LONGTERM CONTRACEPTION BY SUBCUTANEOUS SILASTIC[R] CAPSULES CONTAINING MEGESTROL ACETATE *

Elsimar M. Coutinho
Carlos E. R. Mattos
Ana Rita S. Sant'Anna
J. Adeodato Filho
Maria Conceicão Silva
Howard J. Tatum**

Department of Biochemistry and Obstetrics
Maternidade Climerio de Oliveira
Federal University of Bahia, Bahia, Brazil

** The Population Council, The Rockefeller University, New York

ABSTRACT

Contraceptive effectiveness and acceptability of subcutaneous silastic capsules containing Megestrol Acetate (M.A.) were evaluated in 188 women of childbearing age. The patients were observed for a minimum of 2 and a maximum of 18 months. A total of 1,448 cycles were recorded. In patients bearing 4 implants eleven pregnancies were reported during 1,076 months of use. No pregnancies occurred in the group of patients bearing 5 capsules, during 372 months of use. Data are presented which suggest that in most patients in both groups conception is prevented without inhibition of ovulation.

INTRODUCTION

The use of subcutaneous silastic capsules containing synthetic progestins has been shown to be a practical and acceptable method of long-term contraception (1,2,3). The new technique has the advantage of preventing conception for long periods of time without the consistent inhibition of ovulation. This is possible because the steroid is released slowly in minute quantities which apparently are insufficient to suppress gonadotropin release.

Silastic[R] is a registered trademark of The Dow Corning, Corp., Midland, Michigan.

* 17α-acetoxy-6-methylpregna-4, 6-diene-3, 20-dione.

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Pilot studies with M. A. indicated that effective contraception lasting approximately one year could be obtained with 4 implants each containing 18 mg of the compound. With higher doses ovulation was frequently inhibited thus causing amenorrhea and increasing the incidence of irregular bleeding (1,2).

On the basis of these preliminary observations, the present study which consists of a clinical evaluation of the M.A. implants in a larger group of patients was undertaken.

MATERIALS AND METHOD

Silastic capsules (silastic tubing 602-235, having an O.D. of 2.40 mm) containing approximately 23 mg of M.A. within a filled length of 20 mm were manufactured by the British Drug House, Ltd., London, and were supplied by The Population Council Inc., New York. The capsules were inserted subcutaneously in the upper ventral aspect of the forearm of the patients through an 11-gauge thin walled trocar. Four capsules were inserted in each of 106 normal patients of childbearing age. In another group of 82 patients, 5 capsules were introduced. At the end of 10 to 12 months of use the capsules were replaced by a new set.

Occurrence of ovulation was investigated in randomly selected patients from both groups. The indices which were used to assess the presence or absence of ovulation were (a) basal body temperature curves; (b) endometrial biopsies during one or the other of the two phases of the menstrual cycle; (c) uterine bleeding patterns, and; (d) myometrial activity and the myometrial response to vasopressin. The numbers of patients, tests or cycles studies are shown in Table I.

TABLE I

CRITERIA FOR DETECTION OF OVULATION

	4 implants	5 implants
Basal Body Temperature		
Number of patients reporting	60	52
% of total patients	57	63
Number of cycles	200	120
Endometrial Biopsies		
Proliferative phase (Day 2-7)	20	15
Secretory phase (Day 22 $\pm$ 2)	50	38
Uterine Bleeding Pattern		
Cycles reported	1076	372
Intermenstrual bleeding	37	16
Hypermenorrhea	109	40
Oligomenorrhea	33	7
Amenorrhea	87	26
Myometrial Activity		
Cycles studied	10	10

In addition to the relevant information listed in Table I, each patient provided monthly data regarding the frequency of coitus. Coitus was recorded as having occurred from 2 to 9 times per month. Contraception was limited to that provided by the implants.

RESULTS

Four implants

The patients bearing 4 implants were observed for 1076 months of use. The minimum period of observation was 4 and the maximum 18 months. During this interval 810 cycles were considered to be normal (75%). A menstrual pattern typical of a patient in the group with 4 implants is shown in Figure 1.

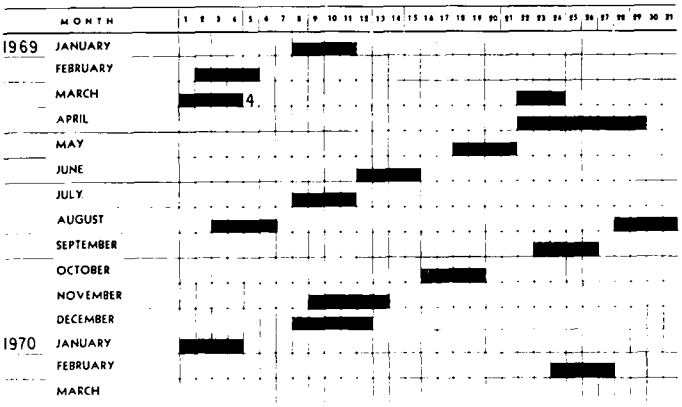

Figure 1

Menstrual pattern of a patient bearing 4 subcutaneous capsules of Megestrol Acetate. Black bars represent menstruation. The capsules were inserted on March 5. Note that the first menstruation which occurred after insertion of the implants was shortened by one day and was advanced by one week. The second menstruation occurred on the expected date but was prolonged, lasting 8 days. Note the regular pattern for the remaining 10 months of the first year of use.

Thirty seven patients (34%) reported intermenstrual bleeding or spotting at least once. Hypermenorrhea (bleeding episodes lasting longer than 6 days) occurred in 43% of the patients in a total of 109 cycles (10%). See Table I. Eleven patients became pregnant during treatment resulting in a pregnancy rate of approximately 10 per 100 patients per year of use (Pearl Index = 12). Five pregnancies occurred after 9 months of use. The other 6 pregnancies occurred between the third and seventh month of use.

Five implants

The patients bearing 5 implants were observed for a total of 372 months. Twenty women of the group were observed for more than 10 months. The maximum period of observation, however, was 13 months and the minimum was 2 months. No pregnancies occurred in this group. As shown in Figure 2, the menstrual pattern for most patients was similar to that of the group bearing 4 implants.

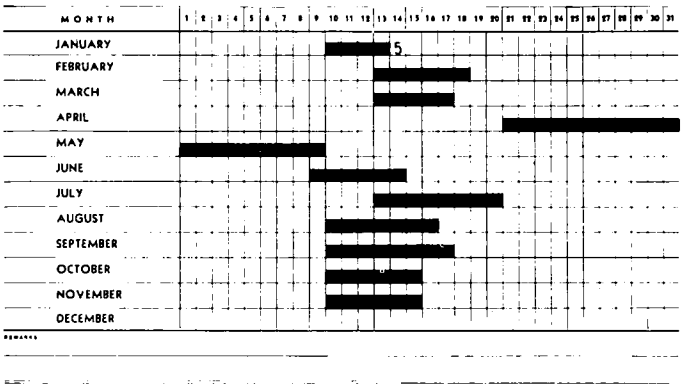

Figure 2

Menstrual pattern of a patient bearing 5 subcutaneous capsules of Megestrol Acetate. The capsules were inserted on January 14. Note that the duration of menstrual bleeding was prolonged by one to three days. An episode of hypermenorrhea lasting 20 days occurred during the third month of use.

In this group intermenstrual bleeding or spotting was reported at least once by 16 patients (16 cycles-19%). Amenorrhea occurred in 15 patients for a total of 26 cycles (7%). Hypermenorrhea was reported by 17 patients (21%) of this group for a total of 40 cycles (11%). See Table I. These abnormal episodes were apparently related to anovulatory cycles and did not occur in ovulatory cycles. By these criteria, 283 cycles were considered to be normal (76%). This phenomenon is also illustrated in Figure 2.

A tabulation of the incidence of factors related to ovulation which occurred in the patients bearing 4 or 5 implants

is shown in Table II.

TABLE II

INCIDENCE OF FACTORS RELATED TO OVULATION

	4 implants	5 implants
Basal Body Temperature		
Number of Biphasic cycles	140	60
Incidence of Biphasic cycles	70%	50%
Endometrial Biopsies (Day 22 ± 2)		
Number of biopsies consistent with date	37	25
Incidence	74%	66%
Bleeding Pattern Consistent With Ovulation		
Number of cycles	810	283
Incidence	75%	76%
Myometrial Activity Consistent With Ovulation		
Number of cycles	7	5
Incidence	70%	50%

Cyclic changes in myometrial activity and pharmacologic reactivity suggestive of unimpaired ovarian function were observed in patients from both groups. The number and incidence of cycles studied in this manner which were consistent with ovulation are shown in Table II. The myometrial pattern illustrative of ovulation is shown in Figure 3.

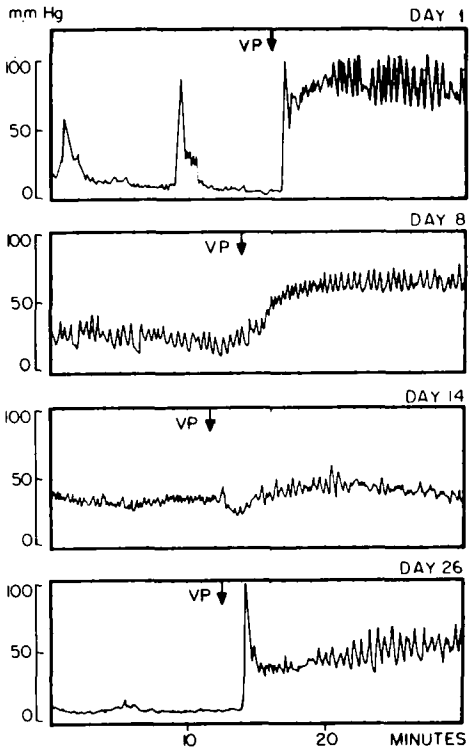

Figure 3

Uterine activity and myometrial response to vasopressin of a patient bearing 4 implants for 7 months. Uterine motility recorded by the microballoon technique (4), in selected days of the menstrual cycle. One unit of vasopressin was injected intravenously at the arrow. Note the positive response during menstruation (Day 1) and its progressive disappearance toward midcycle. On DAY 14 a negative response typical of estrogen domination is recorded, but by DAY 26 the positive response indicative of suppression of estrogen domination by the corpus luteum reappears.

DISCUSSION

The present study confirms previous observations that conception can be prevented by Megestrol Acetate released slowly and continuously from subcutaneous silastic capsules. These data also suggest that the protection provided by this treatment against undesired pregnancy was possible without inhibition of ovulation.

The occurrence of ovulation was indicated by cyclic ovarian function documented by biphasic temperature curves, by a regular pattern of uterine bleeding, and by secretory changes in the endometrium preceding periodic bleeding. Further evidence for the normal ovarian activity was adduced by the demonstration of changes in myometrial sensitivity which are correlated with the presence of a secretory corpus luteum (4). On the basis of these data it has been estimated that between 70 and 80% of the cycles of patients with 4 capsules and 60-70% of the cycles of women with 5 implants were ovulatory.

The abrupt increase in pregnancy rate after 9 months of use indicates that the amount of M.A. released from 4 implants is by then insufficient to afford complete protection. This should be expected in view of the data obtained by radioactive M.A. excretion studies which suggested a slow but steady decline in the daily release of the compound (5). Each of the pregnancies which occurred because of method failure was intrauterine.

Although the number of cycles in the group bearing 5 capsules is still small, it would seem that the greater protection afforded by the additional capsule outweighs the potential disadvantages of a higher dosage for prolonged periods of use. It should be pointed out that the relative infrequency of side effects compares favorably with other modes of administration of steroidal contraceptives such as progestogens by continuous daily oral microdoses. There has been no gross evidence of local tissue reaction to the implanted capsules. In this series, no capsules had to be removed because of adverse reactions other than contraceptive failure.

The present study indicates that long-term contraception by this technique can be recommended as being safe, effective (with proper dosage), and inexpensive.

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