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The performance of levonorgestrel rod and Norplant® contraceptive implants: a 5 year randomized study

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A new contraceptive (LNG rod implants, Jadelle®, Leiras Oy's registered trademark for rod implants) was prospectively evaluated in randomized 5 year comparison with Norplant® (Population Council's registered trademark for contraceptive implants releasing levonorgestrel) capsule implants. The study involved 1198 women at seven centres. No pregnancies occurred in the first 4 years. At 5 years, the cumulative pregnancy rate was 1 per 100 users or less for each regimen. Annual discontinuation rates averaged 11–12 per 100 users ($P > 0.05$), corresponding to 5 year continuation rates of 55.1 for rods and 53.0 per 100 for capsules. Mean annual discontinuation rates for menstrual disturbances were 3.5 and 4.2 per 100 for rod and capsule implants respectively ($P > 0.05$), and mean annual removal rates for medical problems were 3.5 and 3.0 per 100 ($P > 0.05$) respectively. Apart from menstrual problems, headache, weight gain and acne were the principal medical reasons for removal. In proportional hazard analyses, family formation variables, age, parity and desire/non desire for another child, recorded at admission, significantly affected discontinuation rates for major decrement categories and for all reasons combined. Mean rod removal time was half that of Norplant ($P < 0.01$); complications of rod removal were at a lower rate. With these contraceptives indistinguishable in performance except for ease and speed of removal, LNG rod implants appear to be preferable to Norplant for use through 5 years by virtue of relative ease of removal.

Key words: contraception/levonorgestrel/randomized studies/rod implants

Introduction

Up to 6×10^6 women have used contraceptive implants, principally Norplant® (Population Council's registered trademark for contraceptive implants releasing levonorgestrel), since their first regulatory approval 15 years ago (Fraser *et al*., 1998). As reduction in the number of implants was known to facilitate implant placement and removal, the Population Council, in the 1980s, developed a two implant 'rod' system that was equally effective as Norplant implants for a 3 year period, but not for 5 years (Sivin, 1988). However, in non-comparative (Buckshee *et al*., 1993) and comparative clinical trials (Singh *et al*., 1992; Gu *et al*., 1994) among women of low mean body weight, 5 year pregnancy rates and health effects of rod and of Norplant implants were indistinguishable. The difference in results among these large trials was attributed to the greater body weight of women in the Population Council studies.

Further development and distribution of this rod implant was temporarily halted by disappearance from the market of a component needed in its manufacture. When a substitute material yielded equivalent in-vitro levonorgestrel release rates, new clinical trials were initiated, in 1990.

The study detailed below, a 5 year randomized comparative trial of the new rod and Norplant implants has earlier demonstrated the equivalence of the two implant systems for a 3 year period (Sivin *et al*., 1997a) and has led to regulatory approval of the LNG rod implants in Finland, the country of manufacture, and the US. The 3 year randomized trial was extended to 5 years to examine whether the reformulated LNG rod implant would continue to deliver a highly effective drug dose for the longer period, and thus could be viewed as equivalent to the 5 year Norplant capsule implants.

Materials and methods

A set of levonorgestrel rods (LNG rod, Jadelle® Leiras, Turku, Finland) consists of two individual implants, each 2.5 mm in diameter and 4.3 cm in length. Each implant has a drug-releasing core encased in thin-walled silicone rubber tubing. The core contains 75 mg of levonorgestrel and 75 mg of silicone copolymer in a cured mixture. Implant ends are sealed by medical grade adhesive. This reformulated rod contraceptive differs from those manufactured before 1990 in three aspects, the silicone elastomer in the core, the total drug load, and the diameter of each rod. Additionally, procedures for curing the core have been modified. Mean daily levonorgestrel release in the first 5 years is rated as 30 μg. Serum concentrations of the drug in subjects indicated a higher initial release followed by a slow decline (Sivin *et al*., 1997b).

Commercially available Norplant 'soft tubing' implants, now approved in more than 50 countries, served as study controls. A set has six implants, each 2.4 mm in diameter, 3.3 cm in length, containing 36 mg of levonorgestrel. Total drug load is 216 mg per set. Leiras Pharmaceuticals, Turku, Finland, manufactured four production lots

of Norplant and four lots of LNG rod implants for the trials. 'Soft' Norplant implants are made with an encapsulating tubing that contains less inert silica filling than the 'hard' tubing variant which received regulatory approvals in the 1980s. Pregnancy rates with soft tubing capsule implants have been significantly lower than those associated with hard tubing (Sivin, 1988, 1994; Sivin I *et al*., 1998) presumably because 'soft' tubing has higher daily drug release rates during years 3–5.

The protocol and informed consent documents were approved by the institutional ethical review boards at each participating institution, with approvals reviewed annually. In all, 1200 women were scheduled for enrolment with half randomly assigned to each implant. Five clinics were each to enroll 200 subjects and clinics in New York City, USA, and Jyväskylä, Finland, were scheduled to enroll 100 women each.

Subjects were sexually active women in good health, aged 18–40 years, with no contra-indications to Norplant implants and willing to accept random assignment. These volunteers agreed to clinical visits at 1, 3 and 6 months post-placement and half-yearly thereafter, but could withdraw at any time. Histories or current evidence of the following conditions excluded candidates: cancer of any kind, undiagnosed, abnormal genital bleeding, hyperprolactinaemia or bloody breast discharge, hyperlipidaemia, severe cardiovascular problems, mental illness, diabetes mellitus, epilepsy, severe or frequent headaches, pelvic inflammatory disease (PID) since last pregnancy and ectopic pregnancy. Exclusions for PID and ectopic pregnancy were intended to ensure that the fecundity of participants was unimpaired. Candidates initially signed a consent document for a 3 year study duration with provision for extension dependent on pregnancy rates. As cumulative 3 year pregnancy rates were less than one per 100 for each implant regimen, participants continuing at 36 months were requested to sign a new informed consent document to participate up to 5 years.

The protocol stipulated general physical examinations, inspections of the implant site and determinations of pregnancy status at all scheduled visits. At these visits subjects reported on their health, including any hospitalization, since the preceding visit. Pelvic examinations were conducted and cervical smears taken at admission and annually thereafter. To ensure that no pregnancies conceived during study participation had been overlooked, subjects were required to visit their clinic within 2 months of removal to complete the determination of pregnancy status at the end of the study. Adverse event coding followed standard body system delineations (World Health Organization Collaborating Centre, 1993).

Use of other contraceptives was considered a study discontinuation with the exception of short-term employment of non-steroidal contraceptives, e.g. condoms, during treatment of vaginal infections and in a few other transient situations. Oestrogen treatment of a menstrual problem was deemed adjunctive contraception and the subject was considered as discontinued from study by reason of the menstrual problem. Women who adopted other contraceptive methods, e.g. tubal ligation, were considered to have discontinued for a method-related reason when they did not voice their motivation for the change.

Continuation rates in the first 3 years were sufficiently high to ensure that extending the trial would provide reliable data on 5 year pregnancy rates. Given that more than two-thirds of women who enrolled continued through the end of 3 years and no pregnancies had occurred (Sivin *et al*., 1997a), we calculated that if the true cumulative 5 year pregnancy rate of either implant regimen was 1.5 per 100 or less, the chance that we would observe a 5 year pregnancy rate of 3.0 per 100 or more for that regimen was 1% or less.

Simultaneously for a regimen with a true 5 year pregnancy rate of four per 100, the chance of observing a 5 year pregnancy rate of 1.5 per 100 or less was $<1\%$. These considerations, together with the fact that two other trials of the new rod implants were ongoing, led us to believe that the extension of this trial was ethically warranted, in that it could provide sufficiently definitive information about the performance of rod implants over a 5 year term, as well as yielding additional data on the soft tubing Norplant implants.

Differences between implant regimens with respect to characteristics of subjects, removal times and complications were tested by analyses of variance and χ^2 tests. Single decrement lifetables measured survival functions. Differences between lifetable rates were assessed by *t*-tests and log rank procedures. Determinants of discontinuation were examined by.proportional hazard and logistic regression models. Linear regressions tested changes in removal times by duration of use. The cut-off date for this analysis was 31 August 1997, with files updated 1 November 1997.

Subject characteristics

A total of 600 women were scheduled for randomized enrolment to each implant regimen, but two sets of Norplant became contaminated, limiting Norplant enrolment to 598 women. Women randomly assigned to the two implant regimens did not differ in their distributions by age, parity, weight or desire for additional children (Table I).

At no participating institution was the mean admission age >31 years nor was the mean age at any clinic <25 years. Mean parity differed markedly by site, being <2.0 at the Bangkok and New York clinics and almost 5.0 in El Minia, Egypt. Clinics with subjects of low mean parity had high proportions of women who wished, at admission, to have additional children, while the converse was true at institutions with high mean parity. At enrolment, ~20% of the women were uncertain as to whether or not they desired another pregnancy. Mean admission weight was >60 kg at three clinics and <53 kg at one clinic, with an overall mean of 58 kg for each method (Table I).

Results

For 4 years after implant placement no accidental pregnancies occurred. In the fifth year, three women in the LNG rod group became pregnant, as did two Norplant subjects. The corresponding fifth year pregnancy rates were 1.0 and 0.7 per 100 continuing users of the LNG rod and Norplant respectively (Table II). Absent earlier method failures, these were also the cumulative 5 year pregnancy rates. Pregnancy rates for the 5 year period were 0.13 and 0.09 per 100 woman-years of use for LNG rod and Norplant implants subjects respectively. Contraceptive failures occurred to LNG rod subjects weighing 48, 62 and 64 kg, indicating no significant effect of weight as grouped in Table I. On the other hand, both Norplant pregnancies occurred in women who weighed $\geqslant 70$ kg at admission giving a small, but significantly, higher pregnancy rate for that group ($P < 0.001$). Among subjects aged <30 years at admission, the pregnancy rate was 0.15 and 0.16 per 100 woman-years for LNG rod and Norplant subjects respectively. For women aged $\geqslant 30$ years at admission, the pregancy rate was, in the same sequence, 0.11 and 0.00 per 100 years of exposure. One pregnancy in the LNG rod group was ectopic, yielding an ectopic pregnancy rate of 0.4 per 1000 among rod implant users and 0.0 per 1000 for women with Norplant.

A majority of subjects reported menstrual disturbances during the 5 year study course and these were the most frequently given reasons for discontinuation of LNG rod

Table I. Characteristics at admission (percentage distributions)

Age (years)			Parity			Body weight (kg)			Desire for another child		
	LNG rod	N6		LNG rod	N6		LNG rod	N6		LNG rod	N6
<20	4.5	3.9	0	2.3	1.5	<50	18.0	17.9	Yes	24.3	22.2
20–24	21.2	21.2	1	24.9	22.3	50–59	40.5	43.3	Uncertain	20.5	18.2
25–29	34.3	33.4	2	34.9	34.2	60–69	30.2	28.3	No	55.2	59.5
30–34	24.5	26.6	3	20.5	23.3	70–79	8.0	7.4			
35–40	15.5	14.9	4	7.7	7.4	⩾80	3.3	3.2			
			5	9.7	11.4						
All	100.0	100.0		100.0	100.0		100.0	100.0		100.0	100.0
Mean	28.3	28.4		2.45	2.53		58.2	57.8			
Probability		0.616			0.088			0.438			0.308
n	600	598		600	598		600	598		600	598

LNG RC = LNG rod; N6 = Norplant.

Table II. Gross cumulative discontinuation and continuation rates per 100 women using LNG rod or Norplant

Rate or number	Year 3				Year 4				Year 5			
	LNG rod		Norplant		LNG rod		Norplant		LNG rod		Norplant	
	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE
Pregnancy	0.0	–	0.0	–	0.0	–	0.0	–	1.0	0.6	0.7	0.5
Menstrual	11.3	1.4	12.3	1.4	14.5	1.6	15.8	1.6	16.4	1.7	19.2	1.8
Medical reasons	9.6	1.3	7.6	1.2	12.6	1.5	11.0	1.4	15.0	1.7	12.0	1.5
Other, method related	0.4	0.3	1.4	0.5	0.7	0.4	1.4	0.5	1.4	0.6	1.8	0.7
Planning pregnancy	7.7	1.2	7.9	1.2	10.7	1.4	13.3	1.6	14.7	1.7	17.7	1.9
Other personal	4.1	0.9	3.3	0.8	4.8	1.0	5.2	1.0	6.8	1.2	6.9	1.3
Continuation	70.6	1.9	71.1	1.9	63.0	2.0	61.1	2.0	55.1	2.1	53.0	2.1
Percentage lost to follow-up	2.7		2.7		4.0		4.7		7.2		10.2	
Number started year	484		493		410		411		353		339	
Number completed year	410		411		353		339		272		239	

Table III. Discontinuations attributed to menstrual problems

	LNG rod		Norplant		Both
Problem	*n*	%	*n*	%	%
Metrorrhagia	25	4.2	30	5.0	4.6
Menorrhagia, amount increased	18	3.0	20	3.3	3.2
Menorrhagia, duration increased	32	5.3	28	4.7	5.0
Dysmenorrhoea	1	0.2	0	0.0	0.1
Amenorrhoea	3	0.5	11	1.8	1.2
Spotting	3	0.5	4	0.7	0.6
Other	0	0.0	1	0.2	0.1
Total	82	13.7	94	15.7	14.7
Probability (χ^2 test)	0.3442				

implants. Prolonged episodes of vaginal spotting or bleeding, irregular bleeding and perceptions of heavy bleeding were cited by 5, 4, and 3% of LNG rod subjects respectively, as their primary reason for seeking implant removal (Table III). At discontinuation, Norplant subjects cited the same three menstrual disturbances most frequently. Additionally, amenorrhoea led 1.8% of Norplant subjects to request removal. No other menstrual problem was cited as a reason for discontinuation by as many as 1% of women using either implant system. In >90% of the dioscontinuations for menstrual problems with either implant, the subjects rather than the staff made the removal decision.

Cumulative 5 year life-table discontinuation rates for menstrual problems were 16.4 per 100 for the LNG rod group and 19.2 per 100 for the Norplant group (not significantly different, Table II). Annual discontinuation rates ranged from 2.2 to 4.5 per 100 among women with LNG rods and from 3.4 to 5.2 per 100 in the Norplant group. Rate variation by year was not statistically significant for either regimen.

Neither age, parity nor desire for another child at study entry significantly affected menstrual problem discontinuation rates among LNG rod subjects, according to proportional hazard models. Among Norplant subjects, however, univariate and multivariate regression models indicated parity significantly affected the likelihood of discontinuation for menstrual problems ($P < 0.05$).

Cumulative 5 year discontinuation rates for medical reasons were 15.0 and 12.0 per 100 for LNG rods and Norplant respectively (not significantly different, Table II). Annual discontinuation rates for medical reasons ranged from 2.2 to 4.4 per 100 for LNG rod subjects and from 2.1 to 4.1 among women with Norplant, variations that were not statistically significant.

Three conditions, headache, weight gain and acne, jointly represented >50% of the medical removals for each implant type (Table IV). Significant variation by clinic occurred in removals attributed to headache ($P = 0.001$) and to acne ($P < 0.01$), but not to weight gain. Weight gain among continuing users averaged 0.7 kg per year for LNG rod subjects and 0.8 per year for Norplant subjects (Table V). Many subjects

Table IV. Primary medical reason for discontinuation

Condition	Percentage of subjects		
	LNG rod	Norplant	Both
Conditions reported by more than one subject			
Headache	3.50	2.01	2.75
Weight gain	2.33	2.01	2.17
Acne	1.00	0.67	0.83
Hair Loss	0.67	0.33	0.50
Pelvic pain	0.50	0.17	0.33
Depression	0.33	1.00	0.67
Nervousness	0.33	0.00	0.17
Hypertension	0.33	0.50	0.42
Weight loss	0.33	0.00	0.17
Uterine neoplasm/fibroids	0.33	0.33	0.33
Libido decreased	0.17	0.33	0.25
Breast cancer	0.17	0.33	0.25
Conditions reported by a single subject			
Accidental death	0.00	0.17	0.08
Dermatitis	0.17	0.00	0.08
Hypertrichosis	0.17	0.00	0.08
Infection at site	0.17	0.00	0.08
Placement complication	0.00	0.17	0.08
Pain at site	0.00	0.17	0.08
Myalgia	0.17	0.00	0.08
Vertigo	0.17	0.00	0.08
Psychotic depression	0.17	0.00	0.08
Emotional lability	0.17	0.00	0.08
Ulcerative colitis	0.17	0.00	0.08
Dyspareunia	0.17	0.00	0.08
Breast fibroadenosis	0.00	0.17	0.08
Benign brain neoplasm	0.17	0.00	0.08
Myometrial increase	0.17	0.00	0.08
Mastitis	0.00	0.17	0.08
Ovarian disorder	0.00	0.17	0.08
Uterine prolapse	0.17	0.00	0.08
Erythema nodosum	0.00	0.17	0.08
Polyarteritis nodosa	0.00	0.17	0.08
Palpitation	0.00	0.17	0.08
Infectious hepatitis	0.00	0.17	0.08
Upper respiratory tract infection	0.00	0.17	0.08

lost weight compared with baseline, however, and many experienced more substantial weight gain. At the last measurement in the first year, 10% of the women had lost 3–4 kg, while 10% had gained 5–6 kg. At 5 years, 10% had lost 1–2 kg from admission weight while 10% had gained 9–10 kg (Table V).

Medical conditions leading to removal are shown in Table IV. More than two- thirds of the removals for medical reasons were decisions made by the women, rather than by staff recommendations. Removals for 29 different conditions were reported in the first 3 years (Sivin *et al*., 1997a). Later occurring medical discontinuations of LNG rod subjects included hypertrichosis, mood changes and myalgia, while among Norplant subjects newly incident conditions were death from an automobile accident, mastitis, ovarian dysfunction and polyarteritis nodosa. Over the 5 year period, three incident cases of breast cancer were diagnosed, all in women aged 35–40 years at admission. These breast cancer cases represent an incidence of 6.7 per 10 000 years based on the 4478 woman years of observation. A single death occurred, following injuries in an automobile accident. No severe cardiovascular or cerebrovascular diseases were experienced.

In univariate proportional hazard analyses, parity (inversely) and desire for additional children were significantly related to removals for medical reasons in women using LNG rod implants ($P < 0.05$). In multivariate analyses, desire for additional children was the sole significant factor ($P < 0.05$). Discontinuations citing medical reasons were more likely to occur among rod subjects who, at enrolment, desired another child than among subjects who had not wanted or were uncertain about having additional children. Neither age, parity nor desire was significantly associated with medical reasons for discontinuation among Norplant subjects in these regression models.

Removal rates for planned pregnancy proved higher in the fourth and fifth year following placement than in earlier years

Table Va. Mean weight changes from admission

Year	LNG rod			Norplant		
	Mean	SE	*n*	Mean	SE	*n*
1	0.90	0.15	600	0.99	0.15	596
2	2.04	0.18	543	1.91	0.17	538
3	3.12	0.22	460	3.12	0.21	462
4	3.60	0.26	384	3.80	0.23	379
5	3.54	0.26	312	4.14	0.27	302

Table Vb. Weight changes in kg for selected centiles

Year	LNG rod			Norplant		
	10th	50th	90th	10th	50th	90th
1	–4.19	–0.08	5.10	–3.12	0.88	5.56
2	–2.99	1.90	6.73	–2.66	1.87	6.65
3	–2.06	2.76	8.92	–2.01	2.74	8.78
4	–1.49	3.27	9.21	–1.46	3.42	9.71
5	–1.47	3.32	9.23	–1.82	4.23	10.35

Table VI. Cumulative continuation rates per 100 by year by age, parity and desire for children

	Year 3				Year 4				Year 5			
	LNG rod		Norplant		LNG rod		Norplant		LNG rod		Norplant	
Age (years)	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE
<25	64.6	3.9	67.6	3.9	54.7	4.1	55.7	4.2	44.0	4.2	44.8	4.3
25–29	71.4	3.2	68.8	3.3	65.4	3.4	56.9	3.5	57.2	3.5	47.9	3.6
30–40	73.7	2.8	74.9	2.8	66.0	3.1	67.5	3.0	60.0	3.2	61.6	3.1
Significance[a]	NS		NS		NS		NS		$P < 0.01$		$P < 0.01$	
Parity												
0,1	64.1	3.9	63.8	4.1	53.7	4.1	48.6	4.4	42.8	4.2	38.9	4.6
2	70.2	3.2	71.3	3.2	63.8	3.3	63.7	3.4	56.0	3.5	54.3	3.6
⩾3	75.3	2.9	74.7	2.8	68.2	3.1	65.4	3.0	62.0	3.2	59.4	3.2
Significance[a]	NS		NS		$P < 0.02$		$P < 0.01$		$P = 0.001$		$P < 0.001$	
Desire for another child												
Yes	61.0	4.1	62.5	4.3	49.8	4.3	49.0	4.5	38.8	4.3	36.1	4.5
Not sure	61.3	4.4	71.0	4.4	56.3	4.5	60.2	4.8	46.9	4.6	53.1	5.0
No	78.2	2.3	74.3	2.3	71.0	2.5	65.7	2.5	65.0	2.7	58.9	2.7
Significance[a]	$P < 0.0001$		$P < 0.05$		$P < 0.0001$		$P < 0.01$		$P < 0.000001$		$P < 0.0001$	

NS = not significant.
[a]*P* values measure significance of differences among age, parity and desire groups within method and year.

($P < 0.05$ for each regimen). Gross cumulative 5 year discontinuation rates for planned pregnancy were 14.7 and 17.7 per 100 for LNG rod and Norplant subjects respectively (Table II, not significant). For LNG rod subjects age, parity and desire for children were all significant in univariate hazard models ($P < 0.05$), but a desire for additional children, as expressed at enrolment, was the strongest predictor in multivariate models. Parity was the most salient factor affecting removals for planned pregnancy among Norplant subjects.

More than half the women were still using their implants 5 years after admission; cumulative continuation rates were 55.1 and 53.0 per 100 among LNG rod and Norplant capsule subjects respectively (Table II). Annual continuation rates were never less than 86 per 100 for rod subjects nor less than 85 per 100 for women with Norplant (Table VI). During the course of the study, women accumulated 2243.8 years of experience with the rod implants and 2213.5 years with Norplant capsules. Mean duration of use at 5 years was 3.74 and 3.70 years for rod and capsule subjects respectively.

Age, parity and the desire (or not) for additional children significantly affected continuation rates in univariate models for each type of implant ($P < 0.05$), with desire for children dominating in multivariate models, for both regimens. Table VI illustrates the separate impact of these variables on continuation. At 3 years, continuation rates differed significantly by the desire for additional children as stated at enrolment, but not among age or parity groups (Table VI). At 4 years, continuation rates differed significantly by parity groupings, although not so markedly as by desire for children, while age group variation was not significant. Finally, at 5 years, continuation rate differences by age groups became statistically significant, but to a lesser degree than found by parity or desire groups.

At the cut-off date, removal times had been recorded for more than 260 subjects using each regimen (Table VII). Analysis of variance by regimen and year of removal was performed. From incision to closure, mean removal time for the LNG rod implant was 4.8 min, half of the 9.6 min mean in the Norplant group ($P < 0.0001$). Of rod removals, 2% required >15 min; 14% of Norplant removals needed that time and 6.5% required >20 min. Annual mean rod removal times ranged from 4.6–5.0 min, and from 7.8–10.9 min for capsule implants (Table VII). Two-way analysis of variance demonstrated no significant trend toward greater or reduced removal times by year after placement of rod or capsule implants; nor did a one-way analysis of Norplant implants by year. However, regression analysis by month of removal did indicate a significantly decreasing linear trend in monthly removal times for Norplant ($P = 0.035$) but not for the rod implants.

Mean removal times by clinic varied from 1.8 to 7.3 min for rod implants and from 3.4 to 15.7 min for Norplant. Clinics that reported mimimum and maximum removal times for rod implants correspondingly had the minimum and maximum mean removal times for sets of Norplant implants.

Of the 524 removals, 52 (9.9%) were considered to have had complications. Removals afforded some complication in 6.9% of rod and 14.8% of Norplant discontinuations ($P = 0.009$). Duration of use, except as indicated below was not significantly related to the presence or absence of removal complications. Adverse removal events affecting subjects were rare, with only one event per regimen possibly fitting the description of an adverse event. These were failures to locate both rods ($n = 1$) or leaving a small piece of one capsule implant. No woman using the LNG rod or Norplant required multiple incisions for removal, nor was any subject reported to have suffered tissue trauma during removal. Half (17/35) of the Norplant complications were reported by a single clinic ($P < 0.01$) and, somewhat surprisingly, 31% (11/35) of all Norplant removal complications were reported at this clinic in

Table VII. Removal times (min) for LNG rod and Norplant implants

	LNG rod			Norplant			
Year	Mean	SE	*n*	Mean	SE	*n*	*P*
1	4.97	0.48	37	10.96	1.51	39	0.0003
2	4.81	0.47	70	9.79	0.78	56	<0.0001
3	4.88	0.40	64	10.51	0.97	72	<0.0001
4	4.61	0.55	44	8.56	0.69	52	<0.0001
5	4.96	0.57	46	7.82	0.87	44	0.0073
All	4.84	0.22	261	9.59	0.44	263	<0.000001

the third year. The overwhelming majority of reported removal complications involved difficulties experienced by providers because of pericapsular tissue or because of broken or severed implants. These difficulties did not affect subjects except for the greater time needed for removal. The presence of complications increased the time required for removal of Norplant from 8.6 min without complications to 16.1 min with complications ($P < 0.05$). For the LNG rods, removals involving complications averaged 8.0 min in comparison with 4.6 min when no complicating factor was present ($P < 0.05$).

Discussion

Trials during the 1980s revealed two substantive differences between LNG rod and Norplant capsule implants. First, the effectiveness of rod implants, as then manufactured, diminished significantly after 3 years for heavier women. Soft tubing Norplant implants thus provided greater benefits for women seeking longer-term contraception. Second, rates of removal difficulties with rod implants increased with time >3 years and, at several sites, exceeded proportions encountered in Norplant implant removals (unpublished data). These two differences suggested the two products had different contraceptive niches.

The 5 year trial results presented above provide different perspectives. Firstly, long-term removal complications with the new rod implants are markedly fewer than found with Norplant capsule implants, a result attributable to implant redesign and new maufacturing procedures. Secondly, pregnancy rates of these two implant regimens proved to be indistinguishable over 5 years, with both providing a cumulative 5 year pregnany rate of less than 1 per 100 continuing users. The contraceptive effectiveness of each implant regimen appears similar to that of tubal ligation for a 5 year period (Peterson *et al*., 1996).

We noted that the median age of women in this study was lower than that usually observed among women seeking sterilization for birth control, and that age is inversely correlated with pregnancy rates both among sexually active women of reproductive age and among users of contraceptives. Study implant users, aged ⩾30 years at admission, a group more comparable with women seeking sterilization, had a pregnancy rate of 0.5 per 1000 years. While affording similar protection against undesired pregnancy as that given by tubal ligation or vasectomy, these two implant regimens offer nearly immediate restoration of fecundability, an outcome not provided by surgical sterilization methods (Affandi *et al.*, 1987; Sivin, 1988; Sivin *et al*., 1992).

This trial reinforces the indication that levonorgestrel-releasing implants are comparatively free of major health problems. Three incident cases of breast cancer occurred, a rate below that for hospitalization for breast cancer among women of reproductive age in the US (Graves, 1992). Mortality during the trial, one death from an automobile accident, was below the expected two or three deaths, based on mortality statistics for developed countries (US Department of Health and Human Services, 1994). Severe cardiovascular disease or cerebrovascular disease was absent. The single ectopic pregnancy in the study represents a rate of 0.4 per 1000 years of exposure for women with rod implants, and for the two levonorgestrel implant regimens combined, the ectopic pregnancy rate was 0.2 per 1000 years. These rates imply reductions of 80–90% in the risk of ectopic pregnancy compared with non-users of contraception, a strong benefit (Franks *et al.*, 1990, Sivin, 1991a,b; Zhang *et al*, 1994; Meirik, 1997; Skjeldestad, 1997).

In common with intra-uterine devices, implants provide convenience of use, free from daily, monthly or 90-day dependence on re-supply. This convenience and the minimal presence of serious side-effects have yielded continuation rates higher than those associated with any other reversible method, possibly excepting intra-uterine devices, even in the face of prevalent menstrual disturbances (International Committee for Contraception Research, 1978; Sivin *et al.*, 1980; Maragoni *et al*., 1983; Shaaban *et al*., 1983; Meirik, 1997). In the present study, average annual continuation rates were 88.8 per 100 in the LNG rod group and 88.1 per 100 for Norplant subjects. The cumulative continuation rate at 5 years was 55 per 100 for users of the LNG rod implants. This rate appears to reflect the family formation status at entry, as 55% of women with rod implants wanted no additional children. Similarly at entry 59.5% of Norplant subjects wished to have no additional children; and the 5 year continuation rate, 53.0 per 100, was of comparable magnitude. Proportional hazard regression models established that family formation variables, age, parity and desire for children, played significant roles in discontinuation rates not only for planned pregnancy but for menstrual and medical problems and for all reasons combined. The desire for additional children, as expressed at study entry, was the most highly significant family formation factor determining continuation rates.

For several years, concerns have been expressed that implant contraception lends itself to coercion through denial of immedi-

ate access to removal. In Indonesia, which has as many users as the rest of the world combined, a specific concern arose, when the central registry of removals fell far short of the scheduled number. However, a large national probability sample of women then revealed that the registry was deficient. Almost all sampled women reported removals within a week of their request and relatively few women kept implants for >5 years (Fisher *et al*., 1997). Implant convenience, low rates of serious side-effects and family formation variables undoubtedly played strong roles in high continuation rates noted in Indonesia.

More recently, American authors have discussed 'early' or 'premature' discontinuation of implant methods because of side-effects, questioning user satisfaction, method acceptability and cost–benefit ratios, especially as full payment precedes use. Published US studies, however, including several among groups younger than the women in this trial, particularly teenagers, demonstrate, as did the Indonesian study (Fisher *et al*., 1997) that coercion through delay of requested removal is rare while continuation rates have been high, exceeding those of control groups (Crosby *et al*., 1993; Frank *et al*., 1993; Cullins *et al*., 1993; Blumenthal *et al*., 1994; Gerber *et al*., 1994; Polaneczky *et al*., 1994; Dinerman *et al*., 1995; Dugoff *et al*., 1995; Kozlowski *et al*., 1995; Rosenthal *et al*, 1995; Haugen *et al*.,1996; Ricketts, 1996; Berenson *et al*., 1997; Sivin *et al*., 1998). These studies clearly indicate the acceptability and satisfaction of the majority of users with levonorgestrel implants as well as sources of dissatisfaction. High continuation rates with implants combined with great effectiveness provide extended protection against pregnancy and high cost–benefit ratios when compared with pills and injectables (Trussell *et al.*, 1995; Ricketts, 1996).

Counselling received before placement and at scheduled and unscheduled visits thereafter coupled with intrinsic qualities of the method underlie the very high continuation rates that occurred in this study. The great majority of women experienced menstrual disturbances, as previously documented levonorgestrel-releasing implants (Shoupe *et al*., 1991; Biswas *et al*., 1996; Meng and Gu, 1996). Without counselling, undoubtedly a larger proportion of women than than those who terminated for the problem in this study would have done so. Although treatment has been suggested and short-term therapeutic effects of treatment have been satisfactory, data do not as yet yield evidence of markedly improved continuation in the longer term following treatment (Archer *et al*., 1996; Bookasemanti *et al*., 1996; Witjaksono *et al*., 1996). Counselling and continued support from clinic personnel over the 5 year life is an intrinsic part of implant contraception (Vekemans *et al.*, 1997).

Reformulated LNG rod implants afforded providers comparative ease of removal. Providers reported significantly fewer removal difficulties with rods than with capsule implants (6.9 versus 14.8%, $P = 0.009$). No rod removal required >20 min, only 2% required >15 min and mean LNG rod removal time was ~5 min. These are all significant improvements on the removal performance of Norplant implants. Two removal difficulties (0.4%) affecting subjects were reported. Both concerned small implant pieces not removed.

The relative ease of removal of both types of implants in this study is linked to the extensive investigator experience. To achieve similar results new providers require supervised training both in placement and in removal and then need frequent practice of these skills (Sivin and Brown, 1983).

This study has demonstrated an extremely high contraceptive effectiveness for the LNG rod as well as for Norplant capsules over 5 years and a comparable acceptability of the two levonorgestrel implant systems. When regulatory authorities recognize the effectiveness of the LNG implant for a 5 year period of use, the rod implants would appear to be preferable to Norplant for that period by virtue of relative ease of removal.

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