Nonmenstrual adverse events during use of implantable contraceptives for women: data from clinical trials

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Abstract

Contraceptive methods, including implants, do not prevent common symptoms and adverse health events that most people experience. It is difficult, therefore, to decide whether or not the occurrence of symptoms or adverse events that are common can be attributed to use of a contraceptive method or to determine if a given method changes the likelihood of their occurrence. Based on the review of the literature, no apparent differences in the frequency of adverse events are evident between the six-implant or two-rod levonorgestrel systems and the single implant etonogestrel and nomegestrol acetate systems. The most frequent adverse events reported in clinical trials that are probably related to implant use are headaches and acne. Weight gain, dizziness, and mood changes are also frequently mentioned adverse events and are possibly steroid-related. Other possibly related adverse events, although much less frequently reported, are loss of libido, fatigue, hair loss, and other skin conditions. Persistent ovarian follicles that spontaneously disappear are a common event during use of progestin-only contraceptives, and providers should be aware of this condition to avoid unnecessary interventions. Overall, the vast experience reported in the clinical studies reviewed here show that all existing implantable contraceptives are equally safe. This can probably be attributed to the low-hormonal dose delivered by progestin-implant systems. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Contraceptive implants; Adverse events; Norplant; Jadelle; Implanon; Uniplant

1. Introduction

The first clinical trial with progestin-releasing implants was conducted in Santiago, Chile, over 30 years ago [1]. The levonorgestrel (LNG) six-capsule system, currently approved for 5 years of use, was the first to be developed under the name of Norplant by the Population Council of New York. Improvement in technology in the 1980s brought about the development of a two-rod LNG system, Norplant-II, which was reformulated in the 1990s and renamed Jadelle (Leiras Oy, Turku, Finland), with a similar LNG release rate and clinical performance to the Norplant system. A 3-year etonogestrel-releasing implant, Implanon, was developed by Organon (Oss, The Netherlands) between 1982 and 1996. Two single implant models were developed in Brazil in the early 1990s: a 1-year implant releasing nomegestrol acetate (Uniplant) and the other releasing ecometrine (previously known as ST-1435, and currently referred to by the Population Council’s trade name of Nestorone), with an effective life span of 6 months. This last implant will not be included in this review because only one publication, reporting on a single center clinical trial with less than 70 lactating women, exists.

The scope of our review is limited to nonmenstrual adverse events reported in progestin-implant clinical trials. The vast majority of the literature on this subject relates to Norplant, although considerable information exists for the two-rod LNG system, Jadelle, and to a lesser extent for Implanon. Information related to adverse events during use of Uniplant is scarce. Disruption of the menstrual bleeding pattern and serious adverse events are being described in separate articles.

2. Methodological considerations

Contraceptive methods, including implants, do not prevent common symptoms and adverse health events that most people experience. Such symptoms and adverse events also occur during use of any method. It is difficult, there-
fore, to judge in individual subjects whether or not the occurrence of symptoms or adverse events that are common can be attributed to use of a contraceptive method or to determine if a given method changes the likelihood of their occurrence.

On reviewing the available literature on the subject of side effects associated with the use of implantable contraception, we found that most of the published data are from single arm studies (noncomparative trials), a few studies have compared two different implant delivery systems, whereas only studies of Norplant have included controls using nonhormonal methods.

Adverse events are reported in the literature in two different manners, as incidence or percentage of women with complaints during use or as a reason for removal, when the side effect leads to termination.

This review reports the findings of a relatively large number of publications, the majority of which are descriptive studies, reporting adverse events as they were registered in clinical records at a regular follow-up visit or in specific questionnaires. The frequency of adverse events reported in studies obtaining information from specific questionnaires are usually higher than those derived from clinical records. Incidence of adverse events is reported as annual rate per 100 or 1000 woman-years (WY; based both on reported complaints and/or medical findings) or as the percentage of women with complaints without considering the period of exposure. Because a wide variety of procedures have been used to elicit information from users, the incidence of each adverse event or complaint varies widely between studies and from one center to another within a multicenter study. Probably adding to the variability are cultural characteristics of populations such as differences of awareness, perception, and tolerance of adverse events; perspectives of providers; and their interaction with clients.

Removals are more often recorded as total gross or net termination rates for medical reasons, whereas other articles simply report the percentage of the total number of participants that request removal for a specific reason, without considering the duration of use. Removal rates probably indicate the weight, burden, or importance that users attribute to the adverse events and are perhaps the most objective measure to compare differences between implant systems and between centers. The variation in termination rates because of side effects is smaller, yet differences in rates have also been found within different centers.

The difference in duration of use of the implant systems makes a valid comparison between systems difficult because most Norplant studies report findings occurring during 5 years, studies with Jadelle report rates for both 3 and 5 years of use, whereas Implanon studies report mostly rates for 2 years of use, and the only large Uniplant trial reports on 1 year of use. All of these methodological issues need to be considered when reading the data presented below.

### 3. Medical side effects

Apart from menstrual disturbances, which will be the subject of a separate article, the most frequently mentioned side effects in the published clinical trials of any progestogen-releasing implantable contraceptive (IC) are headache; weight gain; acne; dizziness; mood changes, including nervousness and depression; breast tenderness; nausea; lower abdominal pain; hair loss; loss of libido; and pain at implant site (Tables 1 and 2). Complications of insertion and re-

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**Table 1**

Percentage of women reporting specific adverse events in comparative clinical trials with different implantable contraceptives.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Norplant/Jadelle comparative Trial* 3-year results</th>
<th>Norplant/Implanon comparative trial** 3-year results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Norplant n = 598</td>
<td>Jadelle n = 600</td>
</tr>
<tr>
<td>Headache</td>
<td>26.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Acne</td>
<td>5.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Weight gain</td>
<td>12.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>15.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>8.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Mood changes</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Nervousness</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Pain at implant site</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Hair loss</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Sivin I, Viegas O, Campodonico I, et al. [12].
** Urbancsek J [14].
mval, as well as the finding of “follicular cysts,” are also included as adverse events.

3.1. Headache

Headache is the most frequent complaint of users of ICs. The great majority of studies report figures within 10–30%; however, the percentage of women complaining of this condition ranged from 3 to 69% for the different ICs [2–15]. There was great variability by study and by center. The three exceptions in the upper range were two US Norplant studies reporting 43% and 49% of women with complaints [5,6] and the Chilean cohort within the multicenter Implanon study, which reported an incidence of 69% [14,16]. It is difficult to interpret whether these differences are real, or whether they are the result of different methods of obtaining and recording data. The two high rates observed in the US were obtained by using specific follow-up questionnaires applied at 3 months (49%) and 1 year of use (43%) among women returning to the clinic. The high rate observed among users of Implanon in Chile was almost sixfold greater than the mean in all other centers in the same study [14,16]. This very large difference with other centers, which exists not only for headache, but for all complaints, appears to be related to a different definition of the complaint and/or method of obtaining the information.

Other studies have reported annual rates of occurrence of headache per 100 WY. One comparative study between Norplant and a nonhormonal method (TCu 200 intrauterine device; IUD), found a significantly higher incidence of headache among users of Norplant than of IUDs in the first 3 years of use (18.7 vs. 6.9, 17.5 vs. 13.3, and 14.3 vs. 7.1/100 WY for Norplant and IUD in years 1, 2, and 3, respectively) [17]. The Norplant Surveillance study reported a rate of at least one episode of headache or migraine of 11.5 per 1,000 WY with a rate-ratio of 3.44 (95% CI 2.83, 4.18) for current Norplant users compared with nonhormonal controls (p = 0.001) [18]. A smaller study carried out in Egypt reported no difference in the percentage of Norplant and IUD users complaining of headache at the 2-year visit (3.3 vs. 3.7%, respectively) [2]. In a more recent study conducted in the US, the annual rate of occurrence was 16.1/100 WY for the first year, decreasing to an annual rate of 9.7/100 WY during the subsequent years of use [13]. This was not different than an annual rate of 12.8 and 12.0/100 WY reported among Norplant and Jadelle users, respectively, in an international comparative study (Egypt, Chile, Finland, US, Singapore, and Thailand) [12].

The percentage of women removing their IC because of headache was low, ranging from 0.0–5.0%, with no differences between systems (Fig. 1) [7, 12–14, 19–28]. This accounts for about 10–20% of all medical reasons for removal, excluding menstrual disturbances.

From the above review, we conclude that headache is the most frequent complaint among progestin-implant users; it is probably steroid related; there seems to be no difference in the frequency of complaints or rates of removals between implant systems; and overall, less than 5% of all users discontinue for this reason.

3.2. Weight gain

Weight gain is the second most frequently mentioned complaint (not considering menstrual disturbances), and it is probably the side effect most difficult to interpret. Practically every long-term study with any contraceptive method shows an increase in average weight of users. How much of that increase is related to use of the method is very hard to evaluate, without specially designed studies to achieve this purpose. Two controlled studies measured weight over time; one found an increase of 0.7 kg/year in both Norplant and IUD users [17]. The Norplant Surveillance study found a weight gain of 2.5 kg in Chinese women (SE 0.007) over 5 years. This relatively modest weight increase was, however, only 1.0 kg higher than the increase in nonhormonal controls (p < 0.001) [18].

Most studies in which body weight was serially recorded show an average increase of 0.4–1.5 kg/year with all implant systems [4, 9, 10, 13, 17, 20, 23, 24, 29–33]. The weight increase was somewhat higher in two studies of adolescent users of Norplant conducted in the US (2.6 and 3.3 kg after one year of use) [34, 35]. The proportion of women who

Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Crude incidence rate per 1000 WY</th>
<th>Adjusted rate ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11.5</td>
<td>3.44</td>
<td>2.83, 4.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acne</td>
<td>0.9</td>
<td>7.48</td>
<td>2.90, 19.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4.5</td>
<td>6.94</td>
<td>4.57, 10.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>0.96</td>
<td>0.79</td>
<td>0.50, 1.26</td>
<td>0.33</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.2</td>
<td>4.29</td>
<td>3.00, 6.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mood changes</td>
<td>2.8</td>
<td>2.15</td>
<td>1.53, 3.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hair loss</td>
<td>0.3</td>
<td>12.44</td>
<td>1.6, 96.6</td>
<td>0.016</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>1.2</td>
<td>2.64</td>
<td>1.49, 4.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.5</td>
<td>1.66</td>
<td>1.39, 1.97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* International Collaborative Post-Marketing Surveillance of Norplant [18,41].
increased weight was five-fold higher than the percentage of Norplant users who lost weight in studies carried out in Brazil and in the US. Fifty-two percent of Norplant users in Brazil gained more than 3 kg in 3 years, whereas 80% of US users gained more than 1 kg in 5 years. Another large, 5-year Norplant-II study conducted in India reported that 43% of the women increased more than 5 kg, whereas 10% of the women in the multicenter Jadelle trial gained 9–10 kg in 5 years [13,22,26,29]. Only one small study found a decrease of 0.8 kg at 1 year of use of Norplant compared to an increase of 0.06 kg among users of depot medroxyprogesterone acetate [36], and another in Indonesia reported no increase at 2 years of use [32]. In comparative studies with Implanon, 17.6% of Norplant users increased more than 10% in their body weight compared to 20.7% for Implanon [14].

Spontaneous complaints about weight increase were reported by 4% to 22% of women using different ICs [8,12–14]. As with headache, the incidence of complaints was higher in two US Norplant publications (51% and 60%),
which were based on data obtained through questionnaires, and it was 40% in the Chilean cohort within the multicenter Implanon study [6,11,14].

Weight increase led to removal of implants in 0.5–5.6% of women, with no difference between implant systems (Fig. 1) [4,10,12–14,16,19,21,22,24,26,28]. Discontinuation for weight increase, however, is not a good indication of its prevalence, because this phenomenon may be seen as a disadvantage in some populations but as an advantage for others [37].

On the other hand, weight loss was reported as a complaint by up to 3.5% of users [12] and was responsible for discontinuation rates of 0.2% through 1.2% for any of the four IC systems being reviewed [19,20,22,26,27].

In the Norplant Surveillance study the adjusted rate ratio for Norplant compared to controls was significant for both reported weight gain, 6.94 (95% CI 4.57, 10.5), and for reported weight loss, 2.64 (95% CI 1.49, 4.67), p = 0.001 [18].

Summarizing, weight gain has been a consistent finding in all implant clinical trials, but it has also been reported among nonhormonal contraceptive users, suggesting that other factors may also be related, such as the natural increase in weight related to aging.

3.3. Acne, hair loss, and hirsutism

Acne was reported by 3% to 27% of users of any IC in clinical trials [3,5,7,8,12–14,16,27]. In the international comparative study of Norplant and Jadelle, the proportion of women reporting acne was only 5.7% and 5.8%, respectively, whereas in the US Norplant trial, it was 21%, which is similar to a rate of 22% and 18% reported among women in the comparative trial between Norplant and Implanon, respectively [12–14]. However, the objective assessment of acne in a subgroup of women in this study, both before Implanon insertion and at the time of removal, revealed no increase in the proportion of women with this symptom. Furthermore, among women with pre-existing acne, more than half reported improvement during use, whereas the condition worsened in only 10% [14]. In the large US trial, the first year annual rate of occurrence was higher than in subsequent years of use (15.0 vs. 9.8/100 WY) [13].

Hair loss and hirsutism are less frequently mentioned side effects. The publication of the Implanon/Norplant comparative multicenter study did not include these symptoms because they only reported symptoms mentioned by at least 5% of users. The annual occurrence rates of hair loss in the US Norplant trial was 5.2 and 3.5/100 WY in the first and subsequent years of use, respectively [13]. A large Chinese study with Norplant-II reported an annual rate of occurrence of 0.02/100 WY, whereas the international comparative Norplant/Jadelle study reported annual rates of 1.8 and 1.9/100 WY, respectively [12,38]. In two US interview studies, 18–19% of users reported hair loss or abnormal hair growth in the first year of use [6,11]. Hirsutism was even more rarely mentioned, usually pooled together with hair loss. The multicenter Uniplant study did not report any of these symptoms.

In the comparative Norplant/IUD study, the annual rate of occurrence of all skin symptoms, which include acne, hair loss, hirsutism, and other skin problems, was significantly higher among Norplant than among IUD users during the first year of use, but not in subsequent years (8.1 vs. 3.2, respectively, in the first year and 7.8 vs. 9.8, respectively, in the second year) [17]. In the Norplant Surveillance study, the incidence rate of acne was 0.9/1000 WY with an adjusted rate ratio of 7.48 (95% CI 2.90, 19.3) comparing Norplant users with controls, whereas the incidence of hair loss (alopecia) was 0.3/1000 WY with a rate ratio of 12.4 (95% CI 1.60, 96.6) [18]. The incidence rate of inflammatory skin disorders was 3.5/1000 WY (rate ratio 3.09, 95% CI 2.20, 4.32), and for other skin problems the incidence rate was 2.4/1000 (rate ratio 3.35, 95% CI 2.20, 5.12).

The rate of removal in which acne was the reason cited for discontinuation varied from 0% to 2.0% (Fig. 1) [7,12–14,20,25–28], whereas the removal rate attributed to hair loss/hirsutism was 0% to 1.0% among IC users [7,13,21,26,28]. Removal rates for these reasons were not reported in the Implanon/Norplant comparative study, which included only reasons responsible for termination rates greater than 1% [14].

Acne, hair loss, and hirsutism are side effects that are usually attributed to an androgenic effect of progestogens. The significantly more frequent observation of these side effects among Norplant implant users than among nonhormonal controls suggests that these side effects are probably associated with the hormonal component and that they may occur more often in some women in the initial months of use, when the progesterin levels are several-fold higher than in the later months. The available data do not show differences between the implant systems reviewed.

3.4. Dizziness

Between 4% and 11% of users of any IC complained of dizziness [9,12–15,27]. In two controlled studies, the rate of dizziness was higher in Norplant than in nonhormonal controls; 8 vs. 5/100 WY (p > 0.05) and 4.2 vs. 1.2/1,000 WY (p < 0.005; rate ratio 4.29, 95% CI 3.00, 6.15) [17,18]. The annual rate of occurrence was reported as somewhat higher in the first than in subsequent years of use of Norplant (5–8 vs. 3–4/100 WY) [12,13,17]. Dizziness led to removal in a relatively low percentage of women using any IC (0% to 2.3%; Fig. 1) [4,10,14,16,24,26,28,38].

The available data indicates that dizziness is possibly associated with progestogen implant use, but it seldom leads to removal. There does not appear to be any difference between implants.
3.5. Mood changes, nervousness, and depression

Diverse psychological disturbances are also a commonly mentioned side effect of IC use. Nervousness was reported by 6–9% of Norplant and Jadelle users in clinical trials and by 19% Norplant users who responded to a questionnaire in the US [6,7,12]. It was reported by only 1–1.2% of Implanon users, excluding a 30% reported by users of this implant system in the Chilean clinic [14]. The annual rate varied from 4.8 to 10.5/100 WY among Norplant users, slightly, but not significantly, higher than 1.4 to 7.2/100 WY among IUD users in the comparative study [17]. The annual rate in the multicenter Norplant/Jadelle comparative study was of 4.4 and 3.6/100 WY [12], respectively, whereas it was 2.6/100 WY in a large Norplant clinical trial in the US [13]. The annual rate of depression reported in comparative clinical trials was between 1.9 and 2.5/100 WY, which was similar to 0–2.1/100 WY among IUD users [17]. There is one study in which a specific test to measure mood/depression was applied just at the time of initiation of Norplant use and 6 and 12 months later (n = 910). The authors did not find any increase in depression or worsening of the test results after use of Norplant. They also found that the group of women with the lowest score tended to improve after 1 year of use of Norplant implants [39]. Such a study indicates that depression is most likely not induced by the use of ICs.

Mood changes were reported by 10.6% of US users in the large Norplant trial, whereas it was elicited in 16–26% of respondents to questionnaires in the US [3,8,11,13]. This side effect was reported in 1.9–5.4% Implanon users compared to 7.6% among the Norplant comparative group [14]. In the Post-Marketing Surveillance of Norplant, reports of mood disorders were infrequent (2.8/1,000 WY in current Norplant users), but significantly more often reported by current Norplant users than controls (rate ratio 2.15, 95% CI 1.53, 3.02) (p < 0.001) [18].

Mood changes, nervousness, and depression accounted for similarly low rates of removal, 0% to 1.7%, 0.2% to 1.6%, 0.2% to 1.9%, respectively, with no difference by implant system (Fig. 1). [7,13,14,19–21,24,26,28,38]. Overall, it is not easy to interpret whether these symptoms are related to IC use. However, there is a tendency for reports of mood swings, nervousness, and depression to be made more often by women using ICs than by nonhormonal controls.

3.6. Nausea, breast tenderness, loss of libido, and fatigue

Nausea, breast tenderness, loss of libido, and fatigue are seldom reported as reasons for discontinuation; however, they are often reported as complaints. Nausea has been reported as affecting 4% to 12% of users of different ICs [7,10,12–14]. The corresponding percentages were 6.5 for Norplant and 3.8 for Implanon users in the multicenter comparative study of these two implants systems [14]. The annual rate was higher in the first than in subsequent years in the US Norplant trial (7.5 vs. 4.2/100 WY, respectively) [13]. The annual rates for Norplant and Jadelle were of 2.6 and 2.9/100 WY, respectively, in the international comparative study [12]. The Post-Marketing Surveillance of Norplant reported very low rates of nausea (<1/1000 WY) and no significant difference between implant users and users of nonhormonal methods [18].

Breast tenderness is typically reported by 3% to 16% of women using progestogen implants in clinical trials [4,7,12,14,27], but rates of around 30% have been reported [6,11,16]. The annual rates of occurrence were similar for Norplant and Jadelle in non-US and US trials, 3.6 and 4.0/100 WY, respectively [12,13,28]. In the comparative study between Norplant and IUDs, there were no differences in the annual rate of occurrence (3.6–6.3/100 WY and 2.6–7.2/100 WY, for Norplant and TCu200, respectively) [17].

Loss of libido was reported to occur in 2% to 5.4% of users of any IC in clinical trials [12,14,16,40]. The reported annual rate of occurrence was 0.4 to 3.8/100 WY in various Norplant and Jadelle clinical trials, respectively, which was similar to the rate of 0.0–1.4/100 WY reported among IUD users [12,13,17]. The Norplant Surveillance study reported a loss of libido rate ratio of 3.79 for Norplant compared with controls (p = 0.002) [18]. Only one study, conducted among Uniplant users in Chile, had specific questioning regarding libido. They reported no decrease in libido, and the frequency of sexual relation remained unchanged during Uniplant use, in spite of increased irregular bleeding [40].

Fatigue has also been reported by 2.5–4.2% of Norplant and Jadelle users, leading to removal in less than 0.6% of women [2,12,13,19].

The removal rates for the above mentioned symptoms were very low. Loss of libido was a cause for discontinuation in 0% to 0.8% of women, breast tenderness between 0% and 1.0%, and nausea was never above 1.2% (Fig. 1) [10,13,14,19,21,26–28,38].

3.7. Lower abdominal pain

Lower abdominal pain was voiced as a complaint by 7–23% of women using Norplant, Jadelle, and Implanon. The annual rate of occurrence was between 7.3–9.6/100 WY for Norplant and Jadelle users, whereas less than 1.7% of the women had their implants removed for this reason [12–16,26,28]. However, in controlled trials of Norplant and nonhormonal methods, the incidence rates of pelvic pain were higher in IUD users than in Norplant users or in sterilized women [17,41].

3.8. Ovarian cysts

An increased incidence of “ovarian cysts” has been reported since very early in the process of the development of implantable contraception [42]. However, throughout the years it has become perfectly clear that these are not real ovarian cysts, but persistent follicles. Continuous, low-dose progestins do not completely suppress ovarian function.
Dominant follicles develop in response to gonadotrophin secretion, yet the normal ovulatory process is frequently disrupted, and follicle rupture does not occur. The follicular structure will remain and may become enlarged (>30 mm), but will spontaneously disappear within 1–2 months [43, 44].

Several studies of serial sonographic evaluation of the ovaries for periods between 4–6 consecutive weeks have shown that these persistent follicles occur in 56–63% of the cycles with all four implant systems. The maximum diameter of these follicles is usually below 35 mm [45–50].

In a study in which a single ultrasound was performed at a regular clinical visit, the percentage of Norplant users with follicles above 25 mm was 17.6% compared to 4.0% observed among IUD users, and no difference was found by year of use (p = 0.039). In this study, only 40% of these enlarged follicles were detected by clinical, bimanual, vaginal pelvic examination [44].

In large, clinical studies, the finding of an “ovarian cyst” on physical exams has been reported in 2.0–3.0% of Norplant, Jadelle, and Implanon users. The Chilean cohort in the Implanon study reported a higher figure of 9.1% [7,12,16,17,22]. In the Norplant Surveillance study the adjusted rate ratio of ovarian cystic enlargement for Norplant users versus controls was 3.71 (95% CI 2.52, 5.47), whereas there was no difference in the rate of hospitalization or surgery for this condition [41].

Thus, the finding of a persistent follicle at a pelvic or ultrasonographic examination is not an indication for any kind of intervention, except follow-up 1 month later. If a cystic image of the ovary persists for 2 months or longer, it requires further study because it may correspond to a permanent tumor and no longer to a transient functional phenomenon.

4. Insertion and removal related side effects

Side effects related to insertion and removal of the implants have been often neglected in the scientific literature of ICs. Few studies have systematically paid attention to the local discomfort suffered by women during the first few days after the insertion or after removal of implants. Most studies report on more serious conditions, such as infection at the site, which requires removal or spontaneous expulsions.

The incidence of infection reported in the literature varies from 0% to 1.4% [7,13,15,19,33,51–60]. In most Norplant studies the incidence is not greater than 0.5% [13,19,33,51–54], whereas only two studies reported rates 1.0% or over [57,58]. Studies with Jadelle report an infection rate between 0.2–0.3% [22,26], whereas no infection was reported in the Uniplanet trial [10] nor in the Implanon or comparative Implanon/Norplant studies [60]. Most infections occur within the first 2 months of use (65%); however, infections have occurred as late as 2 years after insertion [28,56].

Implant expulsion is frequently the result of infection, but a rate of 0% to 0.6% of spontaneous expulsion without infection has been reported [22,23,28,35,56,59–61]. Expulsions were reported to occur within the first 2 months of use in 35.7% of cases, whereas 70% were reported within the first 4 months of use [56].

Other insertion complications such as bleeding, hematoma, allergy to anesthetic or bandages, dizziness, etc., have been reported by 0.0–1.7% of users [24,26,28,60].

There is one study that systematically evaluated the incidence of signs and symptoms at the site of insertion at 1 week and 1 month after Norplant insertion. Ecchymosis and tenderness were observed in over 30% of the users; 14% had edema, and 8% reported pain at the implant site 1 week after insertion. These symptoms had almost totally disappeared at 30 days after insertion [62]. At about 1 month after Implanon insertion the percentage of women presenting with swelling, redness, pain, and ecchymosis/hematoma was between 0.2% and 1.9%, rates that are very similar and are not lower than those found, in the publication mentioned above, after Norplant insertion [60]. In addition, there were no differences in the percentage of women with post-insertion symptoms in the multicenter, comparative study of Implanon and Norplant [60]. A questionnaire given to Norplant users in Brazil identified a much larger proportion of women declaring to have had pain immediately after insertion (46%), pain requiring oral analgesic medication (29%), swelling (33%), and ecchymosis (60%) [63].

Pain at implant site or arm, as well as numbness in the arm, have been reported with all implant systems, except the large clinical trial with Uniplant, which does not mention this complaint. These spontaneous complaints have been reported by 0.7–7.1% of all implant users, with no apparent difference between devices [8,12–14,16,27,56,60]. The exception to these percentages are a high 16.8% of women in the Chilean cohort of the Implanon study [14] and 28% of the US Norplant users interviewed [6] who report some pain in the implant arm. This pain led to removal in 0.0–2.0% of Norplant users, in 0.0–1.7% of Jadelle users, and it is not reported in the Implanon or Uniplant trials. There have also been reports of skin discoloration in 10.6% of Norplant users [13].

Removal complications, ranging between 0.2–14.8%, have been reported in all studies [13,16,24,26,28,58,60,64]. These complications are mostly due to the formation of a fibrous pericapsular sheath surrounding the implant or to breakage of implants, deeply placed implants, or migration of implants. All these events may lead to more difficult removal and prolonged removal time. In few instances (<0.8%) did these complications affect participants, such as requiring a second incision or not being able to remove all capsules [13,26,64]. Comparative studies between Norplant and Jadelle, as well as Norplant and Implanon, have shown a significantly reduced number of complications with these two newer, systems: 0.2% Implanon removals were reported with complications versus 4.8% in the Norplant.
comparative arm (p = 0.001) [26], whereas 6.9% of Jadelle removals had complications versus 14.8% for Norplant removals (p = 0.009) [60].

One case of keloid formation over the implant site [65], and two cases of peripheral neuropathy causing some paresthesia and numbness [66] have been reported during use of Norplant. Likewise, three cases of ulnar nerve injury associated with removal of Norplant implants have been reported [67,68]. These authors caution about the importance of placing the implants over the medial surface of the biceps brachii and not over the brachial groove because the latter introduces potential for trauma to the ulnar and median nerves [69].

5. All medical terminations excluding menstrual disturbances

The total termination rate because of medical reasons at 5 years ranged from 3.9% to 20.8%, and from 6.0% to 30.5% for Norplant and Jadelle, respectively. In the Implanon studies a total of 1.0–15.0% of users discontinued use for medical reasons at 2 years, whereas in the comparative trial between Implanon and Norplant, the figures were 6.0% versus 7.6%, respectively. In the large 1-year Uniplant trial, a total of 3.4% of users discontinued [10,12–14,16,20,22, 23,26,28,31,38,59,61,70]. In general, these medical terminations accounted for 20–40% of all removals.

6. Factors associated with incidence of side effects

Even though comparative studies between different progestin implants have been relatively small, there seems to be no difference in observed nonmenstrual side effects between the four ICs (with the exception of removal related events that have a higher incidence with the six implant system). This is further illustrated by the results from comparative studies between Norplant and Jadelle and Norplant and Implanon (Table 1) [14,26]. As can be seen in Figs. 2 and 3, the percentage of women reporting complaints as well as the percentage of women terminating use for specific complaints in the two comparative studies were very similar, indicating that the three systems are not different with regards to nonmenstrual side effects. It is noteworthy that, overall, the percentage of women discontinuing for medical reasons is very small compared to the percentage of women with complaints.

The review of the world clinical experience with implantable contraception reveals that, in addition to the described variation in the frequency of complaints by clinics, there is a pattern that clearly differentiates the several regions of the world where the studies have been carried out. This is illustrated by the comparison of the termination rates for medical (nonmenstrual) reasons in Norplant studies carried out in different geographical locations (Fig. 4). The termination rate at 2 years was much lower in Asia (range 0–4.4%), somewhat higher in Africa (all studies except one
between 1–8%), followed by Latin America (5–9%), and finally the US, where the highest rates of complaints are reported (10–16%; Fig. 4) [2,9,12,13,19,23,32,37,55,57,59, 61,70,71].

7. Conclusions

From the review of the published literature it appears that there is no difference in the incidence of adverse events during use of the four systems of ICs currently available. However, the only comparative study between Norplant and Implanon was limited to 184 women in each arm, whereas the comparative multicenter study between Norplant and Jadelle had near 600 women in each arm. No comparative studies of Uniplant have been done. The comparisons of reported adverse events in different noncomparative clinical trials is difficult because the methods for obtaining reports are not standardized. Great variability exists between coun-

Fig. 3. Comparison of frequency of complaints and terminations between Norplant (n = 184) and Implanon (n = 184) users in a 3-year international trial: Scandinavia, UK, Thailand, and Singapore.

Fig. 4. Two-year medical termination rates (excluding menstrual disturbances) reported in various Norplant clinical trials within different geographical regions.
tries and between clinics within countries. This may be due to differences between countries and regions in the incidence and prevalence of symptoms and health conditions [18], but probably adding to the variability are cultural characteristics of populations, such as differences in awareness, perception, and tolerance of adverse events. Another key issue is the interaction of the providers with their clients. There may be differences in the probing for adverse events, and there may also be differences between clinical settings in the willingness or perceived capacity to complain by some users.

The most frequent adverse events during use of ICs, which have been usually reported in the range of 15–25% in clinical trials, are headache, lower abdominal pain, weight gain, and acne. Of these events, headache and acne are probably steroid-related to use, whereas weight gain is possibly related. Lower abdominal pain was observed more frequently among IUD users and sterilized women. Dizziness, breast tenderness, nausea, and mood changes follow in frequency with reports usually ranging from 5% to 12%. Of these, reasonable evidence exists that dizziness and mood changes may possibly be related to steroid use, whereas no scientific evidence is available to relate breast tenderness and nausea to the use of low-dose steroid-releasing implants. Hair loss, loss of libido, and fatigue, which are less frequently reported, usually in the range of 3–9%, may also be possibly related to implant use. The incidence rates reported in the Post-Marketing Surveillance, although about 20-fold lower than in most other clinical trials, have a similar distribution in the adjusted rate ratio between Norplant users and nonhormonal controls for headache, acne, weight gain, dizziness, mood changes, hair loss, fatigue, and weight decrease (Table 2).

It is noteworthy to mention that nonmenstrual related adverse events, although frequently reported, are seldom reason for discontinuation, usually less than 10% of those complaining. Most of these adverse events have each led to discontinuation of the method in less than 5% of the users.

Persistent ovarian follicles that spontaneously disappear are a common event during use of progestin-only contraceptives, and providers should be aware of this condition to avoid unnecessary interventions.

Signs and symptoms related to the immediate post-insertion and removal procedures are rarely evaluated, and reliable information on its incidence is missing. The possible difference in the incidence of insertion site problems and removal complications between one or two implants systems has not been evaluated and should be the object of well designed systematic evaluation.

It is clearly evident from this review that to evaluate the incidence of adverse events of any new steroid contraceptive method, properly designed studies comparing users with nonhormonal contraceptive methods are required. Although randomization is not possible, other means of controlling for possible selection bias and confounding factors should be built into the study design.

Overall, the vast experience reported in the clinical studies reviewed above show that all existing ICs are equally safe. This can probably be attributed to the low hormonal dose delivered by progestin-implant systems.

References


