Pergamon

0960-0760(95)00051-8

J. Steroid Biochem. Molec. Biol. Vol. 53, No. 1–6, pp. 223–226, 1995

0960-0760/95 $9.50 + 0.00

# Subdermal Contraceptive Implants

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**Subdermal contraceptive implants involve the delivery of a steroid progestin from polymer capsules or rods placed under the skin. The hormone diffuses out slowly at a stable rate, providing contraceptive effectiveness for 1–5 years. The period of protection depends upon the specific progestin and the type of polymer. Advantages of progestin implants include long term contraceptive action without requiring the user's or provider's attention, low dose of highly effective contraception without the use of estrogen, and fertility is readily reversible after the removal of implants. The levonorgestrel implant Norplant R system is the only one that has been approved for distribution. The contraceptive efficacy of Norplant is the highest observed amongst the most effective methods with an annual pregnancy rate of 0.2 during the first and second year and 1.1 on the fifth year. Menstrual problems are the main reason for the discontinuation of Norplant and 9% of women stopped using it during the first year of treatment. Other implants are still under development trying to simplify the method by reducing the number of units and to introduce other progestins that may minimize side effects. Norplant-2 was designed to release the same dose of progestin from only two covered rods. Evaluation of 1400 women enrolled, indicates that over 2 years the cumulative pregnancy rate is below 0.5 per 100 women. There are three single implants under development: Nestorone, 3-Keto-desogestrel and Uniplant that are expected to be effective for 1–2 years. Phase II clinical trials with Nestorone have been completed and no pregnancies have been observed in 1570 woman-months of use. Bleeding irregularities occurred in 20–30% of the women but there were only four terminations because of bleeding problems. A multricentric study is ongoing with a newly designed 3-keto-desogestrel implant named Implanon, which releases approx. 60 μg/day of the hormone. The objectives of this study are to assess contraceptive efficacy, safety and acceptability of Implanon. Another multricentric study is ongoing with Uniplant, which releases nomegestrol acetate with a duration of action for only 1 year. The objectives of the trial are to study the endocrine profile of Uniplant users and to evaluate the efficacy and acceptability of the method.**

*J. Steroid Biochem. Molec. Biol.*, Vol. 53, No. 1–6, pp. 223–226, 1995

## INTRODUCTION

Contraceptive implants were originally conceived for long term continuous release of a steroid in order to avoid over and underdosing periods and to liberate the user from the daily attention associated with intermittent administration [1]. The first one to reach the market, known by the name of Norplant has been used now by more than a million women in all continents and over 20 countries, including the U.S.A., have approved its distribution. Other implants are currently under development and purport to simplify the method by reducing the number of units and to introduce other progestins that may minimize side effects.

*Proceedings of the IX International Congress on Hormonal Steroids*, Dallas, Texas, U.S.A., 24–29 September 1994.
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## LEVONORGESTREL CONTRACEPTIVE IMPLANTS

There are two types of levonorgestrel silastic implants, capsules (Norplant) and covered rods (Norplant-2) [2]. Norplant consists of a set of six silastic capsules which release levonorgestrel for more than 10 years although the effective life of the implant is limited to 5 years. The six capsules release initially an average of 70 μg per day of levonorgestrel. After a few months the release stabilizes at around 30 μg per day with a slow decrease over the years [3–5].

Norplant-2 (soon to be submitted for FDA approval), consists of two silastic rods, each 44 mm long, that release levonorgestrel at a higher rate per surface unit as compared to Norplant. the total levonorgestrel load of Norplant and Norplant-2 is 216 and 140 mg respectively, and since the total daily

*Table 1. Norplant. Body weight, levonorgestrel plasma levels and ovulation in Norplant users*

| Body weight (kg) | L-Ng ng/ml X (SE) | Ovulatory status | |
|---|---|---|---|
| | | *n* | % |
| <70 | 0.31 (0.01) | 67 | 44% |
| >70 | 0.22 (0.02) | 30 | 77% |

Blood samples drawn twice a week for 6 consecutive weeks for progesterone and L-Ng levels. Progesterone > 9.0 nmol = ovulatory level. $P < 0.005$ (ovulatory status/body weight).

release is identical, the maximal theoretical life of the latter is about 40% shorter [2, 6, 7].

*Insertion and removal*

Treatment is started within the first week of the menstrual cycle. Implants are placed under the skin in the forearm or upper arm using a N 10 trocar under local anesthesia. The insertion of Norplant by an experienced person takes about 3–5 min and the removal about 10 min. The main advantage of Norplant-2 is that insertion and removal are greatly simplified.

*Levonorgestrel plasma levels*

Plasma levels of levonorgestrel remain within the range of 0.40–0.20 ng/ml up to the 8th year of treatment. After the initial burst, levels fall slowly from 0.35 ng/ml to a mean of 0.28 ng/ml during the first 5 years of use. The sustained release of levonorgestrel, for so many years after a single administration is a remarkable achievement with no precedent in medical pharmacology [4].

The levonorgestrel plasma levels of women treated with Norplant or Norplant-2 are practically coincident during the first year of use. So, we can expect that Norplant-2 may have a similar clinical performance to Norplant although its active life may be shorter [2, 6].

*Contraceptive efficacy*

The contraceptive efficacy of Norplant is the highest observed among the most effective methods. The annual pregnancy rate is 0.2 for the first and second year, 0.9 the third year, 0.5 the fourth year and 1.1 the fifth year [6]. The gross cummulative pregnancy rate per year in 2470 acceptors from ICCR studies is 0.2 for year 1, 0.7 for year 2, 1.9 for year 3 and 4.2 for year five [3, 6].

There is a relationship between body weight and contraceptive effectiveness of Norplant that is evident from the third year of use. Sivin has reported a gross cumulative pregnancy rate at the third year of 0.2 for women below 50 kg, 2.5 for women between 60–69 kg and 6.1 for women over 70 kg [3]. During the fifth year of treatment the pregnancy rate was 1.0 for women below 50 kg and 8.5 for those over 70 kg. During the first 2 years there were no differences in the pregnancy rates.

There is also a relationship between body weight, ovulation and levonorgestrel plasma levels in Norplant users (Table 1). Below 70 kg of weight, the levonorgestrel plasma levels are higher (0.31 ng/ml) and the proportion of ovulatory cycles is lower (44%) than in women over 70 kg of weight (L-Ng 0.22 ng/ml and 77% ovulatory cycles). These differences are statistically significant [6].

Comparative phase III clinical trials with Norplant-2 implants are now in the third year. A total of 1400 women have been enrolled in multicentric studies which will continue through 1996–97. At present, the cumulative pregnancy rate is below 0.5 per 100 women [7].

*Side-effects*

The subjective side-effects reported by Norplant users do not differ much from those reported for other hormonal contraceptive methods. Menstrual problems are the most frequent reason for early discontinuations. They include alterations in the rhythm, periodicity, volume and duration of menstrual flow. Discontinuations for this reason decrease from 9% in the first year of use to 3% in the fifth year (Table 2). By contrast, only 6% of users terminate use in the first year for all other medical reasons, and this rate remains at a similar level during each of the four subsequent years [3].

Among menstrual problems, irregular, frequent bleeding and spotting are the most common. Amenorrhea and oligomenorrhea are the least frequent. Prolonged bleeding is the most disturbing. These changes do not induce anaemia or reduction of iron stores [2–4]. The replacement at 5 years by a new set of implants does not increase the bleeding irregularities [5].

Another side effect is adnexal enlargement which has been sometimes reported as ovarian cysts. A retrospective study conducted in Santiago [8] which included

*Table 2. Terminations. Annual and five-year cumulative rates per 100 users*

| | Pregnancy | Bleeding irregularities | Other medical | Personal | Continuation |
|---|---|---|---|---|---|
| Year 1 | 0.2 | 9.1 | 6.0 | 4.6 | 81.0 |
| Year 2 | 0.5 | 7.9 | 5.6 | 7.7 | 77.4 |
| Year 3 | 1.2 | 4.9 | 4.1 | 11.7 | 79.2 |
| Year 4 | 1.6 | 3.3 | 4.0 | 10.7 | 76.7 |
| Year 5 | 0.4 | 2.9 | 5.1 | 11.7 | 77.6 |
| Cumulative | 3.9 | 25.1 | 22.4 | 38.7 | 29.5 |

28,548 woman-months of use of Norplant detected 62 episodes in 54 women (11%). This rate is higher than the one observed in contemporeaneous Copper T users. In the majority of cases (93%), the enlargement corresponded to functional ovarian cysts up to 5–8 cm, usually asymptomatic which disappear spontaneously within 60 days.

Many studies encompassing non-reproductive endocrine parameters, carbohydrate and lipid metabolism, haematologic, coagulation and other clinical chemistry tests in Norplant users, have shown that the few deviations from the mean pretreatment levels or control group values encountered, rarely fall outside the normal range [4].

*Fertility after removal of implants*

The levonorgestrel half-life in plasma has been calculated as about 40 h (range 13–62 h). After the removal of Norplant, the major part of the steroid is cleared from plasma within 96 h and post-removal conception rates are similar to those observed after the removal of an IUD or after discontinuing the pill [9].

*Post-marketing prospective study*

Since 1987, an international collaborative study called "Post-Marketing Surveillance of Norplant" is ongoing coordinated by the World Health Organization, the Population Council and Family Health International. This is the first prospective study and is being conducted in 8 developing countries (Bangladesh, Chile, People's Republic of China, Colombia, Egypt, Indonesia, Sri Lanka and Thailand). One of the main objectives is to identify any major short-to-medium term side effects of Norplant use that have not been identified in clinical trials. The focus is on side effects of public health importance. Women participating are followed at 6-monthly intervals for 5 years since initiation of the method, irrespective of any change in contraceptive method, health problems or moving away from the study site. The pilot phase was initiated in three countries in 1987 involving 1000 women, but the main phase of the study started in 1989. Half of the 16,000 women recruited for the study use Norplant, 6600 use IUDs and 1400 have been surgically sterilized. The data are being processed at WHO/HRP in Geneva. At the conclusion in 1995, there will be approx. 80,000 woman-years of observation. At this moment, the study shows that multicentre, large scale cohort studies to evaluate the safety of fertility regulating methods are possible in developing countries (O. Meirik, unpublished data).

## A NEW GENERATION OF IMPLANTS—SINGLE IMPLANTS

*Nestorone single implant (ST-1435)*

Nestorone progestin (ST-1435) is a potent 19 norprogesterone derivative (16-methylene-17-α-acetoxy-19-nor-4-pregnene-3,20-dione). It has no estrogenic or androgenic activity and has some advantages for use in contraception: high effectiveness for inhibiting ovulation allowing a single implant version; and lack of effect on lipoproteins [10, 11]. Since it is inactive when given orally, Nestorone appears to be an excellent candidate for contraception in lactating women because the child would be free from the influence of the hormone excreted in the milk [12].

We have recently completed a clinical trial with a single implant containing Nestorone progestin in 70 healthy women of proven fertility who were compared with Copper T users as a control group. The implant tested is a covered Silastic rod 4.4 cm long which delivers 45–50 μg/day. No pregnancies occurred in the 1570 woman-months observed [13].

Nestorone plasma levels declined from 145 to 57 pmol/l throughout the first 2 years of use. The implant demonstrated high effectiveness in inhibiting ovulation. Of 178 cycles studied at various lengths of treatment, 166 (93.3%) showed progesterone plasma levels below 9.5 nmol/l (Table 3). The Nestorone progestine plasma levels in ovulatory cases ranged from 68 to 105 pmol/l. Inhibition of ovulation seems to be the most important mechanism of action of the method. Nonetheless, follicular activity ocurred in the majority of women because estradiol plasma levels were similar or higher than those observed in untreated women with ovulatory cycles. None of the women showed estradiol levels below 100 pmol/l.

The most frequent complaint was again the occurrence of bleeding irregularities. 20–30% of treated women had an increased number of bleeding plus spotting days (more than 10 days) per 30 days interval and this proportion did not improve with time. Nevertheless, the bleeding pattern was well tolerated and there were only four terminations (5.7%) because of bleeding problems. Enlarged follicles, 5–65 mm which disappeared spontaneously within 10 days to 6 weeks, were found during pelvic examination in 8 women (11.4%). The finding of enlarged follicles suggests that the gonadotropic stimulus was not fully inhibited, as has been shown with other progestin-only contraceptive methods. No abnormal changes were observed in plasma lipoproteins or clinical chemistry during treatment [13].

*Table 3. Progesterone plasma levels in women treated with Nestorone implant and in control women*

| | <9.5 nmol/l | | >9.5 nmol/l | | *n*-Samplings | |
|---|---|---|---|---|---|---|
| Group | *n* | % | *n* | % | *n* | % |
| Implant | 166 | 93.3 | 12 | 6.7 | 178 | 100 |
| Control | 0 | 0 | 71 | 100 | 71 | 100 |

Progesterone levels > 9.5 nmol/l = compatible with ovulation. $P < 0.0001$.

*3-Keto-desogestrel subdermal implant*

3-Keto-desogestrel is the biologically active metabolite of the progestin Desogestrel. It has shown no estrogenic, antiinflamatory or mineralocorticoid activity, only weak androgenic and anabolic activity, and strong antiestrogenic activity.

In 1991, we published a study with silastic capsules 4 cm long that released 40 $\mu$g/day and provided 3-keto-desogestrel plasma levels around 0.28 nmol/l. Twenty nine women who received the 4 cm capsule recorded 514 woman-months of use and no pregnancy was observed. The implant induced and increased number of bleeding days, spotting days and bleeding episodes, and was partially effective for inhibiting ovulation. Of 89 blood samples drawn at different weeks of treatment, 17 had progesterone levels compatible with ovulation. From this study it became apparent that 0.29 nmol/l of 3-Keto-desogestrel is the critical serum level for inhibition of ovulation [14].

An open multicentric non-comparative study is ongoing with a newly designed 3-Keto-desogestrel implant named Implanon. It consists of a single covered rod 4 cm long that contains 60 mg of 3-Keto-desogestrel. They are made of a hormone containing ethylene vinylacetate (EVA) core surrounded by an EVA membrane. The initial release rate of these implants is approx. 60 $\mu$g/day after 4 weeks which slowly decreases over time. The required dose is provided for at least 2 years. At our clinic in Santiago 107 women have received Implanon and no pregnancy has been observed in 1121 woman months of use. Out of 10 removals, 3 were due to bleeding problems.

*Uniplant single implant*

One single silastic capsule, containing Nomegestrol acetate, called Uniplant is being tested in a multicentric study. Nomegestrol acetate (3,20-oxo-6-methyl-17-$\alpha$-acetoxy-19-norpregna-4,6-diene) is a 19-norprogesterone derivative which has been available in Europe for several years, being used orally as a progesterone agonist. It has affinity for progesterone receptors and moderate antiestrogenic and antiandrogenic activity. Uniplant implant is a single silastic capsule 3.5 cm long which contains 38 mg of Nomegestrol acetate. The expected release rate is about 75 $\mu$g/day and the duration of use is only 12 months. The insertion and removal are done using the same technique as in Norplant.

The first large study with Uniplant was done in Brazil by Dr Coutinho with 100 women and 1085 woman-months of use of the method [15]. Only one pregnancy occurred resulting in a Pearl Index of 1.1. The main side effect observed was bleeding problems but only three women discontinued because of it. An expanded version of this study has been completed including 345 subjects who accumulated 7430 woman-months of use. Four pregnancies have occurred resulting in a Pearl Index of 0.64.

A multicentric trial involving 9 countries (Brazil, Dominican Republic, China, Nigeria, Chile, Egypt, Indonesia, Cuba and Kenya) is ongoing. At the present, over 10,000 woman-months of observation have been recorded and the most relevant side effect reported is prolonged bleeding.

## CONCLUSIONS

Contraception with subdermal implants offers highly effective protection against pregnancy for several years without continuous attention by the users and it is readily reversible after removal.

Research underway aims at simplifying insertion and removal and taking possible advantage of new progestins. These improvements may be obtained at the cost of a shorter lifespan of the implant.

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