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Post-marketing surveillance of Norplant® contraceptive implants: I. Contraceptive efficacy and reproductive health☆

International Collaborative Post-Marketing Surveillance of Norplant

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Abstract

The subject of this study to examine the safety and contraceptive efficacy of Norplant, we undertook a 5-year study of follow-up of women initiating use of Norplant, intrauterine device (IUD) or sterilization in eight developing countries. Women attending family clinics were enrolled if they consented and were medically eligible to use Norplant, IUD, or female sterilization. Women who chose to initiate use of IUDs or surgical sterilization served as controls and were frequency matched in 5-year age-bands with women who chose to use Norplant. At admission women had a physical examination, and their medical histories, demographic, and socio-economic characteristics were recorded. Follow-up visits were scheduled in the first 6 weeks after admission and semi-annually thereafter for 5 years irrespective of change of contraceptive method. Incidence rate ratios of health events were estimated for initial and current contraceptive method use. This paper reports reproductive health events and contraceptive efficacy. Altogether, 7,977 women initiating use of Norplant, 6,625 of IUD, and 1,419 of surgical sterilization were admitted. Their mean ages at initiation were 28.5, 28.5, and 29.6 years, respectively. More than 99% were married or cohabiting, and parous. Five-year follow-up was completed by 94.6% of the women. By the end of 5 years, the mean duration of first segment use per initiator was 4.16 years for Norplant, 4.10 years for IUDs, and 4.96 years for sterilization accounting for 39,337 woman-years for Norplant, 31,915 for IUDs, and 7,071 for sterilization. The study accumulated 78,323 woman-years of observation. Pearl pregnancy rates for Norplant, copper IUDs and female sterilization were 0.27, 0.88, and 0.17 per 100 woman-years, respectively. Users of Norplant, copper IUDs, and sterilization had rates of ectopic pregnancy of 0.30, 0.68, and 0.13 per 1,000 woman-years, respectively. Major health events related to the reproductive system were rare. Rates of acute PID were significantly lower among Norplant users than IUD users ($p = 0.004$). The rate of ovarian enlargement was significantly higher in Norplant users than controls ($p < 0.001$), but not rates of hospitalization for this condition. Vaginitis and vaginal discharge, and low abdominal pain were significantly less frequent in Norplant users than in the other groups. Bleeding disturbances were more frequent among Norplant users than controls but not anemia. The study confirms the high contraceptive efficacy of Norplant, copper IUDs, and female sterilization. The incidence rates of major reproductive health problems were low. There was no significant excess of serious reproductive morbidity among users of Norplant compared to users of IUDs and sterilization. © 2001 Elsevier Science Inc. All rights reserved.

1. Introduction

Norplant subdermal contraceptive implants continuously release levonorgestrel at low concentrations sufficient to provide effective contraception for 5 years. Regulatory approval of Norplant implants was based on large-scale, well-designed clinical trials, which indicated that Norplant provides effective contraception, with a safety profile similar to that of other steroidal contraceptives, although its use is associated with prevalent bleeding irregularities [1–4]. Premarketing clinical trials, however, are seldom large enough to evaluate the occurrence of rare adverse events that may have public health significance [5]. Moreover, clinical trials are conducted under strict supervision, in circumstances that differ from the usual clinic management, and participants are usually released from follow-up after discontinuation of the method being investigated. Hence, the safety of a method should also be evaluated during its use under usual service conditions and subsequent to its discontinuation since some adverse effects may not be manifest until some time after discontinuation.

In 1985–86, three agencies concerned with reproductive health (Family Health International, FHI; the Population Council; and the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research

☆ Norplant® is the registered trademark of the Population Council for levonorgestrel-releasing capsule implants for protection against pregnancy.

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Training in Human Reproduction, HRP) agreed to evaluate the safety and efficacy of Norplant implants by means of a controlled observational cohort study. The international post-marketing surveillance of Norplant was initiated in 1987 in eight developing countries where this contraceptive had been approved by national regulatory bodies, or approval was pending. The objective was to evaluate, in the short and medium term, the occurrence of health events of public health importance that may not have been detected in the previous clinical trials.

To our knowledge, this is the first large-scale, prospective, multi-country, long-term drug surveillance project in developing countries. The 5-year follow-up study involved women initiating use of Norplant implants or intrauterine devices (IUDs) and women undergoing surgical sterilization. This report describes the methodology of the study and focuses on reproductive health events during and after use of these fertility-regulating methods, the contraceptive efficacy of the methods, and the extent of method continuation. Health effects on other body systems are described in an accompanying paper [6].

2. Materials and methods

2.1. Study design

This was a concurrent cohort study of 5 years' duration in women initiating use of Norplant implants (index subjects), IUDs or sterilization (controls). The study was designed to have sufficient statistical power (80%) to detect a doubling of event rates among implant users from a baseline incidence rate of 1 per 1,000 woman-years (5% significance level, 2-sided test). This required observation of 30,000 woman-years in each of the index and control groups. Enrolment of 8,000 index subjects and the same number of controls was planned, given anticipated method discontinuation rates and losses to follow-up.

The protocol instruments and logistics of the study were reviewed, discussed and modified with potential country coordinators and principal investigators in meetings held before launching the study. The protocol, guidelines for investigators, forms, and logistics were tested in a pilot phase in 1987–1988, engaging a total of 1,500 women in six centers in Chile, Sri Lanka, and Thailand. After revision of the study instruments, the main phase of the study was conducted in 32 family planning clinics in eight developing countries (Bangladesh, two clinics; Chile, two clinics; China, 10 clinics; Colombia, three clinics; Egypt, five clinics; Indonesia, five clinics; Sri Lanka, one clinic; and Thailand, four clinics). Enrolment into the main phase started in January 1989 and was completed in December 1991. Participants in the pilot study were included in the main study. Follow-up was completed in 1997. The study was monitored through frequent visits to the clinics by project coordinators from the three agencies involved, and by the review of all study forms at the coordinating center at WHO in Geneva. Problems and achievements were reviewed in several investigators' meetings.

2.2. Contraceptive methods

Norplant implants consist of six Silastic® capsules which are placed subdermally [1–4]. Each capsule contains 36 mg levonorgestrel. A set of six capsules delivers approximately 30 μg of levonorgestrel per day and provides mean plasma levels that range from 0.35 ng/mL in the first year to 0.29 ng/mL in the fifth year of use [7]. Implants used in this study were manufactured with the so-called "hard tubing" Silastic®.[2,3]. Removal of implants was scheduled at the end of 5 years if they had not been removed earlier. Different models of locally available copper IUDs were provided at all clinics, non-copper IUDs were also used in some countries, notably China and Indonesia, but no progestogen-releasing IUDs were provided. The sterilization procedures preferred by each clinic were applied in the study. Other contraceptive methods were available for women who discontinued their initial method during the course of the study.

2.3. Admission requirements

Women attending family planning clinics who wanted to initiate use of Norplant implants, an IUD or sterilization, were eligible if they were: aged 18–40 years; were living in the catchment area of the clinic; were willing to participate and to attend the clinic semi-annually for 5 years; and if they satisfied medical criteria, valid at the time of initiation of the study, for the use of all three contraceptive methods involved. For each woman choosing Norplant implants, a control subject in the same 5-year age-band (20–24, 25–29 years, etc.) was enrolled.

Medical exclusion criteria were: current clinical evidence of pregnancy, hypertension, jaundice or active liver disease or anemia, as defined according to local standards, history of hypertension, diabetes mellitus, mental illness, epilepsy, severe or frequent headaches, persistent abnormal genital bleeding, ectopic pregnancy, cancer, stroke, thrombophlebitis, thromboembolism, severe cardiovascular problems, or jaundice either during pregnancy or in the preceding year. Breastfeeding women were eligible 6 weeks postpartum.

2.4. Admission procedures

Contraceptive methods available in the clinics and their known side effects were explained to clients. Women who selected Norplant implants, an IUD, or sterilization were informed of the purpose of the study, the importance of recording all health events and of attending the clinic for semi-annual visits during 5 years. Women were also in-

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formed of their right to change contraceptive method at any time if they wished. Although the counseling placed emphasis on the importance of follow-up visits, women were assured of their freedom to withdraw from the study at any time.

At admission, women provided information on their demographic and socio-economic characteristics, on their medical, reproductive, and contraceptive history, and on life-style variables such as alcohol and cigarette consumption. Physical examinations were performed, including breast and pelvic examination, cervical cytology, blood pressure and hemoglobin measurements.

Problems related to method initiation were recorded. Women were provided with a card indicating subject number and clinic identification, the study name, and information that the study was coordinated by WHO. This card was used to record health events when the clients visited health care providers, clinics or hospitals other than those involved in the study.

2.5. Follow-up

Women were scheduled for follow-up visits in the first 6 weeks after admission and every 6 months for 5 years, irrespective of change of contraceptive method. However, since the study was designed to investigate effects associated with longer-term use of the three study contraceptives, women who discontinued their contraceptive method within the first 6 months were no longer followed-up after removal; this also applied to women who became pregnant in the same interval. Women were encouraged to visit the clinic if they had any problems related to their health or contraceptive method. After a change of contraceptive method, additional visits were scheduled according to local practices, but were mandatory for women when selecting Norplant, an IUD, or sterilization. Women using their original Norplant implants at the end of 5 years had the implants removed and were followed-up with a visit at 6 weeks after removal. All other women were released from the study at 5 years.

At all visits, information about the health of the women was obtained through interviews. The interview at semi-annual visits included open-ended questions about general well-being and health complaints, as well as structured questions on current contraceptive method, smoking, last menstrual period (LMP), occurrence of pregnancy, health problems, out- and in-patient medical care, including name and address of care provider(s), clinics and hospitals, surgery and medications. Physical examinations, cervical cytology, blood pressure, and hemoglobin measurements were performed whenever women changed contraceptive method and when medically indicated. Pregnancy was confirmed by pelvic examination, urinary pregnancy tests and, in some centers, by ultrasound examination. Other laboratory tests or procedures were performed only when medically indicated.

Problems related to implant or IUD insertion, to the sterilization procedure or to implant removal, were recorded as well as reasons for discontinuing the initial and subsequent methods.

To facilitate follow-up, in addition to their addresses and telephone numbers, women provided those of husband or partner's workplace, and of two friends or relatives not in the core family. Permission was sought to contact these persons in case of missed visits. At scheduled follow-up visits, inquiries determined whether the subject had moved or planned to move and women were asked about changes in the partner's workplace. Clinics established their own means to trace women who were overdue for scheduled visits. These included phone calls, letters, home visits and/or contacting the partner, relatives or friends, according to procedures agreed upon at admission.

2.6. Ethical aspects

All women had freely selected one of the study methods, and had given informed consent to participate in the study after hearing and reading explanations of the study's purpose, and of the procedures and examinations involved. The study was approved by the ethical review committee of each participating institution and by the Scientific and Ethical Review Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

2.7. Country research teams

Providers in charge of admission and follow-up were physicians, nurses or midwives trained in contraceptive counseling, insertion and removal of Norplant and IUDs, and other clinical procedures. They were trained in the study protocol and procedures, including interviews and record keeping. All were aware of the importance of quality of care to ensure long-term follow-up. Each of the 32 clinics participating in the study had a responsible investigator who reviewed the completeness of forms and checked the coding of diagnoses. All countries had a country coordinator (two in China and Chile) who reviewed the forms of all subjects with health problems.

2.8. Definitions

To achieve uniform review, validation, and coding of health events at center and country levels, and at the overall study level, health events were categorized as "major health event" (MHE) or "other health problem" (OHP). MHEs included deaths and morbid or traumatic events which were potentially life-threatening, required hospitalization or convalescence for a period of at least one month, had physical or mental sequelae, or led to long-term medication (3 months or more). OHPs were defined as events or conditions deviating from normal mental and physical health status, except common colds and minor injuries.

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Information about health events and complaints, including symptoms and signs reported by the women, were recorded and coded by the interviewer according to the International Classification of Primary Care (ICPC) [8] and the International Classification of Diseases 9th Revision, (ICD-9) [9], respectively. The provider also assessed whether the interview or examination had uncovered any health problem or pregnancy. When the information about hospitalizations was incomplete, data were supplemented by extract from hospital case records, including duration of hospitalization, medication, and laboratory examinations, x-ray, surgery and histopathological reports, and discharge diagnosis. Similar additional information was obtained from clinics visited for outpatient care when needed.

Pregnancy was considered a major health event. The date of conception of pregnancies was estimated as 14 days after the onset of the last menstrual period, and adjusted by ultrasound diagnosis or duration of pregnancy as estimated at delivery. The postpartum period was defined as 42 days after a delivery.

Diagnosis of acute pelvic inflammatory disease (PID) (ICD-9 614.0) required oral temperature of at least 38°C, lower abdominal tenderness with guarding, and a pelvic examination revealing either tenderness on cervical motion, adnexal tenderness, or palpable adnexal mass. Women given an outpatient care diagnosis of acute PID but not fulfilling such criteria, were classified as "unspecified" PID (ICD-9 614.9). Women hospitalized for repeated episodes of lower abdominal pain and given a diagnosis of PID but not fulfilling the criteria for acute PID, or who had laparoscopy or laparotomy revealing old pelvic adhesions, were classified as "chronic PID," hospitalized (ICD-9 614.6–7), while outpatient diagnosis of PID among women with repeat episodes or prolonged pelvic pain not fulfilling the study criteria of acute PID, were classified as "other chronic PID", outpatient (ICD-9 614.6–7).

Increased or irregular vaginal bleeding or both (ICD-9 626.2; 626.4; 626.6; 626.8–9) was categorized as severe if it led to hospitalization, or dilatation and curettage, or both. A diagnosis of anemia as a MHE required a hemoglobin value of less than 10 g/dL. Diagnosis of myoma uteri (ICD-9 218) was stratified by whether the myoma(s) was discovered incidentally by systematic screening or by symptoms compatible with myoma followed by clinical examination including ultrasound in some instances. A diagnosis of a neoplastic lesion of the breast (ICD-9 174, 217) required biopsy or other surgery (except one woman with metastatic breast cancer). Benign lesions of the breast requiring surgical biopsy were considered a MHE (ICD-9 217).

2.9. Data management

When pregnancy or health events were recorded, the case form and supplementary information was reviewed by the local principal investigator who coded diagnoses according to ICD-9 and surgical procedures and medications according to International Classification of Procedures in Medicine, ICPM [10]. The country coordinator(s) subsequently reviewed the case forms and classified each event as a MHE or OHP as defined above. Forms were dispatched to WHO, Geneva, where they were checked for completeness and errors before data entry (SB). All study forms and extracts of supplementary information of subjects who experienced a MHE were reviewed by the overall project coordinator (OM), who checked the coding and assessed the validity of the diagnosis. Whenever a diagnosis of a MHE was uncertain, additional information was requested from the clinic before the final diagnosis was given. After data entry, detailed validity and consistency checks were applied. All problems identified were reviewed and resolved by correspondence and/or with visits to the centers. The diagnostic codes of OHPs, as defined above, were given at the clinics and reviewed by the country coordinator(s). When OHPs were analyzed at the ICD-9 three-digit level for reasons described elsewhere [6], the forms and validity of the diagnoses were in several instances reviewed by the project overall coordinator. Thus, for the analyses of OHPs reported in this paper, the three-digit diagnoses were reviewed for myoma uteri (ICD-9 218), benign tumors of the breast (ICD-9 217), diseases of the breast (ICD-9 610–611), inflammatory disease of ovary, fallopian tube, pelvic cellular tissues and peritoneum, and uterus (ICD-9 614–615), and symptoms and signs at site of Norplant insertion and removal.

2.10. Data analysis

This report includes reproductive health events in Norplant users and control subjects from initiation to the last study visit, provided this occurred within 63 months of admission to the study. Data from continuing users of IUDs and sterilized women were censored at that point while Norplant implants were generally removed around the 5-year point. Women who discontinued their contraceptive method within the first 6 study months contributed to event rates as of the time of their last study visit. When women moved out of the area, were lost to follow-up, refused to continue in the study or died, their data were censored as of the time of their last visit or the time of death.

Data have been analyzed both by method in current use and by initial study method. In this paper, incidence rates for reproductive health events are reported according to current method, unless otherwise stated. Observations during the second or subsequent segments of Norplant or IUD use and observations recorded in women who had switched from Norplant to an IUD, or vice versa, contribute to event rates according to the method currently used at the time of the event. When the data were analyzed by method initiated at admission, all events recorded were considered, regardless of changes in contraceptive method or use of no method that occurred during the study.

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2.11. Statistical analysis

Life table methods were used to summarize the cumulative and annual rates of pregnancy according to contraceptive method, and other reasons given for discontinuation, and all reasons combined, treating all other reasons for discontinuation as censored. The cumulative rates reported here are indistinguishable from the cumulative net rates of Chiang or the gross cumulative rates computed using the Tietze-Potter method [11–13]. Women determined to have been pregnant when stopping their contraceptive method for another expressed reason were classified as pregnant at the approximate date of conception, in preference to the originally stated reason and date. The incidence of pregnancies by current contraceptive method was expressed as a Pearl rate (pregnancies per 100 or per 1,000 woman-years) and confidence intervals computed from the Poisson distribution [14].

Incidence rates were expressed per 1,000 woman-years according to the initial method chosen or the method currently used at the time of the event. Only the incidence of first events of a specific type, or within a class of diseases, was considered and thus experience observed in the study after the first occurrence of an event was censored in the calculations for that endpoint. Crude disease incidence rates were computed according to the initial method chosen or the method used at the time of the event. Comparisons between incidence rates (rate ratios) were adjusted for differences between clinics by Poisson regression using STATA [15]. In addition, rate ratios comparing users of different contraceptive methods were adjusted for age of the woman at the start of the study. The rate ratios are given with 95% confidence intervals in parentheses.

3. Results

3.1. Participants and contraceptive methods

Altogether, 16,021 women were enrolled, of whom 7,977 were Norplant users, 6,625 were IUD users, and 1,419 were women undergoing sterilization. Clinics in China recruited 38% of participants; Egypt, Indonesia, and Thailand each enrolled between 11% and 13%, and Bangladesh, Chile, Colombia, and Sri Lanka each contributed between 5% and 8% of the participants (see Annex 1). Two clinics (one in Bangladesh and one in China) recruited only sterilized women as controls. Other clinics (all five in Egypt, six clinics in China, and one each in Bangladesh, Chile, Indonesia, and Thailand) recruited only IUD users as controls. At admission locally available copper IUDs (TCu 220C, TCu 380A, Multiload 250 and 375, or Shanghai V) were provided to 5,996 women in clinics recruiting women initiating use of the IUD or sterilization initiators. In clinics in China and Indonesia 629 women received non-copper IUDs (Lippes Loop, Stainless Steel ring, Mahua ring, Plastic flower, UCD-indomethacin, Uterine cavity shape ring). The tubal sterilization procedures at admission were performed by minilaparotomy (1,073 subjects, 76%), or laparoscopy (307 subjects, 22%). Transcervical chemical sterilization was performed with phenol atabrine (18 subjects, 1%) or quinacrine (two subjects). Other contraceptive methods were available for women who discontinued their initial method during the course of the study.

When all countries were taken together, study and control groups differed moderately in terms of age, age at first union and at first full-term pregnancy, parity, outcome of last pregnancy, educational level, tobacco consumption, and had similar alcohol consumption (Table 1). Although small, most of these differences were statistically significant ($p < 0.001$) given the large study size. Mean age at last birthday before admission was 28.5 years for both Norplant and IUD users while sterilized women were on average 1.1 years older. About 1% of participants were single or separated at admission. IUD users were oldest at the age of first union and of first full-term pregnancy while sterilization subjects were the youngest. IUD users had the lowest parity and sterilized women the highest. Overall, 91.6% of sterilized women had a full-term pregnancy as their last pregnancy outcome, in contrast with 71.5% of Norplant users and 71.1% of IUD users, and induced abortion accounted for nearly all the remaining outcomes. Educational attainment was highest among IUD acceptors while sterilized women had the least schooling. Less than 7% of Norplant and IUD users and 10.6% of sterilized women had ever smoked, less than 5% of participants had ever drunk alcohol, and still fewer women currently smoked or drank alcohol regularly (not shown). Mean weight ranged between 51.7 kg and 55.6 kg, women choosing sterilization being the lightest and those choosing IUD the heaviest. Few women reported previous diseases related to the reproductive organs: an ovarian cyst had been experienced by 0.8%, 0.7%, and 0.5% of women in the Norplant, IUD, and sterilization groups, respectively, while a history of PID was reported by 1.5%, 0.9%, and 1.8% of women in the 3 groups, respectively (not shown).

A higher proportion ($p < 0.001$) of Norplant users had previously used contraception before entering the study than women in the control groups (Table 2). Overall, IUDs, oral contraceptives, barrier methods, and injectables, in descending order, were the methods that had been most frequently used; only 2.5% of the participants had previously used implants.

3.2. Follow-up and years of observation

Of the 16,021 women admitted to the study, 15,161 (94.6%) were followed-up through 5 years (Table 3). A total of 303 users of Norplant or IUDs were released from the study within the first 6 months because they had discontinued the method chosen at enrolment or became pregnant in this interval. Three women in the sterilization group were

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Table 1
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 (%)				<0.001
<Elementary	21.4	13.9	23.8	
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.

also released in the first 6 months because they were pregnant at, or soon after, admission; another woman was released after 12 months because her admission cervical cytology had shown a carcinoma in situ. Thus, 1.9% of the initial acceptors were released in the early course of the study. Of the remaining 15,714 women, 15,161 women (96.5%) completed the 5-year follow-up, with similar follow-up rates for the 3 groups. The study encompassed 78,323 woman-years of observation: 39,337 woman-years (50.2%) in women initiating Norplant; 31,915 woman-years (40.8%) in IUD initiators and 7,071 woman-years (9.0%) in women undergoing surgical sterilization.

The mean duration of follow-up per woman was 4.9 years in Norplant initiators, 4.8 years in IUD initiators and

Table 2
Percentage of women with prior contraceptive use and use of specific methods

Methods used	Study group			p-value
	Norplant	IUD	Sterilization	
No. of subjects	7977	6625	1419	
Any method	85.4	75.9	74.8	<0.001
Oral contraceptives	37.8	28.3	27.6	<0.001
Injectables	19.2	11.2	15.2	<0.001
Implants	3.5	1.5	0.9	<0.001
IUD	37.6	33.9	48.2	<0.001
Barriers	30.2	30.1	11.8	<0.001
Spermicides	6.3	5.4	5.8	0.07
Other	9.5	9.3	7.2	0.02

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Table 3
Number of women admitted, released and followed-up by contraceptive method chosen at admission

	Study group			All subjects
	Norplant	IUD	Sterilization	
Admitted	7977	6625	1419	16021
Released in first 6 months	95	208	4[a]	307
Moved	29	4	0	33
Lost to follow-up	202	238	40	480
Refused to continue	25	10	5	40
Completed follow-up	7626	6165	1370	15161
	(95.6%)	(93.1%)	(96.5%)	(94.6%)
Woman-years	39337	31915	7071	78323

[a] Includes one woman with cervical cancer in situ at admission, released at month 12.

5.0 years among sterilized women (Table 4). The mean number of scheduled follow-up visits was 9.3 per woman with small, though significant, differences between groups ($p < 0.001$) in the number of scheduled, unscheduled, and total visits and in the mean number of physical examinations, pelvic examinations and hemoglobin measurements. Sterilized women had the fewest physical examinations and hemoglobin measurements.

3.3. Removal of the initial method (life table rates)

First segment continuation and termination rates for the 3 methods are shown in Table 5. For 891 women the scheduled removal of Norplant took place shortly after 5 years from insertion, while for most of them (4,348), this occurred shortly before they completed 5 years. For 232 women the Norplant device was not removed within the time frame of the study because of loss to follow-up, refusal, a too late clinic visit, or death. Two clinics had policies requiring IUD removals in the fourth year. Of 701 such removals, 302 women had another IUD inserted during the same visit and are considered, in this analysis, to have continued the first segment. Life table rates were calculated by considering terminations for end of effective life of IUDs and implants as censored observations.

The first segment cumulative life table removal rates for all causes at the end of 5 years were 33.2%, 30.5%, and 27.0% among women initiating Norplant, copper IUDs, and non-copper IUDs, respectively ($p < 0.001$). Norplant subjects stayed with their initial method an average of 4.16 years (standard error [se] 0.02) years while IUD users continued on average for 4.10 years (se 0.02). First segment use of non-copper IUDs, principally in China, was on average 4.23 years (se 0.07) compared with 4.09 years (se 0.02) for copper IUDs. The removal rate for pregnancy in Norplant users included a total of 88 pregnancies, 77 clearly due to method failure (two in the first year, six in the second, 20 in the third, 19 in the fourth and 30 in the fifth year), and 11

Table 4
Follow-up experience by study group

	Study group			All subjects
	Norplant	IUD	Sterilization	
Number of women	7977	6625	1419	16021
Length of follow-up per subject (years)	4.9 ± 0.7[a]	4.8 ± 1.0	5.0 ± 0.6	4.9 ± 0.8
Number of post-admission visits per subject				
Scheduled follow-up				
Year 1	1.5 ± 0.6	1.4 ± 0.6	1.3 ± 0.5	1.4 ± 0.6
Year 2	1.9 ± 0.7	1.9 ± 0.7	2.0 ± 0.6	1.9 ± 0.7
Year 3	1.8 ± 0.7	1.8 ± 0.7	1.6 ± 0.7	1.8 ± 0.7
Year 4	1.9 ± 0.7	1.8 ± 0.7	1.8 ± 0.7	1.8 ± 0.7
Year 5	1.8 ± 0.7	1.7 ± 0.8	1.6 ± 0.7	1.7 ± 0.7
Year 6	0.7 ± 0.5	0.7 ± 0.5	0.8 ± 0.4	0.7 ± 0.5
Total	9.4 ± 1.7	9.2 ± 2.1	9.2 ± 1.7	9.3 ± 1.9
Unscheduled visit	0.7 ± 1.3	0.5 ± 1.0	0.3 ± 0.6	0.6 ± 1.2
Clinical follow-up	1.0 ± 0.5	1.1 ± 0.6	1.1 ± 0.5	1.1 ± 0.5
Procedures				
Physical examination	2.6 ± 2.3	2.5 ± 2.3	2.2 ± 1.8	2.6 ± 2.2
Pelvic examination	2.6 ± 2.3	2.5 ± 2.2	2.2 ± 1.8	2.5 ± 2.2
Haemoglobin measurement	1.5 ± 1.7	1.6 ± 1.7	1.0 ± 1.0	1.5 ± 1.6

[a] Values are mean ± SD.

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where it was not known whether conception took place before or after insertion (n = 6) or removal (n = 5; one in the first year, two each in the third and fourth years). In the IUD groups, no pregnancies were reported to have occurred around the time of insertion.

Bleeding problems were the most frequent medical reason for discontinuation in the Norplant group, leading to a cumulative discontinuation rate of 13.7% at the end of 5 years, significantly higher ($p < 0.001$) than in the copper and non-copper IUD groups, which were 6.4% and 4.7%, respectively. Other medical reasons for discontinuation included a large variety of complaints and health events. Among Norplant users, conditions associated with the use of hormonal contraceptives constituted the majority of reasons for discontinuations. The most frequent of these were headache, weight change, skin changes, mood changes, and breast symptoms or diseases. By contrast, among IUD users, symptoms and diseases of the reproductive tract constituted the majority of medical reasons for removal, pelvic pain, and infection being the most frequent.

Annual first segment life table pregnancy rates and 5-year cumulative life table pregnancy rates (Table 6) were significantly lower ($p < 0.005$) among Norplant users and sterilized women than among IUD users in the first 4 years. Sterilized women had lower pregnancy rates than did Norplant users from the third through fifth years ($p < 0.01$). Norplant pregnancy rates increased with duration of use from around 0.1 per 100 women in the first 2 years to 0.6 per 100 women in the fifth year of use ($p < 0.001$). In contrast, annual pregnancy rates among IUD users declined with longer duration of use ($p < 0.001$). Copper IUDs were 6-fold more effective than non-copper IUDs in the first year ($p < 0.001$) and two-fold more effective in the next 4 years.

3.4. Contraceptive dynamics and outcome of pregnancies

Women discontinued or changed their initial contraceptive method during the course of the study as indicated in Table 7. As a result, the observations include more than 1,000 woman-years of use for each of condom, combined oral contraceptives (COCs) and no method, and shorter accumulations of use with other methods. This permitted an assessment of contraceptive efficacy and ectopic pregnancy rates with study and other methods. Women who were pregnant or in the puerperium accounted for a further 966 woman-years of observation (not shown).

For methods with more than 1,000 woman-years of use and based on all segments of use, Pearl pregnancy rates (intra- and extrauterine pregnancies considered together) were lowest for Norplant implants and female sterilization, 0.27 and 0.17 per 100 woman-years, respectively (Table 8). The pregnancy rates for copper IUDs and COCs were less than 1 per 100 woman-years, while the rate was about 3 times higher among users of non-copper IUDs. The pregnancy rate among users of condoms, 7.4 per 100 woman-years, was substantially higher. Of the total 1,737 pregnancies recorded in the study, the majority (1,134, 65.3%) were among women using no contraceptive method, in whom the pregnancy rate on average was 43.1 per 100 woman-years. The rate was 172 per 100 woman-years among those stopping contraception for want of another child, and 17.7 per 100 woman-years among those who stopped for other reasons.

Seven pregnancies among women using no contraceptive method were ectopic (rate 2.66 per 1,000 woman-years, Table 8). The ectopic pregnancy rate for current users of Norplant, copper-IUDs and sterilization were 0.30, 0.68, and 0.13 per 1,000 woman-years, respectively, compared with 1.30 for those using non-copper IUDs. The proportion of ectopic to total pregnancies was higher for users of Norplant, copper IUDs and non-copper IUDs, than for women using no contraceptive method.

The outcome of pregnancy was known for 1,720 of the 1,737 pregnancies recorded, 603 of which occurred while women were using contraception (Table 9). A total of 1,119 pregnancies were carried to delivery, and 10 of these were multiple births. Among singleton live births, the mean birth weight of the infants of women using no contraceptive method and women using Norplant at the time of conception were similar. The mean birth weight of infants of women with an IUD in utero at conception was lower than that of the infants of non-contracepting women. Similarly, the proportion of low-birth-weight infants was larger, but these differences were not significantly different and were attributable to birth weight differences between clinics. Of the 47 women who conceived with an IUD in utero and gave birth, 42 women (89%) had the IUD removed before 13 completed weeks of pregnancy.

The male-to-female sex ratios of all infants and of infants of women not using any contraceptive method at time of conception, were significantly elevated. The excess of male infants was particularly noticeable in two countries (Bangladesh, Indonesia) where the ratios male-to-female of all births were 2.60 and 2.27 ($p < 0.001$). No malformations at birth were recorded among infants of women who used a contraceptive method at time of conception. Three infants (0.3%) of non-contracepting women had malformations recorded at birth (including one infant with transposition of the great vessels). Most of the 603 pregnancies due to contraceptive failure ended with an induced abortion. The percentage of such pregnancies ending in induced or spontaneous abortion varied for the different contraceptive methods. Two molar pregnancies occurred, one in a Norplant user and one in a condom user.

3.5. Problems at method initiation and discontinuation

Problems during or soon after the 8,146 recorded Norplant insertion were reported in 89 (1.1%) cases; including hematomas (42); inflammatory reactions (36) including one woman with superficial thrombophlebitis close to the insertion site; and complaints of pain, itching or other effects

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Table 5
Reason for removal of the initial method (first segment of use of Norplant implants or IUDs, cumulative net life table discontinuation rates and standard error per 100)[a]

	Year 1		Year 3		Year 5	
	Rate	SE	Rate	SE	Rate	SE
Norplant						
Pregnancy[b]	0.1	0.04	0.5	0.09	1.5	0.16
Excessive bleeding	2.1	0.2	9.4	0.3	13.7	0.4
Other medical	1.4	0.1	5.5	0.3	9.1	0.4
Device complications	0.01	0.01	0.04	0.02	0.04	0.02
Planning pregnancy	0.3	0.1	3.3	0.2	6.8	0.3
Other personal	0.7	0.1	3.9	0.2	7.3	0.3
Method continuation rate	95.4	0.2	79.1	0.5	66.8	0.5
Copper IUDs						
Pregnancy	1.0	0.1	3.0	0.2	4.2	0.3
Excessive bleeding	1.9	0.2	4.7	0.3	6.4	0.3
Other medical	1.0	0.1	4.0	0.3	5.4	0.3
Expulsions	1.7	0.2	3.0	0.2	3.6	0.3
Other device complications	0.05	0.03	0.09	0.04	0.14	0.05
Planning pregnancy	0.9	0.1	5.5	0.3	9.8	0.4
Other personal	0.9	0.1	3.0	0.2	5.3	0.3
Method continuation rate	92.8	0.3	78.8	0.5	69.5	0.6
Non-Copper IUDs						
Pregnancy	6.3	1.0	10.6	1.3	13.0	1.4
Excessive bleeding	0.8	0.4	2.3	0.6	4.7	0.9
Other medical	0.2	0.2	1.1	0.4	1.1	0.4
Expulsions	2.7	0.7	3.9	0.8	4.3	0.8
Planning pregnancy	0.5	0.3	2.0	0.6	5.5	1.0
Other personal	0.2	0.2	0.5	0.3	1.6	0.6
Method continuation rate	89.7	1.2	80.9	1.6	73.0	1.8

[a] Cumulative life table discontinuations rates in percent (standard error) at 365, 1110 and 1826 days since insertion.
[b] Pregnancy rate in Norplant users includes pregnancies where it was questionable if conception had occurred before or after admission (n = 6) or around the time of removal (n = 5).

(11). Problems recorded during or soon after the 8,076 IUD insertions were perforation (1), fainting or dizziness (2), and severe pain (4). Forty-three IUD expulsions were recorded within the first 12 weeks. Problems during and after sterilization procedures were one case of bleeding in the mesosalpinx during laparotomy, excess damage of one tube at cauterization by laparoscopy, 8 wound infections after laparotomy, and two episodes of fever after transcervical chemical sterilization with phenol atabrine paste.

During the course of the study there were 57 diagnoses of pain in limb (ICD-9 729.5) (39 women) and of myalgia (ICD-9 729.1) (18 women) among initial Norplant users, five in IUD users and two in sterilized women. In 32 Norplant users the pain was at the site of the Norplant insertion, for 18 of these women the pain was quoted as a reason for removal of Norplant, in 12 women the symptoms of pain did not lead to removal, and in 2 women the pain occurred after Norplant had been removed. For the other women the site of the pain was not specified (12 women) or the pain was at another site (13 women).

At the end of the study, a total of 7,850 Norplant removals, including second segment removals, had been reported. Of these, 79 (1%) were considered difficult, including 36 cases of broken capsules.

3.6. Reproductive health events

Invasive cancer of the breast was diagnosed in four initial acceptors of Norplant, two of whom were using other contraceptives at the time of detection, and one in a woman initiating IUD use who was also using an IUD at detection of the cancer (Table 10). Four of these women came from China and all had the histopathological diagnosis confirmed by an independent reference pathologist. One woman in Bangladesh had a clinical diagnosis of advanced breast cancer. The overall incidence rate of breast cancer for Norplant initiators was 0.10 per 1,000 woman-years and 0.03 for IUD initiators ($p = 0.21$).

In China, one Norplant initiator had in-situ cancer of the breast and another had a non-invasive phyllodes tumor according to the reference pathologists. Benign tumors of the breast requiring biopsy had similar rates in women initiating Norplant, IUD, or sterilization, the rate ratio for Norplant vs. controls was 1.16 (0.62,2.17), not statistically different from unity. Analysis according to current use of Norplant, IUD or sterilization gave similar results. One Norplant and one IUD initiator each had a breast abscess requiring incision and antibiotic treatment.

One invasive cancer of the cervix was diagnosed in the

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Table 6
First segment annual and cumulative (at the end of 5 years) pregnancy rates per 100 women

	Method			
	Norplant	Copper IUD	Non-copper IUD	Sterilization
Year 1				
Woman-years[a]	7827	5767	593	1409
Events	9	59	39	3
Rate (SE)	0.12 (0.04)	1.02 (0.13)	6.34 (0.98)	0.21 (0.12)
Year 2				
Woman-years[a]	7232	5273	540	1395
Events	6	66	17	3
Rate (SE)	0.08 (0.03)	1.24 (0.15)	3.08 (0.73)	0.22 (0.12)
Year 3				
Woman-years[a]	6558	4816	516	1380
Events	22	38	8	1
Rate (SE)	0.33 (0.07)	0.78 (0.13)	1.54 (0.56)	0.07 (0.07)
Year 4				
Woman-years[a]	5957	4370	496	1368
Events	21	36	8	2
Rate (SE)	0.35 (0.08)	0.81 (0.14)	1.60 (0.54)	0.15 (0.10)
Year 5				
Woman-years[a]	5403	4064	474	1353
Events	30	16	5	1
Rate (SE)	0.59 (0.11)	0.41 (0.10)	1.08 (0.51)	0.08 (0.08)
Cumulative rate at 5 years				
Woman-years[a]	32977	24289	2619	6905
Events	88	215	77	10
Rate (SE)	1.46 (0.16)	4.19 (0.28)	13.00 (1.39)	0.72 (0.23)

[a] Year intervals of 365 days.

course of the study (Table 10), in a sterilized woman in Chile. The incidence of carcinoma in situ of the cervix and cervical dysplasia (not shown) was similar in all groups of contraceptive users whether analyzed by initial or current contraceptive method. No invasive cancers were reported for the corpus uteri including the endometrium, or of the ovary. One sterilized woman in Chile had a choriocarcinoma diagnosed 2 months after the sterilization surgery. The incidence rates of myoma of the uterus, whether incidentally detected or symptomatic, were similar in initiators of Norplant, IUDs, and sterilization groups (Table 10). An analysis according to current use revealed similar results (not shown).

Among women currently using Norplant, the incidence of cystic ovarian enlargement managed on an outpatient basis was almost 4 times that among current users of IUD or sterilization (Table 11). Further stratification according to 4-digit ICD-9 codes of ovarian enlargements by functional cysts (ICD-9 620.0 and 620.1) and other unspecified ovarian cysts (ICD-9 620.2, 620.9) showed a similar pattern (not shown). The incidence of ovarian enlargements requiring hospitalization was not significantly different for current users of Norplant and IUD or sterilization combined; of the hospitalized women, eight Norplant users, five IUD users and one sterilized woman had abdominal surgery.

Incidence rates of acute pelvic inflammatory disease (PID), as defined in the methods section, are shown in Table 11 according to current use of Norplant, IUD or sterilization. Acute PID was more frequent in current IUD users than in users of Norplant or sterilization. The incidence rate of acute PID was 0.2, 0.6, and 0.3 per 1,000 woman-years among current users of Norplant, IUDs, and sterilization, respectively ($p < 0.01$ for the comparison between Norplant and IUD users). Unspecified PID, a less specific diagnosis, was also more frequent in current IUD users than in Norplant users ($p < 0.001$). There was no evidence of a change in incidence of acute or unspecified PID by time elapsed since insertion of the IUD. Adjustment for clinic and age had the effect of slightly increasing the rate ratio for IUD users compared with Norplant users. The frequency of repeated lower abdominal pain classified as chronic PID, whether requiring hospitalization or not, was similar among current users of Norplant and IUDs and occurred at rates in the order of 1 per 1,000 woman-years or less. The incidence of unspecified PID was 1.7-fold higher in sterilized women compared with Norplant users and of borderline significance, but after adjustment for age and clinic the rate ratio was close to 1.0. For the other types of PID there were no significant differences in incidence between sterilized women and Norplant users.

The most common diagnosis in this study was related to excessive or irregular vaginal bleeding (Table 11). Bleeding disorders characterized as excessive, or irregular, or both, occurred at the rate of 64 per 1,000 woman-years among current users of Norplant, almost 3 times that found among current IUD users (25 per 1,000 woman-years) and an order of magnitude larger than reported by sterilized women (7

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Table 7
Contraceptive use dynamics during the study

Current method	Initial method									
	Norplant		Copper IUD		Non-copper IUD		Sterilization		All initiators	
	N[a]	Wyrs	N	Wyrs	N	Wyrs	N	Wyrs	N	Wyrs
Norplant										
First segment	7977	33206							7977	33206
Subsequent segments	80	65	80	169	8	22	1	2	169	258
Copper IUDs										
First segment			5996	24517					5996	24517
Subsequent segments	506	891	714	821	31	60	1	2	1252	1774
Non-copper IUDs										
First segment					629	2660			629	2660
Subsequent segments	121	249	52	109	23	44	3	6	199	408
Sterilization	238	435	133	236	3	7	1419	7041	1793	7719
Injectables	155	183	166	207	12	18	0	–	333	408
COCs[b]	503	758	378	506	14	25	2	2	897	1291
POPs[c]	64	86	64	86	0	–	1	0	129	172
Condoms	812	1208	529	671	85	120	2	0	1428	1999
Spermicides	30	43	21	17	2	1	0	–	53	61
Other methods	91	129	74	103	7	10	2	7	174	249
All methods		37253		27442		2967		7060		74722
No method		1614		987		27		5		2633

[a] N: Number of women using method at least once during the study; Wyrs: woman-years.
[b] COCs: Combined oral contraceptive pills.
[c] POPs: Progestogen-only pills.

per 1,000 woman-years). Altogether, 1,924 (23,6%) Norplant users and 698 IUD users (8.6%) had excessive and/or frequent vaginal bleeding at least once during the course of the study. Despite the frequency of the diagnosis, few women were hospitalized for bleeding problems (Table 11). The incidence of anemia with hemoglobin <10 g/dL was low (1.5 per 1,000 woman-years in current users of Norplant and 2.2 per 1,000 woman-years in users of IUD) and not statistically different. Another 12 current Norplant users and 9 current IUD users had a diagnosis of anemia with

Table 8
Total and intrauterine Pearl pregnancy rates per 100 woman-years and extrauterine pregnancy rates per 1000 woman-years by current contraceptive method (crude rates)

Contraceptive method	Exposure (years)	Total pregnancy			Intrauterine			Ectopic			Ratio of ectopic pregnancy	
		N	Rate[a]	0.95% CI	N	Rate[a]	0.95% CI	N	Rate[b]	0.95% CI	Ratio	0.95% CI
Norplant[d]	33465	89	0.27	(0.21, 0.33)	79	0.24	(0.19, 0.29)	10	0.30	(0.14, 0.55)	0.112	(0.06, 0.20)
Copper IUDs	26292	232	0.88	(0.77, 1.00)	214	0.81	(0.71, 0.93)	18	0.68	(0.41, 1.08)	0.078	(0.05, 0.12)
Non-copper IUDs	3067	85	2.77	(2.21, 3.43)	81	2.64	(2.10, 3.28)	4	1.30	(0.36, 3.34)	0.047	(0.01, 0.12)
Sterilization[d]	7720	13	0.17	(0.09, 0.29)	12	0.16	(0.08, 0.27)	1	0.13	(0.00, 0.72)	0.077	(0.00, 0.36)
COCs	1292	11	0.85	(0.43, 1.52)	10	0.77	(0.37, 1.42)	1	0.77	(0.02, 4.31)	0.091	(0.00, 0.41)
POPs	173	2	1.16	(0.14, 4.18)	2	1.16	(0.14, 4.18)	0	0.00	(0.00, 21.3)	0	(0.00, 0.84)
Injectables	408	1	0.25	(0.01, 1.37)	1	0.25	(0.01, 1.37)	0	0.00	(0.00, 9.04)	0	(0.00, 0.97)
Condoms	1999	148	7.40	(6.26, 8.70)	146	7.30	(6.17, 8.59)	2	1.00	(0.12, 3.61)	0.014	(0.00, 0.05)
Spermicide	61	9	14.75	(6.75, 28.0)	9	14.75	(6.75, 28.0)	0	0.00	(0.00, 60.5)	0	(0.00, 0.34)
Other methods	249	13	5.22	(2.78, 8.93)	13	5.22	(2.78, 8.93)	0	0.00	(0.00, 14.8)	0	(0.00, 0.25)
No method[c]	2633	1134	43.07	(40.6, 45.7)	1127	42.80	(40.4, 45.4)	7	2.66	(1.07, 5.48)	0.006	(0.00, 0.01)
Planning pregnancy	433	744	171.82	(159.8, 184.7)	740	170.90	(158.9, 183.8)	4	9.24	(2.52, 23.7)	0.005	(0.00, 0.01)
Not planning pregnancy	2200	390	17.73	(16.0, 19.6)	387	17.59	(15.9, 19.4)	3	1.36	(0.28, 3.99)	0.008	(0.00, 0.02)

[a] Per 100 woman-years.
[b] Per 1000 woman-years.
[c] Includes women not exposed to the risk of pregnancy while not using contraception, but excludes 966 woman-years during pregnancy and post-partum period.
[d] For 11 (10 intrauterine and one ectopic) of the 89 pregnancies that occurred among Norplant users, it is questionable if they are method failures or not since conception took place close to the time of Norplant insertion (n = 6) or removal (n = 5). In the sterilization group, one pregnancy that may have occurred in the month after or before surgery is included (LMP 6 days before sterilization).

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Table 9
Outcome of pregnancies due to contraceptive failure and among women using no contraceptive method at time of conception

	Norplant	IUD	Sterilization	Inject./OCs	Condoms	Sperm./other	No method
Total number of pregnancies	89	317	13	14	148	22	1134
Livebirths							
Multiple[a]	0 (0.0)[b]	1 (0.3)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	8 (0.7)
Singleton	41 (46.1)	45 (14.2)	3 (23.1)	6 (42.9)	22 (14.9)	9 (40.9)	983 (86.7)
Weight							
Unknown	1	1	1	1	1	0	44
<2500	2 (*5.0*)	5 (*11.4*)	0 (*0.0*)	0 (*0.0*)	0 (*0.0*)	0 (*0.0*)	39 (*4.2*)
≥2500	38 (*95.0*)	39 (*88.6*)	2 (*100.0*)	5 (*100.0*)	21 (*100.0*)	9 (*100.0*)	900 (*95.8*)
mean ± SD	3386 ± 447	3119 ± 461	3475 ± 672	3420 ± 437	3275 ± 381	3141 ± 371	3246 ± 486
Crown-heel length (cm), mean ± SD	50.2 ± 2.4	49.3 ± 2.1	51.5 ± 0.7	48.4 ± 4.8	50.1 ± 1.8	49.9 ± 1.7	49.6 ± 2.6
Sex ratio M/F	1.28	1.37	2.00	1.00	1.44	0.80	1.33
Malformations at birth	0	0	0	0	0	0	3
Stillbirths	2 (2.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (1.1)
Spontaneous abortions	12 (13.5)	22 (6.9)	2 (15.4)	2 (14.3)	5 (3.4)	2 (9.1)	85 (7.5)
Induced abortions	22 (24.7)	224 (70.7)	7 (53.8)	3 (21.4)	118 (79.7)	11 (50.0)	25 (2.2)
Ectopic pregnancies	10 (11.2)	22 (6.9)	1 (7.7)	1 (7.1)	2 (1.4)	0 (0.0)	7 (0.6)
Molar pregnancies	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Unknown	1 (1.1)	2 (0.6)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	13 (1.1)

[a] One triplet pregnancy conceived while using no method resulted in two livebirths and one stillbirth; the remaining multiple pregnancies all resulted in livebirths.
[b] Numbers in parentheses are percentages.

hemoglobin ≥10 g/dL, the rate ratio adjusted for clinic and age was 1.56 (0.66,3.71) (p = 0.315). Amenorrhea, including scanty bleeding, was recorded at least once in 6.0% of current Norplant users, and in 1.3% and 0.9% of current IUD users and sterilized women, respectively. The incidence of amenorrhea among Norplant users (15.5 per 1,000 woman-years) was about five times the rate among controls and the adjusted rate ratio was 5.08 (4.16,6.20).

Cervicitis, vaginitis, and leukorrhea were significantly more often reported as OHPs for current IUD users and sterilized women compared to current users of Norplant (Table 12). The rate ratios adjusted for clinic for these three conditions were 0.59 (p <0.001), 0.62 (p <0.001), and 0.60 (p = 0.002), respectively. The diagnosis of vaginitis include specific diagnosis of candidal vulvovaginitis (ICD-9 112.1) and urogenital trichomoniasis ((ICD-9 131.0), the rate ratios for these specific conditions were similar to the rate ratio for all vaginitis diagnoses combined. Erosion and ectropion of the cervix (ICD-9 622.0) was reported at an incidence rate of 1.28, 1.57, and 2.60 per 1,000 woman-years among current users of Norplant, IUD and sterilization, respectively, the rate ratio for Norplant controls compared to controls users was not statistically different (p = 0.263) (not shown). The incidence rate of dysmenorrhoea among current users of Norplant was 1.5 per 1,000 woman-years, and 3.3 and 11.8 among current IUD users and sterilized women, respectively. Other low abdominal pain (ICD-9 625.8, 625.9) was also more frequent among current IUD users and sterilized women compared with current Norplant users; sterilized women had the highest rate of 2.6 per 1,000 woman-years. Premenstrual tension was reported more frequently among current Norplant users than among current IUD users and sterilized women (p = 0.005). Other gynecological signs and symptoms reported as OHPs were mucous polyps of the cervix (ICD-9 622.7), dyspareunia (ICD-9 625.0), and pelvic congestion (ICD-9 625.5). These were reported at incidence rates of 2 per 1,000 woman-years or less and were not different between the groups. Other single gynecological conditions in the ICD-9 subchapter of Other Disorders of the Female Genital Tract (ICD-9 617–629), except bleeding disorders (ICD-9 626), were reported with incidence rates of less than 1 per 1,000 woman-years and with no particular pattern.

Few cases of syphilis and gonorrhea were reported in this study. The overall rate of syphilis (ICD-9 091) and gonorrhea (ICD-9 098) reported as MHE (six women) or OHP (five women) was 0.14 per 1,000 woman-years. These diagnoses were not associated with any initial or current contraceptive method. Seventeen women had a diagnosis of genital warts (ICD-9 078.1) without any association with contraceptive method.

3.7. Recovery of fertility

During the study, 436 Norplant users and 559 IUD users discontinued the method during the first segment of use, stating that they desired a child. Pregnancy was diagnosed within one year in 214 and 291 of them, respectively. Table 13 shows the recovery of fertility and resumption of contraceptive use for these women during the first year after stopping Norplant or IUD. The overall recovery of fertility within 1 year was low and the proportion of women who conceived within the interval was significantly lower for women stopping use of Norplant than for women stopping use of an IUD (p = 0.02). In

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Table 10
Neoplastic diseases of female reproductive organs by initial use of Norplant, IUD or sterilization; number of events, crude incidence rate per 1000 woman-years, and adjusted rate ratio

Events (severity)	Norplant		IUD		Sterilization		Adjusted[h] rate ratio (Norplant/controls)		
	No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
Breast									
Invasive cancer[a] (MHE)	4	0.1	1	0.0	0		4.07	(0.46, 36.44)	0.21
In situ cancer[b] (MHE)	2	0.1	0		0		∞		
Benign neoplasms, biopsy[c] (MHE)	21	0.5	18	0.6	0		1.16	(0.62, 2.17)	0.65
Ovary									
Benign neoplasms[d] (MHE)	8	0.2	8	0.3	0		1.00	(0.38, 2.67)	1.00
Uterus									
Myoma uteri[e]									
With symptoms (MHE)	21	0.5	12	0.4	4	0.6	1.30	(0.68, 2.49)	0.43
Incidental (OHP)	26	0.7	14	0.4	7	1.0	1.23	(0.69, 2.19)	0.48
Cervix									
Invasive cancer[f] (MHE)	0		0		1	0.1	0.00		
In situ carcinoma[g] (MHE)	6	0.2	4	0.1	3	0.4	0.85	(0.29, 2.53)	0.77

[a] ICD-9 code 174; [b] ICD-9 code 233.0; [c] ICD-9 code 217; [d] ICD-9 code 220; [e] ICD-9 code 218; [f] ICD-9 code 180; [g] ICD-9 code 233.1; [h] adjusted for clinic.

four countries (Chile, Indonesia, Sri Lanka, and Thailand), recovery of fertility was similar for former Norplant and IUD users and in the other four (Bangladesh, China, Colombia, and Egypt) a larger proportion of former IUD users conceived within 1 year. The median interval between removal of the device and the estimated conception date was 9.4 months (se 1.1) in the Norplant group and 6.0 months (se 0.3) in the IUD group. Of the women who discontinued Norplant or IUD stating that they planned pregnancy, 27 (12.6%) and 41 (14.1%) women, respectively, had reinitiated use of a contraceptive method within one year. For 222 former Norplant and 376 former IUD users with parity 0–1, the life-table rate for pregnancy at 12 months was 64.5 (SE ± 3.5) and 66.3 (SE ± 2.9) per 100, respectively ($p = 0.695$). For women of higher parities the rates were lower, and lower among former users of Norplant than of IUDs. Among women aged <30 years the cumulative probabilities of conception at 1 year were 59.4 (SE ± 3.2) and 67.5 (SE ± 2.9) per 100 for former Norplant and IUD users, respectively ($p = 0.063$); for women ≥30 years they were 48.8 (se ± 4.4) and 57.5 (se ± 4.0) per 100 for former Norplant and IUD users, respectively ($p = 0.149$).

3.8. Deaths related to the reproductive system

Two of the 34 deaths recorded, described in the accompanying paper [6], were related to the reproductive system. One initial Norplant user had the device removed 2 years after insertion, used no contraceptive method thereafter and died one year after Norplant removal from sepsis following incomplete septic abortion. The second death occurred in the woman with a clinical diagnosis of metastatic breast cancer.

4. Discussion

This 5-year cohort study which included 16,021 women from eight developing countries, confirms the safety with respect to reproductive health, and the high contraceptive efficacy of Norplant implants, copper IUDs and female sterilization. Incidence rates of adverse reproductive health events were low among women in the study. Acceptance by women of the study and the performance of the clinics ensured high follow-up rates and high method-continuation rates. The intended 30,000 woman-years of observation during use of Norplant and of non-hormonal study methods were exceeded.

The pregnancy rate for Norplant implants was in the lower range of previously reported rates [2,3]. Pregnancy rates for IUDs, interval sterilization and other methods were similar to those reported elsewhere [16–21]. The low failure rate of Norplant was similar to that of female sterilization, and lower than failure rates with other reversible methods, with the exception of injectable contraceptives. The contraceptive efficacy of copper IUDs was significantly higher than that of non-copper IUDs. Low body weight of the women in this study probably contributed to the low rates in Norplant users. We cannot rule out that where induced abortion was illegal or socially undesirable, underreporting of pregnancies terminated by abortion may have occurred. Underreporting would have produced an overestimate of the efficacy of each contraceptive method. The high efficacy of Norplant, female sterilization, and copper-IUDs is particularly important for women living in countries where induced abortion is not permitted by law, where highly efficacious contraceptive methods prevent not only unplanned pregnancies but also adverse health consequences of unsafe abortions.

Rates of ectopic pregnancy varied among current users of contraceptive methods and among groups of non-users. Ectopic pregnancy rates in Norplant and copper IUD users were a tenth and a quarter, respectively, of the rate among non-users (2.66 per 1,000 woman-years). Women planning pregnancy had an ectopic pregnancy rate of 9.24 per 1,000,

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Table 11
Ovarian enlargement, pelvic inflammatory disease, bleeding disturbances and anemia by current contraceptive method; number of events, crude incidence rate per 1000 woman-years and adjusted rate ratio

Events (severity)		No.	Crude rate	Adjusted[h] rate ratio (Norplant/control(s))		
				RR	95% CI	p-value
Ovary						
Cystic enlargement[a], hospitalized (MHE)	Norplant	8	0.2			
	IUD	6	0.2	1.02	(0.35, 2.97)	0.96
	Sterilization	1	0.1	3.76	(0.46, 30.8)	0.22
	Controls	7	0.2	1.40	(0.51, 3.87)	0.52
Cystic enlargement[a], not hospitalized (OHP)	Norplant	106	3.2			
	IUD	27	0.9	3.40	(2.22, 5.21)	<0.001
	Sterilization	7	0.9	4.94	(2.25, 10.9)	<0.001
	Controls	34	0.9	3.71	(2.52, 5.47)	<0.001
Pelvic inflammatory disease PID)						
Acute PID[b] (MHE)	Norplant	6	0.2			
	IUD	18	0.6	0.25	(0.10, 0.63)	<0.001
	Sterilization	2	0.3	1.32	(0.25, 7.06)	0.75
	Controls	20	0.5	0.34	(0.14, 0.85)	0.02
Unspecified PID[c] (OHP)	Norplant	56	1.7			
	IUD	100	3.4	0.45	(0.32, 0.62)	<0.001
	Sterilization	22	2.9	1.02	(0.61, 1.72)	0.93
	Controls	122	3.3	0.54	(0.39, 0.74)	<0.001
Chronic PID, hospitalized[d] (MHE)	Norplant	3	0.1			
	IUD	2	0.1	1.19	(0.19, 7.28)	0.85
	Sterilization	2	0.3	0.86	(0.12, 6.00)	0.88
	Controls	4	0.1	1.09	(0.24, 4.89)	0.92
Chronic PID, outpatient[d] (OHP)	Norplant	24	0.7			
	IUD	18	0.6	1.02	(0.55, 1.89)	0.95
	Sterilization	7	0.9	1.78	(0.75, 4.21)	0.19
	Controls	25	0.7	1.22	(0.70, 2.15)	0.48
Bleeding disturbances						
Excessive/irregular, hospitalized[e] (MHE)	Norplant	8	0.2			
	IUD	6	0.2	1.14	(0.39, 3.31)	0.82
	Sterilization	1	0.1	2.33	(0.28, 19.7)	0.44
	Controls	7	0.2	1.36	(0.49, 3.75)	0.56
Excessive/irregular[e] (OHP)	Norplant	1916	64.3			
	IUD	692	25.3	2.72	(2.49, 2.97)	<0.001
	Sterilization	48	6.5	11.39	(8.49, 15.3)	<0.001
	Controls	740	21.3	3.26	(2.99, 3.55)	<0.001
Amenorrhoea[f] (OHP)	Norplant	491	15.5			
	IUD	104	3.6	4.80	(3.88, 5.95)	<0.001
	Sterilization	17	2.2	6.69	(4.07, 11.0)	<0.001
	Controls	121	3.3	5.08	(4.16, 6.20)	<0.001
Anemia						
Hemoglobin <10 g/dl[g] (MHE)	Norplant	49	1.5			
	IUD	64	2.2	0.78	(0.53, 1.13)	0.19
	Sterilization	5	0.6	1.10	(0.40, 3.02)	0.85
	Controls	69	1.9	0.80	(0.56, 1.16)	0.24

[a] ICD-9 code 620; [b] ICD-9 codes 614.0,615.9; [c] ICD-9 code 614.9; [d] ICD-9 codes 614.1–614.8; [e] ICD-9 codes 626.2,-.4,-.6,-.8,-.9; [f] ICD-9 codes 626.0,626.1; [g] ICD-9 codes 280,285; [h] Adjusted for clinic and age

while those not using a contraceptive method and not planning pregnancy had a low rate of ectopic pregnancy (1.36 per 1,000), presumably because of low exposure to the risk of pregnancy. In users of all other reversible contraceptive methods taken together, the rate of ectopic pregnancy was 0.52 per 1,000 woman-years or about a fifth of the overall rate for women not using a contraceptive method. The proportion of ectopic to total pregnancies in Norplant and copper IUD users was 0.11 and 0.08, respectively, higher than that reported from several other studies [2,3,21–23]. This may reflect the higher average age of the women at the time of pregnancy in the present study compared with most previous studies [22].

Birth outcomes after Norplant method failures were similar to those of women not using contraception at the time of conception. This finding confirms a previous report on the outcome of childbirth among women conceiving while using Norplant [24]. Although infants born following IUD failure appeared more likely to be below 2,500 g at birth, and their mean birth weight was about 200 g less than that

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Table 12
Selected disorders of female genital tract by current contraceptive method; number of events, crude incidence rate per 1000 woman-years, and adjusted rate ratio

Events (severity)	Norplant		IUD		Sterilization		Adjusted[g] rate ratio (Norplant/controls)		
	No.	Rate	No.	Rate	No.	Rate	RR	95% CI	p-value
Cervicitis[a] (OHP)	84	2.5	126	4.3	43	5.6	0.59	(0.45, 0.77)	<0.001
Vaginitis[b] (OHP)	470	14.5	620	22.1	240	33.5	0.62	(0.55, 0.69)	<0.001
Leukorrhoea[c] (OHP)	58	1.7	89	3.1	17	2.2	0.60	(0.44, 0.83)	0.002
Dysmenorrhoea[d] (OHP)	49	1.5	95	3.3	89	11.8	0.33	(0.24, 0.45)	<0.001
Premenstrual tension[e] (OHP)	43	1.3	20	0.7	6	0.8	2.00	(1.23, 3.25)	0.005
Pain, other and unspecified[f] (OHP)	16	0.5	32	1.1	20	2.6	0.37	(0.21, 0.65)	0.001

[a] ICD-9 code 626.0; [b] ICD-9 codes 112.1, 131.0, 616.1; [c] ICD-9 code 623.5; [d] ICD-9 code 625.3; [e] ICD-9 code 625.4; [f] ICD-9 codes 625.8–625.9; [g] adjusted for clinic.

of infants of non-contracepting women, this observation arose from differences of birth weight distributions among the clinic populations rather than from contraceptive method ($p > 0.05$). The rate of removal of IUDs in early pregnancy was high (89%) among those women who became pregnant after IUD failure and gave birth, in compliance with established practice [21].

The deficit of newborn girls, particularly in Bangladesh and Indonesia, could not be accounted for by high reported rates of spontaneous or induced abortions, and was seen equally in women stopping Norplant or IUDs. This suggests that a number of pregnancies with female fetuses may have been selectively terminated and not reported to the study personnel. Survey data from China indicate high sex ratios at birth in most provinces, especially at parities two and higher when prior births were daughters [25] In our study, more than 99% of women were parous, but we did not collect information on sex of previous births

The study found low incidence rates of adverse MHEs of reproductive health character among users of all contraceptive methods, few significant differences were detected between women using Norplant and non-hormonal methods. There were four invasive breast cancers in Norplant users and one in controls with an overall incidence of 0.07 per 1,000 woman-years. The study was not designed to have the statistical power to examine differences in rates of such rare events as reproductive cancers in the age range of women included in this study. Based on reported age-specific incidence rates of breast cancer [26] and the age distribution of the women in this study, an estimated 8.6 breast cancers would have been expected during the 5-year follow-up. Four of the five breast cancers reported in the study were diagnosed in China where an estimated 2.8 breast cancers would have been expected [26]. The incidence of invasive cervical cancer was low (1 case, 0.01 per 1,000 woman-years) compared with the expected 9.5 cases based on age-specific incidence rates of invasive cervical cancer [26]. The low incidence of cervical cancer may be because the women who enrolled in this study came from relatively stable social segments of the population, were married and had low parity, factors that are markers of low risk of cervical cancer [27]. Incidence rates of in situ carcinoma and dysplasia of the cervix were similar among women using Norplant and non-hormonal methods.

The diagnoses of myoma uteri occurred at similar rates in users of Norplant and of non-hormonal methods. The apparent protective effect on myoma uteri from current and recent past use of other hormonal contraceptive methods, such as combined oral contraceptives and depot-medroxyprogestrone acetate reported previously [28,29], was not observed in this study. The incidence of cystic ovarian enlargement was greater among Norplant users than among users of non-hormonal methods, a finding that was expected since abnormal follicular development leading to follicular cysts in Norplant users has been reported by several investigators [30,31]. Most of these cystic enlargements were managed on an outpatient basis. Hospitalizations and surgical treatments for ovarian enlargement were not significantly different for women using Norplant compared with IUD users and sterilized women. Solid benign tumors of the ovary had similar incidence rates among Norplant users and controls.

The overall incidence of PID was low, as reported in other populations attending family planning clinics [32]. Acute PID occurred at the rate of 0.61 per 1,000 woman-years among current IUD users, three times higher than the rate among current users of Norplant. The less strict diagnosis of "other PID," compatible with a less severe inflammatory process of the upper genital tract, also showed lower incidence rates among current users of Norplant compared with users of IUDs and sterilized women. These findings are similar to results of previous observational studies that showed a higher incidence of PID among IUD users compared with users of other contraceptive methods and particularly hormonal methods [21,33,34]. There was no clear pattern of difference in incidence of acute or unspecified PID according to time since insertion of IUD, as reported in previous studies [32,33]. The lower incidence rate of PID in current Norplant users compared with controls may be attributable to changes of the cervical mucus of women using Norplant [35], theoretically making the mucus less penetrable by ascending microbes, or to immunologic mechanisms

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Table 13
Recovery of fertility (first segment)

	Norplant	IUDs	p-value
Number of removals for planning pregnancy	436	559	
At 12 months			
Women who became pregnant			
Number	214	291	
Cumulative life table rate ± SE	55.6 ± 2.6	63.9 ± 2.4	0.02
Women who started contraception			
Number	27	41	
Cumulative life table rate ± SE	10.4 ± 2.0	15.6 ± 2.5	0.10
Number of women observed for less than 12 months for reasons other than pregnancy or contraception	77	128	
Number of women observed through 12 months	118	99	

such as those underlying the protection against chlamydial salpingitis in users of combined oral contraceptives [36]. The incidence of low abdominal pain (chronic PID) was, however, similar and rare (1 per 1,000 woman-years or less) in all groups. Among women undergoing laparoscopy or laparotomy for low abdominal pain, the underlying cause of the condition was pelvic peritoneal adhesions.

Bleeding disturbances were the most common problem among users of Norplant, as reported previously [1–4,37]. Frequent or excessive vaginal bleeding was reported at least once by 24% of current implant users, although it rarely led to hospitalization or anemia. Bleeding was also the most likely reason for implant removal, but nevertheless removal rates for this reason were as low as 2.1 per 100 in the first year of use and 13.7 per 100 at the end of 5 years. This low discontinuation rate of Norplant for bleeding problems may be related to the quality of the counseling and services provided. It is also possible that in this study some women chose to keep the method because they were encouraged to tolerate the inconvenience associated with bleeding problems.

Other common gynecological conditions reported as OHPs, such as vaginitis and leukorrhea, were reported significantly less often among current users of Norplant than among IUD users and sterilized women. Cervicitis was also less frequent among Norplant users. This finding may be attributable to the effect of Norplant on cervical mucus in reducing its amount and making the mucus thicker [35]. As expected, dysmenorrhea and lower abdominal pain of gynecological nature was reported more often among IUD users and sterilized women than in Norplant users. The incidence rates of these complaints were low in women in this study who were nearly all parous. The report of a higher incidence of premenstrual tension, an OHP diagnosis, among Norplant users than in IUD users and sterilized women (Table 12) may be the result of erroneous coding by denoting mood changes and anxiety which were also reported more frequently by Norplant users [6], to the ICD code for premenstrual tension.

Among women who wished for another child and stopped using Norplant or IUD for this reason, the cumulative life table pregnancy rates at the end of the first year after stopping were 55.6 and 63.9 per 100, respectively, and significantly different. Women less than 30 years old and women of low parity had, as expected, higher rates than women of 30 years or older and women of higher parity. The pattern of slightly or moderately higher pregnancy rates among former IUD users compared with former Norplant users was seen among women of younger and older age, and among women with higher parity, but the rates were similar among former Norplant and IUD users with low parity. Although, for women in 4 countries, the recovery of fertility was similar for former Norplant and IUD user. The rates for recovery of fertility in the first year after stopping use of Norplant or IUDs in the present study are lower than those reported from most other studies [2,16,38,39], although one recent study from Indonesia of women stopping use of Norplant or Implanon® reported pregnancy rates similar to those reported here [40]. We can not preclude that in some clinics women who wanted to discontinue the method were encouraged to continue use of Norplant, and that wish for a child, seen as a valid reason for stopping the method by health care providers, was stated by the women as a proxy for some other reason for method discontinuation. It is also possible that a number of pregnancy terminations occurred but were not reported. The present study was not specifically designed to evaluate recovery of fertility after stopping contraception and we have no biologic explanation for the observed delayed recovery of fertility. The apparent low rates observed during the first year in this and the Indonesian study [40] should be evaluated further.

Further information about the 34 deaths recorded in this study is given in the accompanying paper [6]. Two were related to reproductive health conditions.

This study has similarities to other large contraceptive follow-up studies undertaken in developed countries such as the Oxford Family Planning Association study [41], the Royal College of General Practitioners Oral Contraception Study in the UK [42], and the Walnut Creek study in California, USA [43]. All the women were followed-up irrespective of change of contraceptive method. They had admission criteria that resulted in recruitment of mainly

married women with children, from stable, middle to low-middle socio-economic segments of the populations. These three studies relied on passive follow-up with information recorded as women visited their medical practitioners for health care either regularly or spontaneously, although the Oxford study additionally used postal and telephone interviews and traced women lost to follow-up [41]. The practitioners routinely received the reports of hospitalizations, including discharge diagnosis and they reported the findings from the health care visits and the hospital stays to the study coordinators. In one important aspect, the Post-marketing Surveillance of Norplant study was different. This study applied active follow-up procedures, including tracing of women overdue for their scheduled 6 monthly visits and of hospital and outpatient clinics records. This active follow-up was deemed necessary because in most participating countries the infrastructure of the health care services did not include any pre-existing systems for exchange of information between hospitals or outpatient clinics and the family planning clinics, and there was no previous experience except in China, of sustainable follow-up through 5 years. The final outcome of the study depended on ensuring client adherence to the scheduled return visits.

As in other observational studies, bias in reporting and recording health events according to contraceptive use may have occurred. Unlike IUDs and sterilization, the Norplant subdermal implant was a new contraceptive method in most of the communities and clinics involved. Women starting use of Norplant had few relatives or friends with experience of and knowledge about Norplant with whom they could discuss concerns or fears. This may have prompted more frequent visits to health care providers and consequently more reports of symptoms and conditions by Norplant users than by users of IUD or sterilization. Indeed, there were more unscheduled visits to the study clinics by women using Norplant than by users of other contraceptive methods. Bias may also have occurred as more care may have been taken by study providers to elicit responses about complaints and symptoms from women in the index group. Both these biases would lead to higher incidence rates of medical diagnoses among users of Norplant than among users of IUD or sterilization. Moreover, preferential attention may have been paid to symptoms known to be associated with the contraceptive method such as bleeding problems in Norplant users or PID among IUD users. If this latter bias had occurred, it would have magnified differences between groups in the known side effects of the methods studied. However, while these biases may have affected OHP diagnoses, the definition of MHEs was such that these events seem unlikely to be affected by these biases.

For comparison of incidence rates of MHEs and OHPs, all incidence rate ratios were adjusted for differences between clinics, and selected additional factors when relevant, 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 environment in the participating countries and clinics. The design was also robust against the different levels of reporting between the participating clinics. It was not possible to apply uniform criteria for reporting all health problems, but the sensitivity of the systems established in the study makes it likely that MHEs, possibly except for induced abortion, were not missed.

Some differences in socio-demographic and biomedical characteristics of women between contraceptive groups at admission were anticipated since the women had freely chosen their method of contraception. However, additional adjustment for these characteristics (such as educational level) in exploratory analyses had little impact on the estimated incidence rate ratios.

Some clinical service aspects merit comment. The low incidence of problems at Norplant insertion and removal was probably because providers were well trained and had experience in the provision of Norplant. This low incidence appears to confirm the importance of adequate training of providers, both in insertions and removals [4]. Similarly, the rates of expulsion and perforation of copper and non-copper IUDs in this study are at the lowest part of the range of reported expulsion rates at one year for copper IUDs [21]. Virtually all women initiating use of IUD in the study were parous and had a mean age of 28.5 years, characteristics that also contributed to the low IUD expulsion rate.

The high follow-up rates in this study and the high continuation rates for Norplant and IUDs throughout 5 years may be attributable to several factors. Women were explained the purpose of the study and the potential importance it had for developing country women. They cooperated in a remarkable way with the visit schedule, responding positively to the interest shown by the providers about their concerns, health and symptoms experienced during use of the contraceptive methods. Because they wanted long-term contraception, the participants were probably interested in a long-term care program and volunteered themselves as recruits to the study. The participating clinics had experience in research and in the management of the methods provided, and offered good quality services. In addition, the clinics made a great effort to ensure follow-up through tracing women overdue for scheduled visits. Alternative contraceptive methods were available for women who were dissatisfied with their initial choice, and many chose to change. The results of the study indicate that the quality of the services provided affected in a favorable way the performance and continuation rates of provider-dependant methods but some women may have continued with their initially chosen method longer as a result of loyalty to, and encouragement by, the providers.

This prospective post-marketing surveillance study has shown that large-scale, longer term follow-up studies are

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feasible in selected sites in developing countries and that they provide significant information on women's reproductive health. With regard to reproductive health and use of Norplant, the results of the study are reassuring. Norplant has very high contraceptive efficacy. It appears to provide protection against common gynecological complaints such as vaginitis and discharge. The incidence rate of ectopic pregnancy is low and below that associated with use of copper-IUDs and non-use of contraception. The study confirms previous observations of bleeding disturbances and benign ovarian enlargement during use of Norplant and did not document any unexpected reproductive diseases or conditions associated with use of Norplant.

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Annex I
Number of subjects admitted by study group

	Norplant	IUD	Sterilization	Total
Bangladesh				
Dhaka	254	257		511
Khulna	250		252	502
Chile				
Santiago ICMER	226	224		450
Santiago HCSBA	400	281	117	798
China				
Beijing	320	324		644
Changsha	322	325		647
Chongqing	316	319	14	649
Guiyang	316	337		653
Jinan	317	224	98	639
Shanghai SIPPR	168	171		339
Shanghai SMU	319	333		652
Shenyang	315		315	630
Tianjin	315	315		630
Zhengzhou	315	217	99	631
Colombia				
Bogota	200	111	89	400
Cali	150	80	70	300
Medellin	150	101	49	300
Egypt				
Ain Shams	199	201		400
Al Azhar	199	201		400
Alexandria	197	203		400
Assiut	196	204		400
Mansoura	201	199		400
Indonesia				
Bandung	230	186	38	454
Jakarta	300	300		600
Padang	128	119	1	248
Semarang	225	200	25	450
Ujung Pandang	119	146	3	268
Sri Lanka				
Colombo	415	225	157	797
Thailand				
Bangkok Rajvithi	211	204	7	422
Bangkok Siriraj	350	350		700
Chiang Mai	101	98	1	200
Khon Kaen	253	170	84	507
Total	7,977	6,625	1,419	16,021

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