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Risks and Benefits, Advantages and Disadvantages of Levonorgestrel-Releasing Contraceptive Implants

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Contents

Abstract

Levonorgestrel-releasing implants are long acting contraceptives, approved for 5 years of continuous use. Two marketed systems, the six capsule Norplant®[1] and the two rod Jadelle®, have essentially equal rates of drug release, pregnancy and adverse events over 5 years of use. Randomised clinical trials and controlled cohort observations indicate that for the first 3 years, when pregnancy rates are at or almost zero, no other contraceptive system is more effective, although etonogestrel implants provide equal effectiveness. Annual pregnancy rates rise in the fifth year of continuous use but remain below 1 per 100 women. Annual pregnancy rates of Norplant® users remain below 1 per 100 throughout 7 years of continuous use.

Levonorgestrel implants provide low progestogen doses; 40–50 μg/day at 1 year of use, decreasing to 25–30 μg/day in the fifth year. Serum levels of levonorgestrel at 5 years are 60–65% of those levels measured at 1 month of use.

Adverse effects with levonorgestrel implants are similar to those observed with progestogen only and combined oral contraceptives. Risks of ectopic pregnancy, other pregnancy complications and pelvic inflammatory disease are reduced in comparison with those of women using copper or non-medicated intrauterine devices. Risks of developing gallbladder disease and hypertension or borderline hypertension, although small, are about 1.5 and 1.8 times greater, respectively, in women using levonorgestrel implants than in women not using hormonal contraception. Other serious diseases have not been found to occur significantly more frequently in levonorgestrel implant users than in women not using hormonal contraception.

The great majority of levonorgestrel implant users experience menstrual problems, but serious bleeding problems are not more frequent than in controls. Other health problems reported more frequently by levonogestrel implant users than by women not using hormonal contraception in a study of 16 000 women included skin conditions, headache, upper limb neuropathies, dizziness, nervousness, malaise, minor visual disturbances, respiratory conditions, arthropathies, weight change, anxiety and non-clinical depression. Clinical depression is not

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

more frequent in women using implants compared with those not using hormonal contraception (i.e. using intrauterine devices, sterilisation).

Removal problems occur less frequently with Jadelle® than with Norplant®. The mean removal time for Jadelle® is half that of Norplant®.

Levonorgestrel implants in nationally representative scientific samples, in randomised trials, and in controlled cohort studies have continuation rates as high as or higher than any other reversible contraceptive over a duration of 5 years. This would imply that the satisfaction women derive from the contraceptive effectiveness of levonorgestrel implants greatly outweighs the dissatisfaction that may accompany menstrual disturbances and other adverse effects associated with implants.

Levonorgestrel implants are indicated for the prevention of pregnancy; no other therapeutic use is known. The implants are manufactured in two distinct versions; as capsule implants made of silicone tubing filled with levonorgestrel, or as rod implants in which a physical mixture of levonorgestrel and a silicone elastomer is cured and encased by thin-walled silicone tubing. Implants manufactured in Finland are known as Norplant® and Jadelle®. Implants manufactured in China are known as Sinoplant 1 (capsules) and Sinoplant 2 (rods).

Norplant® first received regulatory approval in Finland in 1983. It has been widely available in Southeast Asia for more than 15 years. In the early 1990s, US and the UK regulatory authorities approved the use of Norplant® for up to 5 years of continuous use. Norplant® has been approved for commercial distribution in more than 60 countries worldwide.

Jadelle® received regulatory approval in Finland in 1997, for use over 3 continuous years. In 2000, regulatory authorities in Finland extended the use of Jadelle® to 5 years. In the US, Jadelle® implants were initially approved for use over a duration of 3 continuous years. In 2002, however, the US FDA extended this approval to 5 years continuous use. Jadelle® has also received regulatory approval in Europe (2001). Jadelle has not yet been generally distributed outside of Finland.

Implants of Chinese manufacture (Sinoplant 1 and 2) are thought to be unavailable outside of the Peoples' Republic of China.

Litigation, initially drawn from unrelated concerns in the US about the safety of silicone gel breast implants, has had a strong impact on the demand for contraceptive implants; reducing the number of annual users.[1,2] In 2002, the US distributor of Norplant® ceased its distribution, citing a shortage of components used in manufacture of the system. Nevertheless, estimated worldwide Norplant® usage since 1983 ranges from a likely 7.5 to 8.5 million women to a less likely high of 10 to 11 million.[3]

Levonorgestrel implant safety has been analysed in depth and widely, most notably in a 5-year, controlled cohort study involving 16 000 women.[4] Several reviews have been published which incorporate evaluations of the risks and benefits of levonorgestrel implants.[5-12] The most recent publications review all progestogen (progestin)-only contraceptive implants.[9-12] With respect to publications which cover implant efficacy, acceptability, tolerability or health status, however, an overwhelming bulk of information is focused on implants that release levonorgestrel (as of December 1, 2002, POPLINE listed 1634 citations for the search term 'levonorgestrel implants' or 'Norplant®' and 45 publications for the term 'etonogestrel implant' or 'Implanon®). Norplant® is the only contraceptive

implant for which population-based data on effectiveness and continuation are available from nationally representative scientific samples.

This review provides detailed evaluations of the effectiveness, acceptability and safety of levonorgestrel implants.

1. Designs and Placement

Norplant® is designed as six 3cm capsule implants made of silicone tubing. Each capsule contains 36mg of levonorgestrel, with a total drug load of 216mg. Jadelle® consists of two 4cm rod implants covered with thin silicone tubing. Each rod contains 75mg of levonorgestrel in a silicone elastomer matrix. The total drug load is 150mg. The structure of the rod implant design of Jadelle® permits a greater daily release per unit of surface area compared with that of the capsule design of Norplant®.

The initiation of implant use requires a minor surgical procedure under local anaesthesia to place the implants subdermally in the medial aspect of the non-dominant arm. The removal of the implants, which can be performed at any time, also requires surgical extraction of implants under local anaesthesia.

2. Current Manufacture

Materials used in current manufacture of both Norplant® capsules and Jadelle® rods differ from those employed in the widely studied original models. The silicone rubber tubing in current Norplant® manufacture contains less inert silica than was used in the tubing of the original Norplant®. Tubing with less inert silica is more pliable (or soft) and is associated with lower long term pregnancy rates[5] than tubing with more inert filler which is less pliable (or hard). In the manufacture of Jadelle®, the original elastomer used in forming the rod matrix with levonorgestrel was replaced. This change facilitated linkage with and diffusion of levonorgestrel through the thin walled silicone rubber cover.

Drug release rates for all levonorgestrel implants are slowly reduced with the passage of time. Population Council studies of Norplant® in the 1980s in which the same manufacturing lots of levonorgestrel were used with hard or with soft tubing, showed that soft tubing was associated with significantly lower pregnancy rates, particularly during or after the third year of use, as release rates declined.[5] Therefore the tubing used in all capsule implants was changed to soft tubing to enhance longer term release rates and thereby to reduce pregnancy rates in the third to fifth year of continuous use. Commercial distribution of soft-tubing capsule implants, Norplant®, was first initiated in 1991 in the US.

Changes in the manufacture of rod implants included an increase in drug load from 140mg per set of 2 rods (Norplant® 2) to 150mg per set of two rods and a change of the elastomer used to form Jadelle®'s core. As stated above, the latter change permitted the core to maintain a closer bond with the outer tubing than had been the case with Norplant® 2. This improved bonding increased the release of levonorgestrel from the core, after partial depletion during prolonged use. Improved release rates are confirmed in the results of randomised trials which found that levonorgestrel serum levels were significantly higher in women using Jadelle® compared with women using the original Norplant® 2 rods for more than 2 years. Fourth- and fifth-year serum levels were also higher than had been previously observed for patients receiving Norplant® 2.[13,14]

To date, clinician-authored articles from China have not addressed the question of whether the levonorgestrel implants of Chinese origin have incorporated the design changes that led to enhanced long-term release and extended effective use durations for Norplant® and Jadelle®.[15]

3. Effectiveness and Duration of Use

The principal benefit of contraception with levonorgestrel implants is effectiveness in preventing pregnancy for extended periods after a single administration.

The effectiveness of levonorgestrel implants depends upon the rate at which levonorgestrel is released from the implant surface after placement, and upon the serum levels of levonorgestrel in users. *In vivo* release rates have been estimated by regression analyses of the amount of levonorgestrel extracted from implants in situ after different use durations. The data portray nearly identical Norplant® and Jadelle® release rates throughout most of the 5-year period following placement. At the end of the first year of use, release rates for the two levonorgestrel systems are of the order of 40 to 50 μg/day.[16,17] A slow decline follows to a release rate of approximately 25–30 μg/day at the end of 5 years.[16,17] The similarity of the *in vivo* release rates through 5 years is reflected in the similarity of the cumulative pregnancy rates of Jadelle® and Norplant® through that time (table I).

Serum levonorgestrel levels of Jadelle® and of soft-tubing Norplant® are of the order of 400 pg/mL at the end of 1–3 months of use, and decline gradually thereafter to levels of 250–270 pg/mL at the end of 5 years of continuous use.[16,17] In addition to duration of use, serum levonorgestrel levels in implant users are notably affected by bodyweight.[18] Women weighing ≥70kg have the lowest serum levels and the highest, albeit small, annual pregnancy risks through 5 years. Within 10kg weight groups (as grouped in table II), serum levels at the end of the fifth year of Jadelle® use are approximately 60–65% of those observed at the end of the first month of use.[18] Serum levels measured from hard-tubing Norplant® implants (manufactured in Finland) in extremely long-term Chinese users have been interpreted as indicating that this implant system is likely to remain highly effective for more than 7 years in women weighing <60kg.[19] Serum levels can be expected to vary from study to study in relation to the weight distribution of the participants, and to some extent in relation to the laboratory performing the assays. Effectiveness studies of levonorgestrel implants initiated before 1990 (and completed before 1995) focused largely on hard-tubing Norplant® and on Norplant® 2 rod implants. These earlier implant systems have now been replaced by soft-tubing Norplant® (which was also in limited use before 1990) and by Jadelle®,

Table I. Annual life-table pregnancy rates per 100 women for soft-tubing Norplant® and Jadelle®[16,17]

Soft-tubing Norplant®[a]				Jadelle®[b]			
year	pregnancy rate	SE	number of implant users at risk for pregnancy at year's end	year	pregnancy rate	SE	number of implant users at risk for pregnancy at year's end
1	0.0	0.0	1082	1	0.1	0.1	1217
2	0.0	0.0	930	2	0.1	0.1	1020
3	0.3	0.2	776	3	0.1	0.1	830
4	0.0	0.0	636	4	0.0	0.0	672
5	0.8	0.4	518	5	0.8	0.4	556
6	0.5	0.3	408	6	1.2	0.5	441
7	0.3	0.3	314	7	2.0	0.8	192
8	0.0	0.0	96	8	N/A	N/A	N/A

a 1210 women initiated therapy with soft-tubing Norplant®.

b 1393 women initiated therapy with Jadelle®.

N/A = data not available.

which first entered into large-scale trials in 1990. To examine data related to the effectiveness of levonorgestrel implants for this review, studies presenting such information are arranged in four groups. The first group consists of the Population Council's studies of Norplant® and Jadelle®, initiated in 1990/1991. The second group encompasses all randomised studies of soft-tubing Norplant® or Jadelle® which have used other implants or levonorgestrel-releasing intrauterine devices (IUDs) as comparators. The randomised Population Council studies have also been included in the second group. The third group consists of larger, non-randomised multicentre, cohort studies providing detailed information of hard-tubing Norplant® and on the first rod implant, Norplant® 2. Finally, the fourth group includes two nationally representative samples of women who used Norplant® and who reported their experience retrospectively. Studies in the last group were conducted in the two countries that have had the largest number of levonorgestrel implant recipients, the US and Indonesia.

3.1 Population Council Studies

Population Council studies formed the basis of the initial FDA approval of Jadelle® for 3 years of continuous use, and for subsequent approval (in 2002) for continuous use of Jadelle® for up to 5 years.[13,20-23] These studies also provided data to support a Population Council request to the FDA to grant regulatory approval for an effective life of soft-tubing Norplant® of 7 years of continuous use,[20,21,24,25] a request currently under consideration by the FDA. These studies included a total of 1210 women who received Norplant® and 1393 women who received Jadelle®. One Jadelle® study also included 199 women who received the old Norplant® 2 rod implant.[13]

Table I summarises annual life-table pregnancy rates per 100 women through 8 years of continuous use of the same set of Norplant® implants and 7 years of continuous use of the same set of Jadelle® implants. Users of either levonorgestrel implant system experienced annual pregnancy rates that were at or below 0.3 per 100 women in each of the first 4 years of use. Pregnancy rates in the fifth year were 0.8 per 100 women for each type of implant. In the sixth and seventh years, annual pregnancy rates with Jadelle® continued to increase to 1.2 and to 2.0 per 100 women, respectively. Annual rates above 1 per 100 women are judged unacceptably high in implant users. Thus the Population Council sought and received approval for Jadelle® for 5 years only. The cumulative 5-year life-table pregnancy rate in Jadelle® users is 1.1 per 100 women.[23]

Pregnancy rates in Norplant® users remained below 1.0 per 100 women through 8 years, with sufficient data for the first 7 years to be considered for registration purposes. Like Jadelle®, Norplant® is associated in these studies with a 5-year cumulative pregnancy rate of 1.1 per 100 women and with a 7-year cumulative pregnancy rate of 1.9 per 100 women.[24] Table II exhibits data from the same set of Population Council studies, and shows 5-year cumulative pregnancy rates by 10kg weight groups. For both Norplant® and Jadelle®, higher failure

Table II. Five-year cumulative pregnancy rates per 100 women for soft-tubing Norplant® and Jadelle® by weight group at admission[16,17]

Soft-tubing Norplant®				Jadelle®			
weight (kg)	rate	SE	no. of patients	weight (kg)	rate	SE	no. of patients
<50	0.0	0.0	179	<50	0.9	0.9	212
50–59	0.3	0.3	492	50–59	0.5	0.5	533
60–69	0.6	0.6	344	60–69	1.8	0.9	395
70–79	2.9	2.0	129	70–79	1.4	1.4	175
80+	8.1	4.5	66	80+	1.7	1.7	78

Table III. Pregnancy and continuation rates in randomised trials of levonorgestrel-releasing implants

Reference	Device	No. of patients enrolled	% LFU	Pregnancy rates per 100 women at			Continuation rates per 100 women at		
				1 year	3 years	5 years	1 year	3 years	5 years
Study 1[20,21]	Norplant®	598	10.2	0.0	0.0	0.7	93.1	71.1	53.0
	Jadelle®	600	7.2	0.0	0.0	1.0	93.8	70.6	55.1
Study 2[13,17,18]	Jadelle®	199	3.5	0.0	0.0	2.4	88.3	62.4	39.8
	Norplant® 2	199	2.0	0.0	0.0	N/A	84.8	58.1	N/A
Study 3[27]	Norplant®	450	3.6	0.0	0.0	N/A	98.9	95.7	N/A
	Etonogestrel implant	448	2.0	0.0	0.0	N/A	98.5	92.8	N/A
Study 4[28]	Norplant®	100	0.0	0.0	0.0	0.0 (at year 4)	93.0	77.7	75.6 (at year 4)
	Etonogestrel implant	100	0.0	0.0	0.0	0.0 (at year 4)	96.0	82.7	75.9 (at year 4)
Study 5[15]	Norplant®	998	<1	0.0	0.0	N/A	96.1	87.1	N/A
	Sinoplant 1	1001	<1	0.0	0.1	N/A	96.3	84.9	N/A
	Sinoplant 2	1000	<1	0.0	0.0	N/A	96.1	85.6	N/A
Study 6[29]	Norplant® 2	100	0.0	0.0	0.0	N/A	96.0	69.0	N/A
	Levonorgestrel IUD	100	0.0	1.1	1.1	N/A	90.0	75.0	N/A

IUD = intrauterine contraceptive device; **LFU** = lost to follow-up; **N/A** = data not available.

rates occurred in women weighing ≥60 kg. Pregnancy in levonorgestrel implant users is also associated with age. Younger women experienced higher rates of pregnancy than did women who were aged 30 years or older at study enrolment.[24] An assessment of soft-tubing Norplant® compared on an age-specific basis with a wide range of US tubal sterilisation methods, suggests that for a 7-year period the soft-tubing implant protects against pregnancy as well as tubal ligation.[24,26]

3.2 Randomised Clinical Trials

Table III displays information concerning outcomes in six different randomised trials involving levonorgestrel implants, and permits comparative evaluation of implant regimens. The first tabulated randomised comparison shows that soft-tubing Norplant® capsules and Jadelle® implants were equally effective for up to 5 years of use in the Population Council trials.[20] No pregnancies were recorded in the first 3 years of this trial,[21] which was conducted primarily in developing countries and involved a total of 1198 women. At 5 years, cumulative pregnancy rates were approximately 1 per 100 women for each implant type in the trial. At admission, the mean bodyweight of enrollees was 58.0kg and the mean age was 28.4 years, with no significant difference between Norplant® and Jadelle® recipients with respect to these two variables.

In a second Population Council randomised trial, 199 Jadelle® recipients were compared with 199 women using the older rod system, Norplant® 2.[13] No pregnancies occurred in either group within 3 years of initiating use of either type of implant. Women randomised to the Norplant® 2 implants had them removed at the end of 3 years. Serum levonorgestrel levels in the third year were significantly lower in users of Norplant® 2 than in women with Jadelle® implants.

The remaining four independently published randomised trials shown in table III, involving at least 100 women with levonorgestrel implants and that were initiated in or after 1990, were conducted in China or Indonesia. In two trials comparing the performance of Norplant® with etonogestrel implants over periods of 3 years (Indonesia) or 4 years (China), no pregnancies occurred in users of either implant.[27,28]

Additional information on levonorgestrel capsule implants compared with etonogestrel implants can be found in a summary of studies 3 and 4 from table III and smaller comparisons of approximately 40 women per implant per site.[30,31] A total of 789 women used each type of implant in trials of 2–4 years' duration. No pregnancies were recorded in women using either implant method. 88% of patients were from East or Southeast Asia (70% from the two studies shown in table III).

Study 5, the largest of the randomised trials in table III, was a multicentre comparison of Chinese-made levonorgestrel capsule and rod implants, Sinoplant 1 and Sinoplant 2, and of soft-tubing Norplant® of Finnish manufacture. This trial involved 3000 women.[15,32] In the first 3 years only one pregnancy occurred, that being in the Sinoplant 1 group.[15] At 5 years, no user of soft-tubing Norplant® had become pregnant and the cumulative life-table pregnancy rate for each type of Chinese implant was below 1 per 100 women.[32]

The Chinese data, based on implants presumably similar to the hard-tubing Norplant® capsules and to Norplant® 2, indicate that differences in the cumulative 5-year pregnancy rates between the earlier and current levonorgestrel implant systems are relatively small in women of low bodyweight. The extensively reviewed efficacy data that include levonorgestrel implant studies initiated before 1990,[5,12,33] (and concluded before 1995) remain pertinent today to women of low bodyweight, e.g. populations in East, Southeast- and South Asia and in much of Latin America.

Study 6 in table III was conducted in Beijing, China. Norplant® 2 was compared with a levonorgestrel-releasing IUD for a 3-year period.[29,34] No pregnancies occurred in the Norplant® group, while one pregnancy occurred in the IUD group.

Data examined in this section suggest that for a 3-year period following placement of levonorgestrel implants manufactured in Finland, no reversible implant contraceptive is more effective than soft-tubing Norplant®. However, Jadelle® and the etonogestrel implant Implanon®, appear to be as effective as Norplant® for a period of 3 years' continuous use.

3.3 Large Observational Studies

A multicentre study involving 10 718 women using hard-tubing Norplant® capsules in China led to its regulatory approval there.[35] The 5-year cumulative pregnancy rate was 1.5 per 100 women. Cumulative pregnancy rates declined progressively with age and increased progressively with weight. Median age and weight at admission were 30.5 years and 55kg, respectively. Notably only 3.4% of enrollees weighed more than 70kg at admission. In a prolongation of the study, more than 2400 women continued with the same implant sets for 2 additional years. The cumulative 7-year pregnancy rate was 2.3 per 100.[36]

In China, the Norplant® 2 rod system was approved following an introductory multicentre trial initially involving 1208 women. That trial showed a cumulative 5-year pregnancy rate of 0.5 per 100 women. Mean admission weight was 54.7kg, and over half the women (53%) were aged ≥30 years at enrolment.[37]

A 5-year controlled cohort study involving 16 000 woman, conducted in eight developing countries, the Norplant Postmarketing Surveillance Study (NPMS), assessed the effectiveness and safety of hard-tubing Norplant® in comparison with IUDs or sterilisation.[4,38] Women in the NPMS who initially selected IUDs or sterilisation were age-matched in 5-year groups to women adopting hard-tubing Norplant® in the same month.

Ninety-six percent of women enrolled completed the study. They were seen semi-annually for 5 years, even after discontinuing the initially selected method. Information on effectiveness of contraceptives other than Norplant® and the control methods

was obtained from women who changed to alternative contraceptive methods. The mean age and weight of Norplant® users at admission were 28.5 years and 53.7kg, respectively. Durations of observation of women using Norplant®, copper IUDs, non-medicated plastic or stainless steel IUDs, or sterilisation, were 33 500, 26 300, 3100 and 7700 woman-years, respectively. An additional 1300 and 2000 woman-years were observed during use of combined oral contraceptives and condoms, respectively.

In the first 3 years following contraceptive initiation, hard-tubing Norplant® and tubal sterilisation were equally protective against pregnancy in the NPMS, each having a cumulative pregnancy rate of 0.5 per 100 women.[4,38] Users of hard-tubing Norplant® experienced higher annual failure rates in the fourth and fifth year after method initiation than did women who had undergone sterilisation. Consequently, hard-tubing Norplant® was associated with a significantly higher cumulative 5-year pregnancy rate, 1.5 per 100 women, compared with sterilisation. In the NPMS, despite age-matching of all controls, women using the hard-tubing Norplant® were on average 1.1 years younger than women who had undergone sterilisation, and thus were at somewhat greater risk of pregnancy throughout the study. Pregnancy rates were not adjusted for this age difference. On the other hand, because only a small proportion of Norplant® users weighed ≥70kg, they were at lower risk of pregnancy than women of non-Asian descent, who tend to be heavier.

Hard-tubing Norplant® was substantially more effective than copper or non-medicated IUDs in the NPMS. The 5-year cumulative life-table pregnancy rate for implant users in the NPMS was 35% of the rate for copper IUD users and 11% of the rate for women with non-medicated IUDs. The Pearl pregnancy rate for Norplant® users was a slightly smaller fraction of the Pearl rate for copper IUD users (30%) and for non-medicated IUD users (10%).[38] Implant initiators in the NPMS had significantly ($p < 0.05$) lower pregnancy rates than did individuals who changed from using IUDs or implants to combined oral contraceptives or condoms (table IV).

Of note, in the NPMS, the 5-year cumulative pregnancy rate for hard-tubing Norplant®, 1.46 per 100 women, was nearly identical with that in the large Chinese introductory trial of women of similar weight, 1.53 per 100 women.[35,36] Both cumulative pregnancy rates round to 1.5 per 100 women. Three-year data from the NPMS, and data from the long-term studies of soft-tubing Norplant®, suggest that soft-tubing Norplant® is equivalent to tubal ligation in effectiveness over a 7-year period).[4,24,38]

3.4 Population-Based Effectiveness

Retrospectively determined pregnancy rates for levonorgestrel implants are compared with rates for several other methods of contraception in a population-based scientific sample of US contraceptive users (table IV). In the 1995 National Survey of Family Growth (NSFG), soft-tubing Norplant® implants had the lowest 1- and 2-year failure rates of any contraceptive, including injectable agents.[39,40] In the US, failure rates of implants were approximately one-fourth of those of oral contraceptives. More traditional methods, such as spermicides, the withdrawal method and the rhythm method were all associated with failure rates above 15 per 100 women in the first year and above 20 per 100 women at the end of 2 years, and are therefore not shown in table IV.[39,40]

A nationally representative sample of nearly 3000 women was undertaken in mid-1996 in Indonesia to examine the question of whether Norplant® sets had been removed, as prescribed, after 5 years of use.[41] Interviewed women from 14 provinces, 50 districts and 300 villages were representative of more than 500 000 Indonesians who had initiated hard-tubing Norplant® use between April 1, 1987

Table IV. Cumulative pregnancy rates per 100 women in international multicentre controlled cohort studies and nationally representative samples

Method	USNSFG[39,40]	NPMS[4,38]		Indonesia[41]	
	life-table	life-table	pearl index	life-table	
				max	min
Year 1					
Implant	2.3	0.1	0.1	0.9	0.1
Injection	3.2		0.2		
Copper IUD	3.7	1.0	1.0		
Contraceptive pill	6.9		0.9		
Diaphragm	8.1				
Male condom	8.7		7.4		
Year 2					
Implant	2.3	0.2	0.1	1.0	0.2
Injectable	9.3				
Copper IUD	17.9	2.2	1.2		
Contraceptive pill	12.4				
Diaphragm	16.3				
Male condom	17.6				
Year 3					
Implant		0.5		1.1	0.3
Copper IUD		3.0			
Year 5					
Implant		1.46		1.4	0.5
Copper IUD		4.19			
Initial number of women in study					
Implant	146	7977		2978	
Copper IUD	<100	5996			
All methods	6867	16 021		2978	

IUD = intrauterine contraceptive device; **NPMS** = Norplant® Postmarketing Surveillance Study; **USNSFG** = US National Survey of Family Growth.

and 31 March, 1991, at least 5 years after implant initiation.

Retrospective reporting of pregnancies dated two-thirds as occurring in the first 8 months of use, with one-third in the first 3 months when levonorgestrel blood levels are highest and the method should be most effective. The study authors assumed the majority of these pregnancies were conceived prior to implant placement.[41] Under that hypothesis, the Pearl pregnancy index would be 0.1 per 100 woman-years over the entire duration of use. If, however, all reported pregnancies actually had occurred post-implant placement, the Pearl index during all periods of use would be 0.3 per 100 woman-years. Two pregnancies reported as occurring in the sixth year indicate a pregnancy rate in year 6 substantially below 1 per 100 woman-years. Estimated life-table rates are provided in table IV.

4. Continuation Rates

Continuation rates represent the probability of individuals using the same method for a specified period. Differences of a few percentage points in continuation rates imply larger percentage differences in average durations of use. A continuation rate of 60% per year implies that over a 15-year time horizon, the average duration of use is just under 2 years. A 70% annual continuation rate increases the

average duration not by 17% but by about 40%, with mean use increasing to 2.8 years. An 80% continuation rate implies a mean use duration of 4.5 years, not 14% but about 60% longer than a rate of 70%. With the same 15-year horizon, a continuation rate of 85% translates into an average use of 6 years and 2 months. Of course, continuation rates of reversible methods are unable to match the near 100% annual rates of tubal ligation or vasectomy.

Continuation rates for reversible methods reflect their acceptability, tolerability, the ease with which they may be discontinued and their failure rates. Robust evidence from numerous sources indicates that, when controlled for age, parity and family-building status, implants and IUDs have the highest continuation rates among users of reversible contraceptive methods.[38,40] In Population Council studies of Norplant®,[17] the median duration of use of this implant was 36 months among young, low parity women with stated commitment to spacing pregnancies at admission. This result was less than half of the median duration of use (79 months) of the same implant among women who at study entry had more than two children, intended to have no additional children and were ≥30 years of age.

The 1996 national probability sample of Norplant® users in Indonesia[41] found the annual continuation rate in each of the first 4 years following placement to be an astonishing 96% or higher. More than 90% of the women continued to use the implants for at least 4 years. Attempted compliance with the mandate to remove Norplant® by the end of 5 years lowered the fifth year annual continuation rate to 73%. Accordingly, 66.1% of women used their set of implants for 5 years or more (table V)[41] [6 years after initiation, 90% of women had the implants removed]. These extraordinary continuation figures indicate some misstatement of removal dates, but also reflect Indonesia's unique family planning programme. Sterilisation (which is not endorsed by religious leaders in Indonesia) is not widely practiced and historical continuation rates for IUDs have been high. The absence of sterilisation in Indonesia may explain the high usage of long-acting implants (Indonesian women constitute about half of the world's users of implants) and IUDs in this country.

In a 3-way randomised trial assessing the use of implants of Chinese manufacture (Sinoplant 1 and Sinoplant 2) and the use of Norplant® produced in Finland, Fan and Han have indicated that cumulative continuation rates for these three implant types at 3 years ranged between 85 and 87% (table III).[15] These rates correspond to annual continuation rates of 94.7% or higher.

Data from the NPMS show that the continuation rates over a 5-year period for copper IUD and implants are essentially equivalent (table V).[4,38] At 1 year, continuation rates for implants were slightly higher than those for IUDs. At 3 years, cumulative continuation rates for the two forms of contraception were identical. At 5 years, cumulative continuation rates were 3 per 100 initiators higher for IUDs compared with implants ($p < 0.05$). In the short-term, limitations such as IUD expulsion or implant discontinuation for menstrual disturbances may result in higher discontinuation rates for these long-acting contraceptives. In the longer term, age-matched studies, or age-adjusted studies assessing the use of these contraceptives for 5–7 years post-initiation, have shown that these two methods appear substantially equal in their tolerability or continuation rates.

Table V shows the population-based 1- and 2-year comparative continuation rate data for various types of contraceptives obtained in a nationally representative US NSFG.[39,40] At both the 1- and 2-year points, US users of Norplant® had significantly higher continuation rates than did women employing other reversible methods of contraception. The NSFG estimated that 79.9% of Norplant® users continued to use the implants after 2 years

Table V. Cumulative continuation rates per 100 women in nationally representative samples and international multicentre controlled cohort studies

Method of contraception	USNSFG[40]	NPMS[4,38]	Indonesia[41]
Year 1[a]			
Implant	84.3	95.4	97.9
Contraceptive pill	68.0		
Copper IUD	63.6	92.8	
Diaphragm	57.2		
Injection	55.6		
Male condom	52.7		
Abstinence (rhythm method)	51.2		
Year 2			
Implant	79.9	86.9[b]	95.8
Contraceptive pill	48.7		
Copper IUD	40.8	85.5[b]	
Diaphragm	40.1		
Injection	40.5		
Male condom	34.2		
Abstinence (rhythm method)	33.3		
Year 3			
Implant		79.1	93.5
Copper IUD		78.8	
Year 5			
Levonorgestrel implant		66.8	66.1
Copper IUD		69.5	
Initial number of women in each study			
All methods	6867	16 021	2978

a Only methods with >50% continuation rates at 1 year are shown for US.

b Second year NPMS rates are geometric means of years 1 and 3.

IUD = intrauterine contraceptive device; **NPMS** = Norplant® Postmarketing Surveillance Study; **USNSFG** = US National Survey of Family Growth.

post-initiation. In contrast, <50% of women continued use with other forms of contraception after 2 years. The NSFG found that continuation rates associated with Norplant® were higher than those of methods that are supply-dependent as well as those that do not require resupply, e.g. the rhythm method.

When continuation rates have been adjusted for age, parity and other demographic variables, long-acting methods of contraception are still associated with higher continuation rates than oral contraceptives and other supply-dependent methods.[42] The data from randomised trials have also indicated that the continuation rates are similar between the various implants used, including the several models of levonorgestrel and etonogestrel implants (see table III). This suggests that there is little difference in the acceptability and/or tolerability of these contraceptive implants.

5. Potential Health Risks

For the purposes of this review, quantitatively reliable international data concerning the absolute and relative health risks associated with the use of levonorgestrel implants have been derived principally from a large-scale, 5-year, concurrent cohort NPMS study conducted in eight developing countries.[4,38,43]

Clinical contraceptive trials that are undertaken to gain regulatory approval are rarely large enough

and are seldom conducted over a sufficiently long period to delineate adequately major health risks or benefits of public health significance. The trials that are conducted for the purposes of gaining regulatory approval do produce a full delineation of adverse events; however, few of these adverse events tend to be serious. This is due to the fact that the great majority of patients in contraceptive trials are young, healthy women.

Experience captured in all but the largest or most prolonged contraceptive trials tends to be too small to establish whether the magnitude of any association between serious adverse events and the study drug is stable enough to warrant concern. Recognising this, regulatory agencies require distributors of approved drugs to conduct postmarketing surveillance. However, spontaneous postmarketing case reporting is of limited utility in many countries. Reporting is erratic, denominators are poorly known and controls for case reports are not at hand. Until a new contraceptive becomes sufficiently prevalent, the accumulation of large numbers of cases that would permit the use of standard epidemiological methodology, e.g. the case-control study, will lag considerably behind the need for reliable data.

The NPMS and older controlled cohort studies were of sufficient magnitude and duration to permit delineation of health risks and benefits over a wide spectrum of events.[43-46] Controlled cohort studies of contraceptives embrace broader groups than do clinical trials, but are still likely to enrol and successfully follow patients who are healthier than patients of the general population who are not enrolled or followed. While they address many health issues with appropriate statistical power and minimal bias, cohort studies also face limits related to the rarity of many severe or life-threatening health conditions. For such conditions, case-control studies are superior albeit substantially narrower, and often laggard instruments.

The controlled cohort NPMS provided a wide-ranging assessment of safety and risks associated with levonorgestrel implants, IUDs and sterilisation.[4,38,43] This study was designed to have sufficient (80%) statistical power to detect a doubling of serious adverse events of public health interest, if the base incidence rate in the population was 1 per 1000 woman-years or higher. 8000 women who were using implants as a form of contraception were matched for age (in 5 year groups) to female controls who were using IUDs or who had undergone sterilisation. High continuation rates, 96% completion of 5-year follow-up and accrual of 78 323 woman-years of experience permitted rate ratios (RR) of 2 or more to be deemed statistically significant with base rates in the controls as low as 1 per 2000 woman-years. A large part of what is quantitatively known concerning the health risks and benefits of levonorgestrel implants during or shortly after use is embedded in the results of this study.

RRs are used to approximate the risks of the conditions in implant recipients relative to those in other individuals. RRs significantly below 1.0 reflect reduced risk to Norplant® recipients and RRs significantly above 1.0 reflect increased risk.

5.1 Major Health Events

Potentially life-threatening occurrences, hospitalisations, convalescences of 1 or more months' duration, medication for 3 or more months, events with long-term consequences, or death were considered major health events in the NPMS.[4,38,43]

5.1.1 Intrauterine and Extrauterine Pregnancy

Pregnancies were considered major health events in the NPMS because they most often involve hospitalisation, generally persist for >3 months, and their complications such as ectopic gestation or septic abortion are life threatening. Pregnancies dominated the list of major health events, representing 1737 (62.5%) of the 2780 serious diseases and injuries recorded in the NPMS.[4,38]

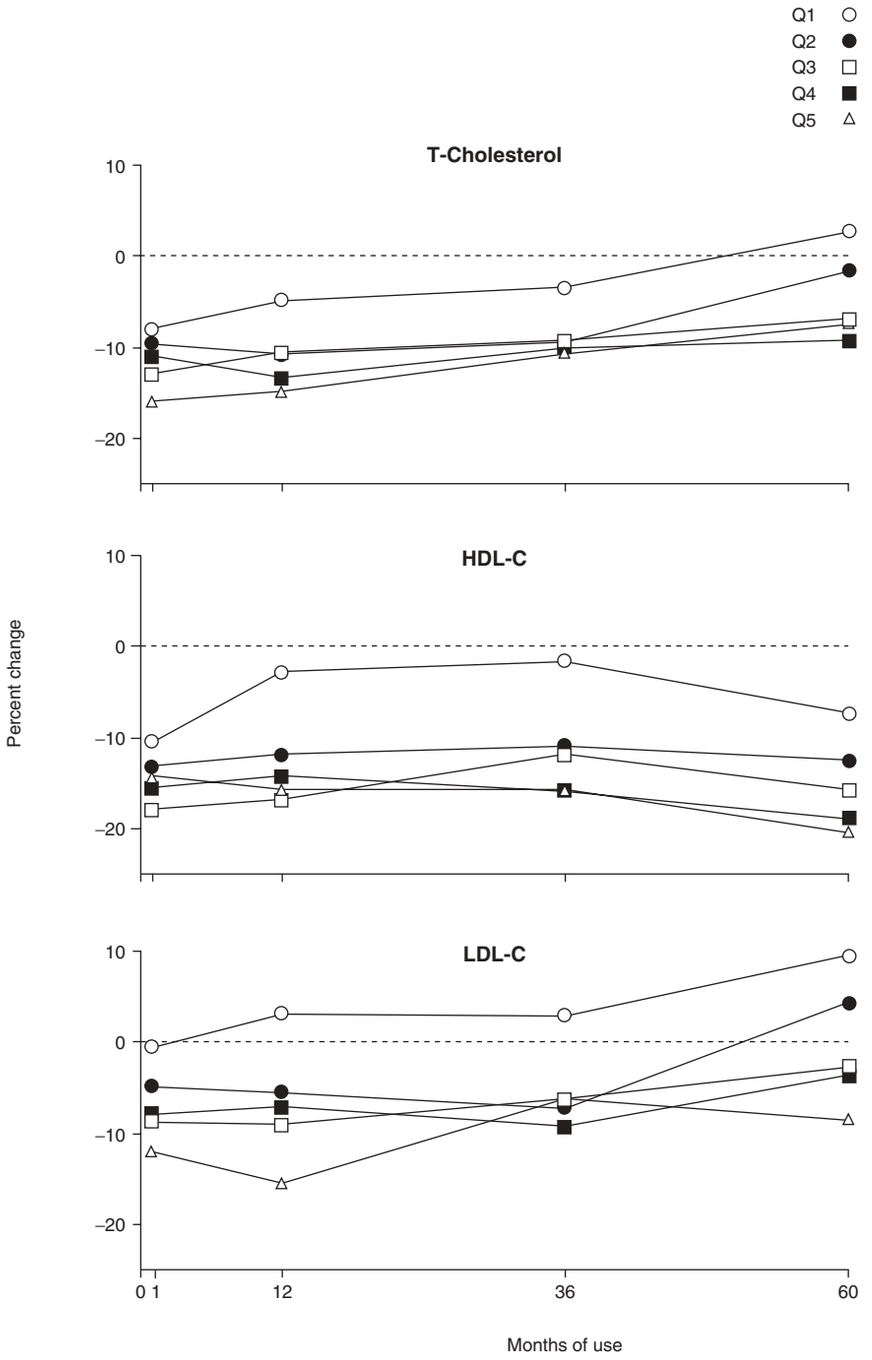

Fig. 1. Percentage change from baseline in total cholesterol (T-cholesterol), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C) by quintile (Q) at baseline. Baseline for each quintile is 0%, and is represented by the dashed line. **Q1** = lowest; **Q5** = highest.

More than one-third (34.7%) of reported pregnancies in the NPMS were due to contraceptive failures. Most pregnancies in women who did not use any form of contraception were characterised as planned, yet one-third (34.3%) were deemed to be unplanned. Contraceptive failures and unplanned pregnancies jointly constituted 57.2% of all pregnancies recorded in the NPMS.[4,38]

According to the data from the NPMS, RRs of accidental pregnancy during implant use were significantly lower than those associated with copper and non-copper IUDs and oral contraceptives. An RR of 1.1, relative to the limited study experience with injectable agents (mainly medroxyprogesterone – Pearl Index 0.25), was not significant. The RR of Norplant® relative to non-users of contraception not planning pregnancy was <0.02. Norplant® provided a substantial, and essentially unmatched benefit to women seeking to avoid an unplanned pregnancy.[4,38]

The risk of ectopic pregnancy was low with levonorgestrel implants. The incidence of ectopic pregnancy in women not using contraception was 2.66 per 1000 woman-years in the NPMS, nine times the incidence in current implant users (RR = 0.11, p = 0.01). Ectopic pregnancy rates per 1000 woman-years were reduced by 56% in Norplant® users when compared with women who used copper IUDs (RR = 0.44, p = 0.03) and by 77% when compared with users of non-copper IUDs (RR = 0.23, p = 0.006).[4,38]

5.1.2 Mortality

Overall mortality incidence in the NPMS was 4.3 per 10 000 woman-years. Mortality rates in women receiving Norplant® were similar to or slightly below (p > 0.05) rates in controls.[4,38,43] Mortality incidence in the NPMS was identical to that noted in the similarly constructed Oxford Family Planning Association cohort study[44] and below rates in two other major contraceptive cohort studies.[45,46] The majority of deaths in the NPMS resulted from violence, through injury, suicide or homicide. One NPMS participant died of septic abortion. She became pregnant after implant removal.

In a large-scale Chinese trial of Norplant®,[35] nine deaths occurred in 44 954 woman-years of observation (2.0 per 10 000 woman-years). Seven of these deaths were as a result of external causes, suicides, industrial accidents and carbon monoxide poisoning. The two disease-related deaths were from miliary tuberculosis and osteosarcoma.

Population Council clinical trials of three levonorgestrel-releasing implants in healthy women, initiated in 1990, accumulated 11 159 woman-years of experience before closure in May 2001.[16,17] A single death, caused by motor vehicle accident, occurred during the study. The mortality incidence was 0.9 per 10 000 woman-years.

One may conclude that levonorgestrel implants do not increase mortality risks as compared with long-acting non-hormonal contraceptive methods, and that mortality rates are very low in women who are healthy at the initiation of use.

5.1.3 Malignancies and Other Neoplastic Conditions

Malignancy rates in the NPMS were low and close to expected values for women of reproductive age.[4,38,43] The 78 000 woman-years of observation had little power to differentiate the incidence of cancer between women using Norplant® and controls. Fifteen malignancies were diagnosed, seven in Norplant® recipients and eight in controls. There were no significant differences between the two groups in terms of malignancy rates or RRs of malignancies (table VI). In total, seven reproductive cancers were recorded. Four were reported by Norplant® recipients, all of which were breast cancers. Three reproductive cancers were diagnosed in controls, of which one was breast cancer.

The risk of developing carcinoma *in situ* of the cervix did not differ between women using Norplant® and controls (RR = 0.85).[4,38,43] Furthermore,

Table VI. Rate ratios of major adverse health events in the Norplant® Postmarketing Surveillance Study (NPMS)

ICD-9 chapter and subchapter	ICD-9 code	Norplant® rate per 1000 woman-years	Rate ratio (to controls)	p-Value
Neoplasms	140–239	1.9	1.08	>0.10
invasive malignancies	140–208	0.2	0.88	>0.10
benign neoplasms	210–229	1.5	1.13	>0.10
carcinoma *in situ*	230–234	0.2	1.13	>0.10
endocrine, nutritional, metabolic-related disorders	240–279	0.6	1.49	>0.10
Disease of blood and blood forming organs	280–289	1.6	0.87	>0.10
anaemia		1.5	0.80	>0.10
Mental disorders	290–319	0.2	1.74	>0.10
Disorders of the nervous system, sense organs	320–389	0.5	2.00	0.07
disorders of the eye and adnexa	360–379	0.2	4.05	0.08
Circulatory system disorders	390–459	1.5	1.40	0.10
Respiratory system disorders	460–519	0.5	1.25	>0.10
respiratory system disorders (other than acute upper respiratory infections)	470–478	0.2	7.08	0.07
Digestive system	520–579	3.0	1.58	0.002
other digestive system	570–579	1.7	1.62	0.01
Genitourinary system (excludes complications of pregnancy)	580–629	2.0	0.96	>0.10
acute pelvic inflammatory disease	614	0.2	0.34	0.02
ovarian cystic enlargement	620	0.2	1.40	>0.10
excessive, irregular bleeding	626	0.2	1.36	>0.10
Disorders of the skin, subcutaneous tissue	680–709	0.2	3.04	>0.10
Disorders of musculoskeletal and connective tissue	710–739	0.4	1.45	>0.10

ICD-9 = International Classification of Diseases 9.

the risk of cervical dysplasia was not significantly different between the two groups. Curtis[47] concluded that to date studies of levonorgestrel implants have found no evidence of increased rates of cancer or of cervical or endometrial changes.

5.1.4 Cardiovascular Disease

Concerns that Norplant® may be associated with stroke arose from spontaneous reporting in the US[48,49] buttressed by association of stroke with oral contraceptives. Cerebrovascular and cardiovascular disease, however, were uncommon in the NPMS.[4,43] No cases of myocardial infarction, one of venous thromboembolism and two of stroke were reported in the implant group; for these three conditions, the observed and expected numbers were close.[4,43] Implant users and controls in the developing country settings of the NPMS had a low prevalence of risk factors for cardiovascular disease. Few were obese, few had hyperlipidaemia or diabetes mellitus; and <7% of subjects had ever smoked tobacco. Except with respect to hypertension, no statistically significant differences were found in the incidence of severe cardiovascular conditions between implant and control groups.

Other epidemiological evidence is consistent with these NPMS data, finding little or no increase in risk of stroke associated with levonorgestrel implant use and odds ratios at or near 1.0, and finding low relative risks of cardiovascular disease associated with low-dose progestogens.[50-53]

Combined oral contraceptives have been associated with hypertension.[45,46] Elevated blood pressures have been reported in users of levonorgestrel implants in clinical trials in developed and developing countries.[4,5,31,32,43,54,55] Lack of adequate numbers of long-term controls hindered assessment from clinical trial and method introduction studies. The magnitude of the NPMS, however, permitted quantitative assessment of the risk of hypertensive disease. In the 5-year NPMS, hypertension, defined as blood pressure exceeding 140/90mm Hg, occurred on two or more occasions at the rate of 0.7/1000 woman-years in implant recipients (RR = 1.78; p = 0.09 vs controls).[4,43] Borderline hypertension, defined as blood pressure greater than 140/90mm Hg recorded once or diastolic pressure above 85mm Hg recorded at least twice, occurred at a rate of 0.6/1000 woman-years in patients receiving Norplant® (RR = 1.85, p = 0.09).[4,43] When women with hypertension or borderline hypertension were considered as a single group, hypertensive disease in patients using implants proved significantly elevated compared with controls (p = 0.02). Because patients using implants had more frequent blood pressure measurements, the finding may partially derive from reporting or information bias. If the finding is valid, the attributable annual risk is about one case per 3000 Norplant® users per year. The low incidence of hypertension in both Norplant® and control groups in the NPMS reflect populations of women with low ponderal indices who have had very low utilisation of tobacco at any time in their lives.

The rarity of severe cardiovascular disease in young women and the paucity of cardiovascular events in studies assessing the use of levonorgestrel-releasing implants means that the empirical evidence by which to judge relative risks of cardiovascular disease in Norplant® users remains weak. Available evidence, however, suggests cardiovascular risks are unlikely to be greatly amplified by use of levonorgestrel implants.

Intracranial hypertension, a rare condition reported in users of combined oral contraceptives, was spontaneously reported to the US FDA after commercial distribution of Norplant® began in 1991.[48,56] It was not observed in the NPMS.

5.1.5 Gallbladder Disease

The risk of gallbladder disease was moderately elevated in patients receiving Norplant® compared with controls, according to the NPMS.[4,43] Reports of gallbladder disease in the NPMS were largely confined to two countries, China and Chile. The incidence rate of gallbladder disease, inclusive of gallstones, acute and chronic cholecystitis, was 1.5 per 1000 woman-years in women who initiated treatment with Norplant®. The RR for women initiating Norplant® implants (1.52), was significantly elevated. Among current Norplant® users in the NPMS, however, the incidence of gallbladder disease did not differ significantly from that in women currently using IUDs in the NPMS or those who had undergone sterilisation at the initiation of or during the surveillance study. As with oral contraceptives, a small risk of gallbladder disease may exist for users of levonorgestrel implants.[57]

5.1.6 Pelvic Inflammatory Disease

The use of Norplant® is associated with a reduced risk for pelvic inflammatory disease (PID) compared with controls. Acute PID in the NPMS was diagnosed at a rate of 0.2 per 1000 woman-years during current implant use (table VI). This incidence, adjusted for clinic and age, produced an RR of 0.25 when compared with current IUD users (p < 0.001). The more frequent, but less serious condition, 'unspecified PID' occurred at a rate of 1.7

per 1000 woman-years in Norplant® users; with an RR of 0.45 compared with IUD controls ($p < 0.001$).[4,38,43] The NPMS data suggest that the strict standards developed over the past two decades concerning suitable patients for IUD insertion may be associated with the low incidence of PID in device users. The data from the NPMS support an earlier WHO study which found a similarly low risk of PID in IUD users.[58] Implant contraception, nevertheless, affords the benefit of significantly better protection against PID than do IUDs.

5.1.7 Mental Health

In the US, Wagner initially raised the possibility of an association between Norplant® and major depression, based on seven case reports.[59,60] Evidence from the NPMS, however, does not support the association based on Wagner's small series.

Rates of mental disorders that necessitated hospitalisation or long-term treatment did not differ significantly between implant initiators and controls in the NPMS. Further, if one were to consider the suicides in the NPMS as cases of major depression, the number of cases in the implant and control groups would not differ by more than 1; thus, the rate ratios of major mental disorders and/or of major depression in the NPMS would both be near unity and neither would prove statistically significant.[4,43]

Analyses of less severe depression and mental disorders in possible association with levonorgestrel implants, reveal the role of familial and social stressors in users of hormonal contraceptives including levonorgestrel implants.[61,62] Nevertheless, in the NPMS diagnoses of less severe mental health disorders (e.g. anxiety) were significantly more frequent in patients receiving levonorgestrel implants (5.4 per 1000 woman-years; RR = 2.7) than in controls.[4]

5.1.8 Other Major Disease Conditions

Spontaneous postmarketing reports, litigation reports and other research have suggested that there are correlations between the major components of levonorgestrel implants (the drug and the silicone elastomer) with connective tissue disease, diabetes mellitus and autoimmune conditions, such as systemic lupus erythematosus and rheumatoid arthritis.[63] The NPMS, however, found no significant differences between implants with respect to any of these conditions. A patient in the IUD group had the only diagnosed case of systemic lupus erythematosus in the NPMS.[4,43] The possibility of a relationship between silicone rubber tubing and connective tissue or autoimmune disease had been raised in connection with US breast implant litigation concerning the effects of silicone gels. Meta-analyses of conducted studies indicate no associations.[63]

5.1.9 Carbohydrate and Lipid Metabolism

Dorflinger,[64] in a recent review of implant effects on carbohydrate metabolism, noted that a majority of studies reported an increase in glucose levels and insulin insensitivity after Norplant® initiation. She suggests disparate studies employing different methodologies in different populations have found minor, rather than clinically significant, changes in glucose levels and insulin sensitivity in healthy women.[65-73]

To date, there have been very few studies published to determine the effects of levonorgestrel implants in women with diabetes mellitus or predisposed to diabetes. The NPMS, conducted in populations with low obesity rates, found no significant difference in terms of the incidence of diabetes mellitus between women using implants and controls.[4,43] Despite this finding, the majority of the cases of diabetes were recorded in the implant group, which may warrant further investigation of this adverse event in patients using implants. The attributable risk of diabetes associated with Norplant® in the NPMS, had it been statistically significant, would be 1 per 7300 women per annum.[4,43] It is of interest to note that of the thousands of adverse events during Norplant® use reported in the US

through MedWatch, fewer than two dozen have concerned diabetes mellitus, suggesting the attributable risk may indeed be small.

Diab and Zaki[73] evaluated the effects of contraceptives on carbohydrate and lipid changes in 80 diabetic women. Twenty women received one of four contraceptives: low-dose oral contraceptives, injectable medroxyprogesterone, Norplant® or the copper T 380A IUD. The authors concluded that, among the four hormonal contraceptive regimens, Norplant® was associated with the least amount of changes in carbohydrate and lipid metabolism.

Numerous articles have attempted to evaluate the effects of levonorgestrel and other progestogen-only implants on lipid metabolism.[64,67,68,72-83] The general consensus from these studies is that levonorgestrel implants initially induce marked reductions in lipid levels. These reductions were generally observed in total cholesterol, low density lipoprotein (LDL)-cholesterol, and high density lipoprotein (HDL)-cholesterol, with greater reductions observed in triglycerides. Data from US clinical trials[16,17] of Norplant® and Jadelle® display lipid percentage changes from baseline for women in each of five quintiles, with changes evaluated at 1 month, and at 1, 3 and 5 years (see figure 1 and figure 2). Women in the lowest quintile at baseline of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides had the least changes from baseline at 1 month and remained closer to the baseline values at 1 and 3 years than did women who had higher baseline levels. Percentage alterations in lipids tended to diminish in magnitude up until at least 3 years following placement of the implants. By 5 years, levonorgestrel-related changes in lipid parameters were minimal. Subsequent to removal, changes from baseline were small and similar to the changes in metabolism that may be expected with aging. The data from different investigators have differed primarily with regard to the extent of changes in lipid parameters that accompany the first months and years of levonorgestrel implant use. The quintile analyses in figures 1 and 2 suggest that these differences may partially or strongly reflect different lipid baselines.

A consensus is emerging that lipid changes during contraception with levonorgestrel implants have little overall impact on cardiovascular risks that may be observed either whilst using implants or subsequent to using implants. This view largely derives from the IUD-controlled WHO study of implants and lipids[74] and earlier data with similar, but less extensive, results.[67,68,72,75-79]

5.1.10 Haemostasis

Studies of haemostasis in women receiving Jadelle® or Norplant® have provided little insight into the effects of these implants on clotting factors.[84-91] Some studies, conducted within the same institution, have produced conflicting results, indicating both increases and decreases in platelet counts.[86-90] Studies have reported varying degrees of the amount by which the platelet counts have changed. On the whole, however, the changes in platelet counts, associated with the use of levonorgestrel implants, appear to be small.[84,85,91]

Thrombocytopenia was reported in clinical trials in China[92] and in postmarketing distribution information in the US[93] of levonorgestrel implants. In the NPMS, thrombocytopenia was diagnosed in three Chinese women receiving Norplant® and in no control participants.[4,43] This difference was not significant. Indeed, the incidence of thrombocytopenia in patients receiving Norplant® in the NPMS was <1 per 10 000 woman-years, similar to that for the general population in the US as determined by national hospital discharge surveys of hospitalised thrombocytopenia cases in the US.[4,43]

5.1.11 Liver Function

Conclusions vary concerning the clinical importance of changes observed when assessing liver function in Norplant® and Jadelle®

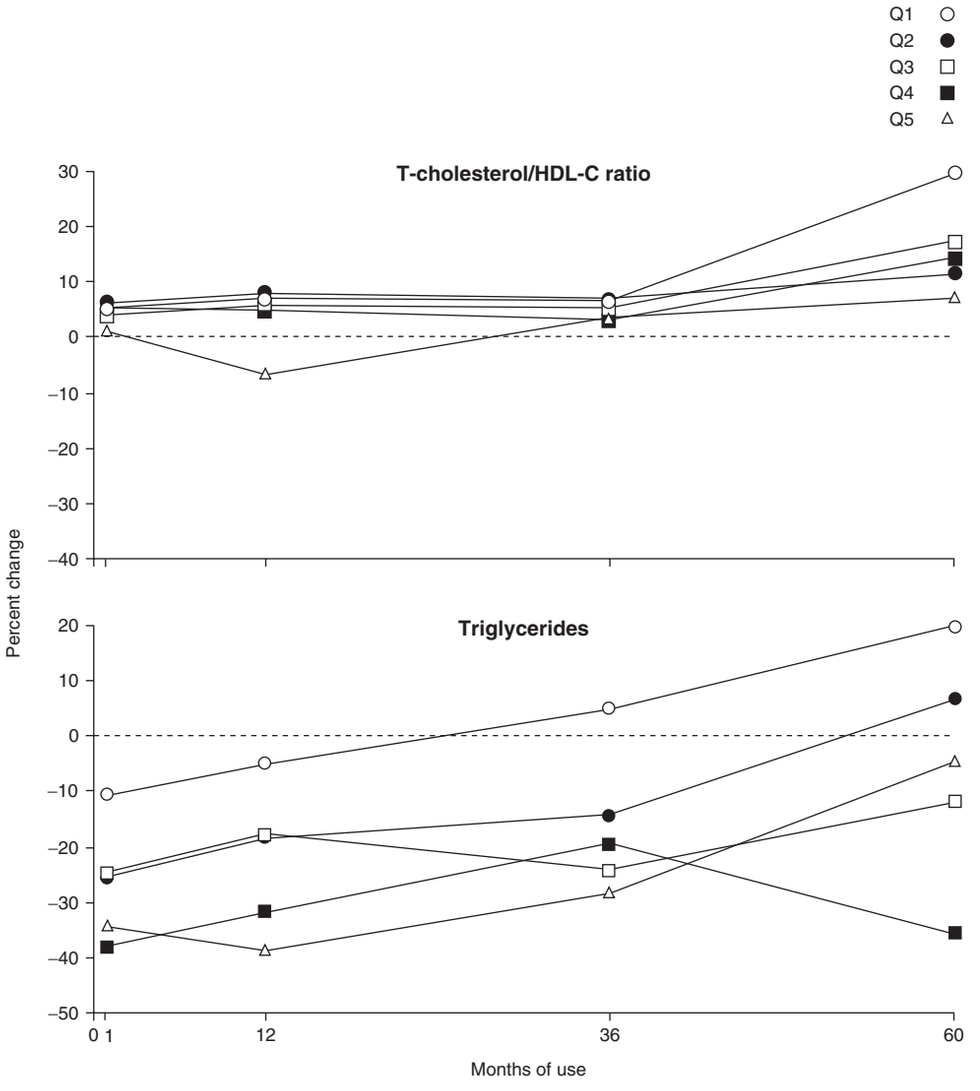

Fig. 2. Percentage change from baseline in total cholesterol/high density lipoprotein-cholesterol (T-cholesterol/HDL-C) ratio and triglycerides by quintile (Q) at baseline. Baseline for each quintile is 0%, and is represented by the dashed line. **Q1** = lowest; **Q5** = highest.

users.[64,67,68,82,84,94] Changes in liver function in women using these implants appear similar to those previously delineated in women using progestogen-only oral contraceptives.[64,95] Abnormal values of liver function are infrequent despite statistically significant increases in mean values in the larger studies.[16,17] In the NPMS neither serious nor non-serious liver conditions were observed at higher rates in Norplant® than in control groups.[4,43]

5.1.12 Bone Mineral Density

Levonorgestrel implant effects, if any, on bone metabolism are small.[96-104] Longitudinal studies have found slight increases in bone mineral density (BMD) in implant users, which matched those of

control subjects not using hormonal contraception[96-101] These results contrasted to decreases in BMD found in users of depot medroxyprogesterone when also studied longitudinally.[96-99,104] A cross-sectional examination of Thai women who had been using levonorgestrel implants or DMPA for 1 year found no statistically significant difference in BMD between the two groups.[102] The study size and design, however, lacked statistical power to find a meaningful difference between groups.

A large cross-sectional WHO study measured BMD in current and past users of Norplant® and in women not using hormonal contraception.[103] The overall BMD of women in the Norplant® group was statistically similar to that of controls. The mean BMD of the ulnar shaft was, however, lower in women who had been currently using Norplant® for 24–36 months than in the controls ($p < 0.05$). Diaz and colleagues[105] have reported on a study of a most vulnerable group – lactating women using levonorgestrel implants. These researchers reported that there was little effect of the drug on bone mass or turnover during or subsequent to lactation.

Banks et al.[104] recently concluded that implant studies have produced conflicting results. The studies outlined in the present review, however, suggest changes in BMD during levonorgestrel implant use are similar to those observed in women not using hormonal contraception. None of the studies indicate marked adverse effects or strong benefits in terms of changes in BMD associated with levonorgestrel implants. Indeed, because estradiol levels fluctuate within normal ranges during levonorgestrel implant use, neither differential gain nor loss of BMD would be expected.

5.2 Other Health Risks

Brache and colleagues have provided a broad review of non-menstrual adverse events during use of progestogen-only implants in clinical trials.[106] These researchers suggest that the intensity of reporting adverse events varies by continent, culture and economic development. Unpublished analyses from the NPMS confirm this statement and extend it to suggest that reports of medical histories and current services vary as well. In the NPMS, reporting was most intense in Latin America, followed by China. With the exception of centres in Bangladesh, reporting intensity was lower in South and Southeast Asia than elsewhere in the NPMS, regardless of the method of contraception initially adopted.[4,38,43] High complaint rates concerning putative effects of a broad range of contraceptives have characterised reproductive health surveys in Bangladesh.[107]

5.2.1 Weight Change

Marked weight changes over a 5-year period are common in women of reproductive age, as metabolic and dietary changes accompany maturation and changes in socio-economic conditions. Weight change, predominantly a gain in weight, is a frequent complaint among patients using levonorgestrel implants.[4,43] Despite the frequency of complaints, few patients (<4%) in long-term studies terminated implant use due to weight gain.[20,22,23,25] In the NPMS over a 5-year period, both reported weight gain and weight loss had significant RRs of 6.9 and 2.6, respectively. The mean weight gain in Chinese patients receiving Norplant® (n = 3000) was 2.5kg. This was 1kg more than the average weight gain of Chinese controls (n = 3000).[4,43] A second, more recent analysis from a large-scale Chinese randomised study reported that women (n = 3000) using either domestic- or foreign-manufactured levonorgestrel implants experienced mean weight changes of 0.6–0.8kg after 3 years of use.[15] Between 49.6 and 52.2% of the women in this study had gained 1kg or more in that time, while between 29.5 and 29.7% had lost 1kg or more.

Weight changes in women of Chinese ethnicity dramatically contrast with the magnitude of change in US women participating in trials. Population Council data have shown that women using levo-

norgestrel implants over a 5-year period experienced mean and median weight increases of 5.2 and 4.7kg, respectively.[16,17] Ten percent of 5-year users in the US experienced weight gains of 12.8kg or more. Dietary habits may explain part of the difference in weight changes exhibited by Chinese and US users of levonorgestrel implants.

5.2.2 Menstrual Disturbances

Pervasive alterations of menstrual function are associated with implant forms of contraception. During the course of using levonorgestrel implants, 75 to 90% of women reported changes in their menstrual patterns.[5] These changes included prolonged episodes of bleeding and/or spotting, irregular bleeding, oligomenorrhoea and amenorrhoea. Heavy bleeding was also reported, however, it was much less common than the other disturbances. Alterations to menstrual patterns represented a substantial proportion of the reasons for discontinuation of implants within 5 years of initiation. In the NPMS, the rates of excessive or irregular menstrual bleeding requiring hospitalisation in patients using levonorgestrel implants were not significantly higher than those for controls.[4,43] On the other hand, complaints concerning excessive, primarily prolonged bleeding or spotting were 3.3 times higher in the implant group than in the control group. The frequency at which amenorrhoea was reported was five times higher in women receiving Norplant® compared with controls.

While bleeding pattern disturbances diminish after longer intervals of levonorgestrel implant use, the prevalence of such problems still remains high.[5] Population Council data suggest that there is a correlation between bodyweight in women using levonorgestrel implants and changes in bleeding patterns. Compared with women of higher weight, women of a lower weight have fewer bleeding episodes and longer bleeding-free intervals, resulting in greater proportions of women with oligomenorrhoea or amenorrhoea. Higher weight is associated with more numerous bleeding days and shorter intervals between bleeding episodes (table VII). These associations appear to hold within as well as between geographic areas. Studies in countries with women of low average bodyweight show high proportions of women experiencing amenorrhoea with Norplant® and with other progestogen-only implants.[108-113] Responses to amenorrhoea during implant use have been quite diverse both among individuals and cultures. Discontinuation rates of implants attributed to amenorrhoea are generally well below those ascribed to prolonged bleeding and spotting (menorrhagia).[5]

Treatment regimens abound for implant-associated bleeding problems.[114-117] These regimens have included oral levonorgestrel, estrogen only, levonorgestrel and estrogen, mifepristone and ibuprofen. While some are effective in the short-term, menstrual problems recur after initial treatment of bleeding pattern disturbances and require treatment anew.

Table VII. Weight-associated bleeding patterns after the first year of use of levonorgestrel implants[17]

Characteristic	Mean for each weight group				
	<50kg (n = 58)	50–59kg (n = 170)	60–69kg (n = 138)	≥70kg (n = 75)	p-Value
No. of bleeding episodes	10.6	11.0	12.4	14.1	<0.01
No. of bleeding days	47.0	48.6	56.3	63.9	<0.01
Duration of bleeding episode (days)	4.8	4.4	4.7	4.5	NS
Longest non-bleeding interval (days)	82.0	74.5	55.8	48.1	<0.01
Longest interval-median (days)	31.4	29.8	25.4	22.6	<0.01

NS = not significant.

Population Council analyses indicate only limited success in long-term implant retention among women who have sought treatment for menstrual disturbances.[16,17]

The incidence of premenstrual tension was twice as great in patients receiving Norplant® as in controls ($p = 0.005$). In contrast, rates of low abdominal pain and dysmenorrhoea were considerably reduced in implant recipients compared with controls ($p \leq 0.001$ each).[4,38]

5.2.3 Haemoglobin and Anaemia

Several studies have assessed haemoglobin changes during levonorgestrel implant use, noting small mean increases in the first 1–3 years.[5,118-121] In Population Council studies conducted in the 1990s, mean haemoglobin levels in 1001 women who received Norplant® and had the implants removed during the course of 7 years increased by 1.8 g/L ($p < 0.0001$) compared with baseline. The increases observed in the first few years tend to be muted after longer durations of use. For instance, women who used implants for a duration of 1–3 years were reported to experience mean increases of 2.2–4.0 g/L in haemoglobin levels. In women who used implants for a longer duration (from 4 to >7 years), however, the increases in haemoglobin levels tended to be less (mean increases ranged from 0.5–1.5 g/L).[17]

Among Norplant® recipients in the 5-year NPMS the incidence of anaemia, defined as haemoglobin <100 g/L, was 1.5 per 1000 woman-years, a rate not significantly different from that in controls (1.9 per 1000 woman-years).[4,43]

5.2.4 Ovarian Cystic Enlargement and Other Genital Tract Conditions

Neither Norplant® nor Jadelle® implants completely suppress ovarian function, even during early use.[7-11] The proportion of women who ovulate or manifest luteal activity increases with the duration of implant use. Luteal activity is defined as rises in progesterone levels that do not reach the threshold considered to be ovulation. Stimulated by follicle-stimulating hormone, ovarian follicles grow, persist, then often fail to regress for several weeks. Such follicles may reach a diameter of 6cm. They may cause pain or may be painful on palpation and may be mistaken for malignancies, ectopic pregnancies or other ovarian problems.

In the NPMS, hospitalisation attributable to ovarian cystic enlargement occurred in patients receiving Norplant® and in controls with the same incidence, 0.2 per 1000 woman-years.[4,38] Complaints of ovarian follicular cystic enlargement, made on an outpatient basis were, however, reported 3.7 times as often in Norplant® recipients (at a rate of 3.2 per 1000 woman-years) than in controls ($p < 0.001$).

Several other reproductive tract disorders evidenced differential effects of the contraceptives used in the NPMS. The incidence rates of leukorrhoea, vaginitis and cervicitis were reduced by about 40% in current implant recipients ($0.001 \leq p < 0.002$ for each).[4,38]

5.2.5 Skin Conditions

Levonorgestrel-associated decreases in sex hormone-binding globulin accompanied by increased circulating levels of androgens could be expected to generate an increased incidence of skin and subcutaneous conditions in women using levonorgestrel implants. In the NPMS, the RR for developing inflammatory skin and subcutaneous conditions (principally contact dermatitis and pruritus) was increased in Norplant® recipients (RR of 3.1) compared with controls. Other skin and subcutaneous tissue diseases (such as acne, alopecia and urticaria) were also increased (RR = 3.4) compared with controls. Incidence rates in the NPMS, however were low for Norplant® users, of the order of four per 1000 woman-years for contact dermatitis or pruritis, and two per 1000 woman-years for alopecia, acne or urticaria.[4] Complaints concerning skin conditions were frequently noted in US postmarketing studies.[122-124] In US trials, slightly less than 1% of

women discontinued the use of levonorgestrel implants because of acne or alopecia.[22,25]

5.2.6 Headache, Dizziness, Malaise, Nervousness and Weight Change

In the NPMS, 88% of all ill-defined conditions, symptoms and signs assigned International Classification of Diseases (ICD)-9 codes 780–789 were recorded as dizziness, malaise/fatigue, weight gain, weight loss and headache. These complaints, ill-defined conditions and symptoms occurred at a rate of 28.4 per 1000 woman-years among Norplant® recipients. The RR was 2.4 when compared with controls. Additionally, Norplant® users reported a feeling of nervousness at a rate of of 1.6 per 1000 woman-years, twice the rate in controls. US levonorgestrel implant studies have observed substantially higher rates for the same set of conditions, both individually and collectively, than did the NPMS.[22,25,122-124] Headache, weight and mood changes have accounted for about half of all non-menstrual medical reasons for discontinuing use of Norplant® and Jadelle® implants in US studies.

5.2.7 Other Health Problems

Significant excess risk of rheumatism, unspecified arthropathies and several respiratory conditions occurred in Norplant® participants in the NPMS.[4,43] The incidence of rheumatoid arthritis, however, did not differ significantly between Norplant® and control method recipients.

6. Placement and Removal Complications

Placement and removal of levonorgestrel implants requires providers be trained to full competence. With respect to placement and removal, Norplant® and Jadelle® are markedly distinct products. Jadelle®'s two rods are easier to place and to remove than are the six capsules that constitute Norplant®.

Norplant® placement in the NPMS was followed by adverse reactions in 1.1% of women using it. Reactions included haematomas, inflammation, pain and one case of superficial phlebitis. IUD insertion complications in the NPMS included one case of uterine perforation, two cases of fainting or dizziness and four cases of severe pain, in addition to expulsions occurring within the following 3 months. Complications of sterilisation procedures included eight wound infections (0.5%), internal bleeding, excessive tubal damage and two episodes of fever.[4,43] The joint occurrence of these events affected 0.7% of women undergoing the procedure. Serious adverse events related to placement appear in the short-term to be of lower incidence in women receiving Norplant® and Jadelle® than in women using IUDs or undergoing sterilisation, as the latter two methods may be associated with uterine perforations, internal haemorrhages or excessive internal damage.[4,43]

There are literature reports of anaphylactic reactions arising from allergic sensitivity to the local anaesthesia given at implant insertion or removal. Infection at the implant site is rare, but its occurrence is not limited to the initial weeks following placement.[125] With both Jadelle® and Norplant® implants, pain or numbness at the implant site may occur. Both transient and persistent pain following placement have been reported. Site pain or numbness was reported by 6.5% of Norplant® subjects in US clinical trials.[25] Discontinuation of implants due to pain at the site were at or near 1% in US trials of Norplant® and Jadelle®.[20,25,123] Population Council trials conducted outside the US reported discontinuation rates due to pain were at one-third the rate of the parallel trials in the US.[20,22] In the NPMS, 57 women (0.7%) were diagnosed with limb pain or myalgia, with 32 indicating pain at the insertion site.[4,43] Eighteen (0.2%) of patients in the NPMS discontinued the use of implants because of pain at the placement site.[43]

Mean removal times for Jadelle® and Norplant® using standard techniques are about 5 and 10 minutes, respectively.[20] Jadelle® implants have a lower incidence of removal complications than do Norplant® implants.[20] In the NPMS, 1.0% of Norplant® removals had complications of any kind. Forty-six percent of these were simply reports of broken capsules.[4,43]

Complicated removals result from peri-implant fibrous tissue, broken implants, deep placement or poorly aligned implants, or placement into muscle tissue. It is generally believed that the more difficult removal cases arise from poor placement. Tissue trauma, wide, long or multiple incisions, or scarring may result. Keloid formation rarely occurs.[126] Long-term use of Norplant® 2 was associated with reports of implant fragility at removal, leading to difficult removals. No such reports have been made in association with Jadelle® or soft tubing Norplant®. Inappropriate placement or inordinately vigorous instrumental searches for non-palpable or deeply placed implants may, in rare instances, lead to nerve damage either during implant use or in the course of removal. Care needs to be taken to avoid tissue or nerve damage in poorly placed or aligned implants.[127-131] No diagnoses of nerve damage occurred during the course of the NPMS or at removal of more than 7500 sets of Norplant® in this study. Removal problems and potential solutions are addressed in a number of papers.[132-137]

While serious adverse events related to placement appear to be fewer with Norplant® and Jadelle®, compared with IUDs or sterilisation, the comparative serious adverse events at removal could potentially be higher with the implants for the reasons that follow. Reversible sterilisation is seldom attempted. After the demise of the Dalkon shield, relatively few reports have appeared in the literature concerning complications of IUD removal. The reports that are found are generally related to broken or missing tails, rather than problems of embedment. Ultrasonography and improved instrumentation aid in the retrieval of IUDs missing tails. Implants are more difficult to remove than to place, particularly when placement is poor. Removal on some occasions may be associated with serious adverse events.[127,129] In the NPMS, however, with over 7500 removals, no serious adverse events were reported.[4,43]

7. Levonorgestrel Implants in Special Population Groups

Several studies have been undertaken on the safety, utility or acceptability of levonorgestrel implants in population subgroups.[138-148] Studies in lactating women who were using levonorgestrel implants were conducted prior to the widespread distribution of implants. Studies in adolescents, of poor or migrant women in more developed countries and of women with asymptomatic HIV were undertaken after general distribution levonorgestrel implants. Immediate post-abortion use of implants has been investigated for safety and acceptability both before and subsequent to widespread distribution.

7.1 Lactating Women: Effects on Infants

Traces of progestogens, taken for contraception, are found in breast milk of lactating women.[138] Controlled studies have examined the effects of levonorgestrel implants on infants of lactating women who initiated Norplant® 4–8 weeks after delivery, a time when breastfeeding of the new infant was well established.[139,140,148] The data from such studies have indicated that levonorgestrel implants have little, if any, effect on infant health and growth; a result different from that when lactating women take combined oral contraceptives.[139,141] Reviews of the effects of various progestogen-only contraceptives on infant health and development (when used by lactating women for extended periods) do not establish the superiority of a specific low-dose regimen or of natural progesterone.[141,142]

7.2 Asymptomatic HIV-1–Infected Women

A cohort of Thai women with asymptomatic HIV-1 infection initiated Norplant® use shortly after abortion or delivery, and were followed for up to 1 year. The investigators concluded that Norplant® had a good safety profile and was effective, well-tolerated and an appropriate method of contraception for these women.[143,144] The investigation did not have contemporary controls.

7.3 Recently Pregnant, Young and Poor Women

Success in delaying or avoiding subsequent pregnancy for 1–2 years has been studied in recently pregnant, young and/or poor women in different settings in the US. Subsequent pregnancies, particularly unwanted pregnancies, were fewer in the Norplant® group compared with women using any other means of contraception or no contraception ($p < 0.05$).[145-147] Because the women in these studies made their own choice of contraception, the results undoubtedly reflect selection effects, but in each study the differences between the groups are impressive. These differences are likely to have been so marked, not simply because of the effectiveness of the implants, but also because of the high continuation rates associated with the implants. Concern has been raised that such results may reflect coercion in the form of refusing removal of the implants at request.[149] This concern, however, seems markedly overblown.[149]

Studies of adolescent and poor women attending family planning clinics in the US and Belgium also note superior continuation rates associated with the choice of levonorgestrel implants.[122-124,150-153] These articles comment on the necessity and utility of giving full counselling and information to all clients about all contraceptive methods available at the clinic, not limiting counselling to the method initially sought by the client. Both as a human right and as a pragmatic way to maintain or improve method and service performance, counselling should be given not only at the initiation of method use, but also at return visits and at the time when a woman may wish to change methods or temporarily cease use of contraception.

7.4 Women Aged >35 Years

One hundred menstruating Thai women over the age of 35 years (mean = 39.7 years) were followed for 1 year after Norplant® placement.[154] Thirty-eight percent experienced amenorrhoea in the year following placement. No adverse health events were reported. The authors suggest that this estrogen-free, highly effective implant should be considered as a form of contraception for women of this age group. The researchers of this study believe that the consideration of the use of levonorgestrel implants in women >35 years of age is neglected by physicians and family planning administrators. This study, however, lacked a control group. With effectiveness comparable to that of sterilisation,[24,26] long-acting levonorgestrel implants may have distinctive advantages for women in the last third of their reproductive life. Population Council and Chinese studies of women initiating use of levonorgestrel implants at or after age 35 years show high tolerability and continuation rates of 90 per 100 per year.[16,20,24,35]

7.5 Post-Abortion Use

Researchers from two studies have characterised immediate post-abortion use of levonorgestrel implants.[155,156] They have found implant use in this circumstance to be associated with few adverse events. However, these studies were limited by small sample sizes. Effectiveness, acceptability and continuation rates associated with the implants were good and comparable with those of levonorgestrel-releasing IUDs.[155]

8. Cost-Effectiveness

The cost effectiveness of levonorgestrel implants and other contraceptives has been examined from two main viewpoints: (i) method costs which includes the costs of the product and the costs of initiation and discontinuation of use as related to a time unit (often the mean duration of use); and (ii) method costs which includes those costs mentioned in (i), to which are added the costs of method failures and adverse effects, and then related to a time unit (often the mean duration of use). Although costs in different settings markedly differ (e.g. between the US public and private sectors, or between costs of pregnancy in lesser or more developed nations), analytical results are perhaps more harmonious than one might expect. Using models that include the cost of pregnancy in the US, Ashraf et al.[157] concluded that sterilisation, IUDs, and levonorgestrel implants, in that order, were the most cost-effective contraceptive methods. A year later using similar models that included costs of method failures, Trussell and colleagues[158] evaluated 15 contraceptive methods. They concluded that over a 5-year period the Copper T 380, vasectomy, levonorgestrel implants and injectable medroxyprogesterone in that order, were the most cost effective. In these analyses, accidental pregnancies with barrier methods, spermicides, withdrawal, and periodic abstinence raised their costs well beyond those of the first four most effective methods. Studies that did not account for the cost of pregnancy or for rates of discontinuation tended to find the long-term costs of IUDs and injectable medroxyprogesterone less costly than levonorgestrel implants.[159-161] These last results included analyses of product costs in Thailand and the US.

Cost-effectiveness analyses yield general guides concerning contraceptive choice to the public, to health authorities and to clinical personnel. They provide less guidance to individuals seeking to make a choice among contraceptives. Young women, i.e. those aged <25 years, who use IUDs, implants or injectable agents will have lower continuation rates and higher failure rates than those stipulated in the models. Moreover, a higher proportion of unintended pregnancies in young women will be simply mistimed rather than unwanted. Women aged 35 years or older will have far higher continuation rates and substantially lower pregnancy rates when using IUDs or implants. As a consequence, the cost effectiveness of these modalities for older women of reproductive age may be even more favourable than that suggested by the analysis of Trussell et al.[158]

Product cost per unit is a major impediment to implant use, particularly in the private sector. Product and placement costs are paid 'up front' at initiation by the consumer. Should a woman, when given appropriate counselling, find that the method is unsuitable for her, she would then be likely, without recourse, to have to pay for expenses incurred in placement and removal and for the drug itself, highly expensive for a short time of use. In the US where many health insurance plans do not reimburse the costs of contraceptive products or services, the comprehensive costs of the method together with the concern about early discontinuation are a deterrent to implant initiation. Purchasers for the public sector may also hesitate to buy, for instance, a thousand sets of implants when, for the same cost, they can purchase many times that number of IUDs or oral contraceptives or condoms.

9. Summary

Norplant® and Jadelle® levonorgestrel implants are among the most effective reversible contraceptives currently available, providing continuous protection against pregnancy for 5–7 years. For women in the last third of their reproductive life, their effectiveness appears to be fully comparable with that of sterilisation.

Placement as well as removal requires competency training. Prospective users need well-informed

counsellors, because in using these, or other progestogen-only contraceptives, sizeable minorities will experience headache, skin problems, dizziness, malaise, mood changes, non-clinical depression, weight change, mastalgia, pelvic pain, and nausea. These effects are similar to those observed when using combined oral contraceptives. Levonorgestrel implants will change menstrual patterns in the great majority of women, as would progestogen-only oral contraceptives. Without adequate pre-counselling concerning menstrual and other adverse effects many women may discontinue their use. In large-scale post-marketing studies, and in US national probability samples, levonorgestrel implants, however, have had high continuation rates, comparable to those of copper IUDs and higher than all other reversible methods of contraception. Apart from counselling, one clear reason that both IUDs and implants have high continuation rates is that they both perform well the task set out for them, averting unwanted or mistimed pregnancies with a minimum of serious health risks and with no need to see health providers for renewed supplies, except at the end of the authorised period of use. Economists in the developed world have shown very favourable cost-benefit ratios in the use of implants and copper IUDs in preventing pregnancies.

A controlled cohort study involving 16 000 women who had used levonorgestrel implants for 5 years has shown there are few safety hazards associated with this contraceptive modality. One additional case of hypertension occurred per year per 3000 Norplant® users than in the same number of IUD users.[4,43] Gallbladder disease was elevated in implant users as compared with controls. This is also the case with oral contraceptives. Conversely, as compared with IUDs, levonorgestrel implants were markedly protective against PID. The NPMS found, however, very low rates of PID in IUD users, an indication of its safety.

Norplant® users have been found to be at no greater risk of life-threatening diseases, of cancers and of cardiovascular disease during long-term use than are IUD users or patients who have undergone sterilisation. The mortality rate in users of levonorgestrel implants does not differ from that in patients using IUDs or those who have undergone sterilisation. The long-term effectiveness of these implants provides women with essentially unmatched protection against serious adverse events associated with pregnancy.

In summary, Norplant®, despite controversies in the US and the UK regarding coercive use among disadvantaged women, adverse effects, and problems associated with its removal, has a good safety profile and is a highly effective and well-tolerated contraceptive for most users.[162] This also applies to Jadelle®.

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