Implantable contraceptives for women

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Progestogen-only implantable contraceptives are used by increasing numbers of women worldwide. This review outlines the evidence accumulated on these methods to date. Reviews of toxicological evaluations, clinical trials, endocrinological, epidemiological and social science studies, as well as operations research and economic evaluation were undertaken in preparation for an Expert Consultation convened by the World Health Organization in 2001. At the meeting, these reviews were further evaluated and the research results summarized in this consensus paper. A large body of evidence demonstrates the high contraceptive effectiveness and safety of the 5-year levonorgestrel-releasing implants Norplant and Jadelle. Information on the 3-year etonogestrel-releasing implant Implanon is more limited, but suggests that this implant has a high contraceptive effectiveness and a satisfactory safety profile. Information available on levonorgestrel-releasing implants manufactured and approved in China suggests that their clinical performance is satisfactory, but was insufficient to allow their full safety assessment. For all implants, there is insufficient information on their use by women with medical conditions. Provision of contraceptive implants requires good quality family planning services and specific provider training.

Key words: contraception/implant/progestogen-only contraceptive/WHO consensus paper

Introduction

The first scientific publication on a contraceptive implant for women releasing a progestogen appeared in 1969 (Croxatto et al., 1969). In 1983, the first implant, Norplant® was approved by the Finnish national drug regulatory authority. Since then, several more implants have been registered (see Table I), and others are under development. Contraceptive implants are now approved in more than 60 countries and have been used by approximately 11 million women worldwide (Bongaarts and Johansson, 2000).

In view of the increasing importance of implant contraception in family planning and the development and approval of new contraceptive implants, the Department of Reproductive Health and Research of the World Health Organization convened a meeting of experts to review data on safety and effectiveness of implantable contraceptives for women. This report details the...
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Table I. Progestogen-only implants registered trademarks (2002)

<table>
<thead>
<tr>
<th>Implant Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elcometrine®</td>
<td>is the registered trademark of the South-to-South Cooperation in Reproductive Health for a single capsule releasing the progestin 16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3, 20 dione.</td>
</tr>
<tr>
<td>Implanon®</td>
<td>is the registered trademark of Organon for a single etonogestrel-releasing contraceptive rod implant.</td>
</tr>
<tr>
<td>Jadelle®</td>
<td>is the registered trademark of Leiras Oy for a set of two levonorgestrel-releasing contraceptive rod implants.</td>
</tr>
<tr>
<td>Nestorone®</td>
<td>is the registered trademark of the Population Council for the progestin 16-methylene-17α-acetoxy-19-nor-pregn-4-ene-3, 20 dione.</td>
</tr>
<tr>
<td>Norplant®</td>
<td>is the registered trademark of the Population Council for a set of six levonorgestrel-releasing contraceptive capsule implants.</td>
</tr>
<tr>
<td>Unimplant®</td>
<td>is the registered trademark of Theramex for a single nomegestrol acetate-releasing contraceptive capsule implant.</td>
</tr>
</tbody>
</table>

Note: only some of these implants are registered products (see text).

The outcome of the meeting and summarises data on the safety and contraceptive effectiveness, programmatic and service aspects, and clients’ perspectives on the currently available contraceptive implants. Background papers commissioned for the consultation provide detailed information on various aspects of implantable contraceptives. They are published in Volume 65(1) of the journal Contraception and are cited in the text where relevant.

Description of implants

Several subdermal contraceptive implants using four different progestogens and two types of non-biodegradable polymers were developed, some of them are registered, and several additional systems are under development (Croxatto, 2002a). The implants are inserted subdermally, under local anaesthesia with use of a trocar, usually in the inner aspect of the non-dominant arm. The daily release rate of steroid declines very slowly throughout the implant life-spans, which are between 6 months and more than 5 years.

Levonorgestrel implants

Norplant® consists of six silicone capsules, and Jadelle® of two silicone rods. Rods differ from capsules in that they contain a matrix which is a cured mixture of steroid crystals and polymer, while capsules contain free steroid crystals. Norplant capsules and Jadelle rods release levonorgestrel at similar rates for 5 years, which is the approved life-span of the two implants. Levonorgestrel serum levels fall fairly rapidly during the first month after insertion and then decline much more slowly through the remaining implant life-span. Serum levonorgestrel level is inversely related to body weight (Diaz et al., 1987a; Sivin et al., 1997). Following implant removal, levonorgestrel is cleared from the circulation within 120h. At the end of 5 years, 69% of the original steroid load remains in the Norplant capsules (Croxatto, 2002a).

The Norplant capsules tested in early studies were made with the so-called hard tubing formulation (Sivin and Moo-Young, 2002). Subsequently, the formulation was slightly modified and referred to as soft tubing. The soft tubing implants release slightly more levonorgestrel per day and have significantly lower pregnancy rates than the hard tubing implants (unpublished data). Since 1991, practically all Norplant capsules have been manufactured with soft tubing.

Contraceptive effectiveness and clinical data of Norplant and Jadelle appear to be almost identical through 5 years of use (Sivin et al., 1998a). Recent data confirm the effectiveness of Norplant up to 7 years (Gu et al., 1995). Levonorgestrel implants manufactured in China were designed to perform as Norplant and Jadelle, and current clinical data seem to confirm this (Fan and Han, 1999).

Etonogestrel implant

The etonogestrel-releasing implant (Implanon®) is a single rod which provides high contraceptive effectiveness for 3 years. Etonogestrel (3-keto-desogestrel) is the biologically active metabolite of desogestrel. It is incorporated into a solid rod of ethylene vinyl acetate (EVA) co-polymer covered by a thin EVA membrane. Maximum serum levels of etonogestrel are attained on day 4 after insertion, and levels then decline slowly over the next 3 years. Low body weight is associated with higher serum etonogestrel levels. After removal, etonogestrel serum levels become undetectable within one week (Huber, 1998).

Nestorone implants

The progestogen Nestorone® (ST1435) is used in a single silicone rod implant under development by the Population Council in the USA, and is designed to be effective for 2 years (Croxatto, 2002a). The same progestogen is used in a single silicone capsule implant (Elcometrine®) licensed for contraception in Brazil for 6-months use (Croxatto, 2002a).

Nomegestrol acetate implant

A single silicone capsule releasing nomegestrol acetate (Unimplant®) has a contraceptive life-span of 1 year (Croxatto, 2002a). There are currently no plans to commercialize this implant.

Toxicology

The contraceptive implantable systems consist of synthetic progestogens and polymer capsules or rods. Toxicological studies of implantable contraceptives therefore need to address both the progestogens and the polymers.

For three of the four progestogens used to date in implantable contraceptives [levonorgestrel, etonogestrel (3-keto-desogestrel), Nestorone], information on the toxicology, including genotoxicity and effects on fetal development of the progestogens, was available from the literature, previous New Drug Applications approved in the USA or data provided by the companies (Jordan, 2002). These sources also contained information on animal carcinogenicity studies for levonorgestrel. For nomegestrol acetate, such information was not available.
Available studies show that levonorgestrel has undergone a thorough toxicological evaluation. Early studies utilizing the oral route of administration to support safety as oral contraceptive were supplemented with additional studies using the parenteral route. No unusual toxicity, genotoxicity, carcinogenicity, or effects on reproduction were noted (Jordan, 2002).

Full toxicological information on etonogestrel is not available and much of the data are derived from the prodrug, desogestrel. The data from toxicity, genotoxicity, carcinogenicity and fetal development studies of desogestrel demonstrated overall safety of the drug in these tests (Jordan, 2002).

Nestorone has been examined for toxicity, genotoxicity and effects on reproduction. The results demonstrate the safety of this steroid in these tests. Nestorone is currently being tested for carcinogenicity (Jordan, 2002).

For nomegestrol acetate no toxicological or carcinogenicity data were available for review by the working group.

The marketed implants Norplant, Jadelle and Implanon have sufficient toxicological data to indicate that the polymers used in them are safe for use. Silicone elastomers (the polymers used in Norplant and Jadelle), with their long-term and widespread clinical use, have additional human data available to ensure safety (Bondurant et al., 2000; Metrik et al., 2001; Shastri, 2002). The carcinogenicity studies reviewed for the polyethylene-co-vinyl acetate (the polymer used in Implanon) indicated that this material is safe for use as judged from these tests (Shastri, 2002). However, clinical data regarding long-term use of this implant are not yet available.

For new implants and generic copies of existing implants, their safety in terms of composition, manufacturing process and leachable substances of polymers needs to be assessed using similar methods to those used for currently marketed implants (International Organization for Standardization, 1997).

In general, the available toxicological data demonstrate that the progestogens in marketed implants are similar in their toxicity profiles in animals, to the progestogens in the approved oral contraceptives. With regard to Norplant and Jadelle, there are extensive toxicological data to support the safety of these products. Implanon has relatively fewer data available, but the toxicological data are sufficient to support the safety of Implanon for human use. Insufficient toxicological information was available for the other products currently under development or manufactured.

Mechanism of action of implantable contraceptives

Levonorgestrel implants

All levonorgestrel implants currently available are comparable in terms of daily dose released; therefore, results of mechanism of action studies conducted in Norplant users apply to all of them (Croxatto, 2002b). Norplant disrupts follicular growth and the ovulatory process, causing a variety of changes that range from anovulation to insufficient luteal function. A small percentage of women have quiescent ovaries. Mean serum estradiol concentrations are usually within the normal range, but sustained levels below 280 pmol/ml and broad peaks above 1.5 nmol/ml have been observed. Luteal activity is uncommon during the first year, but its frequency increases in subsequent years (Croxatto et al., 1982; Alvarez et al., 1996). When luteal activity is present, progesterone levels are significantly lower than normal. Luteal phases are preceded by pre-ovulatory LH and FSH surges that are far smaller and of shorter duration than normal (Brache et al., 1985). This probably jeopardizes the capacity of the oocyte to be fertilized (Croxatto, 2002b).

Both Norplant and Jadelle make the cervical mucus viscous, scanty and virtually impenetrable by spermatozoa, even in the presence of normal or above-normal endogenous estradiol levels (Brache et al., 1985; Croxatto et al., 1987). The endometrium of Norplant users does not exhibit the orderly changes that characterize the normal endometrial cycle regardless of the occurrence of ovulation but, given the above effects on the ovary and cervix, it is unlikely that the endometrial changes contribute to the high contraceptive efficacy of these implants (Croxatto, 2002b).

Etonogestrel implants

A smaller number of studies similar to those of Norplant has been conducted in Implanon users (Croxatto and Mäkäräinen, 1998). Ovulation suppression accounts for almost all the contraceptive effect of Implanon through 3 years. Estradiol levels present considerable inter-individual variation, with mean levels decreasing initially and rising gradually through 3 years of use. Neither consistently low nor consistently high levels have been reported. Impaired cervical mucus and poor sperm penetration may contribute to the high contraceptive efficacy of this implant (Croxatto, 2002b). Endometrial development is suppressed (Croxatto, 2002b).

Nestorone implants

Ovulation suppression is so far the only documented mechanism for pregnancy prevention of these implants (Brache et al., 2000).

Nomegestrol acetate implant

It has been reported that, in the first year of use, this implant blocks ovulation in 86% of the cycles and that it renders the cervical mucus thick and scanty (Croxatto, 2002b).

Suppression and alteration of the ovulatory process and hindrance to sperm penetration through cervical mucus fully explain the high contraceptive efficacy of the implants currently in use, and it is unlikely that endometrial changes contribute to the contraceptive efficacy.

Contraceptive effectiveness

For both Norplant and Jadelle, annual pregnancy rates for each year of use up to the end of 5 years are below or well below 1 per 100 (Glasier, 2002). Five-year cumulative pregnancy rates for both implants are 1.1 per 100. Both the six-capsule and two-rod Chinese implants have similar efficacy to Norplant and Jadelle. Norplant continues to be highly effective up to the end of 7 years (cumulative 7-year pregnancy rate: 1.9 per 100). Pregnancy rates are slightly higher in women aged under 25 years and, beyond 5 years, also in women weighing more than 70 kg (Sivin et al., 1998a).

The reported failure rate of Implanon has been zero. There are insufficient data on the influence of age and weight on the effectiveness of this implant (Croxatto et al., 1999).
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Preliminary studies with Nestorone-releasing implants under development by the Population Council have reported no pregnancies during 2 years of use (Diaz et al., 1995; Massai et al., 2001). In a small study of Uniplant, the 1-year cumulative pregnancy rate was 0.9 per 100 (Coutinho et al., 1996).

A systematic review of contraceptive effectiveness of implants from studies published from 1972 to 1998 was undertaken by the Health Technology Assessment Unit of the National Health Service in the United Kingdom. It found no difference of effectiveness between Norplant and Jadelle up to 5 years, or between Norplant and Implanon up to 3 years (French et al., 2000). The review also indicated lower failure rates for Norplant than for combined oral contraceptives during 1 and 2 years of use.

In the Post-marketing Surveillance of Norplant study, the unadjusted 5-year cumulative failure rates for Norplant (hard tubing), copper IUDs, non-copper IUDs, and sterilization were 1.5, 4.2, 13.0 and 0.72 per 100 respectively (International Collaborative Post-Marketing Surveillance of Norplant, 2001a).

Vaginal bleeding disturbances and implantable contraceptives

As with other progestogen-only methods, vaginal bleeding disturbances are the most common reason given for the discontinuation of implant use, accounting for up to 45% of all reasons in clinical trial settings (Glasier, 2002). Disturbances of vaginal bleeding are almost inevitable in contraceptive implant users (Hickey and d’Arcangues, 2002). They are more common in the first months of use and tend to diminish over time. Although there are individual variations, many women experience prolonged or irregular bleeding or both, during the first year of Norplant and Jadelle use (Fraser et al., 1998). In subsequent years, bleeding patterns tend to improve. Prolonged amenorrhea is infrequent. Whilst many women using Implanon experience prolonged or irregular bleeding or both, a significant proportion experience amenorrhea and infrequent bleeding (Affandi, 1998).

In one Indonesian study, irregular bleeding was common in the first months of use, but by the end of the year up to three-quarters of women experienced a normal regular pattern (Affandi, 1998). Limited information is available regarding Uniplant.

Although bleeding may be prolonged or frequent in women using levonorgestrel-releasing implants, the average total blood loss is similar to or less than that in normally menstruating women (Nilsson and Holma, 1981; Fraser et al., 2000). Most longitudinal studies have found no changes or slight increases in haemoglobin levels among implant users (Task Force for Epidemiological Research on Reproductive Health, 1998; Curtis, 2002), even amongst women who discontinue for bleeding disturbances. In a large cohort study the incidence rate of anaemia in Norplant users was similar to that in controls using an IUD or in sterilized women (International Collaborative Post-marketing Surveillance of Norplant, 2001a). However, in one study ferritin was significantly reduced amongst women who discontinued use for excessive bleeding (Faundes et al., 1987).

The mechanisms of these vaginal bleeding disturbances are complex and still poorly understood, despite a major research effort (Rogers and Salamonsen, 2000). A number of treatments have been proposed, but none has been shown to provide a definitive solution over the long term (d’Arcangues, 2000). However, ethinyl estradiol (either alone or as a combined pill) will terminate a bleeding episode and may help women to cope in the early months of implant use until bleeding patterns improve spontaneously with time (d’Arcangues, 2000).

Common adverse effects

Contraceptive methods of most types, including implants, do not prevent many common symptoms and adverse health events that people experience in their daily lives. Most studies of adverse effects of implant contraceptives have not been comparative trials, making it difficult to assess whether the occurrence of common adverse events can be attributed or not to use of a contraceptive method. Only studies of Norplant have included controls using non-hormonal methods.

The incidence of each adverse event or complaint varies widely between studies because of differences in definitions and collection of the data, differences in cultural characteristics of populations, individual differences in awareness, perception, and tolerance, as well as varying perspectives of providers. Occurrence rates tend to be higher in the first year of use (Brache et al., 2002). So far, studies comparing implants have been relatively small. Few differences in incidence rates of adverse events between implants have been documented (Brache et al., 2002).

Persistent ovarian follicles

Continuous low-dose progestogens do not completely suppress ovarian function. Dominant follicles may sometimes develop, but the normal ovulatory process is frequently disrupted and follicle rupture does not occur. These follicular structures can persist and become enlarged (>30 mm), but usually disappear within 1–2 months (Faundes et al., 1995; Alvarez-Sanchez et al., 2000; Brache et al., 2002). A large cohort study found no difference between users of Norplant and non-hormonal methods in the rate of hospitalization or surgery for this condition (International Collaborative Post-marketing Surveillance of Norplant, 2001a). Providers should be aware of the transient nature of these cysts so as to avoid unnecessary surgery.

Complications of implant insertion and removal

The incidence of infection or expulsion following insertion varies from 0 to 0.5 per 100 insertions, with no apparent differences between systems (Klavon and Grubb, 1990; Brache et al., 2002).

The reported percentages of removal complications have ranged between 0.2 and 7.0% (Brache et al., 2002). Broken or deeply placed implants, and fibrous tissue surrounding the implants have led to difficult and prolonged removals. In a few instances a second incision was required. Comparative studies of Norplant and Jadelle, and of Norplant and Implanon have shown significantly reduced rates of removal complications with the two newer systems, Jadelle and Implanon. Duration of removal procedure is also shorter for Implanon and Jadelle compared with Norplant (Mascarenhas, 1998; Sivin et al., 1998a).

Headache

Headache is a common complaint in women receiving implants (10–30% of users) (Brache et al., 2002). Comparative studies of Norplant and non-hormonal methods have reported 2- to 3-fold...
higher rates of headache among Norplant users (Sivin, 1983; International Collaborative Post-marketing Surveillance of Norplant, 2001b; Brache et al., 2002). Less than 5% of women discontinue implant use because of headache, with no differences between implants (Brache et al., 2002).

Weight change

Weight gain is a frequent complaint among all implant users (4–22%), with reports of 0.4 to 1.5 kg per year, but discontinuation rates are less than 4% for this indication (Brache et al., 2002). However, of two studies with non-hormonal comparison groups, one reported similar weight increase for both groups (Sivin, 1983), and the other showed small but statistically significant excess weight gain of 0.2 kg per year in Norplant users (International Collaborative Post-marketing Surveillance of Norplant, 2001b).

Acne, hair loss, hirsutism and other skin problems

Acne was reported by 3 to 22% of users of any implantable contraceptive (Brache et al., 2002). In a comparative study of Norplant and Implanon, the rates of complaints of acne were similar (Urbancsek, 1998). In a comparative study of Norplant versus non-hormonal methods, complaints of acne were rare, although significantly higher in the Norplant group (International Collaborative Post-marketing Surveillance of Norplant, 2001b). Complaints of hair loss and hirsutism are less frequently reported (Sivin, 1983). The data suggest that there is an association between skin and hair problems and the use of progestogen implants.

Dizziness

Between 4 and 11% of users of any implantable contraceptive complained at some time of dizziness in most studies, but removal rates for this reason are low (0–2.3%) (Brache et al., 2002). In two controlled studies the rate of complaints of dizziness was higher in Norplant than IUD users (Sivin, 1983; International Collaborative Post-marketing Surveillance of Norplant, 2001b).

Mood changes

Mood changes including nervousness and depression, are commonly mentioned side effects of implants ranging, in non-comparative studies, from 1 to 9% (Westhoff et al., 1998; Brache et al., 2002). In comparative studies of Norplant versus non-hormonal methods, rates of nervousness and depression were similar in one study and higher for Norplant compared with controls in another (Sivin, 1983; International Collaborative Post-marketing Surveillance of Norplant, 2001b). Nervousness, depression and mood changes accounted for low rates of removal (<2%), with no difference between implant systems (Brache et al., 2002). It is difficult to know if mood changes are associated with use of progestogen implants; there is a tendency for a higher rate of reporting of mood changes among implant users, but only one comparative study (International Collaborative Post-marketing Surveillance of Norplant, 2001b) found significantly higher rates.

Other complaints

Symptoms such as nausea, breast tenderness, pelvic pain, loss of libido and fatigue have each been reported by small proportions of implant users (Brache et al., 2002). In comparative trials with non-hormonal methods, most of these symptoms have not differed between the two groups, and their incidence probably reflects their occurrence in the general population (Sivin, 1983; Barnhart et al., 1997; International Collaborative Post-marketing Surveillance of Norplant, 2001a,b; Meirik et al., 2001); however, a small effect of the implants cannot always be excluded (International Collaborative Post-marketing Surveillance of Norplant, 2001b). Each of these diverse symptoms typically led to discontinuation in less than 0.5% of users (Brache et al., 2002).

Rare adverse events

Associations between rare health conditions and use of new contraceptive methods are usually not detected in pre-marketing or introductory trials. Evaluations of relationships between contraceptive methods and rare adverse events rely on observational research methodologies, such as cohort and case–control studies (Pettiti and Shapiro, 1989). Few studies have incorporated adequate numbers of participants or length of follow-up to examine adequately the risk of serious conditions with contraceptive implant use. In addition, these studies primarily include women of good health and therefore provide no information about contraceptive implant use in women with pre-existing medical conditions.

Implant users seldom experience serious adverse events. In large prospective studies, overall between 2 and 6% of users have reported adverse events (Urbancsek, 1998; International Collaborative Post-marketing Surveillance of Norplant, 2001b), and in one study, rates of each type of adverse event were less than 2 per 1000 woman-years (International Collaborative Post-marketing Surveillance of Norplant, 2001b). In a pooled analysis, the rates of hospitalization for all adverse events was 20.7 per 1000 woman-years, which was notably less than that expected in the general population (Sivin, 1998).

Invasive neoplasia

The only cohort study to identify invasive neoplasia was too small to adequately assess risk with implant use (International Collaborative Post-marketing Surveillance of Norplant, 2001b). Observations regarding other progestogen-only methods indicate minimal, if any, excess risk of invasive breast neoplasia (Collaborative Group on Hormonal Factors in Breast Cancer, 1996), no excess risk of cervical neoplasia, and protection against endometrial neoplastic disease (World Health Organization, 1993). In three limited short-term implant follow-up studies, no evidence of increased rates of cervical or endometrial changes was found (Curtis, 2002).

Cardiovascular disease

Cardiovascular events have rarely been reported in Norplant or other progestogen-only users, and at rates similar to what would be expected in women of reproductive age (Sivin, 1995; Wysowski and Green, 1995; World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1998; International Collaborative Post-marketing Surveillance of Norplant, 2001b). A large observational study that included 10 718 Norplant users (44 954 woman-years of use) reported no thrombotic or other severe cardiovascular events (Gu et al., 1994).
Clinically significant changes in blood pressure have not been shown with implant use over time or in comparison with IUD use (Sivin et al., 1983b; Shen et al., 1994; Curtis, 2002), with the exception of a large cohort study where an increased rate ratio (RR) of 1.81 (95% CI: 1.12, 2.92) for hypertension and borderline hypertension combined was found for Norplant users compared with non-hormonal users (International Collaborative Post-marketing Surveillance of Norplant, 2001b). The authors estimated that, if this observation is true, then one more case of hypertension would occur per year in every 3000 Norplant users compared with 3000 IUD users.

Mental disorders

No excess risk of severe mental illness was observed among current Norplant users in a large cohort study (International Collaborative Post-marketing Surveillance of Norplant, 2001b).

Diabetes mellitus

In a large cohort study, the incidence of diabetes among Norplant users was 0.2 per 1000 woman-years, which was higher but not significantly different from that in non-hormonal method users (RR 2.42, 95% CI: 0.73, 8.05) (International Collaborative Post-marketing Surveillance of Norplant, 2001b).

Gallbladder disease

In one large cohort study the incidence rate of gallbladder disease was 1.5 per 1000 woman-years for current users of Norplant, which was not significantly different from that in non-hormonal method users (RR 1.31, 95% CI: 0.87, 1.96) (International Collaborative Post-marketing Surveillance of Norplant, 2001b). However, when examining this association by initial contraceptive method used, the RR reached borderline significance (RR 1.52, 95% CI: 1.02, 2.27). This finding of a possible increased risk of gallbladder disease with Norplant use requires further investigation.

Reduced bone mineral density

Cross-sectional, longitudinal or randomized studies have not found any negative effect of Norplant or Implanon on bone density, except for clinically insignificant decreases in short-term users in one large multinational cross-sectional study of Norplant users (Petti et al., 2000; Curtis, 2002).

Pelvic inflammatory disease (PID)

A large cohort study found a decreased incidence of both acute PID (RR 0.34, 95% CI: 0.14, 0.85) and unspecified PID (RR 0.54, 95% CI: 0.39, 0.74) among Norplant users when compared with women using IUDs or in sterilized women, but not when compared with sterilized women alone. Chronic PID occurred at rates of less than 1 per 1000 woman-years for both Norplant and IUD users (International Collaborative Post-marketing Surveillance of Norplant, 2001a).

HIV and AIDS

No studies have evaluated the acquisition or transmission of HIV, or the progression of disease in HIV-positive women, with contraceptive implant use (Curtis, 2002).

Deaths

While no studies have been large enough to assess adequately the risk of death with contraceptive implant use, reported rates are not higher than in other large cohort studies of contraceptive users or general mortality rates in women of reproductive age (Sivin, 1998; International Collaborative Post-marketing Surveillance of Norplant, 2001b; Curtis, 2002).

Metabolic effects

The effects of hormonal contraceptives on metabolic variables are related to the type and dose of the contraceptive steroid. Levonorgestrel-releasing implants have been studied most extensively, while the information on other implants is limited. In particular for Nestorone- and nomegestrol acetate-releasing implants the published information on metabolic variables other than lipids is sparse.

Lipids

Levonorgestrel implants

Total cholesterol and triglycerides generally decrease significantly during the first years of use of the levonorgestrel implants, although values remain within the normal range (Task Force on Long-acting Systemic Agents for Fertility Regulation, 1999; Dorflinger, 2002). Overall, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) appear not to change or show a slight decrease which is largely limited to the first and second years of use (Mascarenhas et al., 1998; Suherman et al., 1999; Task Force on Long-acting Systemic Agents for Fertility Regulation, 1999; Dorflinger, 2002). Levels of apolipoprotein AI decrease in the first and second years of use, while levels of apolipoproteins AII and B remain largely unchanged (Suherman et al., 1999; Task Force on Long-acting Systemic Agents for Fertility Regulation, 1999; Dorflinger, 2002). Ratios of lipids, lipid subfractions and apolipoproteins are inconsistent across studies, and with values largely unchanged during implant use or fluctuating over time (Dorflinger, 2002).

Etonogestrel implants

Limited studies of lipids during etonogestrel implant use have not reported significant changes in total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, apolipoproteins AI, AII and B, and various ratios of lipids, lipid subfractions and apolipoproteins (Mascarenhas et al., 1998; Suherman et al., 1999; Dorflinger, 2002).

Nestorone and nomegestrol acetate implants

Small studies with Nestorone prototype implants and nomegestrol acetate implants have not reported any statistically significant effect on lipid metabolism (Diaz et al., 1995; Dorflinger, 2002).

Carbohydrate metabolism

Fasting glucose and insulin levels were generally normal among implant users (Odlin et al., 1984; Barbosa et al., 1995; Biswas et al., 2001; Dorflinger, 2002). Some studies of levonorgestrel- and etonogestrel-releasing implants showed increased insulin levels during glucose tolerance testing, or during hyperglycaemic clamp assessment, suggesting mild insulin resistance (Dorflinger, 2002).
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**Haemostasis**

The data regarding haemostatic effects during levonorgestrel and etonogestrel implant use are limited and do not demonstrate any consistent changes that are likely to be clinically relevant (Egberg et al., 1998; Dorflinger, 2002). There are no data available for either Nestorone- or nomegestrol acetate-releasing implants (Dorflinger, 2002).

A small number of cases of thrombocytopenia and thrombocytoenic purpura have been reported among Norplant users in the USA and in China (International Collaborative Post-marketing Surveillance of Norplant, 2001b; Curtis, 2002). No other countries reported this condition. Systematic studies have not found significantly decreased platelet counts (Dorflinger, 2002).

Resistance to activated protein C (APC resistance) has been associated with the use of combined oral contraceptives and with increased risk of thrombosis (Vandenbroucke et al., 2001). There is no information on APC resistance during use of any of the currently available progestogen implants.

**Liver function**

Generally, there were no consistent, significant or persistent alterations in liver function tests during the use of progestogen implants, apart from mild elevations within the normal range in mean bilirubin levels (Egberg et al., 1998; Dorflinger, 2002).

**Thyroid hormones**

Five longitudinal and cross-sectional studies with levonorgestrel, etonogestrel and nomegestrol acetate implant systems have found no consistent changes in thyroxine (T4), 3,5,3'-tri-iodothyronine (T3), thyroxine-binding globulin (TBG) and thyroid-stimulating hormone (TSH) (Dorflinger, 2002).

**Return to fertility**

All implants deliver low doses of progestogens that clear rapidly from the circulation after implant removal, with the consequent resumption of ovarian function (Croxatto, 2002b; Glasier, 2002). Fertility declines with age, and some women who have used implants for several years will have become less likely to conceive after implant removal than they were at the time of insertion. Reported 12-month cumulative pregnancy rates for women discontinuing implants in order to become pregnant vary from 76 to 100% (Diaz et al., 1987b; Sivin, 1988; Affandi et al., 1987b; Sivin, 1988; Buckshee et al., 1995; Tseng et al. 1996; Singh and Ratnam, 1997), and do not differ from rates with other contraceptive methods (Diaz et al., 1987b; Glasier, 2002). The exceptions are an Indonesian study (Affandi, 1999) and the multi-country Post-marketing Surveillance of Norplant study (International Collaborative Post-marketing Surveillance of Norplant, 2001a), where the 12-month cumulative pregnancy rates were significantly lower than expected in past implant users, and also in past IUD users (International Collaborative Post-marketing Surveillance of Norplant, 2001a). In the Post-marketing Surveillance of Norplant study, the sex ratio of newborn infants was significantly elevated, particularly in Indonesia, suggesting that underreporting of pregnancies terminated by selective abortion may have occurred (International Collaborative Post-marketing Surveillance of Norplant, 2001a).

**Outcome of pregnancies conceived after and during implant use**

The outcome of pregnancies conceived after removal of levonorgestrel implants has been reported to be no different from that of women stopping other methods of contraception, and no different from normal limits (Diaz et al., 1987b; Sivin et al., 1992).

No increased prevalence rate of malformations at birth or of low birth-weight have been found among infants of pregnancies conceived during maternal use of levonorgestrel implants (Sivin et al., 1998b; International Collaborative Post-marketing Surveillance of Norplant, 2001a). No accidental pregnancies have been reported during use of Implanon (Glasier, 2002).

In the large multi-country Post-marketing Surveillance of Norplant study the rate of ectopic pregnancy in users of levonorgestrel implants was lower (0.30 per 1000 women, 95% CI: 0.14, 0.55) than in women using no contraception (2.66 per 1000 women, 95% CI: 1.07, 5.48) (International Collaborative Post-marketing Surveillance of Norplant, 2001a). However, for pregnancies conceived during levonorgestrel implant use the proportion of ectopic pregnancies to all pregnancies was higher (0.11, 95% CI: 0.06, 0.20) than among pregnancies conceived with no contraception (0.005, 95% CI: 0.00, 0.01) (International Collaborative Post-marketing Surveillance of Norplant, 2001a). Similar findings have been reported elsewhere (Glasier, 2002).

**Breastfeeding**

The effect of progestogen-only implants on breastfeeding duration, milk output and composition, and infant growth is well established, and the results are reassuring. However, small amounts of contraceptive steroids are excreted in breast milk and concerns about the exposure of infants during the first 6 weeks of life persist. These concerns have programmatic implications and require further research.

Levonorgestrel, etonogestrel and Nestorone are all measurable in breast milk, and levonorgestrel has been measured in the serum of breastfed infants. The estimated daily dose received by a child fully breastfed by a mother using implants is in the same range as that estimated for progestogen-only pills (in the nanogram order), and much smaller than that received by infants breastfed by mothers using progestogen-only injectables (in the microgram order) (Diaz, 2002).

When orally administered, Nestorone is rapidly inactivated by hepatic first-pass metabolism. It is unlikely that significant amounts of the biologically active steroid reach the systemic circulation of infants breastfed by mothers using Nestorone, and this may therefore be the preferred progestogen for use during lactation (Massai et al., 2001).

**Users’ perspectives**

Users’ perspectives on a contraceptive method are a reflection of the characteristics of the method including route of administration, mode of action, type and frequency of side effects, and how these affect daily life. Users’ perspectives are also affected by how family planning services providing the method treat their clients, how others perceive the method, and its presentation in the mass media (Bruce, 1987).
Perspectives on advantages of implants

Contraceptive implants have high continuation rates in clinical trial settings, with 5 year continuation rates of Norplant varying between 33 and 78% (Glasier, 2002). A high proportion of users expressed satisfaction (Zimmerman et al., 1990; Widyantoro, 1994; Ortayli, 2002). The most appealing aspects of implant contraceptives to users are the long duration of contraceptive protection, ease of use, high effectiveness, and reversibility (Ortayli, 2002). That implants are not associated with sexual intercourse and that they are placed in the arm rather than in the vagina or uterus, have also been viewed positively (Zimmerman et al., 1990; Sangi-Haghpeykar et al., 2000). Male partners of women using implants reported that the visibility of the implants was reassuring (Sangi-Haghpeykar et al., 2000).

High efficacy and long duration of use make implants a valuable alternative to sterilization for couples who want to preserve their fertility although their family size is completed (Ortayli, 2002). Implants may be a more acceptable long-term method than sterilization in cultures where sterilization is perceived to be related to loss of vitality, or of fertility in afterlife, or is otherwise in violation of religious beliefs (Ortayli, 2002). They are also useful to young women who want to delay childbearing and to women who have contraindications to the use of estrogens. Certain traditions enhance implant acceptability, such as that in Indonesia of inserting objects (so-called ‘susuk’) under the skin to gain strength and beauty, and subdermal placement of therapeutic herbs in Ethiopia (Widyantoro, 1994; Ethiopia Ministry of Health, 2001).

Perspectives on problems of implants

The main complaint of users has been the bleeding irregularities associated with implant use which, apart from being a considerable nuisance, may restrict daily activities and social, religious and sexual practices in some cultures (Zimmerman et al., 1990; Hanhart, 1993; Ortayli, 2002). Concerns and fear of pain with implant insertion and removal, and problems of confidentiality due to the potential visibility of the implants were also reported. Despite expressing dislike of side effects such as bleeding irregularities, many implant users refer on balance to the method in positive terms. This suggests that many users trade the side effects for high effectiveness, convenience and long duration of use (Sangi-Haghpeykar et al., 2000).

Media coverage affected acceptability both positively and negatively. Negative coverage has included alleged but unsubstantiated risks of cancer, the loss of the implanted arm, migrating implants and massive weight gain (Kuiper et al., 1997).

Perspectives on implant services

The user is entitled to a service which provides a choice of methods in an environment which allows dissemination of sound information to support appropriate choices. The service must also offer good technical support with rapid availability of safe implant insertion and removal. In the early years of introduction of implants in some national family planning programmes there were reports of deficiencies in counselling and service provision through all phases of implant use (Zimmerman et al., 1990; Hanhart, 1993; Widyantoro, 1994). Controversies over inadequate counselling have focused attention on the importance of good counselling in all family planning services (Widyantoro, 1994; Ortayli, 2002). In some settings, satisfactory access to removal on request was not always achieved, primarily due to inadequate numbers and distribution of trained providers (Zimmerman et al., 1990; Ortayli, 2002). Access to removal was also constrained because some providers and programme managers wanted to make the implants ‘cost-effective’ by maximizing their duration of use (Zimmerman et al., 1990; Ortayli, 2002).

All provider-dependent contraceptive methods have the potential for being used in an abusive manner. Implants are no more a threat than surgical sterilization which is irreversible, or intra-uterine devices and injectables that can be administered without the knowledge of women (Ortayli, 2002). Policy-makers, programme managers and providers must be well informed on this issue and prevent abusive practices.

Programmatic issues

National contraceptive programmes must ensure the availability, affordability and accessibility of contraceptive services with attention to safety of potential users. Existing implants are highly effective and generally safe, provided that the quality of services fulfils appropriate standards. In order to establish quality in implant contraceptive services, it is necessary to determine the reproductive health needs of communities, the capacity and the readiness of the health delivery system to provide a provider-dependent method, and the capacity to sustain services on a long-term basis in ways that protect the safety and satisfaction of the users (Simmons et al., 1997; Chikamata and Miller, 2002).

Contraceptive implants have been introduced in many family planning programmes successfully, and most acceptors report satisfaction with their experiences of implant use (Ortayli, 2002). Country programmes can benefit from the lessons learned in the early implant introductions, when there was less attention given to adequate planning, sustainability, and quality of services (Hanhart, 1993; Hardee et al., 1994; Ortayli, 2002). The most salient programme corrections proposed are attention to counselling, assurance of removal on request, infection prevention, and increased sensitivity to the disruption of women’s lives caused by unpredictable vaginal bleeding (Chikamata and Miller, 2002).

When introducing or expanding implant services, programmes need to ensure the accessibility of an adequate number of trained, sensitive providers, the necessary equipment, and adequately stocked facilities. One strategy for introducing implants in a way that assures quality is to establish criteria for accreditation of referral centres, to begin slowly, and to expand incrementally. In order to expand and to ensure continuity of implant services, a linkage between facilities that do not or cannot safely provide implant services and the referral centres should be established. Country programmes should also develop mechanisms for notification and reminder of time for removal before implementing implant services. The value of periodic routine visits should be reviewed to determine what is necessary for the protection of the woman’s health and well-being.

The implant systems with fewer capsules or rods greatly facilitate insertion and removal and produce less discomfort to users. Family planning programmes should therefore move as soon as practical to those systems which have been or may be shown to be equally effective and safe as the six-capsule system.
There may be a period of overlap between the use of the six-capsule and the newer methods. Dispensing more than one implant system may pose some challenges for training, counselling, logistics, storage and reporting. Programmes will need to weigh the costs and benefits of increasing options and expanding choice against these challenges.

Requirements for quality implant services

Different cadres of health professionals including physicians, nurse-midwives, nurses and other paramedical personnel can safely provide implants (Affandi et al., 1987a). Their training should be competency-based; the trainees should be authorized for implant services only after they have demonstrated that they can manage all aspects of this service (Chikamata and Miller, 2002). Moreover, training of healthcare providers should be an ongoing process, particularly in settings where staff turnover is high.

Contamination through the use of poorly or non-sterilized instruments risks the spread of infectious diseases. Emphasis should be placed on strict aseptic techniques and on decontaminating, cleaning and sterilization or high-level disinfection of equipment, and proper disposal of sharp instruments and contaminated waste.

Clients need all the information necessary to make an informed choice about implants; this should include costs for insertion and removal, side effects, diminishing efficacy and increasing risks of pregnancy after the scheduled life-span of the implants, and the importance of dual-method use if there is a risk of sexually transmitted infections, including HIV. Clinics providing implants should also provide information materials such as pamphlets, posters and take-home cards. In addition, service providers and community health workers may conduct film shows, lectures, campaigns and other appropriate information activities.

Cost-effectiveness

Implant costs include not only the price of the devices, but the equipment and supplies necessary for the insertion and removal, training costs, time spent with clients for counselling and procedures, follow-up visits for management of side-effects and unintended pregnancies, and the time, personnel and supplies for infection prevention.

With their high effectiveness and long life-spans, implantable contraceptives are likely to be cost-effective in most settings. Studies in the USA and the United Kingdom have demonstrated the cost-effectiveness of implant contraceptives (Trussell et al., 1995; French et al., 2000). In one study, which included method-effectiveness, continuation rates and other costs in the analysis, implants were estimated to be more cost-effective than all other reversible methods except for the Copper T IUD, by the third year of use (Trussell et al., 1995). Cost-effectiveness studies in developing countries are needed.

The cost of contraceptive implant devices is higher than that of other reversible methods. This may change with the ongoing development and manufacturing of cheaper implants. Data on the release rates, equivalence between the new implants and approved products, and quality control of manufacturing procedures of the new implants are essential. The relevance of international patent laws to the inter-country procurement of implants should also be examined.

A more cost-effective approach to implant services can be achieved by decreasing or eliminating unnecessary follow-up visits that do not provide any additional health benefits for the client. It has been demonstrated that services provided by non-physicians improve cost-effectiveness without compromising quality (Affandi et al., 1987a). Costs will also decrease with the newer implants with fewer rods or capsules, which reduce the time needed for insertions and removals.

Conclusion

Published and other available data on implantable contraceptives for women show that for the 5-year levonorgestrel-releasing implants Norplant and Jadelle, there is extensive information, from a large number of studies in developing and developed countries, addressing metabolic and clinical outcomes including adverse effects, service aspects and user’s perspectives. These studies demonstrate the high contraceptive effectiveness and safety of these implants. Information on the 3-year etonogestrel-releasing implant Implanon is more limited, but suggests that the implant has high contraceptive effectiveness and a satisfactory safety profile. The information available on levonorgestrel-releasing implants manufactured and approved in China indicates that the clinical performance of these implants is satisfactory and similar to that of other approved levonorgestrel-releasing implants, but available data were insufficient to allow their full safety assessment. The information available on other implants was too sparse to allow an adequate evaluation. All data on implant safety were generated from studies of a priori healthy women; more information is needed on use of contraceptive implants among women with medical conditions.

The review of data underscored the view that provision of contraceptive implants requires good quality family planning services. Clinics must have facilities to ensure strictly aseptic procedures for the insertion and removal of implants. To provide quality implant services, including timely and safe access to insertion and removal of the implants, an adequate number of providers must have been trained for counselling and have demonstrated technical skills for implant insertion and removal. Where necessary, family planning programmes should develop mechanisms that assist users in timing the removal of the implants at the end of their effective life-span. Implant systems consisting of one to two capsules or rods facilitate insertions and removals, and thus reduce both the discomfort of insertion and removal to users and the personnel costs for family planning clinics and programmes.

References

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