Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant

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Abstract

Objective: To evaluate efficacy, adverse effects, and user continuation rate of an etonogestrel subdermal single-rod contraceptive implant. Methods: A total of 417 healthy volunteers of childbearing age were included in this multicenter trial. After implant insertion, the women were followed up during the 3 years of contraceptive action. At each visit, clinical findings, side effects, and bleeding patterns were recorded. Efficacy and continuation rates were analyzed using the Pearl Index and Kaplan–Meier life tables, respectively. Results: The observation period totaled 958.5 woman-years (27.5 months per woman). The Pearl Index score was 0. Side effects were reported by 44.4% of users, but the proportion had decreased to 16.5% by the end of the study. The continuation rate was 61.4%. The most common reason for early discontinuation (in 21.1% of the participants) was menstrual disturbances. Conclusions: Etonogestrel subdermal contraceptive implants demonstrated high efficacy and an acceptable continuation rate. Counseling potential users explicitly about the side effects will optimize patient success with this long-acting contraceptive.

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1. Introduction

Subdermal contraceptive implants were first developed in 1966. From 1974 to 1980, a system consisting of 6 silastic rods releasing second-generation progestin levonorgestrel proved to be a successful long-
acting contraceptive. Based on this evidence the method was approved for use in Finland in 1983, and afterwards by the rest of the European Community and the United States. The system, called Norplant (Wyeth Pharmaceuticals, Philadelphia, Pa, USA), was evaluated by the Mexican Social Security Institute (IMSS) in 1988 with a total of 1334 subjects [1]. Results showed that these subdermal contraceptive implants were well accepted by both rural and urban women. In spite of its high acceptance and effectiveness, however, the Norplant implant dropped in popularity when reports appeared about the difficulty of removing the contraceptive rods.

Several alternative systems using fewer capsules were designed to facilitate the removal of the subdermal implants. One of these is Implanon (Organon, Oss, the Netherlands), consisting of a single flexible rod of ethylene vinyl acetate 40 mm in length and 2 mm in diameter containing 68 mg of 3-keto-desogestrel (etonogestrel) dissolved in its core. After insertion, serum concentrations of etonogestrel reach ovulation-inhibiting levels (>90 pg/mL) in 8 h, and remain so for up to 3 years [2]. The efficacy and safety profile of this progestin as an oral contraceptive has been established [3]. The results of a meta-analysis of 13 clinical studies of subdermal etonogestrel implants have shown high efficacy (0 pregnancies in 4103 women-years) and good tolerance [4—6]. The present multicenter, prospective, longitudinal study was conducted to evaluate the acceptability and efficacy of this subdermal implant.

2. Materials and methods

Following evaluation and authorization by the IMSS ethics committee, the study was conducted in 9 medical units (7 family medicine units and 2 Obstetrics and Gynecology Hospitals) in greater Mexico City. The sample size was calculated based on the formula for estimating the proportion of variables in the Mexican population, with P set at 0.5. A sample size of 384 women was obtained, and was adjusted later to 417 because a surplus of implants. After 3 years of observation, the implants were extracted and a final assessment was conducted 3 months later. Organon Mexicana provided the implants used in the study. The inclusion criteria were the following: healthy women aged 15 to 49 years, regular menstrual cycles, and informed consent. The exclusion criteria were a World Health Organization medical eligibility criteria for contraceptive use score of 3 or 4 [7]. The participants received a subdermal implant between day 1 and 5 of their menstrual cycle (day 1 being the day of menstruation onset); after the sixth postpartum week; or immediately after an abortion. The implant insertion and retrieval technique has been published elsewhere [8]. The technical difficulty and the time needed for insertion and removal of the implant was recorded.

After insertion, the participants were seen at 1 week, 1 month, 3 months, and every 6 months thereafter until the end of the study. At each visit health status, side effects, and menstrual bleeding patterns were assessed and a gynecological examination with cytologic cervico-vaginal studies was provided as needed. The children of lactating women were followed up on a regular basis as a regular institutional practice, and their growth and development evaluated. To assess the participants' menstrual pattern, they were instructed to record the presence or absence of bleeding (more than 1 sanitary pad per day) or spotting (only 1 pad per day). If bleeding or spotting occurred on one day, it was recorded as a day with flow. Side effects were defined as any discomfort or symptom appearing or increasing in strength or frequency during the study. The participants were instructed to visit the clinic if they experienced any unexplained symptom. Contraceptive efficacy was assessed by the occurrence of pregnancies during the observation period, and any participant suspected of being pregnant was checked for urine choriogonadotropin (CGH). The pregnancy rate was calculated using the Pearl Index (number of pregnancies in a 12-month period of use per 100 women).

Bleeding patterns were analyzed by the method recommended by the World Health Organization, which uses a 90-day reference period from the day of implant insertion [9,10] (Table 1). Normal bleeding was defined as the usual menstrual pattern the participants had before insertion of the implant.

Rate and reasons for discontinuation were analyzed by the Kaplan—Meier method. A follow-up visit was made 3 months after removal of the implant, even by early discontinuers, to assess the return of regular menstrual bleeding and the occurrence of any pregnancy during this implant-free interval.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Bleeding patterns in the 90-day reference period (WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding pattern</strong></td>
<td><strong>WHO definition</strong></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No bleeding</td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>≥1 bleeding/spotting episode during ≥10 days</td>
</tr>
<tr>
<td>Frequent bleeding</td>
<td>&gt;4 episodes of bleeding/spotting</td>
</tr>
<tr>
<td>Infrequent bleeding</td>
<td>&lt;2 episodes of bleeding/spotting</td>
</tr>
</tbody>
</table>
3. Results

Implants were placed in 417 women. Their mean ± SD age was 25.8 ± 5.9 years and mean weight 59.4 ± 9.3 kg, corresponding to a body mass index (BMI) of 24.9 ± 3.9 (calculated as weight in kilogram divided by the square of height in meters). At baseline, 66.5% of the participants had a normal BMI, 19.4% were overweight, 8.9% were obese, and 5.2% were underweight. A high level of education in the sample (61.2% having attended high school) is representative of the population registered at IMSS. Most (87%) had a proven fertility, and most had used another contraceptive method.

The physicians who inserted the implants were asked to evaluate the degree of technical difficulty. Most insertions (95%) were trouble free (they took a mean time of 1 min), and 84% of the women did not experience any discomfort during insertion.

3.1. Contraceptive efficacy

During the study period, which comprised 958.5 woman-years of observation, no pregnancies occurred (Pearl index score = 0). The mean number of months of use was 27.5 per woman.

3.2. Bleeding patterns

The proportion of participants experiencing the side effects observed in the first, second and third years of use, respectively, were amenorrhea (22.9%, 20.3%, and 13.7%); prolonged bleeding (19.7%, 18.9%, and 15.8%); infrequent bleeding (4.9%, 5.3%, and 3.7%), and frequent bleeding (2.9%, 0.8%, and 0.8%) (Fig. 1). Most cycles (66%) were normal at the end of the study.

3.3. Side effects

The proportion of participants experiencing side effects decreased from 44.4% in the third month of the study to 16.5% at 36 months. Table 2 shows the type and incidence of side effects (the participants could report more than one side effect).

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.4</td>
</tr>
<tr>
<td>Local discomfort</td>
<td>9.6</td>
</tr>
<tr>
<td>Mood changes</td>
<td>9.5</td>
</tr>
<tr>
<td>Acne</td>
<td>6.3</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>5.9</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>2.9</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2.8</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>2.7</td>
</tr>
<tr>
<td>Mastalgia</td>
<td>1.4</td>
</tr>
<tr>
<td>Others*</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*<1 >0.5%: weight loss, pruritus, pain in the lower limbs.
<0.5%: galactorrhea, dysmenorrhea, asthenia, melasma, leukorrhea, edema, hot flushes, tachycardia, varicose veins.
3.4. Continuation rates and reasons for discontinuation

Of the 417 women who began the study, 161 (38.6%) discontinued prior to the end of the third year. The net continuation rates were 78.2% at 12 months, 66.7% at 24 months, and 61.4% at 36 months (Fig. 2).

The most common reason for discontinuation was menstrual disturbances, with a cumulative net rate of 21.1%. Prolonged bleeding was the reason for discontinuation in more than half of these cases. Other major discontinuation reasons were desire to become pregnant (8.1%); missed follow-up visit (4.6%); headache (2.8%); weight gain (2.6%), and mood changes (1.5%) (Fig. 3).

There was a mean weight gain of 2.3% at 12 months, 4.5% at 24 months, and 5.5% at 36 months, resulting in a total mean gain of 3.3 kg by the end of the study.

Of the 417 participants, 114 (27.4%) received the implant following a pregnancy, 100 during the postpartum period, and 14 following an abortion. Most women who received it during the postpartum breast-fed their infant during the use of the implant (2 had stillbirths), but it did not seem to affect the quantity of milk. At the end of the study, no harmful effects on their children’s growth or development were observed [11,12]. The continuation rate among implant users in the postpartum was 72% at 3 years, a rate slightly higher than the overall rate of 61.4%, whereas the rate for post-abortion users was only 35.7%.

There were 3 medical reasons for premature removal of the implant: 1 case each of varicose ulcer, uncompensated type 2 diabetes, and multiple sclerosis, all diagnosed after inclusion in the study. The participants were admitted by mistake and their data were not included in the final analysis.

The implant was easily removed in most cases. The mean time required for removal was 3 min; in only 1 case 30 min were reported, because of deep insertion below the subdermal space. It should be noted that this type of problem would not arise with correct insertion.

A total of 217 women (52%) presented to the follow-up visit 3 months after removal of the implant. Of these, 135 (62.2%) chose another contraceptive method and 34 had a new implant inserted. The remaining 82 chose not to use contraception. Of these, 11 (13.4%) were already pregnant and the others were having regular menstrual periods.

4. Discussion

The results of this multicenter study confirm the high contraceptive efficacy of the subdermal implant and its acceptable safety profile, as no pregnancies or serious side effects occurred during the observation period. While there were 3 cases of early removal for medical reasons, no direct causal relationship with the implant could be established because these conditions were already present.
when the implant was inserted. Six of every 10 women who began the study used the contraceptive for the entire 3 years allowed.

The most frequent reason for early discontinuation was menstrual changes (21.1%), as could be expected given the action of this progestin-only method on the endometrium [13]. Interestingly, although the frequency of amenorrhea (range, 26.8—13.7%) was similar to that reported in the literature, 29% of the participants who discontinued did so because of amenorrhea, a much higher rate than in the reported studies (1.8%). An acceptability study [14] showed that those who discontinued most likely because of menstrual changes had a high level of education, as did the participants in the present study.

Over the course of the study, there was an observable trend toward fewer bleeding days per 90-day reference period. The mean number of days of bleeding was 20.3 during the first reference period, and decreased to 11.4 days in the final reference period. This decrease may be perceived as a practical advantage by the women, and it also helps raise their hemoglobin levels [15].

Other investigators have found that candid counseling increases user continuation of long-acting progestins contraceptives [16]. A meta-analysis [6] found the overall incidence of nonmenstrual side effects to be 72%. In the present study, 44.4% of the participants first reported such side effects, but the proportion decreased to 16.5% by the end of the study. Acne (15.3%) was the most common side effect in the meta-analysis, but in the present study only 6.3% of the participants reported experiencing acne. The most common nonmenstrual side effect in our study was headache (24.9%); in the meta-analysis, however, only 8.5% of participants noted experiencing headaches. These differences likely reflect socio-cultural environments that affect interpretation and tolerance of symptoms differently.

Despite the relative high incidence of headache, mood changes, and weight gain, each of these reasons accounted for fewer than 3% of early discontinuations [17]. The fact that no pregnancies were observed in the 51 participants (12.2%) with body weight greater than 70 kg (range, 70—117.5) suggests that implant efficacy is maintained in overweight patients, as was previously reported [18].

In conclusion, the etonogestrel subdermal contraceptive implants were well accepted by Mexican women. The implants were highly effective in preventing pregnancy, and their insertion and removal were uncomplicated. The frequency of side effects was similar to that previously reported for other populations. Bleeding patterns were characteristic of progestin-only contraceptives. After implant retrieval, the fast recovery of regular menstrual patterns and the occurrence of
pregnancies attest to the reversibility of this method.

A candid discussion with implant candidates regarding the pros and cons of this convenient, highly effective method should maximize acceptance and continuation of the single-rod etonogestrel contraceptive implant system.

References
