2. Dziuk, P. J., and Cook, B.: Endocrinology **78:** 208, 1966.
3. Rudel, H., Martinez-Manautou, J., and Maqueo-Topete, M.: Fertil. & Steril. **16:** 158, 1965.
4. Segal, S. J., and Croxatto, Horacio: Presented at the XXIII Meeting of American Fertility Society, April 14-16, 1967, Washington, D. C.
5. Chang, C. C., and Kincl, F. A.: Steroids **12:** 689, 1968.
6. Croxatto, Horacio, Diaz, S., Vera, R., Etchart, M., and Atria, P.: AM. J. OBST. & GYNEC. In press.