Recent developments in contraceptive implants at the Population Council

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Abstract

Development of contraceptive implant methods, when based on established or on new synthetic chemical entities, is a decadal or multi-decadal process. The process often requires the cooperation of numerous investigators for laboratory work, for early Phase II trials, for dose-finding trials, and for Phase III clinical trials. The Phase III work also requires cooperation with a commercial manufacturer and potential distributor of the product. The Population Council has recently completed developmental work on two levonorgestrel-releasing implants, with filings to regulatory agencies that support extended use of Jadelle implants for 5 years and Norplant implants for 7 years. When the developmental process includes establishing the clinical properties of a molecule not yet approved by regulatory agencies, the minimum development time appears to be two decades. The status and rationale of studies of a new Nestorone-releasing, single implant developed by the Population Council for a period of use of 2 years are presented. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Contraceptive implants; Nestorone implants; Jadelle implants; Norplant implants; Contraceptive rods; Implant performance; Contraceptive development

1. Introduction

Over the past decade, the Population Council implant development program has explored implants releasing synthetic hormones to be used by men or by women. Implants for men are addressed to the needs of three different groups: hypogonadal men, men desiring to use contraception, and men seeking hormone replacement therapy. Studies involving implants for men are in early Phase II trials, and although these seem promising, regulatory approvals for general distribution are likely to be at least a decade away. On the other hand, recent Population Council developments of implants intended for use by women are in large Phase II trials, or have been submitted for regulatory approval or have already received it. In consequence, this article focuses solely on contraceptive implants for women.

Both before and after the initial regulatory approvals of contraceptive implants, experience in clinical trials demonstrated the need for and utility of full counseling before and during implant contraception. This will help women evaluate the method before selection and understand the side effects experienced during use. To a large degree side effects of implants are similar to effects associated with combined oral contraceptives and with bleeding patterns associated with the progestin-only pill.

The Population Council’s recent developments have centered on improving the acceptability of implants, increasing their attractiveness, and extending their utility to special groups, such as lactating women or those seeking prolonged use. This developmental effort has taken several directions. These include (a) reducing the number of implants; (b) attempting to reduce side effects by using progestins with improved metabolic profiles; (c) providing implants that are orally inactive and thus, theoretically, safer if used during lactation; and (d) undertaking prolonged clinical trials to examine effective and safe contraceptive lifetimes. Two different progestins, levonorgestrel and Nestorone have been employed for these purposes.

2. Results

2.1. Norplant: six 3-cm levonorgestrel-releasing implants

Norplant, the first approved contraceptive implant has received regulatory approval in more than 60 countries. An
estimated 7–8 million women have used it. Experience with Norplant has repeatedly shown a combination of high contraceptive effectiveness and high continuation rates in clinical trials [1–4], in national probability samples [5], and in cohort studies [6]. In the past decade, the Population Council undertook new Phase III trials of Norplant. These have now confirmed that Norplant manufactured with “soft tubing” is superior in effectiveness to the original version. Soft tubing Norplant has a 5-year gross cumulative pregnancy rate of 1.1/100, which is significantly below the 3.9/100 “hard tubing” implants. Also, these trials now demonstrate that this implant remains effective for 7 years, even when large proportions of participants enter the study at body weights of 70 kg or more. Throughout this 7-year period each annual pregnancy rates is below 1/100. The cumulative pregnancy rate at 7-years is at or below 2/100 for the entire period [7]. The Population Council has submitted these data to the US Food and Drug Administration (FDA) and requested regulatory approval for 7 years of effective use.

2.2. Jadelle: two 4-cm rod implants

A prototype of the current Jadelle implant entered Phase III trials in the mid-1980s [1] in randomized comparison with Norplant for a 3-year period. Although highly effective and with side effects indistinguishable from those of Norplant, this prototype was never registered in the US because manufacture and distribution of critical components ceased as the trials reached their concluding stages. Absent the ability to reproduce the exact product studied in the trials, registration was impossible. By 1990, however, the Population Council had reformulated a two-implant contraceptive system with the use of levonorgestrel. The system was designed to release levonorgestrel at approximately the same daily dose as that released by Norplant for a period of at least 3 years. The drug load of 150 mg levonorgestrel is 69% of that in Norplant implants. Based on clinical data from Phase III trials initiated in 1990, both the Medical Agency of Finland and the US FDA granted approvals in the mid-1990s for use of Jadelle, the name of this system, for a 3-year period. The Population Council’s prolongation of the same set of trials has now led to approvals of Jadelle for 5 years of continuous use in Finland (2000), other Scandinavian countries, France, and other western European countries (2001). Jadelle is currently under review by US FDA as a contraceptive that remains effective for a 5-year period.

Users of the Jadelle implant system in clinical trials have experienced 3- and 5-year cumulative pregnancy rates of 0.3 and 1.1/100 continuing users, respectively [8]. In these trials more than 500 women completed 5 years of continuous use. Annual, single decrement life table pregnancy rates throughout the 5-year period remained below 1/100. The 5-year cumulative pregnancy rate, 1.1/100, was identical with that experienced by women using “soft tubing” Norplant implants in the same set of trials [7]. For the 5-year period, no statistically discernible difference in pregnancy rates was found when women were grouped by body weight, but the very small number of pregnancies precludes firm interpretation.

Compared with Norplant, Jadelle is more easily placed and removed. The manufacturer has developed a kit with a pre-loaded trocar to facilitate implant placement. In comparative and concurrent trials with Norplant, among clinicians using the standard Population Council removal techniques, the mean time required for removal of Jadelle implants was half (48%) of that required for removal of Norplant. Approximately 69% of all removals required 5 min or less [8].

Removal complications were defined to include mechanical problems, which could affect the difficulty of the procedure for the staff but need not have affected the woman, e.g., broken implants, as well as trauma or infection that unambiguously affected the participant. Jadelle reduced removal complications by about 50% compared to Norplant. Reported complications of any kind were noted in the records of 13.5% of participants with Norplant removals and in 6.25% of removals of Jadelle. Complications deemed to have affected women included notations of deep placement, hematoma, long or multiple incisions, multiple clinic visits, or pieces of implants left in situ. Between 2% and 3% of Jadelle participants are reported to have experienced one or more such complications [8].

Women who have used Jadelle and then discontinued for planned pregnancy have experienced normal levels of pregnancy after implant removal. The median time to pregnancy was 3 months from implant removal. Among former Jadelle participants who went to term and had singleton births, there was a slight predominance of girls. These results are similar to results observed for the Jadelle prototype studied in conjunction with Norplant in the mid-1980s [1].

Over the next decade as registration of this product continues, it is expected to replace Norplant in many countries.

2.3. Nestorone implants: a novel molecule with an old history

The Council’s new, single-implant system releases the Nestorone progestin, a 19-norprogesterone derivative, 16-methylene-17α-acetox-19-nor-preg-4-ene-3, 20 dione. Preclinical toxicological studies [9,10] established the safety of this progestin for use in clinical trials. Carcinogenicity studies are in progress.

Two-and-a-half decades ago, Coutinho brought attention to this progestin, then designated as St 1435, and its possible use as a single implant [11–13]. As developed by Coutinho, one capsule implant, with a silicone rubber, rate-limiting membrane, prevented pregnancy for a period of 6–9 months. This duration was clearly too short to provide acceptable contraceptive protection by an implant route.
necessary frequent implant removal and replacement. Several other investigators examined this progestin and found it to be of interest. They characterized the properties of the molecule as it affected pituitary and ovarian function, lipids, blood pressure, clinical chemistries and lactation, and bleeding patterns.

Nestorone is well absorbed from the gastrointestinal tract [14-16], but is biologically inactive because of rapid hepatic first-pass metabolism [16-19]. In addition to Coutinho [11-13], others have shown that the steroid is effective in controlling fertility at low doses when administered parenterally by implants [15,20-24], vaginal rings [25-27], or transdermal gels [28].

Nestorone acts directly on the pituitary-ovarian axis, inhibiting ovulation. This is believed to be its primary contraceptive mechanism [20,21,29]. In a secondary mechanism, Nestorone thickens cervical mucus, rendering sperm penetration more difficult (Croatto, personal communication).

Data indicate that Nestorone has little affect on liver function [21] or on lipid [21,30,31] or carbohydrate [30] metabolism. It is neither estrogenic nor androgenic, but exhibits strong progestational activity [32]. In contrast to commonly used synthetic contraceptive progestins, e.g., levonorgestrel and 3-keto-desogestrel, Nestorone does not bind to the sex hormone binding globulin [32,33] nor to the cortisol binding globulin [33]. Its binding affinity to androgen receptors (ARs) is about 0.2% of that of testosterone, whereas both levonorgestrel and 3-keto-desogestrel manifest considerable binding to AR, approximately 30-70% of testosterone. In binding to progesterone receptors, Nestorone exhibits lesser affinity than does 3-keto-desogestrel but more than levonorgestrel and progesterone. Nestorone, after subcutaneous administration, proved the most potent progestin by the McPhail Index, in pregnancy maintenance and ovulation inhibition in rats. These properties suggest that Nestorone may possess distinct advantages for contraception or hormone replacement therapies [32,34]. The potential advantages relate primarily to oral inactivity and low affinity to ARs. The former quality makes Nestorone potentially suitable as a contraceptive for nursing women [24,35,36]. The latter quality suggests a possible diminution in the incidence of side effects such as acne and alopecia compared with other progestins.

Principal results from a current and three completed clinical trials of Nestorone implants manufactured at the Population Council's laboratories are presented below. The completed studies include a trial of implant designs, a dose-finding study, and a lactation study. The completed studies have not had more than 100 women on a single dosage form at any time. The ongoing trial involves 300 participants at a single dose.

The Council's first Nestorone implant clinical trial examined release rates and effectiveness of two implant designs. In both designs, the implant had a core consisting of a physical mixture of 50%, by weight, Nestorone and 50% silicone rubber elastomer. These cores contained about 80 mg Nestorone. A cellulose, rate-limiting membrane surrounded each core and was, in turn, covered by silicone rubber tubing. In one design the ends of the rods were covered with Teflon barriers and then sealed with a medical adhesive, yielding an overall length of 4.4 cm. The second design did not contain Teflon barriers; the cylindrical implants were 4 cm in length. Implants with Teflon barriers and those without such barriers had outside diameters of 2.5 mm.

This study of Nestorone implants indicated an effective life of about 2 years for both designs. The rate of progestin release consistently suppressed ovulation in the first year. Among women completing 2 years, however, 20% had progesterone levels compatible with ovulation (≥9.5 nmol/L) in the last months of the trial [23]. Serum Nestorone levels averaged above 100 pmol/L (37 pg/mL) in the first 6 months of use for both implant variants. That without Teflon barriers declined to 86 ± 3 pmol/L (32 ± 1 pg/mL) at the end of 2 years, whereas the design with these barriers had serum levels of 57 ± 5 pmol/L (21 ± 2 pg/mL) at 2 years [23]. (Data were not standardized by body weight). No pregnancies occurred in either arm of the trial. The design without Teflon barriers was selected for further trials because it yielded higher serum progestin concentrations at the end of the study period.

A 2-year, dose-finding study, completed in 1997, involved two Nestorone doses, one meant to release at the level exhibited in the earlier trial, and one representing a 50% increase. The latter was intended to minimize the incidence of ovulatory cycles at the end of 2 years. Nestorone was released from a single 4-cm implant for the lower dose or from two 3-cm implants for the higher dose. Drug load for the 4-cm implant ranged from 80 to 86 mg and ranged from 116 to 130 mg in the two-implant system. Enrollment totaled 120 women, 40 at each of three clinics and 60/dose. The mean enrollment age for each group of 60 participants was 27 years, and mean admission weights ranged from 116 to 130 mg in the two-implant system. Enrollment totaled 120 women, 40 at each of three clinics and 60/dose. The mean enrollment age for each group of 60 participants was 27 years, and mean admission weights were 61.2 ± 11.3 kg and 64.7 ± 14.4 kg for the lower and higher dose groups, respectively (p > 0.05).

By fitting data on the amount of unused drug remaining in the implants at the time of removal to the logarithm of days of use, the two-implant sets are estimated to have released 79 and 41 μg/day at 365 and 731 days, respectively. Estimates of daily release of the single implant were 48 and 31 μg/day at the same two points (Table 1). These estimates are based on a few implants removed before the end of the first year, several at the end of the first year, and 70% at the end of the study. Because of the paucity of early removals, the slope of the release rate curves and the relation between doses are both probably better assessed through examination of Nestorone serum levels. These were assayed at the Steroid Research Laboratory of the University of Helsinki.

Serum levels at each time point, also shown in Table 1, represent multiple samplings over a 6-week period. At 1 year the mean assayed concentration at each dose was
Table 1
Mean serum levels and mean release rates estimated from recovered Nestorone implants by dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. of rods and length</th>
<th>Month</th>
<th>Mean serum levels (pg/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Low</td>
<td>1 x 4 cm</td>
<td>41.6</td>
<td>30.2</td>
</tr>
<tr>
<td>High</td>
<td>2 x 3 cm</td>
<td>60.8</td>
<td>44.9</td>
</tr>
<tr>
<td></td>
<td>Ratio B/A</td>
<td>1.46</td>
<td>1.49</td>
</tr>
</tbody>
</table>

*Note: To convert from pg/mL to pmol/L multiply by 2.7.

slightly above 50% of the 1-month mean. At the conclusion of the study, the mean serum level at each dose was somewhat above 40% of the mean at 1 month of use.

A single pregnancy was reported in a woman using the lower dose. The conception date was estimated as Day 734, an event just after the 2-year mark. This pregnancy initiated further redesign of the implant to enhance the drug release rate in the final months of use and thereby provide a few months of additional pregnancy protection to users who for some reason may delay removal.

Adverse menstrual patterns and other medical events were the principal reasons for discontinuation prior to the end of the study. The lower dose implant appeared to have somewhat higher menstrual-related discontinuation rates than did the two-implant regimen. Conversely, the higher dose was found to have a slightly higher termination rate for medical reasons. With the small sample sizes in each group, the differences were not significant. The principal menstrual problem cited at discontinuation was excessive bleeding. Women with a single Nestorone implant experienced, on average, 84 days of bleeding and spotting/year (360 days) compared with 61 days for participants at the higher dose implants (p < 0.0001). On average, 10.9 onsets of bleeding or spotting/year were reported in the lower dose group against 9.4 onsets for the two-implant regimen. A slight but significant overall drop in hemoglobin means of 3.2 g/L occurred in participants with the 4-cm Nestorone implant compared with the baseline measurement.

Adverse events cited by the women that led to implant removal were principally those commonly occurring during use of steroid hormones for contraception, including headache, dizziness, weight and mood change, mastalgia, acne, and alopecia. For each dose, the 2-year cumulative continuation rate was 70/100 (Table 2).

Differences between doses as manifested in reasons for termination reappeared in responses to a set of questions asked of all participants either at the 1-year visit or at an earlier termination. A significantly greater proportion of participants using two, rather than one, implants reported increased (from baseline) headaches during the study period (p = 0.04). Nausea, dizziness, depression, acne, and other skin problems were all reported as having increased during use by slightly greater proportions of participants in the two-than in the one-implant group. Nervousness was the single nonmenstrual adverse event reported to have increased by more participants with the lower than with the higher dose. On the other hand, a significantly greater proportion of participants with the single implant reported an increase in bleeding days than in the two-implant group (p = 0.007), and a lower proportion in the single-implant group noted decreased days of intermenstrual bleeding (p = 0.056).

Table 2
Gross cumulative event rates per 100

<table>
<thead>
<tr>
<th>Event</th>
<th>Low dose</th>
<th>Year 1</th>
<th>High dose</th>
<th>Year 1</th>
<th>Low dose</th>
<th>Year 1</th>
<th>High dose</th>
<th>Year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>4.5 ± 4.4*</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>8.5 ± 3.7</td>
<td>16.9 ± 5.2</td>
<td>1.9 ± 1.8</td>
</tr>
<tr>
<td>Menstrual problem</td>
<td>8.5 ± 3.6</td>
<td>6.7 ± 3.2</td>
<td>15.8 ± 4.9</td>
<td>8.5 ± 3.7</td>
<td>6.1 ± 3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical problem</td>
<td>5.4 ± 3.0</td>
<td>3.6 ± 2.5</td>
<td>7.5 ± 3.6</td>
<td>16.9 ± 5.2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Plan pregnancy</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>4.1 ± 2.8</td>
<td>1.9 ± 1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other personal</td>
<td>1.9 ± 1.8</td>
<td>1.9 ± 1.8</td>
<td>1.9 ± 1.8</td>
<td>1.9 ± 1.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Continuation</td>
<td>85.0 ± 4.6</td>
<td>90.0 ± 3.9</td>
<td>70.0 ± 5.9</td>
<td>70.0 ± 5.9</td>
<td>6.1 ± 3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pregnancy is considered to have occurred in the twenty-fourth month of use in one woman.
The Population Council concluded from this study that it would attempt to develop a single implant releasing a somewhat higher dose than that studied. This conclusion was partially conditioned by the fact that the Council had already developed a two-implant levonorgestrel contraceptive system for women with a 3- to 5-year effective life. A Nestorone dose intermediate to those studied might ensure that the cumulative 2-year pregnancy rate with the resulting system would be close to zero, with a possible margin of effectiveness for several additional months. By somewhat increasing the lower dose, a modest reduction in the incidence of menstruation might be expected, with minimum increase in the common side effects associated with steroidal contraception.

While development of a new Nestorone implant was underway, a second study of the 4-cm Nestorone implant was initiated in postpartum women, and its performance was compared with that of a copper intrauterine device (IUD) enrolled concurrently under the same protocol [24]. Breastfeeding performance and infant growth, as well as standard measures of contraceptive performance were the study's foci. This single center study was undertaken in Santiago, Chile. At 8 weeks postpartum, 200 women were enrolled and divided equally between study and control groups. During the first year the women and their infants were followed monthly. Clinic visits were required quarterly in the second year. Two-year continuation rates were 80-81/100 in each group. No woman in either group became pregnant during the course of contraceptive use. Neither lactational performance nor the pattern of infant feeding nor that of infant growth differed by regimen. The average duration of lactational amenorrhea was 5 months longer in women using the Nestorone implant than in users of the Copper T 380A despite the differences in the duration of full nursing (10 days) and of any nursing (16 days) being small and not significant [24]. Nevertheless, episodes of prolonged bleeding occurred more frequently in the Nestorone group after insertion (both during lactation and after weaning) than occurred in women using the Copper T 380A.

Menstrual problems, headache, and vaginal problems were, in that order, the most frequently voiced complaints in the implant group. Dysmenorrhea, low abdominal pain, and vaginal problems were, in that order, the most frequent complaints of the IUD group. The patterns of lactation and infant growth in this carefully conducted trial provide empirical evidence for the safety for both mother and child of a Nestorone implant when used by lactating women. Continuation rates of Nestorone implant and copper IUD participants in the study were fully comparable for the 2-year period, demonstrating the utility of these implants in the early postpartum period.

2.3.1. Study of a 4.9 cm Nestorone implant

A redesigned implant with an in vitro release of 110–115 µg/day Nestorone, is now in a three-center clinical trial. The trial seeks to determine whether the redesigned implant provides full contraceptive protection for 3–6 months beyond the 2-year period for which effectiveness claims will be filed. Enrollment of 300 women, 100 at each of three clinics was initiated in February 2000 and is completed. The median age at admission was 26 years with half (49.5%) of the women having no or one child. Median body weight was 61 kg, and 4% of participants had a ponderal index in excess of 30.0. Significant differences among clinic populations were noted for age, desire for additional children, weight, and ponderal index.

As of February 15, 2001, 280 women had completed 3 months of the study, and returned for at least one follow-up visit. At that date, approximately 60% of the women enrolled had completed 6 months of use, with a corresponding 6-month continuation rate of approximately 90/100. Through one year, 151 woman-years had been experienced during use. No pregnancies have occurred. In all Population Council studies with Nestorone implants that yield in vitro release rates of 95–115 µg/day, more than 200 women completed 1 year of Nestorone by April 2001 without a first year failure.

In the current multicenter study, women discontinued from the study citing menstrual problems, medical problems, and personal reasons with essentially equal frequency. Sites differed in termination rates in correspondence with young age and expressed desire for additional children. As in the earlier studies of 4-cm single Nestorone implants with similar release rates, users experienced numerous bleeding and spotting days. In the first 180 days, participants, on average, experienced somewhat more than 40 days of bleeding and spotting, with no significant clinic effect. Median duration of bleeding and spotting episodes was 5 days in each of the first two study trimesters (90-day), well below the corresponding means of 9.5 and 7.4 days for the first and second trimester, respectively. In the same two 90-day trimesters, median bleeding episodes lasted 3 days, and mean episode lengths were about 1 day longer.

To date, headache has been the most common complaint of women in this trial followed by pelvic pain and leukorrhea. Other nonmenstrual adverse events cited by more than 5% of study participants included breast pain, rhinitis, genital pruritus, nausea, dizziness, pain at the implant site, and vaginitis. Acne and alopecia, reactions associated with androgenic steroids, have been cited by 3.7% and 0.7% of participants, respectively.

The current trials will be completed early in the year 2003, but key information concerning the pregnancy rate at 2 years should be in hand at the end of 2002.

The Nestorone implant development program has unfolded slowly in the past decade and is rooted in laboratory and clinical studies of the preceding decade. If the implant in current trial performs as hoped for over the duration of the 30-month trial, much work will still be required to translate the production process from the laboratory to industry and to repeat the trials with sufficient numbers to win...
regulatory approvals. Such approvals may require the best part of another decade.

3. Conclusions

It has been almost two decades since contraceptive implants were first approved by a regulatory agency. Several million women have used implants since that time. In clinical and cohort studies and in national probability samples, users of implants have generally had the lowest pregnancy rates and the highest continuation rates of any reversible method of contraception. The latter quality is indicative of good secondary acceptability, i.e., once women begin to use the method, they tend to stick with it more than is the case for other reversible methods despite the well-known menstrual and medical side effects. One may ask why then are not the number of current users larger, and why do we not see a larger variety of contraceptive implants vying to enter the market. There seem to be three or four major reasons for that. Implants are expensive to develop and market; implants require training staff in new techniques; implants are expensive for family planning programs; and implants are expensive for the couple contemplating their use. who re­runs. Today we have highly effective, long- and very long-acting implants.

Today we have highly effective, long- and very long-acting implants. Research and development has reduced the number of implants needed to sustain an effective dose for 1–5 years from six in the case of Norplant to two in the case of Jadelle and to one in the case of the shorter acting implants. It is unlikely that the next decade will show markedly different implant contraceptive from those now marketed or on the verge of being marketed.

Notes

1. Nestorone is the registered trademark of the Population Council for the progestin 16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3, 20-dione
2. Jadelle is the registered trademark of Leiras Oy for a set of two levonorgestrel-releasing contraceptive rod implants.
3. Norplant is the registered trademark of the Population Council for a set of six contraceptive capsule implants releasing levonorgestrel.

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[14] E. Merck AG, Files, Darmstadt, Germany.


