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Levonorgestrel Subdermal Implants

A Review of Contraceptive Efficacy and Acceptability

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Summary

Levonorgestrel 6-capsule subdermal implants (Norplant®) are an effective form of reversible contraception. When implanted under the skin of the upper arm, they release drug into the circulation at a relatively constant rate over 5 years.

Generally, the cumulative pregnancy rate at the end of 5 years' levonorgestrel implant use is less than 2 per 100 users. The implants provide contraceptive efficacy equivalent to, or better than, that provided by other reversible methods (including oral contraceptives). Younger women are more likely than older women to become pregnant while using levonorgestrel implants. Bodyweight was positively correlated with risk of pregnancy in a number of studies, but may not be a factor with the currently available 6-capsule implant formulation. Limited data suggest that a new 2-rod levonorgestrel subdermal system (Jadelle®) is as effective as the more extensively studied 6-capsule system and has a similar tolerability profile.

Fertility returns rapidly after the implants are removed. Use of levonorgestrel subdermal implants is compatible with breast-feeding. In several studies, discontinuation rates were 2 to 15% during the first year of use; cumulative 5-year discontinuation rates ranged from 22 to 64 per 100 women. Despite a substantial incidence of adverse events during therapy, levels of user satisfaction are generally high.

Menstrual abnormalities (increased or decreased menstrual flow, spotting, irregularity and amenorrhoea) affect most women at some time during therapy and are the most frequent reason for discontinuing levonorgestrel implants before the end of 5 years' treatment (incidence of 4.2 to 30.7 per 100 users). Mood changes and headache also may lead to discontinuation. Other reported adverse events include skin reactions (including acne), dizziness and weight gain. Serious adverse events (such as stroke, thrombotic thrombocytopenia and idiopathic intracranial hypertension) have been reported during levonorgestrel implant therapy, but the population incidence is difficult to calculate and causality is unclear.

According to 3 pharmacoeconomic analyses from an institutional or managed-care perspective, all contraceptive interventions result in net cost savings. It is not clear whether levonorgestrel implants provide greater or smaller economic benefits than combined oral contraceptives.

Conclusion. Levonorgestrel subdermal implants provide effective long term contraception. Despite a high incidence of menstrual adverse events, overall levels of user satisfaction are high, and 1-year continuation rates are better than those for combined oral contraceptives. Levonorgestrel subdermal implants are a good choice of contraceptive method in women who desire effective contraception, but who are unable to, or prefer not to, comply with an oral regimen.

1. Introduction: Delivery Systems

Levonorgestrel (fig. 1) is a synthetic, biologically active progestogen, structurally related to 19-nortestosterone, which may be used alone or in combination with estrogens as a female contraceptive. Although levonorgestrel may be administered orally or delivered via an intrauterine device (IUD), the focus of this review is its release from subdermal implants.

Since 1975, when clinical studies of levonorgestrel implants had been initiated in 6 countries,[1] the delivery system has been reformulated a number of times.[2] This review focuses primarily on a system of 6 flexible closed capsules, each 34 by 2.4mm, composed of polydimethylsiloxane, and containing levonorgestrel 36 mg/capsule (Norplant®, 1996)[3] Trials conducted before 1980 used nonstandardised laboratory-manufactured implants;[4] these studies are not considered here, except where they provide important pharmacodynamic or pharmacokinetic data.

Most clinical studies of the 6-capsule system (section 4) used a 'hard tubing' formulation which differs slightly from the reformulated 'soft tubing' system in use since 1990.[5]

Limited clinical data available for a second commercially available levonorgestrel subdermal delivery system (Jadelle®) are presented in section 4.4. This system consists of two implantable 43mm rods, each consisting of a drug-releasing core encased in thin-walled silicone rubber tubing sealed at both ends. The core of each rod consists 50% by weight of levonorgestrel (75mg) and 50% of elastomer. Manufacture of an earlier 2-rod levonorgestrel subdermal system (Norplant®-2) has been discontinued because of the unavailability of one of its components.[6] This formulation is not considered in this review, except where pharmacokinetic and pharmacodynamic data are contributory.

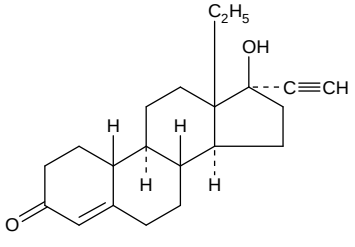

Fig. 1. Chemical structure of levonorgestrel.

2. Pharmacodynamics

2.1 Mechanism of Action

Like other progestogens, levonorgestrel is thought to prevent conception through 3 main mechanisms:

- production of viscous cervical mucus which impairs sperm penetration[7,8]
- inhibition of ovulation by action on the hypothalamus and pituitary to suppress or reduce the surge of luteinising hormone (LH) that triggers ovulation[7,9,10]
- suppression of endometrial function, interfering with implantation of the fertilised ovum[11]

In 1 study, collection of a cervical mucus sample from women using levonorgestrel implants was successful on only 30% of occasions because of the generally low level and viscous nature of the mucus.[8] In contrast, 100% of collections from women not using contraceptive drugs were successful. Penetration of sperm into cervical mucus from implant users was impaired *in vitro* (penetration >10mm in only 4% of samples *vs* 92% of control samples; $p < 0.001$).[8] In 2 studies,[7,8] the average spinnbarkeit of levonorgestrel implant users was 4.1cm (compared with 10.4cm in samples from women not receiving contraceptive drugs[8]). Median cervical mucus scores declined rapidly after insertion of levonorgestrel implants in 42 volunteers: from a baseline score of 6 [according to World Health Organization (WHO) criteria], median scores declined to 5 at 12 and 24 hours and to 2 (considered hostile to sperm penetration) by day 7 after insertion.[12]

The endocrinological profile of women using levonorgestrel implants is characterised by variable suppression of gonadotrophin release, with periodic follicular development, normal (or elevated midluteal peak) estradiol levels and impaired

Table I. Endocrine profile during levonorgestrel implant use: profile of serum progesterone, estradiol, follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels in regularly menstruating users and a control group of ovulatory women not using contraceptive drugs[10]

Subgroup (% of total)	Progesterone profile in second ('luteal') phase of cycle	Estradiol curve	LH	FSH
Levonorgestrel users, n = 31				
Anovulatory (45%)	No elevation	Monophasic	No peak	No peak
Minimal luteal activity (16%)	Small but persistent elevation lasting ≈12 days; peak ≈3 μg/L	Biphasic	Distinct but diminished peak detected in 2 of 5 women	No peak
Luteal activity (39%)	Persistent elevation lasting 12 days; peak ≈9 μg/L	Biphasic	Distinct peak	No peak
Control group, n = 12	Persistent elevation lasting 15 days; peak ≈15 μg/L	Biphasic	Distinct peak	Distinct peak

ovulatory function.[10] An absent or greatly depressed follicle-stimulating hormone (FSH) peak is common, while midcycle LH peaks and elevations in plasma progesterone are small or absent during the second half of the menstrual cycle.[10] Three distinct hormonal patterns corresponding with varying degrees of luteal activity are apparent (table I).

Suppression of luteal activity (indicated by plasma progesterone levels <3 μg/L) may diminish with increasing duration of levonorgestrel implant use: luteal activity was detected in about 18% of cycles during the first year of implant use, increasing to about 60% in year 5.[9]

Overall, more than half of menstrual cycles among levonorgestrel users appear to be anovulatory.[7,9,10] Moreover, ultrasonographic evaluation of ovarian function in levonorgestrel implant users indicated that elevated progesterone levels may frequently be associated with the presence of a persistent, unruptured follicle, rather than normal ovulation.[13,14]

If ovulation does occur in women using the levonorgestrel implants, luteal phase defects, including low estradiol, LH and FSH peaks, may inhibit fertilisation.[10,11] Faundes et al.[10] suggest that the diminished LH surge observed in levonorgestrel users may not be sufficient to induce the first meiotic division necessary to render the oocyte capable of fertilisation.

In ovulatory levonorgestrel implant users, the estradiol curve in the follicular phase of the cycle was similar to that seen in controls, but no midluteal estradiol peak followed the postovulatory fall.[10] In users with minimal luteal activity, the postovulatory fall in estradiol levels was followed by a high midluteal peak. In contrast, the serum estradiol curve was monophasic in levonorgestrel users with no ovulatory activity. In these women, estradiol levels increased continuously during the menstrual cycle (to >1467 pmol/L versus a peak of about 800 pmol/L in control patients), followed by an abrupt drop (over 6 to 7 days) to below control levels. The effects of levonorgestrel on cervical mucus and sperm penetration (discussed earlier) were seen even when circulating estradiol levels were similar to those seen in the late preovulatory phase of the normal menstrual cycle.[8]

Additionally, reduced production of estradiol and progesterone during the luteal phase and the directly antiestrogenic action of levonorgestrel may result in endometrial changes which inhibit the implantation of the ovum and limit the ability of the endometrium to support the implanted ovum.[11] Compared with non-contraceptive users, levonorgestrel implant users had thinner endometrium, which did not exhibit normal phasic changes during the menstrual cycle.

Levonorgestrel did not directly affect oocyte function, nor did it appear to adversely affect early embryonic development in mice.[15]

2.2 Metabolic Effects

2.2.1 Liver Function

At the end of 2 years' treatment, both capsule and (the older) rod subdermal levonorgestrel systems appeared to have some slight effects on liver function in 1 study (n = 200).[16] Both formulations were associated with significant changes in serum bilirubin levels (increased) and total protein and globulin levels (decreased); however, none of the measured changes resulted in levels outside the normal ranges. Bilirubin levels remained 50% above the pretreatment mean values at the end of 5 years, while protein and globulin levels returned to baseline mean values.[17] Alkaline phosphatase levels were unaffected by levonorgestrel. Other studies detected no effect of subdermal levonorgestrel on liver function.[18,19]

2.2.2 Lipid and Carbohydrate Metabolism

Lipid Metabolism

Published studies of 1 to 5 years' duration on the effects of levonorgestrel subdermal implants on lipid metabolism have produced disparate results,[17,20-22] but most have agreed on the following points:

- total triglycerides,[17,20,21] total cholesterol[17,20-22] and high density lipoprotein (HDL)-cholesterol[20-22] are significantly decreased
- low density lipoprotein (LDL)-cholesterol is not significantly affected[17,20-22]

Limited data suggest that serum levels of very low density lipoprotein[21] and apolipoprotein A1[21,22] are reduced after 2 years' levonorgestrel subdermal therapy; levels of apolipoproteins A2 and B were not changed significantly.[21,22]

The 12 to 17% reduction in HDL-cholesterol levels observed during levonorgestrel implant therapy[20-22] might adversely affect cardiac risk profiles, but these changes would be at least partially offset by an approximately 10% reduction in total cholesterol levels. Overall, it appears that the effects of levonorgestrel on serum lipid and lipoprotein metabolism are not likely to be clinically significant.[17]

Carbohydrate Metabolism

In healthy nondiabetic women, fasting blood glucose and basal insulin levels were not altered by the insertion of levonorgestrel subdermal implants.[23,24] Responses to glucose or insulin tolerance tests were not changed to a clinically significant extent after insertion of levonorgestrel implants.[17,25-27] A slight decrease in insulin sensitivity was noted in some,[17,23,25,26] but not all,[24] levonorgestrel implant recipients, suggesting that caution may be warranted in women with, or predisposed to, diabetes mellitus.

2.2.3 Haemostatic Effects

Overall, levonorgestrel implants do not appear to cause a hypercoagulable state.[28] During 5 years' implant use in 97 women, levels of vitamin K-dependent factors II, V and VII were significantly reduced ($p < 0.001$).[28] Levels of other factors did not change significantly; however, prothrombin time was decreased (from 13.5 seconds at baseline to 12.4 seconds at 5 years; $p < 0.001$). Platelet numbers were increased (by 43% from baseline; $p < 0.001$) and platelet aggregation was accelerated (10% increase on preinsertion mean; $p < 0.05$) after 5 years' levonorgestrel implant use.[28] These findings are in contrast with results noted previously during oral contraceptive use (which included increases in factors II, V, VII and X).[29,30] In clinical use, levonorgestrel implants have not been associated with significant increases in cardiovascular events (section 5.2). The effects of progestogens on haemostasis have been reviewed elsewhere in more detail.[31]

2.2.4 Effect on Bone Density

Levonorgestrel implants do not appear to adversely affect bone density. Increases in bone density observed in US adolescent levonorgestrel implant users (2.5 and 9.3% at 1 and 2 years after the initiation of therapy) were similar to increases noted in adolescents who used no hormonal contraceptive during this period (2.9 and 9.5% at years 1 and 2).[32] In this study, combined oral contraceptives were also associated with increased bone density after 1 year (1.5%); no 2-year results were available. Depot medroxyprogesterone injections

(DMPA) were associated with reduced bone density (1.5 and 3.1% at 1 and 2 years).

Six months after the start of treatment in a randomised study in 22 adult women, bone density had increased 2.9% in levonorgestrel recipients, but remained stable in DMPA recipients (–0.41%).[33] In a cross sectional study in Thai women (mean age ≈30 years) who had been using levonorgestrel implants (mean duration 2.5 years) or DMPA (about 5 years), there were no detectable differences in bone mineral density between the 2 groups.[34]

3. Pharmacokinetics

In addition to pharmacokinetic data for the 2 levonorgestrel implant systems currently in use, this section reviews data from studies of earlier levonorgestrel subdermal formulations. Useful information is also available from the levonorgestrel implant prescribing information.[3]

3.1 Absorption and Distribution

Levonorgestrel serum concentrations reach a maximum approximately 24 hours after insertion of the current formulation of 6-capsule implants (mean value 1.6 μg/L).[3] Concentrations decline rapidly during the first month of use and stabilise at about 0.4 μg/L by 3 months after insertion. However, considerable inter- and intraindividual variation occurs, and serum drug concentrations are affected by individual clearance rates and bodyweight, among other factors.[3,35] The levonorgestrel concentrations in this section represent mean values.

A comparison of the 2 levonorgestrel implant formulations currently in use indicated that women using the 6-capsule system had higher drug concentrations during the first week of use than those who used the 2-rod system; however, the difference was statistically significant only during the first 48 hours ($p < 0.05$).[6] Levonorgestrel was detectable in serum 2 hours after insertion of either system. Serum concentrations were highest in the 24-hour sample for the 6-capsule system (mean 1.4 μg/L) and in the 48-hour sample for the 2-rod system (0.77 μg/L).

One month after placement of the levonorgestrel 2-rod system, the mean serum levonorgestrel concentration was 0.44 μg/L.[36] Concentrations remained >0.3 μg/L during the first year of use, but dropped by the end of 3 years' use (mean 0.28 μg/L).

A study of an older 6-capsule system indicated that the release rate of levonorgestrel was highest during the first 16 months after insertion of the subdermal implants (rate not reported); thereafter, through 6.5 years, the release rate was constant, averaging 34.6 μg/day (data published in 1983).[37] In another early study (6-capsule formulation; women enrolled from 1974 to 1979), plasma levonorgestrel concentrations declined steadily up to the eighth year of use ($r = –0.937$; $p < 0.0003$; slope = –0.018).[38] Average plasma concentrations were >0.28 μg/L during the first 5 years, and approximately 0.22 μg/L in year 8.

Bodyweight and serum levonorgestrel concentrations were negatively correlated in studies of both the 6-capsule and 2-rod systems.[6,36] For the 2-rod system, 1-month levonorgestrel concentrations in women weighing >70kg were about 45% lower than those in women weighing <50kg.[36] The decrease in mean serum levonorgestrel concentration with increasing bodyweight is approximately 0.0033 μg/L/kg.[3] These findings may explain the apparent correlation between increasing bodyweight and reduced implant efficacy (section 4.2). However, mean concentrations predict pregnancy only in a statistical sense: although mean levonorgestrel concentrations of 0.21 μg/L have been associated with pregnancy, 20% of women in clinical studies had one or more levonorgestrel concentrations below this value. Despite this, the average annual pregnancy rate in these studies was less than 1 per 100 women.[3]

Other evidence suggests that plasma levonorgestrel concentrations may not correlate with clinical efficacy:[39,40] 19 women who became pregnant while using levonorgestrel implants had plasma concentrations similar to those in 439

women who did not become pregnant (concentrations assessed up to 8 years at intervals before conception and during the cycle) [data from clinical studies published in 1982].[39] Similarly, total plasma levonorgestrel concentrations did not appear to correlate with pregnancy risk in the 8 women who became pregnant of 191 who used subdermal implants for 5 years.[40] However, levonorgestrel is extensively bound to sex-hormone binding globulin (SHBG),[40] and the 8 women who became pregnant in this study had significantly lower ratios of plasma levonorgestrel to SHBG than the remainder of the group (study published in abstract form).[40]

3.1.1 Lactation

Small quantities of levonorgestrel are secreted into breast milk.[41-43] Measured over 1 year in breast-feeding infants whose mothers had had levonorgestrel implants inserted 4 to 6 weeks postpartum, serum levonorgestrel concentrations ranged from 0.31 μg/L (in months 9 and 12) to 0.59 μg/L (month 6) [0.10 and 0.19 nmol/L, respectively].[41,42]

The mean percentage transfer of levonorgestrel from serum of implant users to breast milk during 1 month after insertion was 7%; transfer from breast milk to infant serum was 68%.[42] This finding confirms the 4.9% ratio of infant to maternal serum levonorgestrel concentrations measured during the first month of implant use in another study.[41] For the remainder of the first year of breast-feeding, this ratio ranged from 8.2 to 13.4%.[42]

Use of levonorgestrel implants resulted in higher infant serum levonorgestrel concentrations (mean 0.05 μg/L) than use of levonorgestrel-containing IUDs (mean 0.03 μg/L) or levonorgestrel 30μg oral tablets (peak 0.02 μg/L).[42]

3.2 Metabolism, Elimination and Drug Interactions

Like other steroid hormones, levonorgestrel is metabolised in the liver.[44] Concomitant administration of phenytoin with subdermal levonorgestrel significantly increases the metabolism of the progestogen, thus reducing contraceptive efficacy.[35,45] Other inducers of hepatic enzymes, including carbamazepine, may also increase levonorgestrel metabolism and, hence, may reduce contraceptive efficacy.[46] With the exception of rifampicin and griseofulvin, which are hepatic enzyme inducers, other antibiotics are not thought to reduce the effectiveness of levonorgestrel implants.[46]

After removal of subdermal implants from 12 women, most levonorgestrel was cleared from plasma within 96 hours.[47] The drug appeared to follow first-order elimination, and mean plasma elimination half-life was 42 (range 13 to 62) hours. A positive correlation between levonorgestrel plasma elimination half-life and bodyweight was detected ($r = 0.580$, $p < 0.05$). The rate of elimination did not correlate with either duration of treatment (range 5.5 months to 6 years) or amount of body fat.

4. Clinical Efficacy

Levonorgestrel subdermal implants (6-capsule system) have been evaluated in a number of large noncomparative studies (table II). The mean (or median[48]) age of women at enrolment was 25 to 31 years.[48-55] Mean parity ranged from 1 (in China)[52] to 3.4. Mean weights at enrolment were 44 to 58kg.

Further data are available from 16 282 women in 17 studies (reviewed by Grubb et al.[5]). These studies were conducted in South and Central America, Asia and Africa. Most were previously unpublished, although a small amount of overlap may exist with studies summarised in table II. In addition, a recent consensus statement and review[58] summarised 5-year follow-up data from a post-marketing surveillance study that included 7977 levonorgestrel implant acceptors, along with 6625 women who used an IUD and 1419 who underwent surgical sterilisation.

Several comparisons of levonorgestrel implants with other methods of contraception are summarised in table III. These studies were non-randomised, and there were between-group differ-

Table II. Efficacy and continuation rates of levonorgestrel 6-capsule implants in noncomparative studies with 5 years' follow-up, except where indicated

Reference (country)	No. of women enrolled	Mean age (y)	Cumulative life-table rates (per 100 acceptors)			
			pregnancy		discontinuation	
			1y	5y	1y	5y
Affandi et al.[49] (Indonesia)	437	29	0	1.8	4	22
Akhter et al.[50] (Bangladesh)	600	27	0[a]	0	6.1	59
Chetri et al.[54] (Nepal)	407	29	0.2	0.6	10.1	38.4
Chompootaweep et al.[51] (Thailand)	308	29	0	4.2	2.4	29
Cravioto et al.[55] (Mexico)	533[b]	25	0	0.29 (3y)	14.5	50.4 (3y)
Gu et al.[52] (China)	10 718	30	0.1	1.5	5.9	27.9
Salah et al.[56] (Egypt)	250	33		1.6		41.4
Singh et al.[57] (Singapore)	100	30	0	0	3	40
Tseng et al.[53] (Taiwan)	567	31	0	1.2	10.3	58.6
Vekemans et al.[48] (Belgium)	612	28 (median)	0.3	1.5	13	64

a Two pregnancies (detected at 1 and 4mo after levonorgestrel insertion) were considered to have been conceived prior to implant insertion.

b This was a 3y comparative study with the early 2-rod levonorgestrel formulation that is no longer available. Data reported are only for the recipients of the 6-capsule system.

ences in baseline characteristics in several.[59-61] Therefore, relatively few conclusions about comparative efficacy may be drawn from these investigations. A single published comparison of levonorgestrel 6-capsule implants and the current 2-rod implant formulation is discussed in section 4.4.

4.1 Continuation Rates and User Satisfaction

4.1.1 Continuation

The first determinant of contraceptive efficacy is continuation of use. Unless removed, levonorgestrel implants confer 100% compliance during their normal 5-year lifespan. However, rates of discontinuation before the end of 5 years are substantial. Two to 13% of users discontinued levonorgestrel implants during the first year of use (table II). Of 2129 UK women who received levonorgestrel implants, 15% had opted for removal by the end of year 1.[65] Cumulative 5-year discontinuation rates in table II and in the 17 studies reviewed by Grubb et al.[5] ranged from 22 to 64 per 100 women.

Overall, annual rates of discontinuation appeared to be relatively constant over the 5-year period in most studies,[5,49,51] although a pattern of high rates in years 2 and 3, followed by a return toward first-year discontinuation rates in years 4 and 5, was also reported.[50,57] One explanation for the low year-1 removal rates in these studies and those in table II is that removals occurring on the first anniversary of implant insertion were classified as year-2 removals. (Conversely, most of the 5-year discontinuation rates reported in table II do not include removals coinciding with the fifth anniversary of implant insertion, a time when – in line with current recommendations – most women have the implants removed.)

Although many women elected to discontinue use of levonorgestrel implants because of a desire to become pregnant (section 4.3.3), the primary reasons for early implant removal is most studies were tolerability considerations. The incidence of specific adverse events leading to discontinuation is discussed in section 5.

Demographic Characteristics of Early Discontinuers

A number of demographic characteristics may predict early discontinuation of levonorgestrel implants. Grubb et al.[5] identified age, parity and previous contraceptive use as important factors. However, the statistical significance of these data was not reported, nor was it clear from the published report whether these effects were independent of each other or cultural and geographical factors. Differences in discontinuation rates between women of European and non-European origin in a Belgian study indicated that cultural factors do influence discontinuation rates.[48]

According to a multinational analysis, young women are more likely than their older counterparts to have their levonorgestrel implants removed: women aged ≤24 years had discontinuation rates approximately twice those in women aged ≥35 years in years 2 to 5 of levonorgestrel implant use [cumulative 5-year discontinuation

Table III. Efficacy and discontinuation rates in comparisons of levonorgestrel 6-capsule (LNG-6) subdermal implants with intrauterine devices (IUD), depot medroxyprogesterone (DMPA), combined oral contraceptives (COC) or condoms[a]. Treatments were assigned by patient choice, except where indicated

Reference (country)	No. of women enrolled	Contraceptive	Mean age (y)	Median duration of follow-up (y)	Results at 1 year's follow-up, except where indicated (%)	
					pregnancy rate	rate of discontinuation
Berenson et al.[60] (US)	56	LNG-6	16.9	1	0	9
	56[b]	COC	17.0	1	25	66*
Dinerman et al.[62] (US)	54	LNG-6[c]	16.1	0.5	2 (at 6mo)	13 (at 6mo)
	64	COC[c]	16.3	0.5	20* (at 6mo)	50** (at 6mo)
	48	Condoms[c]	15.9	0.5	17* (at 6mo)	NR
Fakeye [61] (Nigeria)	50	LNG-6	32.8	1	0	6[d]
	22	DMPA	33.7	1	0	55[d]
	184	IUD	30.6	1	0	20[d]
	101	COC	28.5	1	2	13[d]
Marangoni et al. [63] (Ecuador)	283	LNG-6	NR[e]	1	0[f]	12.6[f]
	283[g]	IUD	NR[e]	1	2.4[f]	12.1[f]
Polaneczky et al.[59] (US)	48	LNG-6	16.7	1.3 (mean)	2	2[h]
	50	COC	17.2	1.3 (mean)	38**	57[h]
Singh & Ratnam[64] (Singapore)	39	LNG-6	30.4	5	0[f] (at 5y)	46[f] (at 5y)
	38	IUD	32.9*	5	2.6[f] (at 5y)	47[f] (at 5y)

a With or without spermicide.

b Age-matched case controls treated concurrently, but identified retrospectively.

c Condom use was similar in the 3 groups. Overall, 70% of women reported using a condom at last intercourse, 37% during every intercourse.

d Not including those lost to follow-up. Life-table continuation rates at 1 year were 94, 47, 78 and 28% for users of LNG-6, DMPA, IUD and COC, respectively.

e LNG-6 acceptors were younger than IUD acceptors.

f Rates per 100 users.

g For each woman who accepted LNG-6 implants, 1 IUD (TCu 200) acceptor, prospectively case-matched for parity, was enrolled.

h 12-month discontinuation rates estimated from graph of life-table analysis results ($p < 0.001$ for probability of discontinuation during first 6mo postpartum).

Abbreviation and symbol: NR = not reported; * $p \leq 0.01$, ** $p \leq 0.001$ *vs* levonorgestrel users.

rates of >70 *vs* <40 per 100 users (values estimated from graph)].[5] A similar pattern of age-related discontinuations emerged in Belgium.[48] However, in US studies, adult and adolescent levonorgestrel implant users appeared to have similar discontinuation rates and durations of use.[66-68] Reported reasons for implant discontinuation were also similar in adolescent and adult US women.[67] Why younger age should be predictive of higher discontinuation rates in the multinational studies, but not in US studies, is unclear. The US studies were possibly too small and follow-up too short (6 to 21 months)[66-68] to show a statistically significant difference.

Lower parity at insertion also correlated with higher discontinuation rates in the multinational studies.[5] Women with 1 or no children had discontinuation rates approximately twice those of women with 4 to 6 births at the time of insertion (statistical significance not reported).

Women with no history of contraceptive use appeared to be less likely to discontinue use of levonorgestrel implants than those who had previously used nonhormonal methods.[5] The latter group, in turn, were less likely than previous users of hormonal methods to discontinue levonorgestrel implant use.

Comparative Continuation Rates

Compared with users of other contraceptive methods, levonorgestrel subdermal implant users generally appeared to have higher continuation rates,[59-62,69-71] although few comparative data are available and randomised studies have not been conducted. The 1-year life-table continuation rate among women who chose to use levonorgestrel subdermal implants (93.7%) was higher than that among users of IUDs, DMPA or oral contraceptives (78, 47 and 28%, respectively).[61] Significant differences between groups at baseline, including a higher level of education among levonorgestrel implant acceptors, may have affected continuation rates. In another study,[63] 1-year discontinuation rates were approximately 12% in levonorgestrel recipients and case-matched TCu 200 IUD users. Five-year results reported by Singh and Ratnam[64] indicate that similar proportions of levonorgestrel implant and copper T380 IUD users discontinued their contraception (table III).

A review of 137 studies[48] reported median 1- and 2-year discontinuation rates of 10 and 21%, respectively, for levonorgestrel implant users; corresponding rates among IUD users (17 and 24%), oral contraceptive users (42 and 63%) and users of injectable methods (41 and 65%) were higher.

Among US adolescents, discontinuation rates during the first year of administration were much lower in those who accepted levonorgestrel implants than in those who used oral contraceptives (table III).[59,60,69,70] In 1 study, a 9% 1-year rate of discontinuation among levonorgestrel implant users was attributable entirely to adverse events (section 5).[60] In contrast, discontinuations among age-matched oral contraceptive users were more frequent (66%, $p = 0.01$) and were mostly because of poor compliance or an exhausted supply of pills. Similar results were obtained in other studies which had only 6 months' follow-up[62,69] and in retrospective reviews of postpartum or postabortion contraceptive use by US adolescents.[70,71]

4.1.2 User Satisfaction

Levels of satisfaction with levonorgestrel implants were generally high.[54,55,72] Of 533 women who received levonorgestrel 6-capsule subdermal implants in a Mexican study, 374 were asked at the discontinuation visit about their level of satisfaction with the product.[55] Of these, almost 85% described their experience as excellent or good, and 87% preferred the method to the last contraceptive they had used. Not surprisingly, women who opted for removal of the implants later in therapy were more likely to report positive experiences. Conversely, women discontinuing use of the implants during years 1 or 2 were more likely to have had less positive experiences. Good or excellent experiences were reported on discontinuation by 73, 74, 89 and 95%, respectively, of women who had the implants removed in years 1, 2, 3 and subsequently. 'Regular' experiences were reported by 20, 24, 11 and 5% of women; bad or unacceptable experi-

ences by 7, 2.4, 0 and 0% (Ma. Cravioto, personal communication).

Other studies assessed the levels of satisfaction among women who continued use of levonorgestrel implants for the full 5-year term.[54,72] 100% of 155 Nigerian or Ghanaian women who used levonorgestrel implants for a full 5 years reported having a favourable (9.9%) or very favourable (90.1%) experience with the implants.[72] The experiences of 195 women who did not complete 5 years' treatment were not recorded, but were presumably less positive.

At 15 months' follow-up, 74% of 42 US adolescents who chose levonorgestrel implants after a first pregnancy, compared with 38% of 42 who chose to use oral contraceptives, reported themselves 'very satisfied' with the method chosen ($p < 0.05$).[59] 95 and 79%, respectively, would recommend their chosen method of contraception. Similar results in US adolescents and adults have been reported elsewhere.[68,69]

4.2 Prevention of Pregnancy

Women using levonorgestrel 6-capsule subdermal implants experienced few accidental pregnancies in any study. In most large published trials, the cumulative 5-year pregnancy rate was <2 per 100 women continuing treatment (table II). However, in a study in Thailand, 4.2 per 100 women became pregnant during 5 years' therapy.[51] Data reviewed by Grubb et al.[5] generally confirm these findings. In the 17 studies, first- and second-year pregnancy rates, respectively, did not exceed 0.6 and 2.4 per 100 women. Five-year pregnancy rates ranged from 0 to 7 per 100 women.

In the largest study (n = 10 718),[52] the cumulative pregnancy rate after 5 years was 1.5 per 100 women continuing treatment (fig. 2). The annual pregnancy rate in this study rose from 0.1 per 100 users in the first year to 0.6 in the fifth year of use ($p < 0.001$ for trend) [fig. 2]. During a voluntary continuation phase of this study in which the implants were not removed at the end of year 5, annual pregnancy rates in years 6 and 7 appeared to stabilise at approximately 0.4 per 100 woman-years.[73] However, continuation of levonorgestrel implant use beyond 5 years is not recommended (section 6.3).

Pregnancy rates during levonorgestrel implant use decreased significantly with increasing age at enrolment in this study.[52] Cumulative 5-year pregnancy rates among women aged <25, 25 to 29, 30 to 34 and 35 to 40 years were 3.0, 1.7, 1.5 and 0.7 ($p < 0.02$).[52] Additional data from 2470 women confirm this relationship (reviewed by Sivin[74]).

Bodyweight correlated positively with annual and cumulative pregnancy rates in studies that used the older, 'hard-tubing' formulation.[4,5,52] In the largest study, 5-year cumulative pregnancy rates of women who weighed, respectively, <50, 50 to 59, 60 to 69 and ≥70kg at enrolment were 0.8, 1.5, 2.1 and 4.6 per 100 ($p < 0.0001$).[52] Pooled efficacy data comparing 5-year cumulative pregnancy rates between women <50kg and those ≥50kg and those <60 and ≥60kg showed a similar pattern ($p < 0.01$ for both comparisons; n = 16 282).[5] However, data presented by Sivin[74] indicate that although a relationship between bodyweight and efficacy is evident in women using the older hard-tubing 6-capsule levonorgestrel formulation ($p < 0.05$; n =

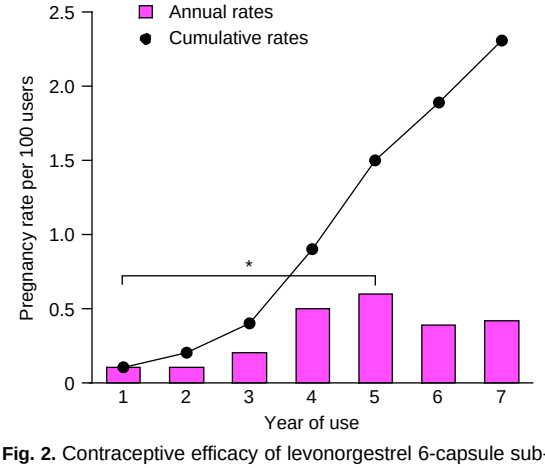

Fig. 2. Contraceptive efficacy of levonorgestrel 6-capsule subdermal implants: annual and cumulative pregnancy rates during years 1 to 5[52] and 6 and 7.[73] Of 10 718 women enrolled, 7554, 3622 and 2433 completed years 5, 6 and 7, respectively. *Symbol:* * $p < 0.001$ for trend of increasing annual pregnancy rate in years 1 to 5.

2470), no such relationship appears to exist with the soft-tubing formulation now in use.

Low cumulative pregnancy rates for levonorgestrel implants reported in table II (1-year rates ≤0.3 per 100 women) compare favourably with rates reported previously for other contraceptive methods.[75] Two nonrandomised comparative studies[59,62] and a case-control study[60] in US adolescents appeared to indicate that levonorgestrel implants were more effective than combined oral contraceptives (approximate 1-year pregnancy rates: 0 and 2 *vs* 25 and 38%) [table III]. In a Nigerian study, women who chose contraception with levonorgestrel implants, DMPA or IUDs experienced no pregnancies during the first year of use.[61] In contrast, 2 of 101 women who chose to use oral contraceptives became pregnant during this period (table III). Five-year follow-up of levonorgestrel implant and copper T IUD users indicated similar pregnancy rates for the 2 methods (0 and 2.6 per 100 users, respectively) [table III].[64]

4.3 Pregnancy Outcome, Lactation and Return of Fertility

4.3.1 Unintended and Ectopic Pregnancy

Because unintended pregnancy during levonorgestrel implant use was uncommon, only limited data are available to assess whether use affects pregnancy outcomes.

One study[53] reported that a high proportion of pregnancies which occurred during levonorgestrel implant use were ectopic (1 of 3); however, larger data sets did not suggest such an effect (17 reported pregnancies in pooled data; none ectopic).[51,76] In the largest published study, 4 pregnancies were ectopic (approximately 3.1%).[52] The overall rate of ectopic pregnancy in this study was 0.09 per 1000 woman-years. Postmarketing surveillance data indicated an ectopic pregnancy rate of 0.3 per 1000 woman-years among levonorgestrel implant recipients, compared with rates of 0.7 and 0.1 per 1000 woman-years, respectively, in IUD users and surgically sterilised women (n = 7977, 6625 and 1419).[58]

Based on these data, the possibility of ectopic pregnancy should be considered in women who become pregnant while using levonorgestrel implants.[77] However, it is important to note that, because of the overall contraceptive efficacy of the implants, the absolute risk of ectopic pregnancy among levonorgestrel implant users is certainly lower than that of the general population of women of reproductive potential.

4.3.2 Lactation and Infant Growth

Pharmacokinetic data indicate that levonorgestrel transfer from maternal to infant serum via breast milk is low (section 3.1.1). In 1 clinical study, it appeared that levonorgestrel implant use did not adversely affect lactation or infant growth: of 65 breast-feeding women who chose to receive levonorgestrel implants and 55 who opted to receive the copper T 380Ag IUD (both inserted on day 55 postpartum), 81 and 73%, respectively, were still exclusively breast-feeding on postpartum day 150.[43] The average weight of infants belonging to levonorgestrel implant- and IUD-using mothers, although initially significantly lower in the former group, did not otherwise differ significantly during this period (average weight at 153 days was 7503 *vs* 7741g).

Data from large nonrandomised studies conducted by the WHO support these findings. 2466 nursing mothers at 7 centres in 5 countries (Egypt, Thailand, Kenya, Chile and Hungary) chose to receive either progesterone-only contraception (levonorgestrel implants, progesterone-only oral contraceptive pills, DMPA or injectable norethisterone) or nonhormonal contraception at 6 weeks postpartum. Monthly follow-up including a large number of anthropometric measurements and infant development tests revealed no consistent differences in infant growth[78] or development[79] between the 2 groups during the first postpartum year. Results from smaller comparative studies are consistent with these findings.[80,81] It is not known whether the neonate may be at risk from exposure to steroid hormones prior to 6 weeks postpartum. Therefore, use of levonorgestrel implants should probably not be initiated before this time.[82]

4.3.3 Return of Fertility after Discontinuation

The desire to become pregnant led 6 to 25% of women in published studies to discontinue use of levonorgestrel implant before the end of 5 years' treatment.[50,51,53-55,57] Fortunately, prior use of levonorgestrel implants does not appear to affect subsequent fertility: in a trial with the now discontinued 2-rod levonorgestrel implant formulation, 20% of women who desired pregnancy became pregnant within 1 month of removal of the implants.[83] One-year conception rates were generally ≥78%.[53,57,83] Not surprisingly, increasing age correlated with reduced success in becoming pregnant in the first year after levonorgestrel implant removal.[83,84] In 1 study, women <30 years of age were more likely than those aged >30 years to conceive during the first year after implant removal (83 *vs* 67%; $p < 0.05$); however, this difference was no longer statistically significant after 2 years (90 *vs* 81%).[83]

Pregnancy rates among women who discontinued levonorgestrel subdermal implants to become pregnant were not different from those among women who discontinued levonorgestrel-releasing or Copper TCu 380Ag IUDs for the same reason (83, 84 and 77% success rates, respectively, at 1 year among 62, 91 and 103 women).[84] Duration of levonorgestrel subdermal implant use did not correlate with success rates.[84]

Although the total number of pregnancies after levonorgestrel implant removal was relatively small, these pregnancies appeared to be associated with usual rates of normal full-term deliveries (≥90%).[57,83]

4.4 Efficacy of the Levonorgestrel 2-Rod System

In a randomised comparison, the efficacy of the newer 2-rod levonorgestrel implant system appeared to be similar to that of the older, more extensively studied 6-capsule system.[85] This international multicentre study included 1198 women and was designed to detect a difference in cumulative pregnancy rates of 2 per 100 between the 2 products. In fact, no pregnancies were reported in either group through 3 years' follow-up. Three-year cumulative discontinuation rates were also similar between groups (about 29 per 100 women in each group). Adverse events (principally menstrual problems) accounted for most discontinuations (section 5).

In a smaller study, no pregnancies occurred among 199 women who used the levonorgestrel 2-rod system for up to 3 years.[36]

5. Tolerability

Tolerability data for levonorgestrel subdermal implants are available from the same sources as clinical results (for the 6-capsule system) reviewed in section 4. Most large studies reported the incidence of discontinuation of levonorgestrel implants due to adverse events; fewer studies reported the incidence or severity of adverse events in the total population of implant recipients. Moreover, rates of adverse events are likely to be affected both by cultural factors and by the method of data collection (i.e. elicited or volunteered complaints, general or specific questionnaires, etc.).

Data reviewed here are primarily from women who received the levonorgestrel 6-capsule system. In a comparison of levonorgestrel 2-rod (the newer system) and 6-capsule implants (section 4.4), the incidence of medical complaints, including menstrual abnormalities, appeared to be similar in us-

Table IV. Adverse events reported[a] by US adolescent users of levonorgestrel 6-capsule implants (LNG-6) and age-matched case controls who received combined oral contraceptives (COC)[60]

Adverse events	Incidence (% of users) at 12mo	
	LNG-6 (n = 56)	COC (n = 56)
Menstrual irregularities[b]	73*	5
Amenorrhoea	6	0
Increased appetite	33	42
Perception of weight gain	56	42
Emotional problems	26	5
Headaches	26	42

a Reports elicited during follow-up visits through the use of an event-specific questionnaire.

b Excluding amenorrhoea.

Symbol: * $p < 0.01$ *vs* COC.

ers of the 2 systems.[85] Levonorgestrel implants appeared to be less well tolerated than oral contraceptives (principally because of menstrual disturbances) in US adolescents, although no randomised comparative studies have been conducted (table IV and sections 5.1.1 and 5.2).

Of 766 US women who used levonorgestrel subdermal implants for 1 year, most experienced at least 1 adverse event (fig. 3).[86] In the studies summarised in table II, adverse events led to removal of the implants in 8 to 43% of women after 5 years.[49,51-54,57,87] Menstrual irregularities accounted for by far the largest proportion of these discontinuations (section 5.1).

Immediate (<48 hours) postpartum insertion of levonorgestrel implants was well tolerated, although implant recipients experienced more frequent bleeding irregularities and headaches than women who underwent tubal ligation in the same postpartum period.[88,89]

5.1 Menstrual Disturbances

Menstrual complaints, including increased or decreased menstrual flow, spotting, irregularity and amenorrhoea, are the most common cause of early discontinuation of levonorgestrel subdermal implants.[5,49,50,52,53,57,85] The 5-year cumulative incidence of discontinuation because of menstrual complaints ranged from 4.2 to 30.7 per 100 acceptors.[49-51,54]

Little information is available about the 5-year incidence of menstrual abnormalities that did not lead to discontinuation. However, it appears that nearly all women experience bleeding abnormalities at some time during levonorgestrel implant use.[3] Spotting, irregular bleeding and longer periods are the most common complaints. Of 215 women who received levonorgestrel implants and maintained bleeding records, 27% had regular bleeding cycles (bleeding every 21 to 35 days) during the first year of use; 66% had irregular cycles and 7% were amenorrhoeic (>3 months with no bleeding or spotting).[90] By the fifth year of use, the corresponding proportions were 62.5, 37.5 and 0% (n = 46 in year 5). About three-quarters of the implants used in this study were an early formulation.[90] Data from a larger trial (n = 600) also suggested that the percentage of women with amenorrhoea decreases with successive years of treatment (about 30% at the end of year 1 *vs* 6% of women who remained in the study at the end of year 5); however, the percentage of early removals which were due to amenorrhoea increased with successive years (to 50% in year 5).[50]

Analysis of bleeding complaints by trimester during the first year of levonorgestrel implant use showed that complaints of reduced bleeding decreased in frequency throughout the year, but complaints of increased bleeding and irregularity remained relatively constant.[91] In this study women were asked if they had any complaints relating to levonorgestrel therapy, but were not asked specifically about bleeding problems. About 20% of women had bleeding complaints in any given 3-month period; however, although the total number of women complaining of bleeding problems did not change, most of those complaining of these problems in any 3-month period had not had complaints in previous trimesters. The proportion of bleeding complaints that resulted in implant removal increased during the year.

In the pooled data presented by Grubb et al.,[5] the incidence of discontinuation because of menstrual irregularities more than doubled between the end of years 1 and 2 in 13 of 17 studies. Similarly, 4.2 women per 100 discontinued levonorgestrel implants because of menstrual complaints during the first year of use, compared with 6.7 per 100 at the end of year 2 in the largest single published study (n = 10 718).[52] Discontinuation rates for menstrual complaints declined significantly between years 1 to 3 and years 4 and 5 (p value not reported) [fig. 4]. In this study, the 5-year proportion of women who terminated levonorgestrel implant therapy because of amenorrhoea was considerably lower than the overall incidence of amenorrhoea.[52]

There appears to be an inverse correlation between menstrual abnormalities and contraceptive failure. In 2 studies carried out with (mainly) older

Fig. 3. Incidence of adverse events among US recipients who continued levonorgestrel implant therapy for 1 year (n = 766) or opted for early removal (n = 200) [adverse event reports elicited by questionnaire]. *Symbols:* * $p \leq 0.05$, ** $p \leq 0.01$ between continuers and discontinuers.[86]

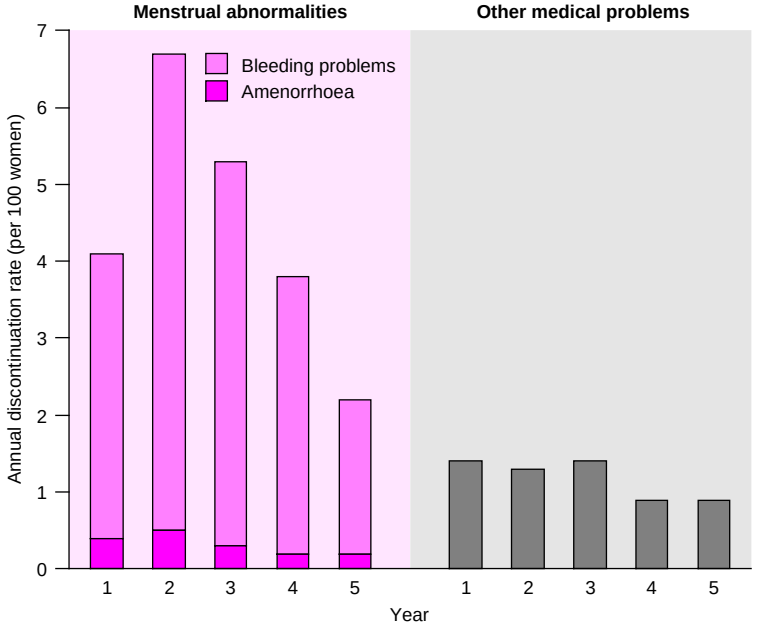

Fig. 4. Annual discontinuation rates for menstrual abnormalities and other medical problems among 10 718 levonorgestrel implant users.[52]

levonorgestrel implant formulations, pregnancies were reported in 19 of 458[39] and 10 of 234 women;[90] all except 2 of those who became pregnant in these 2 studies had had regular bleeding patterns prior to conception ($p < 0.05$ for pregnancy rate between users with regular bleeding and those with irregular bleeding/amenorrhoea in 1 study[90]). Luteal activity is associated with regular menstrual cycles. Only 3 of 31 levonorgestrel implant users with luteal activity had menstrual cycles of abnormal duration (either long or short); the remainder had normal cycles (24 to 45 days).[92]

5.1.1 Compared with Other Contraceptive Methods

Menstrual irregularity occurred significantly more often among US adolescent levonorgestrel implant recipients than among similar users of oral contraceptives.[60,62,69] After 6 months in 1 study, menstrual irregularity or spotting was significantly more likely among levonorgestrel implant users than oral contraceptive users [70 *vs* 31%; odds ratio 5.2; 95% confidence interval (CI) 2.5 to 11].[69] The former group was significantly more likely to report an increase in the length of the menstrual period, the number of days of spotting per month or the severity of menstrual cramps. Levonorgestrel implant users were also more likely to report heavier menstrual flow, although this difference was not statistically significant (odds ratio 1.5; 95% CI 0.7 to 48).

Implant recipients were also significantly more likely than parity-matched users of TCu 200 IUDs to discontinue use of their chosen method of contraception because of menstrual problems in 1 study (7.3 *vs* 2.3 discontinuations per 100 women at 1 year; $p < 0.05$).[63] Similarly, levonorgestrel implant users reported changes in menstruation much more frequently than users of TCu 380Ag IUDs.[93] However, in another study similar proportions of implant and IUD recipients (primarily TCu 200 IUDs) discontinued their respective methods because of menstrual problems (4 and 6.5%), but menstrual problems led to much higher

rates of discontinuation (55%) among women who had chosen DMPA contraception.[61]

5.1.2 Hormonal Management of Excessive Bleeding

Prolonged or frequent bleeding during use of levonorgestrel implants may be controlled or reduced through the use of oral hormonal therapy.[94,95] Supplementation of levonorgestrel subdermal therapy with 20 days' levonorgestrel/ethinylestradiol combination oral contraceptive treatment resulted in fewer total days of bleeding (mean 2.6) than supplementation with 20 days of ethinylestradiol therapy (mean 5.4; $p < 0.0001$).[95] Both hormonal therapies were more effective than placebo (mean 12.3 days of bleeding; $p < 0.00001$) in this randomised comparative trial ($n = 150$). Bleeding was more likely to stop within 3 days during combination oral contraceptive therapy (91% of users) than during ethinylestradiol monotherapy (67%; $p < 0.01$) or placebo administration (15%; $p < 0.0005$). Other hormonal regimens may also be appropriate for management of excessive bleeding during levonorgestrel implant use.[96-100]

5.2 Other Adverse Events

After menstrual complaints, the most common adverse event which led to discontinuation of levonorgestrel implant therapy was headache;[49,52,53,55,85] however, the overall incidence of discontinuations for this reason is low. Gu et al.[52] reported 10.9 discontinuations because of headache per 10 000 woman-years of treatment.

Caution is indicated in levonorgestrel implant recipients who develop persistent or severe headache. Although causality is uncertain, a number of levonorgestrel implant users have developed idiopathic intracranial hypertension (pseudotumour cerebri)[55,101] [Alder et al.[101] reported 2 cases and a total of 56 in the databases of various monitoring agencies]. Therefore, the presence of papilloedema in women who develop persistent or severe headache while using levonorgestrel implants is cause for referral to a neurologist. Levonorgestrel implants should be removed from women diagnosed with this condition.

After 1 year, the incidence of increased appetite, perceived weight gain, emotional problems and headaches did not differ significantly between US adolescents who chose levonorgestrel implants and those who chose oral contraceptives.[60] In a retrospective chart review of 150 women who received levonorgestrel implants, DMPA or combined oral contraceptives (50 women in each treatment group), mean 1-year weight changes were small and clinically unimportant in all groups (i.e. <1kg).[102] Similarly, body mass index in 75 levonorgestrel users did not change over 5 years.[103]

Because psychiatric disturbances, including major depression, panic disorder, agoraphobia and obsessive-compulsive disorder, have been reported in levonorgestrel implant users who had no prior history of such conditions,[49,104,105] levonorgestrel implants should be discontinued in previously well patients who develop these conditions.

Between 1991 and 1993, the US Food and Drug Administration received 14 reports of stroke in levonorgestrel implant users.[106] From such reporting, it is difficult to calculate the true incidence of stroke in this population or to determine whether the relative risk of stroke in levonorgestrel recipients is increased, decreased or unchanged compared with that in the general population of women of child-bearing potential.[106-109] Similar difficulties surround the interpretation of 3 reports of thrombotic thrombocytopenia and 39 reports of pseudotumour cerebri made during the same period.[106]

Acne, dizziness, hirsutism, alopecia mastalgia and nausea and vomiting may occur during levonorgestrel implant use.[3] During postmarketing surveillance of the first year of implant use, more than 5% of patients reported breast discharge, abdominal discomfort, cervicitis, vaginitis and leukorrhoea.[3] Other rare adverse events with uncertain causality which have led to discontinuation of levonorgestrel implants include peripheral neuropathy and myasthenia gravis.[110,111] Levonorgestrel implants are inserted in the vicinity of several major nerves, and arm pain is a relatively com-

mon adverse event (7 to 10% reported incidence).[110,112,113] Skin reactions may also develop over the insertion site.[114]

Prospectively collected postmarketing surveillance data reviewed elsewhere[58] indicated 'no significant excess' of malignant neoplastic disease or cardiovascular events (myocardial infarction, stroke, venous thromboembolism) in levonorgestrel implant users compared with women who used IUDs or who were surgically sterilised.

About 20% of levonorgestrel implant users develop persistent unruptured follicles, which may become as large as 5 to 7cm.[58] These follicles generally regress in 1 to 2 months without therapy, but may be associated with abdominal discomfort.

5.3 Insertion and Removal Complications

Techniques for insertion and removal of levonorgestrel 6-capsule subdermal implants are discussed in section 6. During the first year of levonorgestrel implant use, approximately 5.9% of women (n = 2674) experienced insertion site complications, although the incidence varied widely between countries and clinics within a country.[115] Local reactions accounted for most of these events (4.7% overall), with infection or expulsion accounting for smaller proportions (0.8 and 0.4%, respectively). Most insertion site infections occurred during the first month of follow-up; the majority of expulsions and local reactions occurred during the first 3 months of levonorgestrel implant use.[115] Insertion site complications were uncommon after the first year of use.[5]

Removal complications were reported in 4.5% of 3416 women in 11 countries.[116] The incidence in individual countries ranged from 0 to 11%. Complications were commonly caused by implants which broke during removal or were embedded below the subdermal plane. The most important risk factors which predicted removal complications were complications at insertion and infection at the implant site at, or before, the time of removal. On questioning, 48% of women in a Texas study reported significant pain during implant removal.[117] Figures such as this are likely to be affected by the method of data collection (particularly elicited versus volunteered responses). Among 125 UK women asked to rate the degree of discomfort during implant removal on a scale from 1 (no discomfort) to 7 (unbearable pain), the median discomfort score was 2 (range 1 to 7).[118]

Mechanical removal difficulties were reported in similar proportions of levonorgestrel 6-capsule and 2-rod recipients in a randomised study which included 1198 women (10.9 and 7.8%).[85] Postmarketing surveillance of levonorgestrel implant use in >16 000 women revealed a frequency of 10.1 difficult removals per 1000.[58]

Anaphylactoid reactions shortly after levonorgestrel implant insertion[119] and removal[120] are probably attributable to hypersensitivity to the local anaesthetic agent. Normal screening and precautions for use of local anaesthetics should be observed during levonorgestrel implant insertion and removal.

6. Dosage and Administration

Levonorgestrel implants should be inserted or removed only by personnel who have received (or are receiving) training in proper insertion and removal techniques. Complications associated with levonorgestrel implant insertion and removal are discussed in section 5.3. This section presents information on the insertion and removal of the 6-capsule system, except where indicated.

6.1 Counselling and Support

Appropriate counselling, both before levonorgestrel implant insertion and after the development of adverse events, is essential.[58,96,121] Emphasis of the potential for altered menstrual bleeding patterns (section 5.1) is an important aspect of preinsertion counselling. Other potential adverse events, particularly insertion site infection and mood changes, should also be explained. When appropriate, implant users should be counselled as to precautions against sexually transmitted diseases.

The continued availability of counselling during follow-up may increase user satisfaction and reduce the incidence of premature discontinua-

tions.[96] However, levonorgestrel subdermal therapy should be initiated only if facilities exist to provide for elective early discontinuation of the implants. Each woman must understand at the time of system insertion that this option is available.

6.2 Insertion

Levonorgestrel implants are inserted under the skin in the inner aspect of the nondominant (i.e. usually left) arm approximately 6 to 8cm above the fold in the elbow. Before insertion, the skin is cleansed, and local anaesthetic is infiltrated into the incision area. After a 2mm skin incision has been made with a scalpel, the capsules are placed subdermally through a trocar in a radial (fan) pattern in the direction of the axilla.[46]

Insertion of the capsules through a sharpened trocar without use of a scalpel caused no more complications (pain, tenderness, oedema/swelling, ecchymosis or defective scar) than the standard insertion technique.[122] Neutralising the acidity of the local anaesthetic used in insertion may reduce insertion pain.[123]

US prescribing guidelines suggest that implants should be inserted during the first 7 days of the menstrual cycle.[3] For later insertion, recommended practice includes use of an additional, nonhormonal method of contraception for 7 days and exclusion of pregnancy beyond the fifth day of the menstrual cycle or after abortion. A recently published study indicated that backup contraception was not necessary >3 days after levonorgestrel implant insertion.[82] Some evidence (section 5) suggests that levonorgestrel implant insertion ≤48 hours postpartum is well tolerated.

6.3 Removal

Levonorgestrel 6-capsule implants should be removed ≤5 years after insertion, although efficacy may be maintained beyond 5 years (section 4.2). The 2-rod formulation has been approved for ≤3 years' use;[4] data to support a longer duration of effect may yet emerge. If infection develops at the insertion site, antibiotic treatment should be initiated. If infection persists, the capsules should be removed.[3]

The recommended removal method involves cleansing and anaesthetising the skin and extraction of the capsules with small forceps through a 4mm incision made at the apex (i.e. pointed end) of the fan.[46] The removal procedure may be carried out at any time in the menstrual cycle; loss of contraceptive efficacy should be assumed to be immediate. If all capsules cannot be removed at the first attempt, a second procedure should be carried out after the incision has healed. If the woman wants to continue using levonorgestrel implants, a second set of capsules may be placed through the removal incision, and oriented in the same or opposite direction.

Reported mean removal time for the levonorgestrel 6-capsule system was 12.3 minutes, with a mean of 30 minutes in women who experienced removal complications.[116] Mean removal time in another study was 34 minutes.[117] In a comparison of levonorgestrel 6-capsule and 2-rod implants (section 4.4), mean removal time for the latter system was significantly faster (10.4 *vs* 4.9 minutes; $p < 0.001$).[85]

Several nonstandard removal techniques have been described for the levonorgestrel 6-capsule system.[124-129] In particular, randomised studies have shown that removal of levonorgestrel capsules using the 'U' technique[125] is faster and less likely than standard removal methods to result in broken capsules.[125,130,131] Methods for removal of deeply inserted, nonpalpable implants have also been described.[132,133] x-Rays,[132,134,135] fluoroscopy,[136] ultrasonography,[135,137-140] computer tomography[141,142] and compression mammography[143] may be used to locate nonpalpable implants in some instances.

7. Pharmacoeconomic Analyses

Three studies have examined the pharmacoeconomic implications of subdermal levonorgestrel (6-capsule) use in the US.[144-146] All attempted to compare the costs or cost savings associated

with a variety of contraceptive options. Each included:

- the acquisition cost of the drugs (or costs of surgical procedures)
- costs of physician visits and routine ongoing monitoring and contraception-related healthcare expenses
- the cost of adverse events and the cost of contraceptive failure (normal vaginal delivery, miscarriage and abortion).

Efficacy assumptions and discontinuation rates were based on previously published studies and the levonorgestrel implant prescribing information. Because none of these models attempted to estimate the economic effects of contraception from the user or societal perspectives, indirect costs of unplanned pregnancy (such as lost income and expenses related to child-rearing) were not included.

Results from these studies have been inconsistent; it is therefore difficult to clearly assess whether levonorgestrel implants are more or less cost effective than other contraceptive methods.

A cost-benefit analysis comparing levonorgestrel implant therapy, DMPA, oral progestogen tablets and oral estrogen/progestogen tablets (from the perspective of a managed-care organisation) indicated that all resulted in net economic benefits.[144] The savings were greatest with DMPA ($US2.87 per patient-day of pregnancy prevented) [1992 dollars]. Both oral formulations resulted in savings of approximately $US2.79 per patient-day of pregnancy prevented, and the levonorgestrel implants produced the smallest savings: $US1.64 per patient-day of pregnancy prevented. A sensitivity analysis (10% variation of drop-out rates for each product) did not change the overall ranking of the drugs. The smaller economic benefit calculated for levonorgestrel implants was a result of 2 main factors: a lower estimated number of days of pregnancy prevented per year (based on a 60% discontinuation rate for levonorgestrel recipients at the end of 5 years, which appears consistent with discontinuation rates presented in section 4.1.1) and higher fixed costs for the implants (i.e. costs for procedures such as implantation and removal).

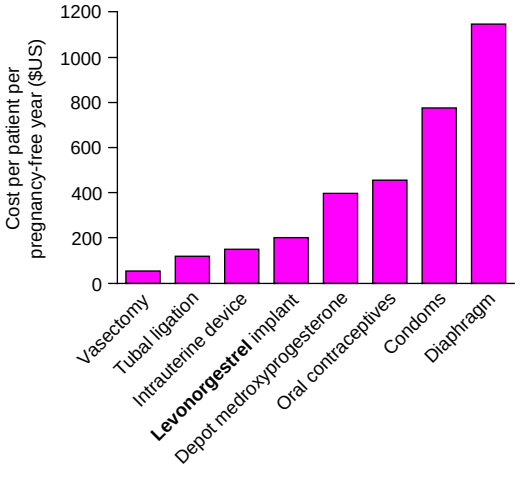

Fig. 5. Cost-effectiveness of levonorgestrel implants. Comparison with 7 other contraceptive methods expressed as cost per user per pregnancy-free year (from an institutional perspective). Includes costs of treatment, medical care, adverse events and method failure (1992 US dollars).[145]

A cost-effectiveness analysis estimated the net direct cost per pregnancy-free year (from an institutional perspective) of 8 contraceptive methods: levonorgestrel implants, DMPA, IUDs, oral contraceptives, condoms, diaphragms, vasectomy and tubal ligation.[145] In this model, vasectomy was the most cost-effective contraceptive method, followed by tubal ligation ($US55 and $US118 per woman per pregnancy-free year, respectively) [1992 dollars]. Of the reversible methods of contraception, the IUD and levonorgestrel implants were most cost-effective ($US150 and $US202 per user per pregnancy-free year) [fig. 5]. Oral contraceptives and other methods of contraception were more costly. The relative cost effectiveness of the methods was unaltered when comparative costs were calculated assuming that each method would be used for 15 years (costs discounted by 5% per year to the present value).

In addition to the costs mentioned above, this model estimated savings accrued per year from the beneficial effects of certain contraceptive methods (e.g. the reduced ectopic pregnancy rate with progestogen therapy and protection against benign ovarian cysts from combined oral contraception).

For levonorgestrel implants, failure rates were assumed to vary between 0.2 and 1.6% per year over 5 years and continuation rates were assumed to be 81% after year 1 and approximately 77% per year thereafter. A variety of sensitivity analyses did not alter the cost-effectiveness ranking of levonorgestrel implants relative to other methods in the analysis. Overall, the cost of method failure had the greatest effect on relative cost effectiveness of the 8 methods.

As in the above study, a cost-effectiveness analysis by Trussell et al.[146] indicated that barrier methods of contraception and oral contraceptives were more costly than levonorgestrel implants, IUDs, DMPA and vasectomy. This model estimated cost savings per user (from both managed care and public payer perspectives) and number of pregnancies avoided over 5 years for each of 15 contraceptive methods: tubal ligation, vasectomy, oral contraceptives, levonorgestrel implants, DMPA, progesterone-T IUD, copper-T IUD, diaphragm, male condom, female condom, sponge, spermicides, cervical cap, withdrawal and periodic abstinence. Costs were estimated from a variety of US sources and years (1990 to 1993). Over 5 years, copper-T IUDs, vasectomy, levonorgestrel implants and DMPA prevented approximately 4 pregnancies, with associated cost savings of $US13 000 to $US14 500 over no contraception. Oral contraceptives, progesterone-T IUDs and tubal ligation were each associated with savings of $US12 000 to $US13 000 for a similar number of pregnancies avoided. Other methods resulted in both smaller net savings and fewer pregnancies prevented. However, a major limitation of this model was the assumption that no discontinuations occurred for any method prior to 5 years, even if adverse events or unintended pregnancy developed.

It should be noted that levonorgestrel implant acquisition and other direct healthcare costs may vary between countries. Therefore, caution is necessary when attempting to interpret these studies from a non-US perspective.

8. Place of Subdermal Levonorgestrel in Contraception

The availability of safe, effective contraception may be one of the defining technological advances of the twentieth century. Nevertheless, unintended pregnancy remains a risk for many women. Of 5.4 million pregnancies in the US in 1994, almost half (49%) were accidental.[147] These pregnancies have substantial social and economic costs, and low-income women are more likely than their wealthier counterparts to have an unintended pregnancy.[147]

According to the recently published Norplant® Consensus Statement,[58] more than 6 million women worldwide have used levonorgestrel subdermal implants. More than 55 000 have participated in clinical trials. Overall, the implants provide extremely good contraceptive efficacy: cumulative 5-year pregnancy rates were <2 per 100 women in most studies (section 4.2). Failure rates decrease with age and appear, at least with older levonorgestrel implant formulations, to increase with increasing bodyweight.

Efficacy rates reported for levonorgestrel implants compare favourably with those reviewed by Hatcher et al.[148] for other reversible methods of contraception (table V). And, unlike oral contraceptive therapy, compliance with implants is 100%. Thus, levonorgestrel implants may be especially suited for use by women who have low rates of compliance with oral contraceptive regimens.

Unlike estrogen-containing contraceptives,[149] levonorgestrel implants do not interfere with lactation (section 4.3.2). They also do not appear to interfere with growth of breast-fed infants. The WHO and several other major family planning groups support the use of progesterone-only contraception during lactation, but recommend that it be initiated not earlier than 6 weeks postpartum.[82,149]

Like other systemic methods of contraception, levonorgestrel implants provide no protection against sexually transmitted disease. However, levonorgestrel implants did not reduce self-reported condom use among US adolescents.[59,150]

Table V. Efficacy and continuation rates of various contraceptive methods among US women[75,148]

Method	Accidental pregnancy rate (% of women in first year of use)		Continuation rate at 1y (%)
	perfect use[a]	typical use[b]	
Levonorgestrel implants	0.09	0.09	81
No contraception	85	85	
Spermicides	6	21	43
Periodic abstinence	1-9	20	67
Withdrawal	4	19	
Diaphragm	6	18	
Condoms, male	3	12	
Condoms, female	5	21	
Combined oral contraceptive pills	0.1	7[c]	75[d]
Progesterone-only pills	0.5		
IUD, copper T 380A	0.6	0.8	≈80
DMPA	0.3	0.3	70
Female sterilisation	0.4	0.4	100
Male sterilisation	0.1	0.15	100

a Perfect use requires that the method is used consistently and correctly.

b Typical use reflects the full range of use patterns, including perfect use and absolute noncompliance.

c Calculated from reference[75]. Type of 'pill' formulation not specified; may also include progesterone-only formulations. Rate corrected for abortion (uncorrected rate was 5%).

d 1y continuation rate in developing countries may be only 40-60%.

Abbreviations: DMPA = depot medroxyprogesterone injection; IUD = intrauterine device.

The most common adverse event during levonorgestrel implant therapy is abnormal menstruation, including amenorrhoea. Nearly all women experience menstrual disturbances at some time during levonorgestrel implant therapy. Headache appears to be the next most common adverse event leading to discontinuation of therapy. Although a high proportion of women request removal of their implants before the end of 5 years' treatment, 1-year continuation rates appear to be better than those for oral contraceptives. Implant removal results in rapid return of fertility.

The link between other hormonal contraceptives and the risk of cardiovascular disease (venous thromboembolic events, stroke and myocardial infarction) has been controversial, and a clear picture slow in emerging. The best available evidence, reviewed elsewhere,[151-153] suggests that use of combined oral contraceptives containing estrogen and (levonorgestrel or norethisterone) progestogens is associated with an increased risk of venous thromboembolism compared with no contraceptive use (absolute risk 15 versus 5 to 11 per 100 000 women per year). The risk with newer progestogens (e.g. desogestrel or gestodene) appears to be somewhat higher. However, a number of biases may have affected these calculations, including possible differences in underlying risk between women receiving second and third generation progestogens.

Smoking and age >35 years are recognised independent risk factors for cardiovascular disease in oral contraceptive users.[152,154] Limited data suggest that progestogens administered in combination with estrogen <50 μg/day increase the risk of ischaemic or haemorrhagic stroke, but not to a statistically significant extent.[153]

The relevance of any of these findings to the relative risk of cardiovascular disease with levonorgestrel subdermal implants is unknown. Pharmacodynamic data suggest that levonorgestrel implant use does not markedly alter the serum lipid profile and has only small effects on haemostasis (section 2.2). A prospective postmarketing surveillance study detected no significant increase in cardiovascular events in levonorgestrel implant users compared with women using nonhormonal methods of contraception (section 5.2).

US pharmacoeconomic models designed from the institutional or managed-care perspective indicate that all contraceptive strategies are associated with net cost savings compared with no contraception (section 7). Whether savings associated with levonorgestrel implants are larger or smaller than those associated with other contraceptive methods is less clear. For example, levonorgestrel implants were more cost effective than oral contraceptives in 2 analyses, but less cost effective in a third.

Thus, levonorgestrel implants are a good choice of contraceptive method for women with contraindications to estrogen therapy, including those with increased risk for venous thromboembolism,

myocardial infarction or cerebrovascular events and for lactating women who want to continue breast-feeding (>6 weeks postpartum). Levonorgestrel implants should not, however, be initiated in women with active thromboembolic disorders. Nor should women with liver disease, a history of idiopathic intracranial hypertension or undiagnosed vaginal bleeding receive the implants. Preexisting pregnancy should be ruled out before insertion of the implants. All potential recipients of levonorgestrel implants should be counselled about the potential for adverse events. Prior to insertion, it is important to ensure that facilities exist for removal of the implants, and that potential recipients understand that they can request removal of the implants at any time.

Conclusion. Levonorgestrel 6-capsule subdermal implants are a highly effective way of providing continuous contraception. Notwithstanding a high incidence of menstrual abnormalities, 1-year continuation rates with the implants appear to be better than those with other methods of contraception. Limited clinical data suggest that the newer 2-rod levonorgestrel subdermal system is associated with similar efficacy and tolerability to that of the 6-capsule formulation. Levonorgestrel implants are suited for use by women who want to use a hormonal contraceptive during breast-feeding. In women who desire effective, reversible contraception, but who are unable (or unwilling) to comply with an oral regimen, levonorgestrel subdermal implants are a good choice of contraceptive.

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