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Post-marketing surveillance of Norplant® contraceptive implants: II. Non-reproductive health

International Collaborative Post-Marketing Surveillance of Norplant

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Abstract

This controlled cohort study aimed to evaluate the safety and efficacy of Norplant contraceptive implants in developing countries. Women initiating Norplant implants were index subjects and women initiating intrauterine devices (IUDs) or surgical sterilization were controls. Consenting participants at 32 clinics in eight developing countries were admitted and followed-up every 6 months for 5 years. Major and less serious health events during follow-up were recorded. Incidence rate ratios of health events adjusted for clinic were estimated for initial and current method use. This paper reports non-reproductive health events. The study involved 7,977 women initiating use of Norplant, 6.625 of IUD, and 1,419 of sterilization. Five years follow-up was completed for 94.6% of the women. The study accumulated 78,323 woman-years of observation. The initial method chosen accounted for 84.4% or more of observed woman-years in users of Norplant, IUD, or sterilization. Twenty-two of the recorded 34 deaths were due to accidents, suicide or homicide. Few deaths or major health events were due to cancer or acute cardiovascular diseases and were not associated with the contraceptive method used. The incidence rates of major health events were low and with two exceptions, there was no significant excess risk of serious morbidity for Norplant users compared with controls; among Norplant initiators gallbladder disease occurred at an incidence rate of 1.5 per 1,000 woman-years and was weakly associated with use of Norplant (rate ratio 1.52 [95% C.I. 1.02, 2.27]). For current Norplant users compared to controls, the rate ratio of a combined variable of hypertension and borderline hypertension was significantly elevated (1.81, [1.12, 2.92]). The occurrence of less serious health events was also low and several of them were significantly more often reported among Norplant users. Headache-migraine, weight gain, mood disturbances, pruritus, eczema, and acne had incidence rates among Norplant users of 11.5, 4.5, 2.8, 1.5, 1.4, and 0.9 per 1,000 woman-years, respectively, and were significantly higher than in controls. Respiratory health problems, nonspecific symptoms, and several ill-defined conditions were also significantly more often reported for Norplant users, but some of the excess incidence may be attributable to reporting and detection bias. The study confirms the safety with respect to serious disease of Norplant, IUDs, and sterilization.

1. Introduction

Randomized clinical trials of hormonal and other contraceptives are typically not of sufficient size to detect rare non-contraceptive effects [1]. Nevertheless, knowledge of rare side effects is especially important for contraceptive methods that are used for long periods by young and healthy women, in contrast to drugs used by ill persons, usually for shorter periods. Data from large post-marketing surveillance studies are needed to supplement those from clinical trials. Such large-scale follow-up studies of hormonal and other contraceptive methods have detected numerous beneficial and adverse non-contraceptive effects of public health significance [2–4].

For these reasons, when Norplant contraceptive implants [5,6] were introduced in developing countries, three agencies concerned with reproductive health proposed an international surveillance study of women who chose to use this method. The objective was to identify whether any important health effects occurring within 5 years after initiating Norplant use had escaped detection in clinical trials. The study was conducted in 8 developing countries where Norplant approval by drug regulatory bodies was completed or pending.

The study involved women starting use of Norplant im-

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plants, of intrauterine devices (IUDs), and of sterilization. This report focuses on non-reproductive health effects related to use of Norplant, IUDs, and female sterilization for fertility regulation. Contraceptive efficacy and reproductive health events are described in an accompanying paper [7].

2. Materials and methods

The methods have been described in detail elsewhere [7]. The following summary includes aspects relevant to the results described in this paper. This was a concurrent cohort study of 5 years duration in women initiating use of Norplant implants (index subjects), intrauterine devices (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 1,000 woman-years (95% significance level, two-sided test). This required observation of 30,000 woman-years in each of the index and control groups. Enrollment of 8,000 index subjects and the same number of controls was planned, given anticipated method discontinuation rates and losses to follow-up. After approval by the World Health Organization (WHO) and by local ethical review committees in each of 32 family planning clinics in eight developing countries (two in Bangladesh, two in Chile, 10 in China, three in Colombia, five in Egypt, five in Indonesia, one in Sri Lanka, and four in Thailand) enrollment proceeded from 1987 to 1991. Follow-up of all subjects was completed in 1997.

All 32 clinics provided Norplant, 17 offered sterilization by locally preferred methods, and all but 2 offered IUDs (copper or non-copper, but not progestogen-releasing devices). Women 20–40 years old were eligible if they lived in the catchment area, 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 (e.g., 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. Women wishing to change methods or stop method use did so, but follow-up continued for 5 years. Women who discontinued or became pregnant in the first 6 months, however, were released from follow-up for insufficient exposure to the initial method.

Breast and pelvic examination, cervical cytology, 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 in- and out-patient medical care, surgery and medications were reviewed. Implants were removed at the end of 5 years. The former Norplant users returned 6 weeks later to ensure recording of removal complications.

Complaints, symptoms and diseases uncovered by interview, physical examinations, tests or from diaries, were coded locally according to the International Classification of Disease, 9th revision (ICD-9) [8]. Country coordinators reviewed all health problems, verified diagnoses and classified each as a major health event or another health problem. Major health events (MHE) were potentially life-threatening events or events requiring hospitalization or convalescence of at least one month, or those leaving physical or mental sequelae or leading to medication for 3 months or more, or death. Pregnancy was considered a major health event. Other less serious health events were classified as other health problems (OHP). The MHE diagnosis of diabetes mellitus (ICD-9 250) was based on elevated fasting glucose levels and treatment with antidiabetic drugs or diet or both, and was confirmed by a glucose tolerance test. Essential hypertension (ICD-9 401) was considered a MHE when the systolic blood pressure (BP) was >140 mm Hg and the diastolic BP was >90 mm Hg on more than one occasion, on different days, or if antihypertensive medication was prescribed. Borderline hypertension, an OHP, was defined as systolic BP>140 mm Hg and diastolic BP>90 mm Hg on one occasion, or diastolic BP>85 mm Hg on more than one occasion. Gallbladder disease (ICD-9 674–5) was a MHE if cholecystectomy was performed, or if the disease was symptomatic and gallstones were confirmed by x-ray or ultrasound examinations. Mental disorders (ICD-9 290–316) were considered a MHE when the individual was hospitalized or prescribed long-term therapy, and as an OHP in all other cases. Forms were dispatched to the co-coordinating center at WHO and rechecked. The project overall coordinator reviewed all MHE diagnoses, accepting a diagnosis only after receipt of adequate documentation.

Some OHP diagnoses were reviewed at the co-coordinating center. These were 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 health problem diagnoses deemed potentially serious.

The analysis of the MHEs focuses on, but is not restricted to, health events and conditions which fulfilled at least one of the following criteria: more than five events within an ICD-9 subchapter in a given contraceptive initiator group associated with a rate ratio for Norplant compared with controls greater than 2.0 or less than 0.5, or previously reported as an adverse effect of hormonal contraceptive use. The analysis of OHPs focused on, but was not restricted to, events or conditions that met the last of these criteria or if the adjusted rate ratio at the ICD-9 subchapter level was significantly different from unity. For some ICD-9 subchapters identified by the rate

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Table 1
Number of women recruited by country and contraceptive method

Country	Norplant	IUD	Sterilization	Total	Percent
Bangladesh	504	257	252	1013	6.3%
Chile	626	505	117	1248	7.8%
China	3023	2565	526	6114	38.2%
Colombia	500	292	208	1000	6.2%
Egypt	992	1008	0	2000	12.5%
Indonesia	1002	951	67	2020	12.6%
Sri Lanka	415	225	157	797	5.0%
Thailand	915	822	92	1829	11.4%
Total	7977	6625	1419	16021	100.0%
Percentage	49.8%	41.3%	8.9%	100.0%	

ratio screen, the analyses are restricted to specific ICD-9 three- or four-digit codes that were most frequently reported in the subchapter or accounted the difference of the incidence rates. Because five MHEs in a given contraceptive group would be well below the level chosen for statistical power (1 per 1,000 woman-years or more than 30 events in the Norplant group), and because numerous significance tests have been conducted, the p-values should be interpreted in a conservative manner. Incidence rates were expressed per 1,000 woman-years. Only first events of a specific type within a specific ICD-9 chapter, subchapter, or three-digit code of diseases were considered and thus that woman's experience in the study after the first event was censored in the calculations for that endpoint. The total number of women experiencing events in analysis of subchapters may exceed the number of women with at least one event in analysis of the chapter since only the first event of a particular type in the chapter was counted in this analysis. Similarly, for the analyses of ICD-9 three- and four-digit codes, the total number of women experiencing at least one event at the more detailed level may exceed the number with at least one event at the subchapter level. The ratio of incidence rates of Norplant users and controls (rate ratio) was used for comparisons between event rates. The rate ratios were adjusted for differences between clinics and for selected other factors as described in the tables, by means of Poisson regression using STATA (StataCorp 1997. Stata Statistical Software: Release 5.0. College Station, TX, USA: Stata Corporation). The rate ratios are given with 95% confidence intervals in parenthesis.

3. Results

3.1. Participants

Altogether 16,021 women, including 7,977 Norplant users, 6,625 IUD users, and 1,419 women undergoing sterilization, were admitted to the study (Table 1). Overall, the Norplant and IUD study groups were similar, but the sterilized women were approximately one year older at admission and twice as likely to have had two or more deliveries (Table 2). The sterilized women also were 1 to 2 years younger on average both at first union and at first delivery, and they were much less likely to have experienced higher education. All groups had similar tobacco and alcohol consumption. Less than 7% of Norplant and IUD users and 10.6% of sterilized women had ever smoked, and less than 5% of participants had ever drunk alcohol. Fewer still were current smokers or drank alcohol regularly. A minority of women reported pre-existing health problems (Table 3). A larger proportion of Norplant initiators had previously used hormonal contraceptives (60.5%) than those initiating use of IUD (41.0%) or sterilization (43.7%).

3.2. Discontinuations from the study

A total of 307 (1.9%) women were excluded from further participation in the study within the first 6 months because they had discontinued the initial method or became pregnant within this interval (95 Norplant users, 208 IUD users, four sterilized women of whom two were pregnant at admission, one became pregnant in the first month, and one because the cervical cytology taken at admission was suggestive of cervical malignancy). Of the remaining 15,714 women, 15,161 (96.5%) completed the 5 years of follow-up. The losses were due to 513 women (3.2% of total participants) who moved out of the area or were lost to follow-up (231 Norplant users, 242 IUD users, and 40 sterilized women) and 40 (0.3%) women who refused to continue in the study (25 Norplant users, 10 IUD users, and five sterilized women).

3.3. Scope of the study

The study accumulated 78,323 woman-years of observation, 39,337 (50.2%) in women initiating Norplant use, 31,915 (40.7%) in women initiating IUDs, and 7,071 (9.0%) in women undergoing sterilization. The mean length of follow-up per woman was 4.9 (SD 0.7) years in Norplant initiators, 4.8 (SD 1.0) in IUD initiators, and 5.0 (SD 0.6) in

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Table 2
Characteristics of women at admission

	Study group			p-value
	Norplant	IUD	Sterilization	
No. of subjects	7977	6625	1419	
Age (%)				
<25 years	18.6	19.3	13.3	
25–29 years	39.9	40.4	36.6	
30–34 years	29.9	27.5	36.4	
>35 years	11.6	12.9	13.7	
Age (years)[a]	28.5 ± 4.5	28.5 ± 4.7	29.6 ± 4.1	<0.001
In union (%)	99.1	98.9	99.3	
Age at first union (years)[a]	21.1 ± 3.9	22.0 ± 3.8	19.9 ± 3.8	<0.001
Age at first delivery (years)[a]	22.4 ± 3.9	23.2 ± 3.8	21.2 ± 3.6	<0.001
Parity (%)				
0	0.6	0.7	0.1	
1	47.1	57.2	1.3	
2	25.6	20.2	48.6	
>2	26.8	22.0	50.0	
Parity[a]	2.1 ± 1.6	1.9 ± 1.5	2.9 ± 1.3	<0.001
Outcome of last pregnancy (%)				<0.001[c]
Delivery	71.5	71.1	91.6	
Abortion	28.1	28.5	8.4	
Ectopic/molar	0.1	0.1	0.0	
Never pregnant	0.3	0.4	0.0	
Education level (%)				
<Elementary	21.4	13.9	23.8	<0.001
Elementary	22.2	18.2	47.5	
Secondary	42.1	48.1	24.2	
Higher[b]	14.3	19.8	4.5	
Ever smoked (%)	6.9	5.6	10.6	
Ever drank alcohol (%)	5.0	4.2	4.2	
Body weight (kg)[a]	53.7 ± 10.5	55.6 ± 11.0	51.7 ± 9.8	<0.001

[a] Mean ± SD.
[b] Includes technical and university education.
[c] Comparing delivery with other outcomes.

sterilized women [7]. The majority of women continued to use their initially chosen method throughout the follow-up period and this accounted for 84.4% of the observed woman-years for Norplant initiators, 85.2% for IUD initiators, and 99.6% for sterilized women. There were small but statistically significant differences between the 3 groups in the total number of scheduled or unscheduled visits and in the mean number of visits in each study year [7].

Table 3
Percentage of women reporting histories of specified health conditions by initial contraceptive method

Condition	Norplant	IUD	Sterilization
High BP in pregnancy	3.9	4.3	3.0
Gallbladder disease	1.2	1.5	0.8
Jaundice	0.9	1.2	0.6
Tuberculosis	0.4	0.8	0.4
Ovarian cyst	0.8	0.7	0.5
P.I.D.	1.5	0.9	1.8
Urinary tract infection	7.6	6.3	8.9
Renal disease	1.9	1.6	2.6
Allergy	6.7	5.9	6.8
Other serious disease	3.2	3.5	3.2

3.4. Major health events (MHEs) and other health problems (OHPs)

The incidence of MHEs according to ICD-9 chapter and initial contraceptive method is shown in Table 4. The most commonly reported non-reproductive MHEs were neoplasms, diseases of blood and blood forming organs, and of the digestive system. A total of 971 (6.0%) of the women reported at least one MHE not arising from pregnancy or the reproductive system and 14,993 (93.6%) reported at least one non-reproductive OHP. Further details on the number of women experiencing at least one MHE or one OHP within specific ICD-9 subchapters, and the associated crude incidence rates and adjusted rate ratios are listed by initial contraceptive method in Appendixes 1 and 2, respectively.

The following text and tables present further details on the incidence of MHEs and OHPs. The description follows

Table 4
Major health events by ICD-9 chapters and by initial use of Norplant, IUD or sterilization

ICD-9 chapters		ICD-9 codes	Norplant			IUD			Sterilization		
			W/years	Events	Rate	W/years	Events	Rate	W/years	Events	Rate
I	Infectious and parasitic diseases	001–139	39154	55	1.4	31826	34	1.1	7053	6	0.9
II	Neoplasms	140–239	39166	74	1.9	31789	58	1.8	7048	10	1.4
III	Endocrine, nutritional and metabolic diseases and immunity disorders	240–279	39288	24	0.6	31880	13	0.4	7060	3	0.4
IV	Diseases of blood and blood forming organs	280–289	39178	63	1.6	31773	71	2.2	7065	2	0.3
V	Mental disorders	290–319	39317	9	0.2	31910	3	0.1	7062	2	0.3
VI	Diseases of the nervous system and sense organs	320–389	39282	20	0.5	31905	5	0.2	7054	5	0.7
VII	Diseases of the circulatory system	390–459	39212	58	1.5	31843	31	1.0	7050	10	1.4
VIII	Diseases of the respiratory system	460–529	39288	21	0.5	31886	11	0.3	7067	1	0.1
IX	Diseases of the digestive system	520–579	38994	117	3.0	31735	63	2.0	7042	11	1.6
X	Diseases of the genitourinary system	580–629	39143	78	2.0	31752	68	2.1	7047	12	1.7
XII	Diseases of the skin and subcutaneous tissue	680–709	39319	6	0.2	31911	2	0.1	7071	0	0.0
XIII	Diseases of the musculoskeletal system and connective tissue	710–739	39295	16	0.4	31900	8	0.3	7065	3	0.4
XIV	Congenital anomalies	740–759	39328	3	0.1	31911	2	0.1	7070	1	0.1
XVI	Symptoms, signs and ill defined conditions	780–799	39326	6	0.2	31915	0	0.0	7071	0	0.0
XVII	Injury and poisoning	800–999	39257	31	0.8	31880	21	0.7	7061	6	0.8

Number of events, woman years, and crude incidence rate per 1000 woman-years.

the order of the ICD-9 codes. The results are presented according to initial contraceptive method, and where relevant by current method.

3.4.1. Chapter I: infectious and parasitic diseases (ICD-9 001–139)

The most frequent MHEs were Tuberculosis (ICD-9 010–018) and Other Diseases Due to Viruses and *Chlamydiae* (ICD-9 070–079) (Appendix 1). Twenty-two of the 29 diagnoses of tuberculosis referred to the respiratory tract, 1 bone or joint case each was in Norplant and IUD initiators, there were two cases of other organ tuberculosis in Norplant initiators and 3 in IUD initiators. In the latter subchapter there were 23, 17, and 3 cases of viral hepatitis (ICD-9 70) among women who had initiated use of Norplant, IUD, and sterilization, respectively; the rate ratio for Norplant initiators compared with controls was 1.16 (0.64, 2.12).

OHPs in the subchapters of Other Diseases Due to Viruses and *Chlamydia* (ICD-9 070–079), Mycoses (ICD-9 110–118), and of Other Infectious and Parasitic Diseases (ICD-9 130–136) (Appendix 2) were dominated by lower genital tract infections of papilloma virus, candidiasis, and trichomonas, respectively, and are described in the accompanying paper [7], as are the MHEs and OHPs of the subchapter of Syphilis and Other Venereal Diseases (ICD-9 090–099). The subchapter of Intestinal Infectious Diseases referred largely to amoebiasis (ICD-9 006) (66 cases) and other protozoan diseases (ICD-9 007) (15 cases). The subchapter of Helminthiasis (ICD-9 120–125) included 15 cases of filarial infection (ICD-9 125.0, 125.9), all in women who had initiated Norplant and reported from one center in Sri Lanka, 13 were current users at time of infection.

3.4.2. Chapter II: neoplasms (ICD-9 140–239)

Eight non-reproductive malignant neoplasms (MHEs) were diagnosed during the study. Three were in Norplant initiators (nasopharynx, unspecified ICD-9 147.9, lung cancer ICD-9 162.9, and non-Hodgkin's lymphoma ICD-9 202.8). Five were in women initiating use of an IUD (gastric cancer ICD-9 151.2, carcinoid of appendix ICD-9 153.5, rectal cancer ICD-9 154.1, thyroid cancer ICD-9 193, and acute monocytic leukemia ICD-9 206.0). Seven reproductive organ malignant neoplasms (five of the breast, one cervical cancer, and one choriocarcinoma) are described in the accompanying paper [7].

One-hundred-and-thirteen benign neoplasms of various types and 15 carcinoma in situ, all classified as MHEs, occurred with equal frequency in Norplant users and controls (Appendix 1). Ninety-four of these benign neoplasms refer to the genital organs and are described in the accompanying paper [7]. Other benign neoplasms were of the thyroid gland (ICD-9 226) (six in Norplant initiators and six in IUD initiators); five cases of hemangioma (ICD-9 228.0), 4 of the liver (2 Norplant initiators, one each in IUD and sterilization initiators, all in China); and one of the skin. The remaining benign neoplasms were tumors of the liver and biliary tract, of retroperitoneum, of thorax, of kidney, and lipoma without any particular pattern of distribution according to contraceptive groups. The 15 carcinoma in situ were all related to the reproductive organs and are described in the accompanying paper [7]. Another 58 benign neoplasms not subject to biopsy, were classified as OHPs, 50 of these were reproductive organ neoplasms and are described elsewhere [7]. The rest were two or less cases by contraceptive group and included lipomas, skin tumors, and benign tumors of the thyroid gland. One IUD initiator had an OHP diagnosis of neurofibromatosis (ICD-9 237.7) on one occasion and no symptoms or complaints at follow-up (Appendix 2).

3.4.3. Chapter III: endocrine, nutritional and metabolic diseases and immunity disorders (ICD-9 240–279)

MHEs relating to Disorders of the Thyroid Gland (ICD-9 240–246) occurred with nearly equal frequency in Norplant initiators and controls (Appendix 1), and with similar distribution of ICD-9 3-digit diagnoses for initiators of Norplant and of IUD or sterilization. Of 16 MHE reports of Diseases of Other Endocrine Glands (ICD-9 250 -259), 12 were diabetes mellitus (ICD-9 250), nine in Norplant initiators (eight current users), two in IUD initiators (three current IUD users) and one in a sterilized woman. The crude incidence rate was higher in current Norplant users compared with controls (Table 5), but the crude and adjusted rate ratios for Norplant users compared with controls were not significantly different. After adjustment for clinic, age and body weight, the rate ratios were slightly altered but remained not significant compared with IUD users ($p = 0.12$), sterilized women ($p = 0.98$) or both ($p = 0.15$). Similar relationships were observed when the assessment was done according to initial contraceptive method (data not shown).

OHPs in the subchapter of Disorders of the Thyroid Gland (ICD-9 240–246) included 10 diagnoses of thyroid gland disorders in current Norplant users and 3 in current IUD users and sterilized women, 8 of these women (7 Norplant users and one control) had a diagnosis of nontoxic goiter (ICD-9 240,241) ($p = 0.08$). OHP diagnoses in the subchapter Other Metabolic and Immune Disorders (ICD-9 270–279) were dominated by diagnosis of obesity (ICD-9 278), a diagnosis assigned to 49 Norplant initiators and 33 controls with a rate ratio of 1.45 (0.93, 2.25) ($p = 0.10$); for current Norplant users compared with controls the rate ratio was 1.71 (1.08, 2.73) ($p = 0.02$) based on 44 Norplant users and 30 controls. These women were from Chile (52), Colombia (16), Egypt (10), and 2 or less from China, Indonesia, and Sri Lanka. Their mean body mass index was 30.9 (SD 4.3) kg/m^2. For further results regarding weight and weight gain see also ICD-9 chapter XVI.

Table 5
Selected major health events and other health problems by current contraceptive method

Events	Norplant		IUD		Sterilization		Adjusted[h] rate ratio (Norplant/controls)		
	No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
Diabetes mellitus[a] (MHE)	8	0.2	3	0.1	1	0.1	2.42	(0.73, 8.05)	0.15
Mood disorders[b] (OHP)	94	2.8	35	1.2	17	2.2	2.15	(1.53, 3.02)	<0.001
Migraine[c] or headache[d] (OHP)	376	11.5	62	2.1	80	10.6	3.44	(2.83, 4.18)	<0.001
Hypertension[e] (MHE)	24	0.7	11	0.4	4	0.5	1.78	(0.93, 3.40)	0.08
Borderline hypertension[f] (OHP)	20	0.6	9	0.3	3	0.4	1.85	(0.90, 3.78)	0.09
Cholelithiasis[g] and other disorders of gallbladder[h] (MHE)	50	1.5	36	1.2	8	1.0	1.31	(0.87, 1.96)	0.19

Number of events, crude incidence rate per 1000 woman-years and adjusted rate ratio.
[a] ICD-9 code 250; [b] ICD-9 code 300,311,799.2; [c] ICD-9 code 346; [d] ICD-9 code 784.0; [e] ICD-9 code 401, see text for definition; [f] ICD-9 code 574; [g] ICD-9 code 575; [h] adjusted for clinic; for "diabetes mellitus" also adjusted for age and body weight.

3.4.4. Chapter IV: diseases of blood and blood-forming organs (ICD-9 280–289)

Of the 136 MHE reports under this chapter (Appendix 1), 118 were iron deficiency anemia (ICD-9 280) and are described in the accompanying paper [7]. Thrombocytopenia (ICD-9 287.5) was diagnosed in three Norplant initiators, all in China and all current Norplant users at the time of diagnosis. The crude incidence rate for current use of Norplant was 0.09 (0.02, 0.26) per 1,000 woman-years. Twelve Norplant and nine IUD initiators had an OHP diagnosis of iron deficiency anemia (ICD-9 280) [7], other OHPs were cases of other diseases of blood and blood forming organs (ICD-9 289) which were equally distributed among Norplant users and controls.

3.4.5. Chapter V: mental disorders (ICD-9 290–316)

Mental disorders requiring hospitalization or long-term therapy (MHEs) comprised three cases of schizophrenia (ICD-9 295), three of manic-depressive disease (ICD-9 296), three cases of hysteria (ICD-9 300.1), single cases of neurotic depression (ICD-9 300.4), anorexia nervosa, (ICD-9 307.1) and acute confusion (ICD-9 293), and two ill-defined diagnoses (ICD-9 298.0 and 306.2). Nine of these 14 MHEs were Norplant initiators and the adjusted rate ratios for Norplant users compared with controls were 1.72 (0.58,5.13) for initiator groups and 1.13 (0.33,3.92) for current use. Neither rate ratio was significantly different from unity.

OHP diagnoses of anxiety (ICD-9 300.0) or depression (ICD-9 311) in the subchapter Neurotic Disorders and Personality Disorders (ICD-9 300–316), or of nervousness (ICD-9 799.2) in the subchapter Unknown Causes of Morbidity and Mortality (ICD-9 797–799) referred to below, were reported by 94 current Norplant users, 35 current IUD users, and 17 sterilized women. These three diagnoses were analyzed jointly as mood disorders (Table 5). Compared with current IUD users, Norplant users reported significantly more events of mood disorders (rate ratio 2.15 (1.53, 3.02 [p <0.001]). Similar relationships were observed when the assessment of these conditions was done according to initial use (data not shown). The subchapter includes the diagnosis of frigidity (ICD-9 302.7) that was reported by 23, 6, and 1 women during use of Norplant, IUD, and sterilization, respectively, the rate ratio was 3.79 (1.63,8.85) (p = 0.002). One-hundred-thirty-eight women had a diagnosis of psychalgia (ICD-9 307.8), a condition that in ICD-9 is defined as pains of mental origin, e.g., headache or backache, when a more precise medical or psychiatric diagnosis cannot be made [8]. A diagnosis of psychalgia was recorded in 95 current users of Norplant, 38 current IUD users, and 1 sterilized women with an incidence rate of 2.9 per 1,000 woman-years among Norplant users and a rate ratio of 3.11 (2.14,4.52) (p <0.001). Other OHP diagnoses with incidence rates of 0.3 per 1,000 woman-years or less in current users were anorexia nervosa (ICD-9 307.1) with a rate ratio for current Norplant users compared with controls of 1.60 (0.49,5.23), and sleep disorders (ICD-9 307.4) which had a rate ratio of 7.94 (1.78,35.5).

3.4.6. Chapter VI: diseases of the nervous system and sense organs (ICD-9 320–389)

There were few MHEs in this chapter of ICD-9 diagnoses. The most frequent MHEs were Disorders of the Eye and Adnexa (ICD-9 360–379) (Appendix 1). Of the 10 MHEs reports in this category, eight were among Norplant initiators and included one case of retinal vascular occlusion, 1 focal chorioretinitis, one each of glaucoma and cataract, one foreign body (with blindness of the afflicted eye) and one suspected optic neuritis associated with hyperthyroid thyroiditis, and two cases of keratitis. One IUD initiator had a diagnosis of macular changes and another of eyelid abscess.

Most OHPs of this ICD-9 chapter were reported in the subchapter Other Disorders of the CNS (ICD-9 340–349), and the most frequently reported OHP was migraine (ICD-9 346). It was reported for 83 current Norplant users, two current IUD users and 31 sterilized women. Altogether 65% of the migraine diagnoses were from three centers in Co-

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lombia where migraine outnumbered common headache (ICD-9 784) by a factor of 12. Therefore, diagnosis of migraine and common headache was combined. The rate ratio for migraine and common headache combined, was 3.44 for current Norplant user compared to controls ($p = 0.001$) (Table 5). Similar relationships were observed when the assessment was done according to initial contraceptive method (data not shown). One woman had an OHP diagnosis of chorea (ICD-9 333.5) reported once, she had no symptoms or complaints at follow-up visits (Appendix 2).

OHPs in the subchapter Disorders of the Peripheral Nervous System (ICD-9 350–359) were relatively infrequent (17, 3, and 1 in Norplant initiators, IUD initiators and sterilized women, respectively), but significantly more common in Norplant initiators (Appendix 2). There were no differences between the groups in facial nerve disorders (ICD-9 351) including Bell's palsy (two and three in Norplant initiators and controls, respectively). There were five cases of mononeuropathies of the upper limb (ICD-9 354), and seven cases of inflammatory and toxic polyneuropathies (ICD-9 357), all these 12 cases were in Norplant initiators, the conditions being all of short-term nature. OHP disorders of the eye included a variety of conditions affecting 34 Norplant initiators and 17 controls ($p = 0.01$) (Appendix 2). Five women (four current Norplant users and 1 current IUD user) experienced refraction problems (ICD-9 367). The rate ratio 2.58 (0.47, 14.16) was not significantly different from unity ($p = 0.27$). Eight women (seven current Norplant users and one sterilized woman) had short-term visual disturbances and low vision (ICD-9 368 and 369,2) associated with fatigue, headache or both, the rate ratio for Norplant compared with controls was 9.46 (1.16, 77.0) ($p = 0.04$). There were a total of 19 cases of conjunctivitis and blepharitis (ICD-9 372–373) among current users of Norplant (12), IUD users (6), sterilization (1), the rate ratio was 2.00 (0.79, 5.10). Two cases of borderline glaucoma (ICD-9 365.0) were reported in Norplant initiators. Eight cases of strabismus (ICD-9 378) were reported, seven of which were from one clinic, the 8 cases were equally distributed among contraceptive groups. The remaining eight OHPs in the subchapter were single cases of specific disorders.

In the subchapter on Diseases of the Ear and Mastoid Processes (ICD-9 380–389), 19 of the 37 reported OHP diagnoses referred to vertigo and other disorders of the vestibular system (ICD-9 386), the incidence rate in current Norplant users was 0.3 per 1,000 woman-years and the rate ratio was 1.66 (0.65, 4.22).

3.4.7. Chapter VII: diseases of the circulatory system (ICD-9 390–459)

The most frequent cardiovascular disease reported as MHE was Hypertensive Diseases (ICD-9 401–405) (45 cases), followed by Diseases of Veins, Lymphatics and Other Diseases of the Circulatory System (ICD-9 451–459) (22 cases) (Appendix 1). The incidence rate of hypertension (ICD-9 401) as defined, was 0.72 per 1,000 woman-years in current Norplant users, almost double the rate found among current IUD-using controls (0.38 per 1,000 woman-years) (Table 5). Adjustments for clinic, age or body weight or both, did not change the rate ratios appreciably. No significant differences in the incidence of hypertension were found according to initial use of Norplant, IUD or sterilization (data not shown). The rate ratio for borderline hypertension as defined above, for current use of the contraceptive methods was similar to the ratio for hypertension (Table 5). The rate ratio for hypertension and borderline hypertension combined, was 1.81 (1.12, 2.92) ($p = 0.02$). The mean number of blood pressure measurements, adjusted for clinic, during the course of the study was higher in Norplant initiators (2.7) compared with women initiating IUD (2.5) or sterilization (2.1) ($p < 0.001$).

No myocardial infarctions (ICD-9 410) were reported during 78,323 woman-years of observation. Two Norplant initiators had an OHP diagnosis of ischemic heart disease reported (Appendix 2). The condition was reported once for each of them, the 2 women had no complaints or symptoms at subsequent follow-up visits. An OHP diagnosis of cardiac dysrhythmia (ICD-9 427) was reported during current use of the three methods for 24 Norplant users, nine IUD users, and five sterilized women; the incidence rate was 0.7 per 1,000 woman-years among Norplant users, and the rate ratio for Norplant users compared with controls was 1.92 (0.99, 3.71).

Cerebrovascular Diseases (ICD-9 430–438) included one ischemic (ICD-9 434) and one hemorrhagic (ICD-9 431) stroke, both among Norplant users in China. The overall incidence rate for ischemic and hemorrhagic stroke combined was 0.05 (0.01, 0.18) per 1,000 woman-years.

Diseases of Veins, Lymphatics, and Other Diseases of the Circulatory System (ICD-9 451–459) included one MHE case of idiopathic deep vein thrombosis of the lower extremities (ICD-9 451.1) confirmed by Doppler examination, in a first segment Norplant user. Pulmonary embolism was excluded by lung scan. The incidence rate was 0.03 (0.00,0.14) per 1,000 woman-years of Norplant use. The other MHEs in this category included operations on varicose veins of the lower extremities (ICD-9 454) (6) and hemorrhoids (ICD-9 455) (12). Neither was more common in initial or current Norplant users compared with controls. Also in this category were two women with upper extremity superficial phlebitis (ICD-9 451.8) (one in conjunction with Norplant insertion and one in association with parasite infection), and one woman with pelvic varicose veins (ICD-9 456.5).

The most frequently reported OHP was varicose veins of the legs (ICD-9 454) with 30, 4, and 13 cases in current users of Norplant, IUD and sterilization, respectively, with a rate ratio of 2.38 (1.31, 4.32) for Norplant users compared with controls. OHP diagnoses of hemorrhoids (ICD-9 455) and of varicose veins of other sites (ICD-9 456) were infrequent, with incidence rates of 0.5 per 1,000 woman-years or less and rate ratios of 0.39 (0.14, 1.08) and 0.74 (0.27, 2.04), respectively.

3.4.8. Chapter VIII: diseases of the respiratory system (ICD-9 460–519)

With one exception, the MHEs in this ICD-9 chapter were equally distributed in Norplant users and controls. The exception was eight cases of other diseases of the upper respiratory tract (ICD-9 470–478) for which the adjusted rate ratio for Norplant users compared with controls was 7.08 (0.87, 57.5) ($p = 0.07$) (Appendix 1). These cases were all hospitalized and reported from China. They included one case each of chronic sinusitis (ICD-9 473.9) and tonsillitis (ICD-9 474.0), two of swelling of the nasal concha (ICD-9 478.0), three cases of polyp of the vocal cord (ICD-9 478.4), all these in current Norplant users, and one case of other vocal cord disease (ICD-9 478.5) in a current IUD user.

The most frequently reported OHPs in this ICD-9 chapter were Acute Respiratory Tract Infections (ICD-9 460–466), which were significantly more often reported in Norplant initiators compared with controls. The three-digit codes were evenly distributed within the subchapter. All ICD-9 three-digit codes except tonsillitis (ICD-9 463) and acute bronchitis (ICD-9 466) were reported more often in initial or current Norplant users than in controls (Appendix 2). Other Diseases of the Upper Respiratory Tract (ICD-9 470–478) were also more often reported among Norplant initiators, the most frequent OHPs in this subchapter were chronic pharyngitis (ICD-9 472), chronic sinusitis (ICD-9 473), and allergic rhinitis (ICD-9 477). There were 49 OHPs under these three 3-digit ICD-9 codes. The incidence rates for chronic pharyngitis (ICD-9 472) and chronic sinusitis (ICD-9 473) combined were 0.4, 0.3, and 0.1 per 1,000 woman-years for current Norplant users, current IUD users and sterilized women, respectively, with an adjusted rate ratio of 1.46 (0.62, 3.47) ($p = 0.39$). With respect to allergic rhinitis (ICD-9 477), the incidence rates were 0.3, 0.3, and 0.1 per 1,000 woman-years for current Norplant users, current IUD users and sterilized women, respectively, and the adjusted rate ratio was 0.90 (0.37, 2.20) ($p = 0.82$).

Pneumonia and Influenza (ICD-9 480–487) were rarely reported as MHEs (eight cases in Norplant initiators and five in controls) (Appendix 1). OHPs in this subchapter were significantly more likely in Norplant initiators compared with controls (rate ratio 3.24, (1.89, 5.56) ($p < 0.001$)) (Appendix 2). There were 51, 15, and 3 cases in Norplant initiators, IUD initiators and sterilized women, respectively. Of these, 35, 8, and 1 case, respectively, had a diagnosis of influenza (ICD-9 487) with an incidence rate of 0.9 per 1,000 woman-years in Norplant initiators and a rate ratio of 4.79 (2.30, 9.99). Data were similar when analyzed according to current use.

OHPs for Chronic Obstructive Pulmonary Disease (ICD-9 490–496) were reported significantly more often in Norplant initiators (Appendix 2). The most frequent disorders were chronic bronchitis (ICD-9 491) (17 Norplant initiators and 5 controls) with an incidence rate of 0.4 per 1,000 woman-years in Norplant initiators and a rate ratio of 3.39 (1.25, 9.18), and asthma (ICD-9 493) (19 Norplant initiators and 5 controls) with an incidence rate of 0.5 per 1,000 woman-years in Norplant initiators and a rate ratio of 3.75 (1.40, 10.0). The results were similar when analyzed according to current use.

3.4.9. Chapter IX: diseases of the digestive system (ICD-9 520–579)

This chapter included two of the most commonly reported MHEs, gallbladder disease and appendicitis. Appendicitis (ICD-9 540–543) was reported in 56 women, and the rates were not significantly different for Norplant users and controls, evaluated either by initial (Appendix 1) or by current use (not shown).

Of the 110 MHE diagnoses in the subchapter Other Diseases of the Digestive System (ICD-9 570–579), 101 referred to gallstones (ICD-9 574) and other disorders of the gallbladder including acute and chronic cholecystitis (ICD-9 575). The incidence rates of gallbladder disease were 1.5, 1.2, and 1.0 per 1,000 woman-years for current Norplant users, IUD users and sterilized women, respectively (Table 5). Adjustment for past history did not materially alter the rates (not shown). After adjustment for clinic, the rate ratios for gallbladder disease were not significantly different from unity comparing current Norplant users with IUD users ($p = 0.23$), sterilized women ($p = 0.47$) or all controls ($p = 0.19$). In the analysis by initial contraceptive method, the adjusted rate ratio for Norplant users compared with controls was 1.52 (1.02, 2.27) ($p = 0.04$).

OHP diagnoses of the subchapters of Diseases of the Digestive System were common, none of the adjusted ratios of incidence rates in Norplant compared with controls were significantly different from unity. Diagnoses in the subchapter of Oral Diseases (ICD-9 520–529) was dominated by caries (ICD-9 521) (27 cases) and gingival and periodontal diseases (ICD-9 523) (16 cases), the rate ratios of these 2 ICD-9 codes for initial Norplant users compared with controls were 0.91 (0.43, 1.94) and 2.24 (0.78, 6.46), respectively, and the incidence rate among Norplant initiators was 0.3 per 1,000 woman-years for both ICD-9 codes. The results were similar when analyzed by current method. The majority of OHP diagnosis of the subchapter of Diseases of the Esophagus, Stomach and Duodenum (ICD-9 530–537) referred to gastric ulcer (ICD-9 531), duodenal ulcer (ICD-9 532), gastritis and duodenitis (ICD-9 535), and disorders of function of stomach including dyspepsia (ICD-9 536). There was considerable overlap of these diagnoses and they were therefore analyzed combined. The rate ratio of these four ICD-9 diagnoses combined for current Norplant compared with current IUD users and sterilized women was 1.43 (1.08,1.88) based on 110 users of Norplant, 53 of IUD and 39 sterilized women; the incidence rates were 3.3, 1.8, and 5.1 per 1,000 woman-years, respectively. When analyzed by initial contraceptive method the rate ratio was 1.25 (0.97,1.61) based on 136 Norplant users and 108 controls.

Table 6
Contact dermatitis, pruritus, alopecia, acne, and urticaria by current contraceptive method

Events (severity)	Norplant		IUD		Sterilization		Adjusted[f] rate ratio (Norplant/controls)		
	No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
Contact dermatitis and other eczema[a] (OHP)	47	1.4	12	0.4	3	0.4	3.53	(1.97, 6.32)	<0.001
Pruritus and related conditions[b] (OHP)	49	1.5	23	0.8	3	0.4	2.21	(1.37, 3.55)	0.001
Alopecia[c] (OHP)	11	0.3	1	0.0	0		12.44	(1.60, 96.6)	0.016
Acne[d] (OHP)	30	0.9	5	0.2	0		7.48	(2.90, 19.3)	<0.001
Urticaria[e] (OHP)	17	0.5	6	0.2	0		3.07	(1.21, 7.81)	0.018

Number of events, crude incidence rate per 1000 woman-years and adjusted rate ratio.
[a] ICD-9 code 692; [b] ICD-9 code 698; [c] ICD-9 code 704.0; [d] ICD-9 code 706.0-.1; [e] ICD-9 code 708; [f] adjusted for clinic.

In the subchapter Other Diseases of Digestive System (ICD-9 570–579), the most common OHP diagnoses were gallstones (ICD-9 574) and cholecystitis (ICD-9 575); these were analyzed together. The incidence rate for Norplant initiators was 0.5 per 1,000 woman-years based on 20 cases, and the rate ratio for initial use of Norplant compared with controls was 1.54 (0.77,3.10), with similar results when analyzed by current method.

3.4.10. Chapter X: diseases of the genitourinary system (ICD-9 580–629)

Diseases and disorders of the female pelvic organs and genital tract (ICD-9 614–629) are reported in the accompanying paper [7]. The 3 MHEs reported in the subchapter on Nephritis and Nephrosis (ICD-9 580–589) were acute glomerulonephritis in IUD initiators (Appendix 1). Diagnoses of Other Diseases of the Urinary System (ICD-9 590–599) were generally equally distributed among Norplant users and controls, although there were seven MHE reports of kidney and ureter calculus among current Norplant users, none among IUD users and two in sterilized women, giving an adjusted rate ratio for Norplant users compared with controls of 4.09 (0.85,19.7). There were five cases of pyelonephritis (ICD-9 590) in current Norplant users and eight in current IUD users and none in sterilized women with an adjusted rate ratio of 0.70 (0.23, 2,15).

OHPs in these subchapters were dominated by reports of urinary tract infections. There was one case of pyelonephritis reported as OHP among IUD users and none among Norplant users or sterilized women. Renal and ureter calculus were reported as OHP in 12 current Norplant users, in four current IUD users, and none among sterilized women, the adjusted rate ratio was 3.43 (1.11, 10.6) (p = 0.03). Lower urinary tract infections (ICD-9 595 and 599.0) were reported as an OHP in 132 current Norplant users, in 108 current IUD users, and in 51 sterilized women with incidence rates of 4.0, 3,7, and 6.7 per 1,000 woman-years, respectively, and a rate ratio for Norplant users compared with controls of 0.97 (0.77, 1.23).

3.4.11. Chapter XII: diseases of the skin and subcutaneous tissue (ICD-9 680–709)

There were eight MHEs in this ICD-9 chapter, including two cases of abscesses in the leg (ICD-9 682.6), two of contact dermatitis (ICD-9 692.9), and one of each alopecia (ICD-9 704.0) and urticaria (ICD-9 708.8) in Norplant initiators, and one case each of lupus erythematosus (ICD-9 695.4) and other disease of skin (ICD-9 709.8) in IUD initiators (Appendix 1).

Numerous OHPs were recorded (Appendix 2). For Infectious Conditions of the Skin (ICD-9 680–686) the rate ratios were not significantly different from unity. The analysis focused on diagnosis in the subchapters Other Inflammatory Conditions of Skin and Subcutaneous Tissue (ICD-9 690–698) and Other Disease of Skin and Subcutaneous Tissue (ICD-9 700–709) which were significantly more frequently reported among Norplant initiators. The most common three-digit codes in the former subchapter were contact dermatitis (ICD-9 692) (48 Norplant initiators and 17 controls), and pruritus and related conditions (ICD-9 698) (57 Norplant initiators and 23 controls). The number of women, crude rates and adjusted rate ratios by current use for contact dermatitis and for pruritus are shown in Table 6. Diagnoses of atopic dermatitis (ICD-9 691) (11 cases) and of dermatitis due to ingested substances (ICD-9 693) (9 cases) were more frequently recorded among current Norplant users (p = 0.03 and p <0.001, respectively), while occurrence of psoriasis (ICD-9 696) (11 cases) was not significantly different from that among controls. Similar results were found for analyses by initial contraceptive method.

Other Disease of Skin and Subcutaneous Tissue (ICD-9 700–709) includes conditions that had previously been reported as possibly associated with use of Norplant such as alopecia, hirsuitism, and acne. Incidence rates and rate ratios of alopecia (ICD-9 704.0) and acne (ICD-9 706.0–1) are shown in Table 6. Hirsutism (ICD-9 704.1) was reported by 4 women, all were current Norplant users (incidence rate 0.1 [0.03, 0.31] per 1,000 woman-years). The crude incidence rate for urticaria (ICD-9 708) was

0.5 per 1,000 woman-years in current Norplant users with an adjusted rate ratio of 3.07 (1.21, 7.81) (Table 6).

3.4.12. Chapter XIII: diseases of the musculoskeletal system and connective tissue (ICD-9 710–739)

The subchapter Arthropathies and Related Disorders (ICD-9 710–719) includes diffuse diseases of connective tissue (ICD-9 710) where three women had a MHE diagnosis. Systemic lupus erythematosus (ICD-9 710.0) was diagnosed in an IUD initiator 4 years into the study. Systemic sclerosis (ICD-9 710.1) was diagnosed in a Norplant initiator after 3 years in the study. Dermatomyositis (ICD-9 710.3) was diagnosed in an IUD initiator 4 months after the initial insertion. Other MHEs in this subchapter were nine cases of rheumatoid arthritis (ICD-9 714) and two cases of internal derangement of the knee (ICD-9 717). For the nine cases of rheumatoid arthritis and other inflammatory polyarthropathies (ICD 714), the crude incidence rates were 0.18, 0.03, and 0.14 per 1,000 woman-years in Norplant initiators, IUD initiators and sterilized women, respectively; the adjusted rate ratio was 3.46 (0.72, 16.6) ($p = 0.12$). The findings were similar when the analysis was done by current contraceptive method (not shown).

The rate ratio for OHPs in the subchapter Arthropathies and Related Disorders (ICD-9 710–719) was 2.60 (1.34, 5.05) (Appendix 2). The majority of these OHP reports were in the ICD-9 3-digit categories Other and Unspecified Arthropathies (ICD-9 716) (11 cases in Norplant users and two in IUD users), and other and unspecified disorders of joint (ICD-9 719) (10 cases in Norplant users, two in IUD users and one in a sterilized woman).

The OHP diagnoses in the subchapter Dorsopathies (ICD-9 720–724) were more frequent in Norplant initiators than among controls and of borderline statistical significance (Appendix 2). The ICD-9 code Other and Unspecified Disorders of the Back (ICD-9 724) was by far the most frequent 3-digit code encompassing 85, 93, and 87% of the diagnoses in initiators of Norplant, IUD, and sterilization, respectively. The most frequent ICD-9 4-digit codes were lumbago (724.2) and unspecified backache (ICD-9 724.5).

The rate ratio for OHPs in the ICD-9 subchapter Rheumatism, Excluding the Back (ICD-9 725–729) was 4.71 (2.93,7.56) ($p < 0.001$) (Appendix 2). Of the 93, 16, and 5 OHP diagnoses in Norplant initiators, IUD initiators and sterilized women, respectively, 65, 7, and 3, respectively, referred to the three-digit diagnosis of other disorders of soft tissues (ICD-9 729) including myalgia and pain in limb. Among the 65 Norplant initiators with this diagnosis, the myalgia and pain specifically referred to the arm of the Norplant insertion in 32 women as reported in the accompanying paper [7].

3.4.13. Chapter XIV: congenital anomalies (ICD-9 740–759)

During the study six congenital anomalies were discovered and reported as MHEs, the rate ratio for Norplant initiators compared with controls was not significantly different from unity. These anomalies refer to one case of preauricular sinus (ICD-9 744.4), one atrial septal defect (ICD-9 745.5), one megacholedochus (ICD-9 751.6), one dislocation of the hip (ICD-9 754.3), one occult spina bifida (ICD-9 756.1), and one thyrolingual cysts (ICD-9 759.2). The OHPs reported as congenital anomalies referred to one case of liver cyst, one bicornuate uterus, one each of rotated and of cystic kidney, one nasal septum abnormality, one pes planus, and four women with supernumerary nipples, seven of these OHPs were in initiators of Norplant and three of IUD.

3.4.14. Chapter XVI: symptoms, signs, and ill-defined conditions (ICD-9 780–799)

The codes in this section of the ICD-9 comprise symptoms that are not defined as a diagnosis classifiable elsewhere in the ICD-9 coding system [8]. The subchapter included 6 MHEs, all among Norplant initiators (Appendix 1). The MHEs included one case of syncope (ICD-9 780.2), two cases of dizziness and giddiness (ICD-9 780.4), one of hepatomegaly of unknown etiology (ICD-9 789.1), and one of non-specific abnormal liver function tests (ICD-9 794.8). These five MHEs were all reported from China. The sixth was a woman who died from sudden cardiorespiratory failure (ICD-9 798.1).

The subchapter on Symptoms (ICD-9 780–789) had the largest number of OHPs in each contraceptive group (Appendix 2). The analysis focused on ICD-9 four-digit codes with the largest number of diagnoses. Dizziness and giddiness (ICD-9 780.4) and malaise and fatigue (ICD-9 780.7) were significantly more often diagnosed in current Norplant users compared with controls (Table 7), although the crude incidence rate of the latter diagnosis was more than 3-fold higher in sterilized women compared with current Norplant users. Of the 279 cases of malaise and fatigue (ICD-9 780.7) in current Norplant users, 55 and 216 originated from clinics in Dhaka and Khulna, Bangladesh, respectively. The clinic in Dhaka had exclusively IUD initiators and the Khulna clinic exclusively sterilized women as controls. The adjusted rate ratios for this diagnosis (ICD-9 780.7) for Norplant initiators compared with controls in Dhaka and Khulna were 3.57 and 1.25, respectively, and for current Norplant users compared with controls 3.77 and 1.11, respectively.

The incidence rates of common headaches (ICD-9 784.0) other than migraine were 9.1, 2.1 and 7.2 per 1,000 woman-years, respectively, in current Norplant users, current IUD users and sterilized women. Due to apparent inconsistencies in the classification of migraine and common headache, the 2 diagnoses were analyzed together (Table 5), (see Chapter VI). Nausea and vomiting (ICD-9 787.0) were uncommon in all contraceptive initiator groups. The crude incidence rates were 0.30, 0.17, and 0 per 1,000 woman-years in current Norplant users, IUD users and sterilized women, respectively, with an adjusted rate ratio of 2.20 (0.75,6.46).

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Table 7
Dizziness, malaise, reported weight gain, and loss by current contraceptive method

Events (severity)	Norplant		IUD		Sterilization		Adjusted[e] rat ratio (Norplant/controls)		
	No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
Dizziness[a] (OHP)	141	4.2	35	1.2	3	0.4	4.29	(3.00, 6.15)	<0.001
Malaise, fatigue[b] (OHP)	279	8.5	26	0.9	203	27.9	1.66	(1.39, 1.97)	<0.001
Reported weight gain[c] (OHP)	149	4.5	26	0.9	0		6.94	(4.57, 10.5)	0.001
Reported weight loss[d] (OHP)	39	1.2	16	0.5	1	0.1	2.64	(1.49, 4.67)	0.001

Number of events, crude incidence rate per 1000 woman-years and adjusted rate ratio.
[a] ICD-9 code 780.4; [b] ICD-9 code 780.7; [c] ICD-9 code 783.1; [d] ICD-9 783.2; [e] adjusted for clinic.

Weight gain and weight loss were reported significantly more frequently in current Norplant users than in current IUD users and sterilized women (Table 7). No cases of weight gain were reported among sterilized women and one sterilized woman reported weight loss. In China, 94% of subjects had body weight recorded at baseline and at 5 years. For current Norplant users, the average weight increase was 2.5 kg [standard error (SE) 0.07] compared with 1.5 kg (SE 0.08) for controls ($p < 0.001$). The crude incidence rates of abdominal pain (ICD-9 789.0) were 0.96, 1.40, and 0.26 per 1.000 woman-years in current Norplant users, IUD users and sterilized women, respectively. The adjusted rate ratio for current Norplant users compared with controls was 0.79 (0.50,1.26) ($p = 0.33$).

In the subchapter of Ill-defined and Unknown Causes of Morbidity and Mortality (ICD-9 797–799), reports were twice as frequent for Norplant users compared to controls (Appendix 2). The subchapter included 60 reports of nervousness (ICD-9 799.2), one of debility (ICD-9 799.3), and 33 coded as other ill-defined or unknown causes (ICD-9 799.8, 799.9). The diagnosis of nervousness (ICD-9 799.2) was analyzed together with anxiety and depression in the subchapter Neurotic Disorders and Personality Disorders (ICD-9 300–316), see Chapter V and Table 5. For ill-defined morbidity the incidence rate in Norplant initiators was 0.6 per 1.000 woman-years, the adjusted rate ratio was 1.86 (0.92, 3.73).

3.4.15. Chapter XVII: injury and poisoning (ICD-9 800–999)

There were 52 injuries and 6 accidental poisonings classified as MHEs (Appendix 1). The overall rate ratios for controls compared with Norplant users were not significantly different from unity. The most frequent type of injury was fractures of the lower limbs (ICD-9 820–829), 8 in Norplant users and 8 in controls. Sixty-nine injuries and 47 accidental poisonings were classified as OHPs, both reported consistently but not significantly more often in Norplant initiators (Appendix 2).

3.5. Deaths

There were 34 deaths among study subjects, 26 while still using the initial method (Table 8). Twenty-two of the 34 deaths were due to accidents, including falls, and accidental poisonings (11), suicides (8), and homicide (3). Of the eight women who died from suicide, one had a history of recent hospitalization for mental disease while none of the other 7 women had any report of previous or concurrent psychiatric disease or mood changes. Deaths due to disease were caused by cancers of breast, lung, rectum, and stomach, acute monocytic leukemia, non-Hodgkin's lymphoma, intracranial hemorrhage, bronchial asthma, status epilepticus, unspecified secondary cardiomyopathy, sudden ill-defined cardiorespiratory failure, and septic abortion. The woman who died from status epilepticus was a Norplant user who had failed to inform study personnel about her history of epilepsy when she was admitted to the study. The death caused by septic abortion was in a woman who had discontinued Norplant one year prior to the abortion. Mortality rate ratios for Norplant initiators compared to controls, adjusted for clinic were 0.86 (0.44, 1.69) ($p = 0.67$) for all deaths, 1.23 (0.34, 3.70) ($p = 0.84$) for deaths due to accidents and accidental poisonings, 0.33 (0.34, 3.70) ($p = 0.18$) for deaths due to suicides, and 1.98 (0.60, 6.57) ($p = 0.27$) for deaths due to disease.

4. Discussion

This study involving 16,021 women in developing countries, and nearly 80,000 woman-years of observation, confirms the safety of Norplant implants, IUDs and sterilization with regard to serious health problems. The incidence of first MHE unrelated to pregnancy, was 13.3 per 1,000 woman-years, 1,043 events in 78,323 woman-years in the analysis by subchapter (Table 4). The observed events were not unexpected among women of reproductive age. Differences between index subjects and controls in the frequency of MHEs were generally small and seldom statistically significant.

The overall incidence of major health events in this study is relatively low. In part this may be because women admitted to the study underwent screening and had no history, signs or symptoms of pre-existing major medical problems, and they were thus less likely to experience any severe medical events compared with women in an unselected population. Furthermore, utilization of hospital and ambulatory care services by women is generally lower in developing countries [9]. We

Table 8
Causes of death by age, months in study, initial contraceptive method and method at time of death

Cause	Age	Months in study	Initial method	Last method
External				
Suicide				
	25	27	IUD	IUD
	37	53	IUD	Condom
	32	38	IUD	None
	24	16	Norplant	Norplant
	34	36	Norplant	Norplant
	23	57	Sterilization	Sterilization
	24	36	Sterilization	Sterilization
	31	11	Sterilization	Sterilization
Accidental: motor vehicle accidents, falls, poisonings	35	15	IUD	IUD
	19	13	IUD	IUD
	24	41	IUD	IUD
	28	58	IUD	IUD
	31	43	Norplant	Norplant
	20	15	Norplant	Norplant
	36	58	Norplant	None
	31	14	Norplant	Norplant
	23	52	Norplant	Norplant
	21	45	Norplant	Norplant
	36	36	Sterilization	Sterilization
Homicide				
	24	1	IUD	IUD
	30	33	IUD	Sterilization
	25	20	Sterilization	Sterilization
Cancer				
Rectum	32	53	IUD	IUD
Stomach	30	39	IUD	IUD
Leukemia	29	52	IUD	IUD
Breast	32	41	Norplant	COC
Lung	34	42	Norplant	None
Lymphoma, non-Hodgkin	21	58	Norplant	Norplant
Cardiovascular				
Haemorrhagic stroke	26	47	Norplant	Norplant
Cardiomyopathy	37	21	Sterilization	Sterilization
Ill-defined cardio-respiratory failure	35	35	Norplant	None
Other				
Epilepsy	23	51	Norplant	Norplant
Asthma	27	17	Norplant	Norplant
Septic abortion	23	41	Norplant	None

cannot exclude that MHEs were under-reported. However, women in this study had frequent contact with the participating clinic, the MHEs were defined as relatively severe health events that are likely to be reported by clients in family planning clinics, especially when the providers specifically ask about such events. Moreover, the follow-up rate for women scheduled for 5 years follow-up, was above 96% at the completion of the study, and losses to follow-up were largely due to women moving out of the catchment area of the clinics and, to our knowledge, not for medical reasons.

Baseline differences at admission between contraceptive groups in their socio-demographic and biomedical characteristics were anticipated among women who had freely chosen a reversible or permanent contraceptive method. The sterilized women, for example, were on average older, of higher parity, and had less formal education than the other groups. Baseline differences did not substantially influence the incidence rates of non-reproductive health events in exploratory analyses incidence rates adjusted for baseline characteristics were very similar to the crude rates. All incidence rate ratios were adjusted for differences between clinics, consistent with the design of the study whereby women undergoing IUD insertion or sterilization, age-matched to the Norplant initiators, were enrolled as a comparison group within each clinic. This was in anticipation of the substantially different social conditions and health care characteristics in the participating countries and clinics. For specific diseases and conditions, additional adjustment was made when relevant.

The possibility of differential reporting of MHEs by initial contraceptive method remains possible. Norplant was a new method in most of the countries involved. Previous studies have shown that women using the newest method, or their health care providers, may be more alert to potential problems [2–4]. Women initiating use of Norplant attended more scheduled follow-up visits than IUD or sterilization initiators ($p < 0.001$). Norplant and IUD initiators had more general physical and pelvic examinations and hemoglobin measurements than sterilized women ($p < 0.001$), though these differences were small [7]. The frequency of blood pressure measurement was also higher in Norplant users ($p < 0.001$). The concept of MHEs was defined a priori and referred to serious morbidity, and the MHE records were reviewed by the country coordinator(s) and at the study coordinating center to achieve uniformity of recording. At the coordinating center, the medical review of the documentation for MHEs was done with the reviewer unaware of the contraceptive method at time of the event.

The methodology of this observational cohort study was similar to large contraceptive follow-up studies undertaken in developed countries. These include the Oral Contraception Study of the Royal College of General Practitioners [2] and the Oxford Family Planning Association study [3] in the UK, and the Walnut Creek Study in California [4]. In these studies controls were frequency matched by age [2,4] and area of residence [3,4], and the enrolled women continued under observation whether or not they changed their contraceptive method. The admission criteria of these studies were such that all [2] or a large majority [3,4] of the women were married. However, the Norplant Post-Marketing Surveillance study differed from previous studies with respect to follow-up procedures, previous studies relying largely on medical practitioners to report to the study coordinators whenever enrolled women attended for health care or were hospitalized. By contrast, this study traced hospital and outpatient clinics records when major health events were reported. Moreover, the study applied active follow-up procedures, tracing women who were overdue for their scheduled 6-monthly visits in contrast to 2 of the previous studies [2,4]. Active follow-up was planned because reliable attendance at family planning clinics was uncertain in developing countries, there was no precedent, except in China, for follow-up through 5 years, and exchange of information between hospital-based services and the family planning clinics involved in the study was not well organized.

4.1. Deaths

The majority of deaths recorded in this study (22 of 34) were due to accidents, suicide or homicide. Few deaths were due to disease, such as cancer or cardiovascular diseases and there was no association with the contraceptive method used. One death due to septic abortion occurred in a woman who had stopped contraception a year earlier. The overall mortality in this developing countries study (34 deaths per 78,323 woman-years, 0.43 per 1,000 woman-years) can be compared with early reports from 3 previous developed country studies: the Royal College of General Practitioners study, reported in 1974 a mortality rate of 0.73 deaths per 1,000 woman-years [2]; the Oxford Family Planning Association study reported in 1976 a rate of 0.43 per 1,000 woman-years [3], and the Walnut Creek study reported in 1980 a rate of 1.33 per 1,000 [4]. More deaths in this study were due to accidents, suicide or homicide (22/34, 65%) than in the Royal College of General Practitioners study (22/69, 32%) [2]. In the Oxford Family Planning Association study the women were almost 2 years older on average and 16 of 24 deaths (67%) were due to cancer or cardiovascular disease [3] compared with 9 of 34 (26%) in this study.

4.2. Major health events

Malignant neoplastic and cardiovascular disease are serious long-term health concerns for contraceptive users. Results from this study are generally reassuring with respect to both although they are based on small numbers. The incidence of breast cancer (reported elsewhere [7]) was below that expected in the countries concerned, and non-reproductive malignant neoplasms were rare and followed no clear pattern. Cardiovascular events were infrequent. There were two strokes, one deep venous thrombosis, and no myocardial infarctions. All three events occurred in Norplant users. The incidence of cardiovascular events in this study may reflect the screening of eligible women, their low rates of obesity and low frequency of smoking (less than 10% of women had ever smoked). An estimate of the expected number of events was derived from cardiovascular incidence profiles for women in developing countries who have no cardiovascular risk factors; that is, women free from hypertension, diabetes mellitus, and hyperlipidemia who do not smoke or use oral contraceptives [10]. Adjusted for the age and country distribution of the women in this study, an expected 0.1, 2.7, and 2.6 myocardial infarctions, strokes (all types) and venous thromboembolisms, respectively, would have occurred in cases of 78,323 woman-years. The corresponding expected number of cases among 39,337 woman-years of Norplant use were 0.05, 1.3, and 1.3 for myocardial infarctions, strokes and venous thromboembolisms, respectively.

Another factor contributing to few cardiovascular events might be the low incidence of hypertension: approximately 0.7, 0.4, and 0.5 cases per 1,000 woman-years in current Norplant and IUD users and sterilized women, respectively. Although the overall incidence of hypertension was low, the adjusted rate ratio for current Norplant users compared with controls was 1.78 ($p = 0.08$), and the rate ratio for hypertension and borderline hypertension combined was significantly higher for current Norplant users ($p = 0.02$). The higher frequency of hypertension among Norplant users

could, in part, reflect reporting bias since blood pressure measurements were more frequent among index subjects than among controls. Oral contraception, usually at higher dose levels, has been associated with an increased risk of hypertension [2]. In one study, oral contraceptive users but not Norplant users had higher diastolic blood pressures than IUD using controls [11]. If the observed difference in hypertension incidence between Norplant and IUD users were true, then in theory one more case of hypertension would occur per annum in approximately 3,000 Norplant users than in a similar number of IUD users.

The possibility that Norplant use might be associated with an increased risk of stroke was raised in a 1995 publication on spontaneous reporting in the United States [12]. However, a pooled analysis of data from 2 population-based case-control studies found that the odds ratio for stroke in current Norplant use compared with non-current use was 1.0 (0.1, 9.2) after adjustment for age [13]. Despite the size of the present study, the data were still insufficient to estimate relative rates, but the results are consistent with the findings from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, where the odds ratios for all strokes in women using oral and injectable progestogen-only contraceptives, were 1.01 (0.60, 1.69) and 1.07 (0.62, 1.86), respectively [14]. This study's data are consistent with other epidemiologic studies, jointly indicating no material increase in risk of stroke with Norplant use.

Effects of Norplant on glucose tolerance have been reported previously. Non-insulin dependent diabetes was a medical reason for implant removal in an Egyptian study [15]. Also, in a 3-year clinical trial, two of nine women tested had impaired glucose tolerance, one in the clinical diabetes range, although subsequent tests after removal of Norplant were within the normal range [16]. Larger long-term studies of Norplant have not identified women developing diabetes while using Norplant [5,6], perhaps because increases in glucose and insulin levels remain within normal limits during use of Norplant, they peak at 12 months and usually decrease with time according to one study [17]. Eight women using Norplant and three controls in this study developed diabetes, an overall incidence of 0.15 per 1,000 woman-years, well below the power of the study to detect doubling of an incidence rate from 1 to 2 per 1,000, comparing one contraceptive initiator group with another. If the observed difference in diabetes incidence between Norplant and IUD users were true, then in theory, 7,300 women using Norplant would experience one more case of diabetes per annum than a similar number of IUD users. It is not clear from this study whether the higher diabetes incidence in current Norplant users compared with current IUD users is causally associated with use of Norplant. Further evaluations are needed to resolve this question.

Among the more frequent non-reproductive MHEs were cholelithiasis and appendicitis. The rate ratio for gallbladder disease, including cholelithiasis (ICD-9 574) and other disorders of the gallbladder (ICD-9 575), for initiators of Norplant v. initiators of IUD or sterilization, was significantly elevated (rate ratio 1.52, $p = 0.04$), but not for current users (rate ratio 1.31, $p = 0.19$) (Table 5). Use of combined oral contraceptives has been reported to be weakly associated with gallstone disease and cholecystitis in some studies, but not all [18]. It has been proposed that oral contraceptive use precipitates the clinical manifestation of already existing gallstones, with or without enhancement of gallstone formation [19]. It is not known if the apparent association is due to the estrogen or the progestogen component, or both, of the oral contraceptives [18]. The data from this study are compatible with a weak association between use of Norplant and gallbladder disease, similar to that observed for combined oral contraceptives.

Less-frequent MHEs included severe mental disorders, systemic lupus erythematosus, rheumatoid arthritis, and thrombocytopenia. The study did not confirm concerns about an excess risk of major depression among Norplant users, concerns that were based on seven cases described in two previous reports [20,21]. The study also did not confirm concerns about silicone implant-related risks of connective tissue disorders, concerns that have been refuted by recent large meta-analyses [22]. In the present study there was no Norplant-associated risk of systemic lupus erythematosus or other diseases in the ICD-9 3-digit category of diffuse diseases of connective tissue. Rheumatoid arthritis was diagnosed somewhat more often among Norplant initiators than among controls but the difference was not statistically significant. Other studies have found that use of combined oral contraceptives is associated with reduced risk of rheumatoid arthritis, but it is unclear if the association is real [23]. More enigmatic is the issue of thrombocytopenia, which occurred in 3 Norplant users in China but no case in controls, with an overall incidence in Norplant users of approximately 9 per 100,000 woman-years. One previous Chinese study reported 8 cases among 301 users of Norplant 2 [24], a levonorgestrel-releasing implant similar to Norplant. To our knowledge there are no incidence figures for this disease from China or other developing countries. The annual incidence rate of hospitalization for thrombocytopenia for women in the United States is estimated to be 2.6 to 7.4 cases per 100,000 women aged 15–44 years [25], comparable with the incidence rate of this study.

4.3. Other health problems

The intensity of reporting OHPs varied between countries and between clinics within countries. Several factors may have influenced this variability. Differences between countries and regions in the incidence and prevalence of symptoms and health conditions may have contributed to the variation. Social and cultural views of health conditions and their symptoms may also have played a role as shown by Murray and Chen who reported how self-perceived indicators of specific morbidities vary widely between states in India [26]. Between clinics there may have been differ-

ences in the probing for the presence of health problems, or different thresholds for which complaints and symptoms resulted in assigning a medical diagnosis or both. Examples of clustering of OHP diagnoses to certain clinics were all diagnoses of fatigue and malaise among sterilized women, 99.5% of the 203 reports were from 1 clinic, and 7 of 8 diagnoses of strabismus were reported from 1 clinic. Also, within clinics the frequency of reporting of OHPs was dependent on the local principal investigators who assigned diagnostic codes at the clinic level. In some clinics investigators were replaced in the course of the study that led to changes in the intensity of reporting of OHPs. Conditions and diseases in the OHP category may also have been misclassified with regard to ICD-9 codes, which theoretically should lead to bias toward unity of the rate ratios for OHPs. For these reasons OHP diagnoses were primarily analyzed at the level of ICD-9 subchapters, but attempts were made to identify specific 3-digit or 4-digit ICD-9 codes to which any differences possibly could be attributed.

For 14 of the ICD-9 subchapters, including ICD-9 Chapter IV, of non-reproductive OHPs reported in this paper, the adjusted rate ratio was significantly larger for women initiating Norplant compared with controls. In none of the subchapters was the rate ratio significantly less than unity. This imbalance in the distribution of the rate ratios may be due to chance, confounding, bias, causal relationships, or a combination of these. Chance is an unlikely explanation for the skewed distribution of the rate ratios, the probability of the observed distribution under the null hypothesis of no difference was small ($p < 0.0001$). Confounding is a possible explanation for the higher rate of reports among Norplant initiators. There were differences in demographic and social characteristics between initiators of Norplant, IUDs and sterilization (Table 2). For Norplant and IUD initiators these differences were generally small albeit statistically significant. The sterilization initiators who were relatively fewer, were on average older, had higher parity, and less formal education than the other two groups. While confounding by choice of method may have influenced the rate ratios of OHPs for Norplant compared with all controls, it is not likely that the effect of confounding has been large in the comparison between Norplant and IUD initiators. Moreover, when rate ratios were adjusted for clinic, additional adjustment for baseline characteristics did not materially influence them.

In four ICD-9 subchapters, it could be expected that more diagnoses would be recorded in Norplant users than in controls according to previous observations and a causal association is plausible. These were the subchapter Neurotic Disorders (ICD-9 300–316) which includes anxiety and depression (ICD-9 300–311), the subchapter Other Disorders of the CNS (ICD-9 340–349), which includes migraine (ICD-9 346), the subchapter Other Diseases of the Skin (ICD-9 700–709) which includes alopecia, hirsuitism and acne, and the subchapter Symptoms (ICD-9 780–759) which include headache (ICD-9 784). All these diagnoses have previously been reported to be associated with Norplant [5,6].

Of the remaining 10 subchapters, four were in the ICD-9 chapter Diseases of the Respiratory System (ICD-9 460–529), 2 each in the ICD-9 chapters of Diseases of the Nervous System and Sense Organs (ICD-9 320–389) and Diseases of the Musculoskeletal System and Connective Tissue [710–739], and one each in the ICD-9 chapters Diseases of the Skin and Subcutaneous Tissue (ICD-9 690–698); and Symptoms, Signs and Ill-defined Causes of Morbidity (ICD-9 780–799). The 10 subchapters include common diseases and conditions, some of which refer to unspecific symptoms and conditions. Attempts to identify diseases and conditions within these subchapters to which the elevation of the rate ratio could be attributed were largely fruitless. In most instances the detailed analysis of ICD-9 three- and four-digit codes within the subchapters showed that the ICD-9 3- and 4-digit codes referred to unspecific diagnosis, e.g., arthropathies and related disorders (ICD-9 710–719), rheumatism, excluding the back (ICD-9 725–729), and ill-defined and unknown causes of morbidity (ICD-9 797–799), or that the diagnoses were distributed over a large number of ICD-9 codes without any pattern, e.g. acute respiratory tract infections (ICD-9 460–466), disorders of the eye (ICD-9 360–379). It may be that use of Norplant is associated with vague and general symptoms, which are difficult for women and their health providers to define precisely, and that the symptoms therefore were assigned to unspecific diagnostic categories.

It is likely that the elevated rate ratios of OHPs for Norplant users can in part be attributed to bias. For the women and providers in all the participating centers Norplant was a relatively new contraceptive method, and moreover being implantable, it was a new principle for administrating a contraceptive hormone. The novelty of the method may have meant that women were more alert to report on symptoms and signs, and providers to record these. Similar tendencies to reporting and recording biases were reported from other observational cohort studies of combined oral contraceptives when these were a new contraceptive method [2–4], and particularly from the Royal College of General Practitioners Study on oral contraceptives [2] that, like the present study, recorded all health events regardless of severity. The higher incidence rates of unspecific OHP diagnoses such as influenza, chronic bronchitis, dyspepsia, kidney and ureter calculus, and unspecified pain (psychalgia) which were all unexpectedly significantly more often reported for Norplant users, may be due to reporting and recording biases. Slightly higher rates of attendance of Norplant initiators to scheduled and unscheduled visits, and of having medical examinations [7], indicate surveillance bias, but the higher attendance rate may also have been a reflection a real need for consultation with health care providers.

Some of the diseases and conditions unexpectedly reported as OHPs at a significantly higher rate among Nor-

plant users have the common denominator of atopic diathesis although they appear in unrelated ICD-9 subchapters. The subchapters relating to Other Diseases of the Upper Respiratory Tract (ICD-9 470–478), to Chronic Obstructive Pulmonary Diseases (ICD-9 490–496), and to Other Inflammatory Conditions of Skin (ICD-9 690–698), include conditions such as nasal congestion and rhinitis, asthma, eczema, and pruritus that are embraced in the concept of atopic diathesis. Acute urticaria (ICD-9 708) is also a component of atopic diathesis. All but one of these conditions (allergic rhinitis, ICD-9 477) were significantly more often reported among Norplant users than among controls. This pattern of distribution of OHP diagnoses indicates that use of Norplant may well be associated with atopic conditions, perhaps in a subgroup of susceptible women. The design of this study, however, does not allow any further in-depth evaluation of the apparent association and studies of a different design are needed to further examine the possible causality of the observation.

Among the most frequent non-reproductive OHPs within three- or four-digit ICD-9 diagnostic codes were migraine and headaches, weight gain, and mood disturbances. Migraine and common headache analyzed as a combined variable, were significantly more common in current Norplant users compared with controls. In previous studies, headache was the second most common reason for women to discontinue Norplant use [27], in a study in the United States the incidence of headache was 78 per 1,000 woman-years [28]. The incidence of migraine and headache among current Norplant users in the present study was much lower (11.5 per 1,000 woman-years). Reports of both weight gain and weight loss were significantly more common in Norplant users than controls, but again the overall incidence was low (4.5 and 1.2 reports per 1,000 woman-years) for weight gain and weight loss, respectively, in Norplant users. Judging from the data from China on measurements of weight at admission and at the end of the study, the average weight gain was 1.0 kg more among Norplant users than in controls. Mood changes including anxiety, depression, and nervousness were also more likely in Norplant users, and once again the incidence was low (2.8 reports per 1,000 woman-years). The health problems headache, weight gain and mood disturbances and several other complaints found to be associated with use of Norplant in this study such as frigidity and pruritus, have been reported to be related to use of other hormonal contraceptives [29].

Less commonly reported OHPs analyzed at the ICD-9 three-digit level occurring more frequently among Norplant users were visual disturbances, skin disorders (hirsutism, alopecia, acne, pruritus, and urticaria). Seven cases of visual disturbances were reported in Norplant users and one in controls, and the p-value (0.04) for the difference should be interpreted with caution, given the number of significance tests that have been done in these analyses. Similar transient visual disturbances have been reported to be associated with combined oral contraceptives [29]. As to more serious eye diseases, a recent report on eye disease from the Oxford Family Planning Association and Royal College of General Practitioners studies concluded that only retinal vascular lesions were more likely in current and recent users of oral contraception [30]. Among skin conditions reported in the present study, dermatitis and eczema, pruritus and urticaria were reported at an incidence rate of <1.5 per 1,000 woman-years among Norplant users, and were unexpectedly more commonly noted among Norplant users than among controls. Of perhaps more concern are the skin disorders that potentially could represent increased androgenic activity, hirsutism, alopecia and acne. Hirsutism and alopecia were rare. Acne was reported by 35 women of whom 30 were Norplant users ($p < 0.001$). In previous studies acne was the most commonly reported skin problem, but the incidence rate for acne in the present study was two orders of magnitude lower than in one previous report (0.90 per 1,000 woman-years in this study compared with 7% in the first year of Norplant use in a study from the USA) [6]. Nevertheless, the higher rate in Norplant users in this study is consistent with the earlier report. The mechanism for development of acne remains unclear. Norplant use appears to reduce SHBG and total testosterone levels, while free testosterone remains unchanged, and no significant differences were seen in androgen measurements between Norplant users with and without acne [31].

Other observations in this study were 24 women with episodes of pain in the arm of the Norplant insertion during use it the implants, and 13 cases of filariasis infection among current Norplant initiators in Sri Lanka. Pain at the site of the insertion of Norplant has been reported in previous studies of Norplant although these studies did not distinguish between pain reported at insertion, during use, or removal [32]. The incidence of pain in this study was low—3 per 1,000 Norplant insertions—and transient. The excess of filariasis infections in Norplant initiators in Sri Lanka, is unlikely to be due to chance ($p < 0.001$). Unless the observation of the excess infection rate is attributable to confounding and bias, the explanation may be complex and perhaps relate subtle immunologic changes similar to those thought to alter susceptibility to filarial [33] and nematodes infestations [34].

5. Conclusion

The Post-Marketing Surveillance of Norplant study shows that multi-center, large-scale cohort studies to evaluate the safety of fertility regulating methods are feasible in developing countries. The observations exceeded the planned 30,000 woman-years for each of the Norplant and control groups. For less serious health concerns, findings from this study indicate that use of Norplant in developing country settings is associated with a variety of symptoms and conditions ranging from headaches, mood changes, respiratory tract and skin problems. The excess incidence

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rates of these symptoms and conditions possibly attributable to use of Norplant users were low, generally in the order of 1 to 2 per 1,000 woman-years or less, although for migraine and headaches, and unclassifiable symptoms the excess incidence rates were higher. It was, however, not possible to determine to what extent the excess incidence of many these less serious conditions is causally attributable to use of Norplant or to reporting bias. With respect to serious medical conditions the study results were reassuring. There was no excess morbidity for serious conditions such as cancer and cardiovascular disease, but the number of disease endpoints was small. Apart from a weak association between use of Norplant and gallbladder disease and possibly increased blood pressure, Norplant was not related to any material risk of serious morbidity compared with IUDs and female sterilization.

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Appendix 1
Major health events by ICD-9 sub-chapters and by initial use of Norplant, IUD or sterilization

ICD-9 sub-chapters	ICD-9 code	Norplant		IUD		Sterilization		Adjusted[a] rate ratio (Norplant/controls)		
		No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
I-Infectious and parasitic diseases										
Intestinal infectious diseases	001–009	3	0.1	3	0.1	0		1.06	(0.21, 5.25)	0.95
Tuberculosis	010–018	17	0.4	10	0.3	2	0.3	1.39	(0.66, 2.92)	0.38
Zoonotic bacterial diseases	020–027	0		0		0				
Other bacterial diseases	030–041	1	0.03	0		0		∞		
Poliomyelitis and other non-arthropod-borne viral diseases of CNS	045–049	1	0.03	0		0		∞		
Viral diseases accompanied by exanthem	050–057	1	0.03	0		0		∞		
Arthropod-borne viral diseases	060–066	1	0.03	1	0.03	0		0.91	(0.06, 14.5)	0.95
Other diseases due to viruses and chlamydiae	070–079	24	0.6	17	0.5	3	0.4	1.21	(0.67, 2.20)	0.52
Rickettsioses and other arthropod-borne diseases	0.80–088	1	0.03	0		1	0.1	0.89	(0.06, 14.2)	0.93
Syphilis and other venereal diseases	090–099	2	0.1	4	0.1	0		0.48	(0.09, 2.65)	0.40
Other spirochaetal diseases	100–104	0		0		0				
Mycoses	110–118	0		0		0				
Helminthiases	120–129	3	0.1	0		0		∞		
Other infectious and parasitic diseases	130–136	2	0.1	0		0		∞		
Late effects of infectious and parasitic diseases	137–139	1	0.03	0		0		∞		
II-Neoplasms										
Malignant neoplasm of										
lip, oral cavity and pharynx	140–149	1	0.03	0		0		∞		
digestive organs and peritoneum	150–159	0		3	0.1	0		0.00		
respiratory and intrathoracic organs	160–165	1	0.03	0		0		∞		
bone, connective tissue, skin and breast	170–175	4	0.1	1	0.03	0		4.07	(0.46, 36.4)	0.21
genitourinary organs	179–189	0		0		2	0.3	0.00		
other and unspecified sites	190–199	0		1	0.03	0		0.00		
lymphatic and haematopoietic tissue	200–208	1	0.03	1	0.03	0		1.00	(0.06, 16.00)	1.00
Benign neoplasms	210–229	60	1.5	48	1.5	5	0.7	1.13	(0.78, 1.63)	0.53
Carcinoma in situ	230–234	8	0.2	4	0.1	3	0.4	1.13	(0.41, 3.12)	0.81
Neoplasms of uncertain behaviour	235–238	0		0		0				
Neoplasms of unspecified nature	239	0		0		0				
III-Endocrine, nutritional and metabolic diseases and immunity disorders										
Disorders of thyroid gland	240–246	12	0.3	9	0.3	2	0.3	1.07	(0.47, 2.42)	0.87
Diseases of other endocrine glands	250–259	11	0.3	4	0.1	1	0.1	2.23	(0.78, 6.42)	0.14
Nutritional deficiencies	260–269	0		0		0				
Other metabolic and immunity disorders	270–279	1	0.03	0		0		∞		
IV-Diseases of blood and blood-forming organs	280–289	63	1.6	71	2.2	2	0.3	0.87	(0.62, 1.21)	0.41
V-Mental disorders										
Organic psychotic conditions	290–294	1	0.03	0		0		∞		
Other psychoses	295–299	5	0.1	1	0.03	1	0.1	2.40	(0.46, 12.4)	0.30
Neurotic disorders, personality disorders	300–316	3	0.1	2	0.1	1	0.1	0.97	(0.20, 4.81)	0.97
Mental retardation	317–319	0		0		0				

VI-Diseases of the nervous system and sense organs									
Inflammatory diseases of the CNS	320–326	1	0.03	0		1	0.1	0.93	(0.06, 14.8)	0.96
Hereditary and degenerative CNS disorders	330–337	0		0		0				
Other disorders of the CNS	340–349	4	0.1	0		2	0.3	2.03	(0.37, 11.1)	0.41
Disorders of the peripheral nervous system	350–359	3	0.1	3	0.1	1	0.1	0.75	(0.17, 3.35)	0.71
Disorders of the eye and adnexa	360–379	8	0.2	2	0.1	0		4.05	(0.86, 19.1)	0.08
Diseases of the ear and mastoid process	380–389	4	0.1	0		1	0.1	3.89	(0.43, 34.8)	0.23
VII-Diseases of the circulatory system										
Acute rheumatic fever	390–392	4	0.1	1	0.03	1	0.1	1.87	(0.34, 10.2)	0.47
Chronic rheumatic heart disease	393–398	2	0.1	2	0.1	2	0.3	0.50	(0.09, 2.76)	0.43
Hypertensive disease	401–405	27	0.7	14	0.4	4	0.6	1.49	(0.82, 2.71)	0.19
Ischaemic heart disease	410–414	0		0		0				
Diseases of pulmonary circulation	415–417	0		0		0				
Other forms of heart disease	420–429	9	0.2	9	0.3	2	0.3	0.82	(0.34, 1.98)	0.66
Cerebrovascular disease	430–438	2	0.1	0		0		∞		
Diseases of arteries, arterioles and capillaries	440–448	0		0		0				
Diseases of veins, lymphatics and other	451–459	15	0.4	6	0.2	1	0.1	2.07	(0.84, 5.07)	0.11
VIII-Diseases of the respiratory system										
Acute respiratory infections	460–466	3	0.1	2	0.1	1	0.1	1.01	(0.20, 5.00)	0.99
Other diseases of upper respiratory tract	470–478	7	0.2	1	0.03	0		7.08	(0.87, 57.5)	0.07
Pneumonia and influenza	480–487	8	0.2	5	0.2	0		1.61	(0.53, 4.91)	0.41
Chronic obstructive pulmonary disease and allied conditions	490–496	3	0.1	3	0.1	0		0.96	(0.19, 4.77)	0.96
Pneumoconioses and other lung diseases	500–508	0		0		0				
Other diseases of respiratory system	510–519	0		0		0				
IX-Diseases of the digestive system										
Diseases of oral cavity, salivary glands and jaws	520–529	0		0		0				
Diseases of oesophagus, stomach and duodenum	530–537	12	0.3	8	0.3	0		1.51	(0.62, 3.68)	0.37
Appendicitis	540–543	33	0.8	18	0.6	5	0.7	1.42	(0.83, 2.41)	0.20
Hernia of abdominal cavity	550–553	3	0.1	1	0.03	1	0.1	1.43	(0.24, 8.58)	0.69
Noninfective enteritis and colitis	555–558	1	0.03	1	0.03	0		1.00	(0.06, 16.0)	1.00
Other diseases of intestines and peritoneum	560–569	2	0.1	1	0.03	0		2.02	(0.18, 22.3)	0.57
Other diseases of digestive system	570–579	68	1.7	36	1.1	6	0.9	1.62	(1.10, 2.38)	0.01
X-Diseases of the genitourinary system										
Nephritis, nephrotic syndrome and nephrosis	580–589	0		3	0.1	0		0.00		
Other diseases of urinary system	590–599	17	0.4	12	0.4	3	0.4	1.13	(0.56, 2.25)	0.74
Disorders of breast	610–611	1	0.03	1	0.03	0		1.00	(0.06, 15.9)	1.00
Inflammatory disease female pelvic organs	614–616	16	0.4	19	0.6	4	0.6	0.68	(0.36, 1.28)	0.23
Other disorders of female genital tract	617–629	46	1.2	33	1.0	6	0.8	1.15	(0.75, 1.77)	0.51
XII-Diseases of the skin and subcutaneous tissue										
Infections of skin and subcutaneous tissue	680–686	2	0.1	0		0		∞		
Other inflammatory conditions of skin/subcutaneous tissue	690–698	2	0.1	1	0.03	0		2.04	(0.19, 22.5)	0.56
Other diseases of skin and subcutaneous tissue	700–709	2	0.1	1	0.03	0		2.03	(0.18, 22.4)	0.56
XIII-Diseases of the musculoskeletal system and connective tissue										
Arthropathies and related disorders	710–719	10	0.3	3	0.1	1	0.1	2.48	(0.78, 7.91)	0.13
Dorsopathies	720–724	3	0.1	2	0.1	2	0.3	0.74	(0.17, 3.33)	0.70
Rheumatism, excluding the back	725–729	1	0.03	3	0.1	0		0.33	(0.03, 3.22)	0.34
Osteopathies/chondropathies/acquired muscular deformities	730–739	2	0.1	0		0		∞		
XIV-Congenital anomalies	740–759	3	0.1	2	0.1	1	0.1	0.98	(0.20, 4.85)	0.98
XVI-Symptoms, signs and ill-defined conditions										
Symptoms	780–789	4	0.1	0		0		∞		
Nonspecific abnormal findings	790–796	1	0.03	0		0		∞		
Ill-defined/unknown causes of morbidity/mortality	797–799	1	0.03	0		0		∞		
XVII-Injury and poisoning										
Injury	800–959	28	0.7	20	0.6	4	0.6	1.15	(0.67, 1.98)	0.62
Poisoning/toxic effects/complications of care	960–999	3	0.1	1	0.03	2	0.3	0.96	(0.19, 4.75)	0.96

Number of events, crude incidence rate per 1000 woman-years and adjusted rate ratio.

[a] Adjusted for clinic.

Appendix 2
Other health problems by ICD-9 sub-chapters and by initial use of Norplant, IUD or sterilization

ICD-9 sub-chapters	ICD-9 code	Norplant		IUD		Sterilization		Adjusted[a] rate ratio (Norplant/controls)		
		No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
I-Infectious and parasitic diseases										
Intestinal infectious diseases	001–009	44	1.1	18	0.6	39	5.6	0.76	(0.52, 1.13)	0.18
Tuberculosis	010–018	0		0		0				
Zoonotic bacterial diseases	020–027	0		0		0				
Other bacterial diseases	030–041	2	0.1	1	0.03	0		1.94	(0.18, 21.4)	0.59
Poliomyelitis and other non-arthropod-borne viral diseases of CNS	045–049	0		0		0				
Viral diseases accompanied by exanthem	050–057	11	0.3	17	0.5	0		0.63	(0.30, 1.35)	0.23
Arthropod-borne viral diseases	060–066	1	0.03	2	0.1	0		0.46	(0.04, 5.10)	0.53
Other diseases due to viruses and chlamydiae	070–079	12	0.3	12	0.4	0		0.99	(0.44, 2.20)	0.97
Rickettsioses and other arthropod-borne diseases	080–088	0		1	0.03	0		0.00		
Syphilis and other venereal diseases	090–099	2	0.1	3	0.1	0		0.65	(0.11, 3.87)	0.63
Other spirochaetal diseases	100–104	0		0		0				
Mycoses	110–118	141	3.6	138	4.4	25	3.6	0.84	(0.67, 1.05)	0.13
Helminthiases	120–129	26	0.7	8	0.3	12	1.7	1.19	(0.67, 2.14)	0.55
Other infectious and parasitic diseases	130–136	120	3.1	111	3.5	32	4.5	0.79	(0.62, 1.01)	0.06
Late effects of infectious and parasitic diseases	137–139	0		0		0				
II-Neoplasms										
Malignant neoplasms	140–208	0		0		0				
Benign neoplasms	210–229	32	0.8	18	0.6	8	1.1	1.22	(0.73, 2.05)	0.45
Carcinoma in situ	230–234	0		0		0				
Neoplasms of uncertain behaviour	235–238	0		1[b]	0.03	0		0.00		
Neoplasms of unspecified nature	239	0		0		0				
III-Endocrine, nutritional and metabolic diseases and immunity disorders										
Disorders of thyroid gland	240–246	10	0.3	2	0.1	1	0.1	3.19	(0.88, 11.6)	0.08
Diseases of other endocrine glands	250–259	11	0.3	6	0.2	5	0.7	0.96	(0.42, 2.22)	0.93
Nutritional deficiencies	260–269	4	0.1	1	0.03	0		3.96	(0.44, 35.4)	0.22
Other metabolic and immunity disorders	270–279	53	1.4	28	0.9	6	0.9	1.53	(0.99, 2.35)	0.05
IV-Diseases of blood and blood-forming organs	280–289	26	0.7	14	0.4	0		1.93	(1.01, 3.71)	0.05
V-Mental disorders										
Organic psychotic conditions	290–294	1	0.03	0		0		∞		
Other psychoses	295–299	11	0.3	7	0.2	3	0.4	1.10	(0.47, 2.59)	0.83
Neurotic disorders, personality disorders	300–316	209	5.4	71	2.2	18	2.6	2.70	(2.11, 3.46)	<0.001
Mental retardation	317–319	0		0		0				
VI-Diseases of the nervous system and sense organs										
Inflammatory diseases of the CNS	320–326	0		0		0				
Hereditary and degenerative CNS disorders	330–337	1[c]	0.03	0		0		∞		
Other disorders of the CNS	340–349	96	2.5	9	0.3	30	4.3	2.50	(1.73, 3.63)	<0.001
Disorders of the peripheral nervous system	350–359	17	0.4	3	0.1	1	0.1	4.65	(1.56, 13.8)	0.01
Disorders of the eye and adnexa	360–379	34	0.9	13	0.4	4	0.6	2.13	(1.19, 3.82)	0.01
Diseases of the ear and mastoid process	380–389	24	0.6	10	0.3	3	0.4	1.83	(0.93, 3.60)	0.08
VII-Diseases of the circulatory system										
Acute rheumatic fever	390–392	0		1[d]	0.03	0		0.00		
Chronic rheumatic heart disease	393–398	0		0		0				
Hypertensive disease	401–405	28	0.7	15	0.5	4	0.6	1.48	(0.82, 2.64)	0.19
Ischaemic heart disease	410–414	2[e]	0.05	0		0		∞		
Diseases of pulmonary circulation	415–417	0		0		0				

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Other forms of heart disease	420–429	27	0.7	10	0.3	7	1.0	1.59	(0.87, 2.92)	0.13
Cerebrovascular disease	430–438	0		0		0				
Diseases of arteries, arterioles and capillaries	440–448	4	0.1	0		0		∞		
Diseases of veins, lymphatics and other	451–459	57	1.5	27	0.8	13	1.8	1.40	(0.93, 2.10)	0.10
VIII-Diseases of the respiratory system										
Acute respiratory infections	460–466	226	5.8	118	3.7	46	6.6	1.38	(1.13, 1.69)	<0.01
Other diseases of upper respiratory tract	470–478	36	0.9	18	0.6	2	0.3	1.78	(1.03, 3.08)	0.04
Pneumonia and influenza	480–487	51	1.3	15	0.5	3	0.4	3.24	(1.89, 5.56)	<0.001
Chronic obstructive pulmonary disease and allied conditions	490–496	54	1.4	16	0.5	4	0.6	2.67	(1.60, 4.46)	<0.001
Pneumoconioses and other lung diseases	500–508	1	0.03	0		1	0.1	0.98	(0.06, 15.7)	0.99
Other diseases of respiratory system	510–519	5	0.1	0		0		∞		
IX-Diseases of the digestive system										
Diseases of oral cavity, salivary glands and jaws	520–529	34	0.9	23	0.7	1	0.1	1.42	(0.84, 2.39)	0.19
Diseases of oesophagus, stomach and duodenum	530–537	144	3.7	82	2.6	33	4.7	1.24	(0.97, 1.59)	0.08
Appendicitis	540–543	6	0.2	3	0.1	0		1.98	(0.49, 7.92)	0.33
Hernia of abdominal cavity	550–553	6	0.2	2	0.1	2	0.3	1.46	(0.41, 5.16)	0.56
Noninfective enteritis and colitis	555–558	29	0.7	24	0.8	4	0.6	1.02	(0.61, 1.72)	0.93
Other diseases of intestines and peritoneum	560–569	53	1.4	30	0.9	26	3.7	0.93	(0.64, 1.36)	0.71
Other diseases of digestive system	570–579	25	0.6	13	0.4	2	0.3	1.68	(0.88, 3.18)	0.11
X-Diseases of the genitourinary system										
Nephritis, nephrotic syndrome and nephrosis	580–589	0		0		0				
Other diseases of urinary system	590–599	192	4.9	130	4.1	44	6.3	1.09	(0.89, 1.34)	0.42
Disorders of breast	610–611	330	8.6	160	5.1	35	5.0	1.71	(1.43, 2.04)	<0.001
Inflammatory disease female pelvic organs	614–616	628	16.7	676	22.6	232	35.3	0.65	(0.59, 0.72)	<0.001
Other disorders of female genital tract	617–629	2701	89.3	1129	39.8	184	27.9	2.55	(2.38, 2.72)	<0.001
XII-Diseases of the skin and subcutaneous tissue										
Infections of skin and subcutaneous tissue	680–686	37	0.9	17	0.5	6	0.9	1.58	(0.94, 2.66)	0.08
Other inflammatory conditions of skin/subcutaneous tissue	690–698	137	3.5	40	1.3	5	0.7	3.09	(2.20, 4.32)	<0.001
Other diseases of skin and subcutaneous tissue	700–709	93	2.4	25	0.8	3	0.4	3.35	(2.20, 5.12)	<0.001
XIII-Diseases of the musculoskeletal system and connective tissue										
Arthropathies and related disorders	710–719	32	0.8	8	0.3	4	0.6	2.60	(1.34, 5.05)	0.01
Dorsopathies	720–724	183	4.7	103	3.3	46	6.6	1.23	(0.99, 1.53)	0.06
Rheumatism, excluding the back	725–729	93	2.4	16	0.5	5	0.7	4.71	(2.93, 7.56)	<0.001
Osteopathies/chondropathies/acquired muscular deformities	730–739	24	0.6	9	0.3	5	0.7	1.69	(0.87, 3.27)	0.12
XIV-Congenital anomalies	740–759	7	0.2	3	0.1	0		2.33	(0.60, 8.99)	0.22
XVI-Symptoms, signs and ill-defined conditions										
Symptoms	780–789	1030	28.4	272	8.7	226	34.5	2.35	(2.11, 2.62)	<0.001
Nonspecific abnormal findings	790–796	28	0.7	25	0.8	1	0.1	1.04	(0.61, 1.78)	0.88
Ill-defined/unknown causes of morbidity/mortality	797–799	63	1.6	28	0.9	3	0.4	2.02	(1.32, 3.11)	0.001
XVII-Injury and poisoning										
Injury	800–959	41	1.0	23	0.7	5	0.7	1.46	(0.90, 2.35)	0.13
Poisoning/toxic effects/complications of care	960–999	28	0.7	16	0.5	3	0.4	1.42	(0.79, 2.55)	0.23

Number of events, crude incidence rate per 1000 woman-years and adjusted rate ratio.

[a] Adjusted for clinic; [b] ICD-9 code 237.7; [c] ICD-9 code 333.5; [d] ICD-9 code 390; [e] ICD-9 code 414.8.

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References

[1] World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction. Guidelines for the toxicological and clinical assessment and post-registration surveillance of steroidal contraceptive drugs. Geneva: World Health Organization, 1987.

[2] Royal College of General Practitioners. Oral Contraceptives and Health, London: Pitman Medical, 1974.

[3] Vessey M, Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception—an interim report. J Biosoc Sci 1976;8:373–427.

[4] Ramcharan S, Pellegrin FA, Ray RM, Hsu P-J. The Walnut Creek Contraceptive Drug Study: a prospective study of the side effects of oral contraceptives. J Reprod Med 1980;25:346–72.

[5] Sivin I. International experience with NORPLANT and NORPLANT-2 contraceptives. Stud Fam Plann 1988;19:81–94.

[6] Sivin I. Contraception with NORPLANT implants. Human Reprod 1994;9:1818–26.

[7] International Collaborative Post-Marketing Surveillance of Norplant. Post-Marketing surveillance of Norplant contraceptive implants: I. Contraceptive efficacy and reproductive health. Contraception 2001; 63:167–186.

[8] World Health Organization. International classification of diseases, 9th revision. Geneva: World Health Organization, 1977.

[9] Craft N. Women's health is a global issue. BMJ 1997;315:1154–7.

[10] Farley TMM, Collins J, Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease: an international perspective. Contraception 1998;57:211–30.

[11] Shen Q, Lin D, Jiang X, Li H, Zhang Z. Blood pressure changes and hormonal contraceptives. Contraception 1994;50:131–41.

[12] Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. Obstet Gynecol 1995;85:538–42.

[13] Petitti DB, Siscovick DS, Sidney S, Schwartz SM, et al. Norplant implants and cardiovascular disease. Contraception 1998;57:361–2.

[14] World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Contraception 1998;57:315–24.

[15] Rizk DE. Subdermal levonorgestrel implants. Three years' experience in Cairo, Egypt. J Reprod Med 1995;40:638–44.

[16] Diaz S, Pavez M, Robertson DN, et al. A three-year clinical trial with levonorgestrel silastic implants. Contraception 1979:19:557–73.

[17] Konje JC, Otolorin EO, Ladipo OA. Changes in carbohydrate metabolism during 30 months on Norplant. Contraception 1991;44: 163–72

[18] Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. Am J Publ Health 1993:83:1113–20.

[19] Kaye CR. The Royal College of General Practitioners' Oral Contraceptive Study: some recent observations. Clin Obstet Gynaecol 1984; 11:759–86.

[20] Wagner K, Berenson A. Norplant-associated major depression and panic disorder. J Clin Psych 1994;55:478–80.

[21] Wagner K. Major depression and anxiety disorders associated with Norplant. J Clin Psych 1996;57:152–7.

[22] Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 2000;342:781–90.

[23] Haze JM, van Zeben D. Oral contraception and its possible protection against rheumatoid arthritis. Ann rheum Dis 1991;50:72–4.

[24] Du MK, Zheng HM, Chen HC, Chow LP. Study of Norplant implants in Shanghai: three-year experience. Int J Gynaecol Obstet 1990;33: 345–57.

[25] Graves, EJ. Detailed diagnosis and procedures, National Hospital Discharge survey 1987–1988-1989–1990. National Center for Health Statistics, Vital Health statistics 13, (107) 1991; 13, (107) 1991; 13, (108) 1991; 13, (113) 1992.

[26] Murray CJL, Chen LC. Understanding morbidity change. Pop Develop Rev 1992;18:481–503.

[27] Fraser I.S, Tiitinen A, Affandi B, Brache V, et al. Norplant consensus statement and background review. Contraception 1998;57:1–9.

[28] Sivin I, Mishell DR, Darney P, Wan L, Christ M. Levonorgestrel capsule implants in the United States: a 5-year study. Obstet Gynecol 1998;92:337–44.

[29] Hatcher RA, Trussel J, Stewart F, et al. Contraceptive technology, 16th ed. New York: Irvington Publishers, Inc, 1994.

[30] Vessey MP, Hannaford P, Mant J, Painter R, Frith P, Chappel D. Oral contraception and eye disease: findings in two large cohort studies. Br J Ophthalmol 1998;82:538–42.

[31] Olsson SE, Odlind V, Johansson E. Androgen levels in women using Norplant implants. Contraception 1986;34:157–67.

[32] Sivin I, Alvarez Sanchez F, Diaz S, et al. Three-year experience with Norplant™ subdermal contraception. Fertil Steril 1983;39:799–808.

[33] Luder CG, Schulz-Key H, Banla M, Pritzes S. Immunoregulation in onchocerciasis: predominance of Th1-type responsiveness to low molecular weight antigens of *Onchocerca volvulus* in exposed individuals without microfilaridermia and clinical disease. Clin Exp Immunol 1096;105:245–53.

[34] Elliot AM, Nakiyingi J, Quigley MA, French N, Gilks CF, Whitworth JAG. Inverse association between BCG immunization and intestinal nematode infestation among HIV-1-positive individuals in Uganda. Lancet 1999;354:1000–1.

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