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ONE YEAR CONTRACEPTION WITH A SINGLE SUBDERMAL IMPLANT CONTAINING NOMEGESTROL ACETATE (UNIPLANT)

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ABSTRACT

One single silastic capsule containing nomegestrol acetate, Uniplant, was inserted subcutaneously in 100 women of reproductive age who desired to avoid conception. Insertions and removals of the capsules were made in the gluteal region following intracutaneous local anesthesia with 2% procaine. Eighty women completed one year of use. Eleven women bore the implant for 6-11 months. A total of 1,085 women-months were recorded. One pregnancy occurred, resulting in a Pearl Index of 1.1. Bleeding episodes similar to menstruation occurred in all women but the degree of regularity varied from subject to subject. Amenorrhea developed in the range of 14-18% during the first six months of use but declined to less than 10% during the last six months. Menorrhagia likewise was higher in the first six months (18% in the first month) but fell to less than 10% during the last six months. Spotting was 5% or less. Of the twenty women who did not complete one year of use, nine discontinued because they found other methods were either more practical or less revealing. Three discontinued because of bleeding irregularities, three desired to become pregnant, one became pregnant. Other complaints included dizziness, headache, increased blood pressure, loss of libido, painful breasts and nausea. Over half of the women indicated their desire to continue using the single implant as a contraceptive.

INTRODUCTION

That silastic capsules containing a progestin could be used effectively to prevent conception in women for long periods of time was shown in studies carried out simultaneously in Brazil and Chile twenty years ago (1,2). The drug used in these early studies was megestrol acetate (M.A.). The number of capsules of M.A. required to provide full contraceptive protection was in excess of four, a number considered too high for just one year of contraception (3,4). Several compounds were later identified which could provide contraception for longer periods of time. Norgestrienone protected for two years, norethindrone for three years and levonorgestrel for five years or longer (5,6). In every case, however, six or more capsules were required for full protection. Effective contraception was achieved with a single capsule of ST-1435 but the duration of the effect lasted only six months (7). The present report describes our experience with nomegestrol acetate (3,20-oxo-6-methyl-17-alpha-acetoxy-19-norpregna-4,6-diene), a close relative of both ST-1435 and megestrol acetate with an affinity for

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progesterone receptors and moderate antiestrogen and antiandrogen activity. The drug has been available in Europe for several years, being used orally as a progesterone agonist (8).

MATERIAL AND METHODS

The implants were hand-made from medical grade dimethylpolysiloxane (Silastic) tubing, catalogue number 602-265, made by Dow Corning, Midland, Michigan. Segments measuring 39 mm of total length (35 mm of filled length) and 2.4 mm in diameter were used to make the implants. The segments of silastic tubing were filled with 38 mg (±10%) of crystalline, finely-ground nomegestrol acetate (3,20-oxo-6-methyl-17-alpha-acetoxy-19-norpregna-4,6-diene; Theramex, France) and sealed at both ends with silastic medical adhesive, type A. Steam sterilization, which proved effective in previous studies with silastic implants, was used (6). In pilot studies implants were analyzed before and after steam sterilization and it was confirmed that no alteration occurred in the steroid content of the implant during this procedure.

Following intracutaneous local anesthesia with 2% procaine, one single capsule was inserted subcutaneously in the gluteal region of 100 healthy women of childbearing age (86 women were less than 30 years of age), all sexually active and who preferred this method of contraception to other methods available in the clinic, such as the pill or the intrauterine device. Only women having regular menstruation were accepted. An 11-gauge trocar (Beckton Dickison & Co., Rutherford, N.J.) was used for insertion of the Uniplant. At the end of the study or at any time following discontinuation, the capsule was removed, with the help of a small forceps, through an incision made with the trocar. Removals were also preceded by local anesthesia with 2% procaine.

In order to measure the amount of residual nomegestrol acetate, implants removed from patients who discontinued at different time intervals and at the end of the study were cleaned with physiological saline solution, dried in a desiccator and weighed. An estimate of the amount of the compound released between the various time intervals was based on the reduction in weight of the used capsule. Endocrine profiles which included measurements of progesterone, estradiol, LH and FSH by radioimmunoassay were established for twenty subjects. These studies will be reported in a separate paper. Bleeding patterns were recorded on a diary card which was checked by the physician every month. Amenorrhea was defined as a non-bleeding interval of 45 days or longer. Intermenstrual bleeding was defined as a light or moderate bleeding occurring between two periodic menstrual-like bleeding episodes. Menorrhagia is defined as heavier or prolonged menstrual bleeding. Ultrasound assessment of the uterine cavity and B-HCG RIA were carried out in patients who developed amenorrhea in order to investigate the possibility of pregnancy. Blood pressure and weight were measured monthly.

The selection of the 35 mm capsule length was based on a pilot study carried out in a small group of volunteers which indicated that a 20 mm capsule allowed ovulation in all subjects, whereas 40 mm inhibited ovulation in most women. It was estimated that the 35 mm capsule, although unable to inhibit ovulation in all cycles, would be sufficient to prevent conception through other antifertility mechanisms. The finished product was named the "Uniplant". Whenever applicable, Student's T test was used to establish statistical significance.

RESULTS

Eighty patients completed one year of use. Eleven women bore the Uniplant for 6-11 months, and only nine patients had the implant removed before six months of use. A total of 1,085 women months of use were recorded. Only one pregnancy occurred, resulting in a Pearl Index of 1.1. Bleeding episodes similar to menstruation occurred in all patients but the degree of regularity varied from patient to patient. Among the 80 women who completed one year of use, the mean number of bleeding episodes was 12.24 (S.E. 0.29), with an average duration of the bleeding runs of 5.24 days (S.E. 0.11). Table I shows the bleeding characteristics of these women while Figure 1 shows the individual bleeding patterns of the first 20 women having completed one year of use. Amenorrhea occurred in 19 of 100 women (19%) in the first 45 days of use. The occurrence of amenorrhea diminished during the following months, being 8.8% at six months and only 4.7% at eleven months (Fig.1). Intermenstrual bleeding, likewise, began at 11% during the first month of use, declining steadily to 6% at 6 months, and to only 1% during the last month of use. Spotting was noted in 4% of patients during the first month of use and in less than 2% of patients in month 6.

No significant increase in blood pressure occurred during Uniplant use. In fact, a significant ($p=0.029$) decrease in systolic blood pressure from 109.6 to 105.8 mmHg was recorded for this group of patients. The mean body weight at admission of 56.2 kg increased to 57.3 kg at the end of one year. This increase of 1.1 kg was found to be statistically significant with $p=0.0005$. Fig. 2 shows weight and blood pressure before and at 12 months.

Of the twenty women who did not complete one year of use, nine discontinued because they preferred other methods of contraception. Three discontinued because of bleeding irregularities, two because of weight increase, three desired to become pregnant, one became pregnant, one because of dizziness and one because of dysmenorrhea. Other complaints included headache (5%), increase in blood pressure in one patient, loss of libido (2%), painful breasts (3%) and nausea (4%).

Implants removed at various time intervals of use indicate that nomegestrol acetate is released at the rate of approximately 100 mcg daily during the first three months of use. This rate declines

T A B L E I

NOMEGESTROL ACETATE IMPLANT (UNIPLANT)

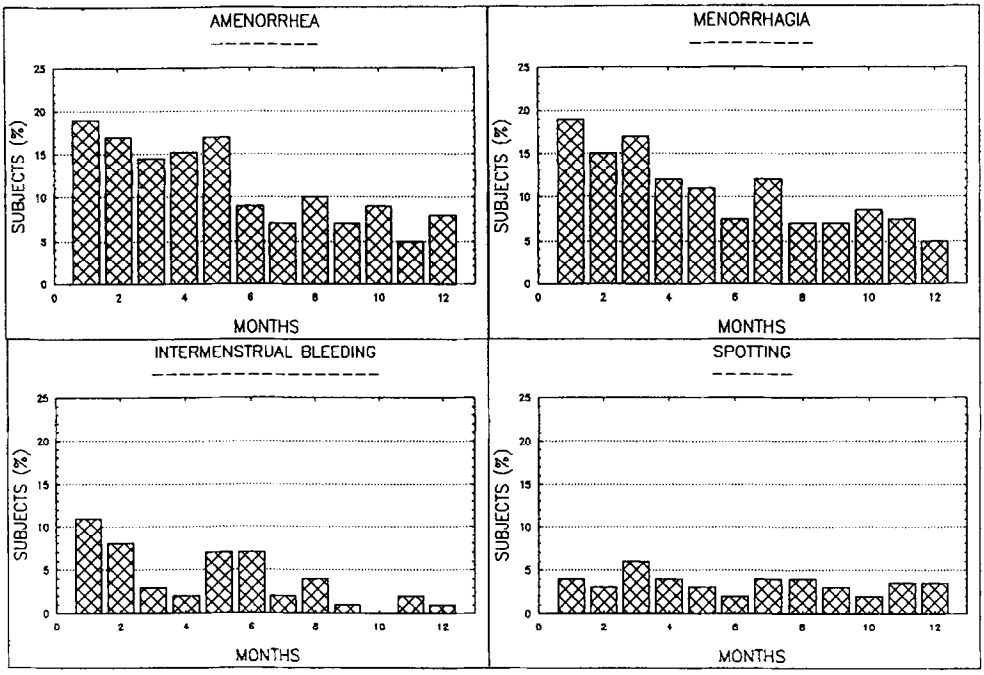
Menstrual Pattern during 12 months of use (N=80 women)

VARIABLE	MEAN	S.E.
Number of bleeding runs*	12.24	0.29
Average duration of runs (days)	5.24	0.11
Total bleeding days	64.19	2.75
Total spotting days	7.24	1.50
Bleeding and spotting days	71.42	3.22
Average non-bleeding interval (days)**	24.51	0.60
Average episode length (days)***	29.80	0.60
Longest bleeding run (days)	10.70	0.92
Longest non-bleeding interval (days)	57.86	4.13

* A bleeding run is one or more consecutive days of bleeding (excluding spotting) and the usual concept of the menses and of breakthrough bleeding.

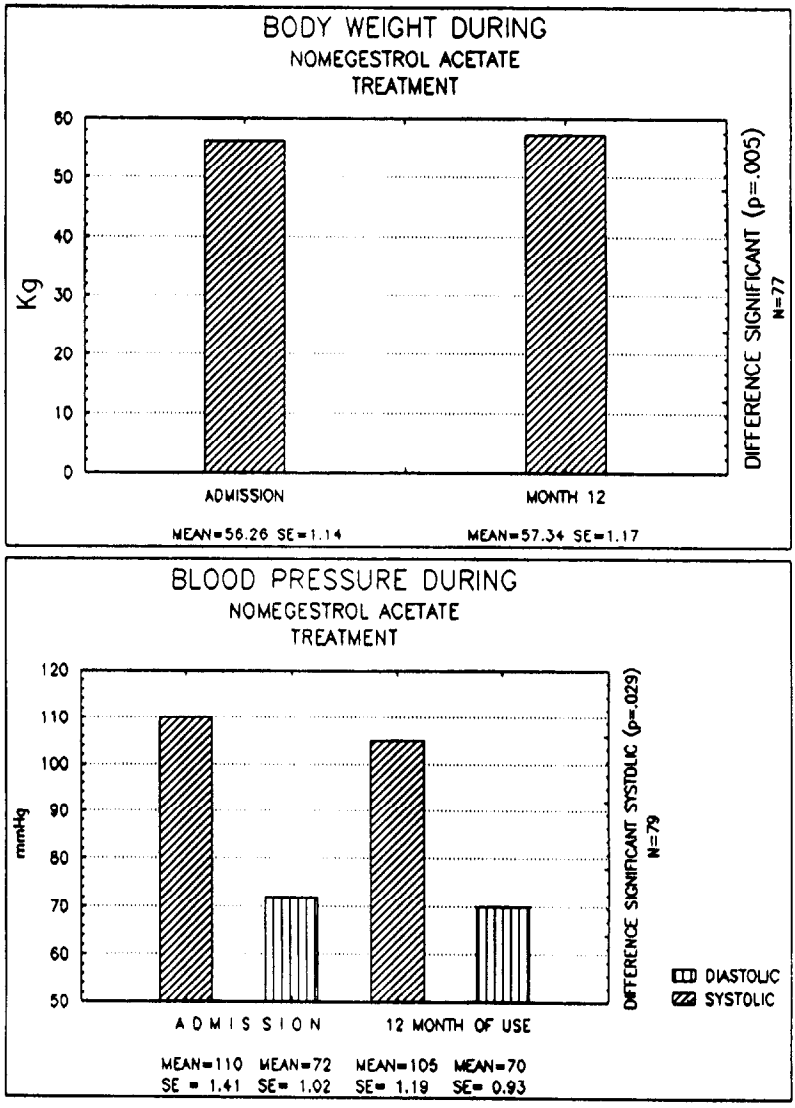
** A non-bleeding interval is the interval between two bleeding runs.

*** An episode includes a bleeding run and a non-bleeding interval.



F I G U R E 1

Bleeding irregularities during nomegestrol acetate single implant use in the first 20 subjects to complete one year of treatment. The figure on amenorrhea shows the percentage of patients who failed to bleed at the expected date. Note the decline in the incidence of both amenorrhea and menorrhagia. Note also the low incidence of intermenstrual bleeding and spotting.



F I G U R E 2

Mean body weight and blood pressure in women bearing Uniplant. Note small but significant increase in body weight. Note also reduction in both systolic and diastolic blood pressure.

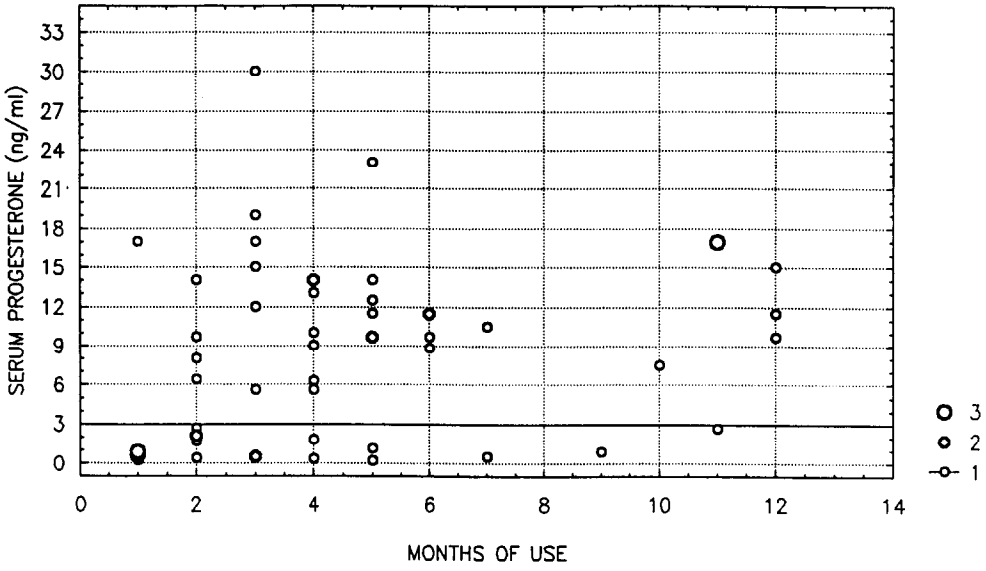


FIGURE 3

Progesterone levels in 60 cycles of the first 20 women bearing Uniplant who completed one year of use; 4 subjects were studied for 7 cycles, for a total of 28 cycles; 16 subjects were studied for 2 months, for a total of 32 cycles; 36 of these cycles were suggestive of ovulation whereas 24 cycles had progesterone values below 3 ng/ml.

to 70 mcg daily during the last nine months of use. Implants removed after 13 to 14 months of use presented some residue of nomegestrol acetate which varied from 2 to 10 mg, indicating that the protective effect may last over 12 months. Endocrine profiles carried out in 12 subjects revealed progesterone levels higher than 3 ng/ml, suggestive of ovulation, in 36 out of 60 cycles. The values of progesterone found in these cycles are shown in Fig. 3.

COMMENTS

The present study shows that one single implant of nomegestrol acetate prevents conception in women for as long as one year. The Uniplant releases amounts of nomegestrol acetate which do not seem to be sufficient to inhibit ovulation consistently but probably exert a contraceptive action at the peripheral level. A reduction in the amount of cervical mucus has been observed in patients using the nomegestrol acetate implant and alterations in its physico-chemical properties may interfere with sperm penetration as shown in patients using other progestin-only contraceptive regimens. A study of the changes in cervical mucus volume and composition in Uniplant users is being conducted in a larger group of women and will be reported in the near future.

Most patients are pleased with the treatment as indicated by the fact that more than half of the women completing one year of use requested a new capsule. Studies now in progress will evaluate the acceptability of the method for more prolonged use. The new method will be especially suitable for women who dislike the amenorrhea induced by other long-acting injectables or implants, such as Norplant, and who prefer to maintain a periodic bleeding similar to menstruation.

Acknowledgement

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