

# Safety and Efficacy of Levonorgestrel Implant, Intrauterine Device, and Sterilization

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NORPLANT

**Objective:** To evaluate safety and efficacy of levonorgestrel-releasing contraceptive implants (Norplant; Leiras Oy, Turku, Finland) in developing countries.

**Methods:** We used controlled cohort methodology. Women attending family planning clinics in eight developing countries selecting Norplant were enrolled, together with women of similar age choosing intrauterine devices (IUDs) or surgical sterilization. Participants were interviewed and examined at semi-annual visits and followed-up for 5 years regardless of change of contraceptive methods. Incidence rate ratios of health events were estimated for initial and current method use.

**Results:** Altogether, 7977 women initiated Norplant, 6625 IUD, and 1419 sterilization. The overall follow-up rate was 94.6% and 78,323 woman-years of observation were accumulated. Pregnancy rates for Norplant, copper IUDs, and sterilization each averaged less than 1 per 100 woman-years.

*From the United Nations Development Programme (UNDP)/United Nations Population Fund (UNFPA)/World Health Organization (WHO)/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland, and The Population Council, New York.*

*Supported by Family Health International (Research Triangle Park, NC), The Population Council (New York, NY), The Rockefeller Foundation (New York, NY) and UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (Geneva, Switzerland).*

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*Norplant is the registered trademark of the Population Council for levonorgestrel-releasing contraceptive capsule implants.*

With two exceptions, no significant excess risk of serious morbidity was detected for Norplant users compared with controls. The incidence of gallbladder disease was higher in women who initiated Norplant use than in controls (rate ratio 1.52, 95% confidence interval [CI] 1.02, 2.27), as was the incidence of hypertension and borderline hypertension in current implant users (rate ratio 1.81; CI 1.12, 2.92). Other new findings were increased risks of respiratory diseases and decreased risks of inflammatory disease of the genital tract in Norplant users compared with IUD users and sterilized women.

**Conclusion:** The study confirms the safety with respect to serious disease and the high contraceptive efficacy of Norplant, copper IUDs, and sterilization. (Obstet Gynecol 2001; 97:539-47. © 2001 by The American College of Obstetricians and Gynecologists.)

Norplant implants (Leiras Oy, Turku, Finland) continuously release levonorgestrel at low concentrations sufficient for effective contraception for 5 years.<sup>1</sup> Regulatory approval of Norplant implants was based on clinical trials indicating a safety profile similar to that of other steroid contraceptives,<sup>1,2</sup> but such trials are seldom sufficient to evaluate rare adverse events of public health significance. Postmarketing surveillance studies of contraceptives have provided important supplements to regulatory trial data, detecting beneficial and adverse effects of public health importance.<sup>3-5</sup> We report findings from a multicenter cohort study of safety and efficacy of Norplant, intrauterine devices (IUDs), and sterilization in developing countries. Fuller details of methods and results will be published elsewhere.

## Materials and Methods

This concurrent cohort study of 5 years' duration followed women initiating use of Norplant implants (index subjects), IUDs, or sterilization (controls). The study

was designed to have at least 80% power to detect a doubling of event rates among implant users from a baseline incidence rate of 1 per 1000 woman-years (95% significance level, two-sided test). Given anticipated method discontinuation rates and losses to follow-up, the study required 8000 index subjects and 8000 controls. After approval by the World Health Organization (WHO) and by local ethical review committees of 32 family planning clinics in eight developing countries, enrollment proceeded from 1987 to 1991. Follow-up was completed in 1997.

All 32 clinics provided Norplant, 17 offered sterilization by locally preferred methods, and all but two offered IUDs (copper or noncopper, but not progesterone-releasing devices). Enrollees were women 20–40 years old, living in the catchment area, who agreed to attend the clinic 6 weeks after enrollment and semi-annually thereafter for 5 years, and were medically eligible for use of any of the three study methods. Exclusion criteria were those applicable to both Norplant and IUDs. For each Norplant subject, a control in the same 5-year age group (eg, 20–24 years) selecting an IUD or sterilization was enrolled. Participants were encouraged to visit the clinics for unscheduled consultations when needed and maintained diaries of contacts with other health providers and facilities. Except for women who discontinued or became pregnant in the initial 6 study months, follow-up continued for 5 years, regardless of whether women discontinued contraception or changed methods.

Breast and pelvic examinations, cervical cytology, and blood pressure and hemoglobin measurements were performed at admission, at contraceptive method change, and when medically indicated. Laboratory tests and diagnostic procedures were performed when medically indicated. At all visits, health information was obtained from interview and diaries of inpatient and outpatient medical care. Surgery and medications were reviewed. Implants were removed at the end of 5 years. Former Norplant users returned 6 weeks later to ensure recording of removal complications.

Complaints, symptoms, and diseases were coded according to the International Classification of Disease, 9th revision (ICD-9).<sup>6</sup> Country coordinators reviewed all health problems, verified diagnoses, and classified each as a major health event or another health problem. Major health events were potentially life-threatening events that required hospitalization, convalescence of at least 1 month, or medication for 3 months or more, left sequelae or led to death. Pregnancy was a major health event. All study record forms were dispatched to the coordinating center at WHO and rechecked. The project coordinator reviewed all major health events, accepting a diagnosis only after receipt of adequate documenta-

tion. Other specific health problem diagnoses—diabetes mellitus; diseases of the eye and adnexa; hypertensive disease; gallbladder disease; myoma uteri; benign tumors and other diseases of the breast; inflammatory diseases of ovary, fallopian tube, pelvic cellular tissues and peritoneum, and uterus; congenital anomalies; and other diagnoses deemed potentially serious—were also reviewed at WHO.

Incidence rates for first events were calculated by the initial method selected and by method in use when the event occurred. Results are primarily presented by initial contraceptive method because the initial method accounted for 84.4% or more of the contraceptive exposure. For health events theoretically or empirically associated with current use of a method, results are presented by method used at the time of the health event. Rate ratios (with 95% confidence intervals [CI]) represent the disease incidence rate in the Norplant group divided by that in the control group. All rate ratios were adjusted for clinic using Poisson regression (STATA 5.0; Stata Corp., College Station, TX).

Health events were analyzed according to ICD-9 subchapters, which group allied diseases, minimizing misclassification effects. Tabular analyses focus on major health events and other health problems with statistically significant rate ratios, and conditions previously reported to be associated with use of hormonal contraception. Because of numerous significance tests, *P* values require cautious interpretation.

## Results

Altogether 16,021 women were recruited, including 7977 Norplant, 6625 IUD (5996 copper IUD, 629 noncopper IUD), and 1419 sterilization initiators (Table 1). Clinics in China enlisted 38% of participants; Egypt, Indonesia, and Thailand each enrolled between 11% and 13%; Bangladesh, Chile, Colombia, and Sri Lanka each contributed between 5% and 8%. Table 1 presents characteristics and follow-up of subjects by initial contraceptive choice. At completion of 5 years, 94.6% of the 16,021 initiators were still in follow-up. Total experience was 78,323 woman-years. Norplant initiators attended more scheduled follow-up visits and had more blood pressure measurements than controls (each *P* < .001). Use of the initial method chosen accounted for 84.4%, 85.2%, and 99.6% of observed woman-years in participants initially selecting Norplant, IUDs, and sterilization, respectively.

Norplant, IUDs, and sterilization initiators used their initially selected method an average of 4.2, 4.1, and 5.0 years, respectively. Implant initiators had a significantly higher 1-year continuation rate than did copper IUD initiators, but continuation rates at 3 years did not differ

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**Table 1. Characteristics of Women at Admission and Extent of Follow-Up**

Characteristic/item	Method used at admission				P	
	Norplant	IUD	Sterilization	All controls	N vs I vs S*	N vs controls†
Number of women	7977	6625	1419	8044		
Age (y)	28.5 ± 4.5	28.5 ± 4.7	29.6 ± 4.1	28.7	<.001	<.05
Age at first delivery (y)	22.4 ± 3.9	23.2 ± 3.8	21.2 ± 3.6	22.8	<.001	<.001
Parity	2.1 ± 1.6	1.9 ± 1.5	2.9 ± 1.3	2.1	<.001	0.15
Body weight (kg)	53.7 ± 10.5	55.6 ± 11.0	51.7 ± 9.8	54.9	<.001	<.001
Last pregnancy full term (%)	71.5	71.1	91.6	74.7	<.001	<.001
Secondary/higher education (%)	56.4	67.9	28.7	61.0	<.001	<.001
Ever smoked (%)	6.9	5.6	10.6	6.5	<.001	0.31
Ever drank alcohol (%)	5.0	4.2	4.2	4.2	<.001	<.001
Ever used contraception (%)	85.4	75.9	74.8	75.7	<.001	<.001
Ever used oral contraceptives (%)	37.8	28.3	27.6	28.2	<.001	<.001
Censored for early discontinuation (%)	1.2	3.1	0.3	2.6	<.001	<.001
Moved, refused follow-up, or lost to follow-up (%)	3.2	3.8	3.2	3.7	<.001	0.10
Completed full 5-y follow-up (%)	95.6	93.1	96.5	93.7	<.001	<.001
Woman-years of observation	39,337	31,915	7071	38,986		
Woman-years per woman in study	4.9	4.8	5.0	4.8		

\* P value for differences between Norplant, IUD, and sterilization initiators (2 df).

† P value for differences between Norplant initiators and controls (1 df).

and at 5 years were higher for IUD than for implant initiators (Table 2). Annual pregnancy rates during implant, copper IUD, and sterilization use were less than 1 per 100 woman-years. The 5-year cumulative life table pregnancy rate of copper IUD subjects was markedly less than that of women who used noncopper IUDs, but higher than that of implant subjects (each  $P < .001$ ) (Table 2).

Ectopic pregnancy rates were below 1.0 per 1000 woman-years among current users of sterilization, implants, and copper IUDs, and significantly below the rate of 2.7 per 1000 woman-years in women using no contraception at time of conception.

The study recorded a total of 34 deaths, 0.43 per 1000 woman-years, of which 16 occurred among Norplant initiators. Twenty-two deaths were caused by accidents ( $n = 11$ ), suicides ( $n = 8$ ), and homicides ( $n = 3$ ).

Disease-related deaths were from cancers of the breast, lung, rectum and stomach, acute monocytic leukemia, non-Hodgkins lymphoma, intracranial hemorrhage, bronchial asthma, status epilepticus, secondary cardiomyopathy, sudden ill-defined cardiorespiratory failure, and septic abortion. The adjusted rate ratio for overall mortality by initial method for Norplant compared with controls was 0.86 (CI 0.44, 1.69). Adjusted rate ratios for disease-related or other causes of death were not significant.

With the exception of pregnancy (mostly after cessation of contraception), all incidence rates of major health events or serious diseases by ICD-9 subchapters were below 2 per 1000 woman-years. With the exception of digestive system diseases, none of the rate ratios of ICD-9 chapters and subchapters differed significantly from unity with respect to serious disease. Detailed

**Table 2. Five Year Rates (per 100) of Discontinuing Initial Study Method**

Reason/item	Norplant		Copper IUD		Noncopper IUD		Sterilization	
	Rate	SE	Rate	SE	Rate	SE	Rate	SE
Pregnancy*	1.5	0.2	4.2	0.3	13.0	1.4	0.7	0.2
Menstrual problems	13.7	0.4	6.4	0.3	4.7	0.9	0.0	0.0
Other medical	9.1	0.4	5.4	0.3	1.1	0.4	0.0	0.0
Expulsion	0.0	0.0	3.6	0.3	4.3	0.8	0.0	0.0
Device complications†	<0.1	<0.1	0.1	<0.1	0.0	0.0	0.0	0.0
Planning pregnancy	6.8	0.3	9.8	0.4	5.5	1.0	0.2	0.1
Other personal reasons	7.3	0.3	5.3	0.3	1.6	0.6	<0.1	<0.1
All reasons	33.2	0.5	30.5	0.6	27.0	1.8	1.0	0.3
Method continuation rate	66.8	0.5	69.5	0.6	73.0	1.8	99.0	0.3

SE = standard error.

Cumulative life table discontinuation rates per 100 at 1826 days.

\* Rate includes 11 pregnancies in which conception may have occurred before admission ( $n = 6$ ) or immediately subsequent to removal ( $n = 5$ ).

† Includes expulsion of implants.

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**Table 3. Major Health Events by ICD-9 Chapters and Selected Subchapters**

	ICD-9 codes	Norplant		Controls		Adjusted* rate ratio (Norplant/controls)		
		Events	Rate <sup>†</sup>	Events	Rate <sup>†</sup>	RR	95% CI	P
Neoplasms	140-239	74	1.9	68	1.8	1.08	(0.78, 1.51)	.64
Invasive malignancies	140-208	7	0.2	8	0.2	0.88	(0.32, 2.43)	.81
Benign neoplasms	210-229	60	1.5	53	1.4	1.13	(0.78, 1.63)	.53
Carcinoma in situ	230-234	8	0.2	7	0.2	1.13	(0.41, 3.12)	.81
Endocrine, nutritional and metabolic	240-279	24	0.6	16	0.4	1.49	(0.79, 2.81)	.22
Disease of other endocrine glands	250-259	11	0.3	5	0.1	2.23	(0.78, 6.42)	.14
Nervous system and sense organs	320-389	20	0.5	10	0.3	2.00	(0.93, 4.27)	.07
Eye and adnexa disorders	360-379	8	0.2	2	0.1	4.05	(0.86, 19.08)	.08
Circulatory system	390-459	58	1.5	41	1.1	1.40	(0.94, 2.08)	.10
Hypertensive disease	401-405	27	0.7	18	0.5	1.49	(0.82, 2.71)	.19
Vein and lymphatic disease	451-459	15	0.4	7	0.2	2.07	(0.84, 5.07)	.11
Digestive system	520-579	117	3.0	74	1.9	1.58	(1.18, 2.11)	.002
Other diseases, digestive system	570-579	68	1.7	42	1.1	1.62	(1.10, 2.38)	.01
Genitourinary system	580-629	78	2.0	80	2.1	0.96	(0.70, 1.30)	.77
Inflammatory, female genital tract	614-616	16	0.4	23	0.6	0.68	(0.36, 1.28)	.23
Other diseases, female genital tract	617-629	46	1.2	39	1.0	1.15	(0.75, 1.77)	.51
Musculoskeletal and connective tissue	710-739	16	0.4	11	0.3	1.45	(0.67, 3.12)	.35
Arthropathies and related disorders	710-719	10	0.3	4	0.1	2.48	(0.78, 7.91)	.13

ICD-9 = International Classification of Diseases, 9th Revision; RR = relative risk; CI = confidence interval.

\* Adjusted for clinic.

† Rate per 1000 woman-years.

analyses of ICD-9 3-digit and 4-digit diagnoses of major health events showed, with few exceptions, no pattern of significantly increased or decreased risk among users of the different contraceptive methods.

Table 3 shows, by ICD-9 chapters and subchapters, incidence rates and rate ratios for major health events for which previous reports have indicated possible modification of risk by hormonal contraception or for which further analysis showed significant differences of the rate ratio. Rates of invasive neoplasms did not differ by contraceptive group. Cases included five breast malignancies, four in Norplant initiators. Benign neoplasms were classified as major health events, and carcinoma in situ occurred at similar rates in Norplant users and controls. Nine of 12 diagnoses of diabetes mellitus (subchapter Other Endocrine Glands) were in Norplant initiators (eight current users) (Table 3); the rate ratio adjusted for clinic, age, and weight for current use of Norplant was 2.42 (CI 0.73, 8.05). Results were similar when analyzed by initial contraceptive method.

Eight diagnoses in Norplant initiators of Eye and Adnexa Disorders (ICD-9 360-379) included single cases of retinal vascular occlusion, focal chorioretinitis, glaucoma, cataract, foreign body, suspected optic neuritis associated with hyperthyroid thyroiditis, and two of keratitis. One case each of macular changes and eyelid abscess occurred in controls.

Circulatory System Diseases included one ischemic and one hemorrhagic stroke, both in implant users. Hypertension, defined as blood pressure greater than

140/90 mmHg on more than one occasion, was diagnosed at a higher rate in current implant users (0.7 per 1000 woman-years in Norplant users) than in controls (0.4 per 1000 woman-years) (rate ratio 1.78; CI 0.93, 3.40). Borderline hypertension, another health problem diagnosis, defined as systolic blood pressure exceeding 140/90 mmHg on one occasion or diastolic pressure exceeding 85 mmHg more than once, had similar incidence rates as hypertension, and a similarly elevated, but nonsignificant rate ratio of 1.85 (CI 0.90, 3.78). The rate ratio for hypertension and borderline hypertension combined was 1.81 (CI 1.12, 2.92). One current Norplant user developed deep vein thrombosis of the leg. Other major health event diseases of veins were dominated by surgery for varicose veins and hemorrhoids, neither condition showing significant differences between Norplant users and controls.

In the subchapter Other Diseases of the Digestive System, 101 diagnoses referred to gallbladder diseases (gallstones, acute and chronic cholecystitis, 61 in Norplant initiators) with an adjusted rate ratio of 1.52 (CI 1.02, 2.27). For current Norplant users and controls, incidence rates of gallbladder diseases were 1.5 and 1.1 per 1000 woman-years, respectively, with an adjusted rate ratio of 1.31 (CI 0.87, 1.96).

Inflammatory Diseases of the Genital Tract included acute pelvic inflammatory disease (PID) as previously defined.<sup>7</sup> The incidence was less than 1 per 1000 woman-years. Acute PID was diagnosed in current implant users at one-third the crude rate in current IUD users

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with an adjusted rate ratio of 0.25 (CI 0.10, 0.63). Diagnoses of acute PID not meeting the criteria given above were classified as "unspecified" PID, another health problem diagnosis, with a rate ratio of 0.54 (CI 0.39, 0.74) for current implant users compared with all controls. Comparison between current users of Norplant and IUDs gave a similar result.

Hospitalization for ovarian cysts or excessive bleeding (subchapter Other Female Genital Tract Diseases) occurred with similar frequency in implant and control groups. Arthropathies and Related Disorders included one diagnosis each of systemic lupus erythematosus in an IUD initiator, systemic sclerosis in a Norplant initiator, and dermatomyositis in an IUD initiator. Nine cases of rheumatoid arthritis occurred with an incidence rate in Norplant users of 0.2 per 1000 woman-years and a nonsignificant rate ratio of 3.46.

Table 4 provides data on other health problems, incidence rates, and adjusted rate ratios of the 17 ICD-9 subchapters in which the rate ratio for Norplant users differed significantly from unity. Sixteen subchapters had rate ratios significantly above unity and one was significantly below 1.0. We examined which diagnosis(es) accounted for the differences in incidence rates (see Table 4).

Diagnoses of anxiety or depression largely accounted for the excess incidence in Norplant users in the subchapter Neurotic and Personality Disorders. Difficulties in distinguishing between migraine (ICD-9 346) and common headache (ICD-9 784) led us to combine them. The adjusted rate ratio for migraine-headache for Norplant users was 3.44 (CI 2.83, 4.18). In the subchapter Eye and Adnexa Disorders, seven current Norplant users and one sterilized woman had short-term visual disturbances and low vision associated with fatigue, headache, or both, with a rate ratio of 9.46 (CI 1.16, 77.0).

In the Acute Respiratory Tract Infections subchapter, diagnoses were evenly distributed, all 3-digit codes except tonsillitis and acute bronchitis were reported more often in initial or current Norplant users than in controls. Conditions leading to elevated rate ratios for Norplant subjects in other subchapters of respiratory diseases are detailed in Table 4. Unspecified mammary dysplasia and signs and symptoms of the breast (subchapter Disorders of the Breast) were reported significantly more often for Norplant initiators than controls, with rate ratios of 1.56 (CI 1.24, 1.97) and 1.93 (CI 1.39, 2.70), respectively.

Norplant users had significantly lower incidence rates of Inflammatory Disease of Female Pelvic Organs. Adjusted rate ratios with current use of Norplant for unspecified PID, cervicitis, and vaginitis were all significantly below unity with rate ratios between 0.45 and

0.62. Norplant users experienced significantly higher rates of amenorrhea and premenstrual tension, but lower rates of dysmenorrhea and low abdominal pain, than did controls. Norplant subjects experienced higher rates of contact dermatitis and pruritus and of alopecia, acne, and urticaria, than controls in diagnoses in two subchapters of Skin and Subcutaneous Tissue. The subchapter Rheumatism, Excluding the Back encompassed 65 diagnoses of other disorders of soft tissues (ICD-9 729) in Norplant initiators, and included 32 women locating the disorder to the arm of the implant.

Five symptoms—dizziness, malaise and fatigue, weight gain, weight loss, and headache—accounted for 88% of Norplant-associated events in the subchapter Symptoms. Current Norplant users had significantly elevated rate ratios for each of the five symptoms. In China, where 94% of subjects had body weight recorded at baseline and at 5 years, the average weight increase was 2.5 kg in current Norplant users compared with 1.5 kg in controls ( $P < .001$ ). The diagnosis nervousness (ICD 799.2) accounted for the elevated rate ratio of the subchapter Ill-defined and Unknown Causes of Morbidity and Mortality.

## Discussion

Based on a 5-year follow-up of women with long-term exposure, this study provided quantitative evidence of the safety of Norplant implants, IUD contraception, and tubal sterilization. We found no differences between Norplant and controls with respect to major disease, with three exceptions. Differences concerned moderately elevated risks in Norplant initiators of gallbladder disease (rate ratio 1.52), of raised blood pressure (rate ratio 1.81) in current Norplant users, and lower risk of acute pelvic infection (rate ratio 0.34), also in current implant users. Norplant, copper IUDs, and sterilization provided excellent protection against unplanned pregnancy and considerably reduced the risk of ectopic pregnancy. Each of these three contraceptive methods had annual pregnancy rates averaging less than 1 per 100 woman-years. The reversible methods, Norplant and IUDs, had annual continuation rates above 90 per 100 women entering each year.

The incidence of major health events was low. Women admitted to the study were screened and had no history, signs, or symptoms of pre-existing major medical problems, presumably making them less likely to experience severe disease than an unselected group. Although underreporting of major health events cannot be excluded, semi-annual visits made it relatively unlikely that major events would be forgotten. Additionally, the follow-up rate was high (94.6% of initiators were observed for 5 years). Differing from two previous

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**Table 4. Other Health Problems by Selected ICD-9 Subchapters**

Diagnosis	ICD-9 codes	Diagnoses principally contributing to rate ratio (ICD-9 code)	Norplant		Controls		Adjusted* rate ratio (Norplant/controls)		
			No.	Rate†	No.	Rate†	RR	95% CI	P
Mental disorders									
Neurotic and personality disorders	300-316	Anxiety (300.0), depression (311)	209	5.4	89	2.3	2.70	(2.11, 3.46)	<.001
Nervous system and sense organs									
Other disorders of the central nervous system	340-349	Migraine (346)	96	2.5	39	1.0	2.50	(1.73, 3.63)	<.001
Peripheral nervous system	350-359	Upper limb mononeuropathies (354), inflammatory and toxic polyneuropathies (357)	17	0.4	4	0.1	4.65	(1.56, 13.84)	.01
Eye and adnexa	360-379	Visual disturbances (368), low vision (369.2)	34	0.9	17	0.4	2.13	(1.19, 3.82)	.01
Respiratory system									
Acute respiratory infections	460-466	Acute respiratory infections (460-6)	226	5.8	164	4.3	1.38	(1.13, 1.69)	.01
Other diseases of upper respiratory tract	470-478	Chronic pharyngitis (472), chronic sinusitis (473)	36	0.9	20	0.5	1.78	(1.03, 3.08)	.04
Pneumonia and influenza	480-487	Influenza (487)	51	1.3	18	0.5	3.24	(1.89, 5.56)	<.001
Obstructive pulmonary diseases	490-496	Chronic bronchitis (491), asthma (493)	54	1.4	20	0.5	2.67	(1.60, 4.46)	<.001
Genitourinary system									
Disorders of breast	610-611	Unspecified dysplasia (610.9), signs and symptoms (611.7)	330	8.6	195	5.1	1.71	(1.43, 2.04)	<.001
Inflammatory disease of female pelvic organs	614-616	Unspecified PID (614.9), cervicitis (616.0), vaginitis (616.1)	628	16.7	908	24.9	0.65	(0.59, 0.72)	<.001
Other disorders of female genital tract	617-629	Dysmenorrhea (625.3), premenstrual tension (625.4), low abdominal pain (625.8,-9), bleeding disorders (626.2,-4,-6,-8,-9)	2701	89.3	1313	37.5	2.55	(2.38, 2.72)	<.001
Skin and subcutaneous tissue									
Other inflammatory conditions of skin and subcutaneous tissue	690-698	Contact dermatitis (692), pruritus (698)	137	3.5	45	1.2	3.09	(2.20, 4.32)	<.001
Other diseases of skin and subcutaneous tissue	700-709	Alopecia (704.0), acne (706.1), urticaria (708)	93	2.4	28	0.7	3.35	(2.20, 5.12)	<.001
Musculoskeletal system and connective tissue									
Arthropathies and related disorders	710-719	Unspecified arthropathies (716), unspecified joint disorders (719)	32	0.8	12	0.3	2.60	(1.34, 5.05)	.01
Rheumatism, excluding the back	725-729	Other disorders of soft tissues (729.1,-5)	93	2.4	21	0.5	4.71	(2.93, 7.56)	<.001
Symptoms, signs, and ill-defined conditions									
Symptoms	780-789	Dizziness (780.4), malaise and fatigue (780.7), weight gain (783.1), weight loss (783.2), headache (784.0)	1030	28.4	498	13.2	2.35	(2.11, 2.62)	<.001
Ill-defined and unknown causes of morbidity and mortality	797-799	Nervousness (799.2)	63	1.6	31	0.8	2.02	(1.32, 3.11)	.001

ICD-9 = International Classification of Diseases, 9th Revision; RR = relative risk; CI = confidence interval; PID = pelvic inflammatory disease.

\* Adjusted for clinic.

† Rate per 1000 woman-years.

similar studies,<sup>4,5</sup> this study actively traced all women overdue for scheduled visits and traced hospital and outpatient clinic records when events were reported. We cannot rule out that where induced abortion was illegal or socially undesirable, underreporting of pregnancies terminated by abortion may have occurred. Underreporting would have produced an overestimate of the efficacy of each contraceptive method.

Baseline differences between women choosing long-term contraception or sterilization did not substantially influence incidence rates of nonreproductive health events. Rates adjusted for baseline characteristics were similar to crude rates. All rate ratios were adjusted for clinic, in anticipation of substantially different social conditions and health care characteristics in the participating countries and clinics.

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Differences in reporting of health events among contraceptive groups are possible. Norplant was a new method, women may have been more alert to report signs and symptoms during implant use and providers more likely to record them than with familiar contraceptive methods, as reported from similar studies.<sup>3-5</sup> Norplant users also attended more scheduled follow-up visits than controls. However, reporting of less serious disease (other health problems) is more likely to have been affected by such bias than more serious disease (major health events). The concept of a major health event was defined a priori and referred to serious conditions. Whether or not a health event was considered a major health event was indicated by country coordinators who were experienced clinicians; the project coordinator made the final decision to classify a health problem as a major health event without knowledge of the woman's initial or current contraceptive method.

The intensity of reporting of diagnoses varied between countries and between clinics within countries. True differences in disease incidence contributed to the variation; for example, gallbladder diseases were reported almost exclusively from Chile and China. Differences in self-perceived morbidity between cultures and regions,<sup>8</sup> differences in staff diligence in probing, and differences in prevalent rumors about different contraceptive methods would also contribute to enhancing variation, particularly for other health problems. Clustering of diagnoses also occurred. Colombian centers with 6.2% of the study's participants reported 65.4% of all migraine but only 1.6% of other headaches. Intense reporting of other health problems such as headache or malaise by sterilization participants in Bangladesh resulted in higher overall incidence rates for these conditions in sterilization than in IUD subjects. High rates of symptom reporting have been found previously in sterilization users in Bangladesh national surveys.<sup>9</sup> Moreover, in absence of central review of most other health problem diagnoses, these do not have the same consistency across countries as major health event diagnoses. In view of such limitations, conclusions based on other health problems may be substantially more tenuous than those based on major health events.

Most deaths in the study were due to accidents, suicide, or violence, and few were due to health problems. Two deaths were related to the reproductive system; one woman initiating Norplant had the implants removed and died 1 year later from septic abortion, and one woman died from clinically diagnosed breast cancer. All-cause mortality was 0.43 per 1000 woman-years, similar to that found in comparable studies in developed countries.<sup>3-5</sup>

This study had low statistical power with respect to cancer and severe cardiovascular disease. Nonreproductive cancers were rare and seem to have no specific pattern. Five breast cancers occurred, an overall incidence rate of 0.07 per 1000 woman-years. Based on reported age-specific incidence rates of breast cancer<sup>10</sup> and the age-distribution in this study, 8.6 breast cancers would have been expected during follow-up. Four of the five breast cancers were diagnosed in China, where 2.8 breast cancers would have been expected.<sup>10</sup>

The three serious cardiovascular events that occurred in Norplant subjects provide little evidence of increased risk. Expected events in 39,337 woman-years of exposure were 1.3, 1.3, and 0.05 cases of stroke, venous thromboembolism, and myocardial infarction, respectively,<sup>11</sup> and two, one, and zero events were observed. Concerns that Norplant may be associated with increased risk of stroke derived from spontaneous reporting in the United States.<sup>12</sup> However, one study from the United States<sup>13</sup> indicated an odds ratio for stroke of 1.0 during current Norplant use, and odds ratios of 1.01 and 1.07 were found in a multicenter case-control study of women using oral and injectable progestogen-only contraceptives, respectively.<sup>14</sup> The present study's data are consistent with other epidemiologic studies, jointly indicating no material increase in risk of stroke with Norplant use. The overall incidence of hypertension was low in all contraceptive groups. When hypertension was combined with borderline hypertension, the rate ratio was significantly elevated. Because users of Norplant had more frequent measurements, the elevated rate ratio may partially reflect reporting bias.

Investigators have reported effects of Norplant on glucose tolerance,<sup>15</sup> but long-term trials have not previously reported Norplant users developing diabetes.<sup>12</sup> We found a small and nonsignificant excess in the incidence of diabetes. Several other postulated associations of disease with these levonorgestrel-releasing silicone rubber implants were not confirmed. These include associations of Norplant use with major depression<sup>16</sup> and with severe connective tissue diseases from silicone exposure.<sup>17</sup> No association was found between use of Norplant and severe depression, although mood disorders were more frequent, as also reported for other hormonal contraceptives.<sup>4,18</sup> Systemic lupus erythematosus was not associated with use of Norplant silicone implants in this study, in agreement with a recent meta-analysis.<sup>17</sup> Rheumatoid arthritis was diagnosed more often in Norplant initiators than controls, but the difference was not statistically significant. This elevation contrasts with some studies that found combined oral contraceptives to protect against rheumatoid arthritis, although it is unclear if the protective effect is real.<sup>19</sup>

The rate ratio for gallbladder disease was significantly elevated for Norplant initiators compared with controls. Use of combined oral contraceptives has been reported to be weakly associated with gallstone disease.<sup>20</sup> The data from this study are compatible with a similarly weak association between Norplant use and gallbladder disease. As previously observed, thrombocytopenia occurred in Norplant users in China.<sup>2</sup> The three cases we found did not represent a significant increase when compared with controls, and the incidence in Norplant subjects was similar to what can be estimated from hospital discharge studies in the United States.

We suspect that the elevated rate ratios for several diagnoses categorized here as "other health problems" are due to an unknown extent to reporting bias. However, the results reconfirm several established findings. Among these are the associations of Norplant with increased risks of irregular or excessive menstrual bleeding, amenorrhea, and ovarian cystic enlargement not requiring hospitalization. Headache, mood disturbances, including anxiety and depression, breast symptoms, and weight gain have been linked previously with hormonal contraceptives,<sup>18</sup> and were among the more frequent other health problems. These problems were all reported significantly more frequently in Norplant than in control groups. Short-term visual disturbances related to headache have been associated with oral contraceptive use<sup>18</sup> and were observed among a few current Norplant users. The risk of unspecified PID, dysmenorrhea, and low abdominal pain was found to be about half as great or less in Norplant users than in controls. We also observed contact dermatitis and other eczema, pruritus, and urticaria more frequently in the implant group. Problems of acne and alopecia have previously been reported for Norplant users.<sup>1,2</sup>

The study provided novel findings that several lower genital tract disorders, namely cervicitis, leukorrhea, and vaginitis, were significantly less frequent in implant than in control groups. Findings of increased risk in Norplant users of several respiratory conditions, for example influenza, chronic bronchitis, and asthma, are similarly novel.

This postmarketing surveillance study has demonstrated the feasibility of large multicenter cohort studies in developing countries. The data indicated low incidence rates for most health problems of a less serious nature, but demonstrated a pronounced tendency toward higher incidence rates among Norplant users. For more serious health events, the findings were generally reassuring. For health concerns such as diabetes and thrombocytopenia, and for postulated silicone-related disease, the results suggest there is little or no association with Norplant use. There was no substantive

evidence of increased risk of cancer and cardiovascular disease, but the absolute number of events was small. Apart from a weak association between Norplant use and gallbladder disease, and possibly increased blood pressure, Norplant was not associated with any material risk of major morbidity compared with IUDs and female sterilization.

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*Received June 16, 2000.*

*Received in revised form December 5, 2000.*

*Accepted December 7, 2000.*

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