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Long-Term Reversible Contraception

Twelve Years of Experience With the TCu380A and TCu220C

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Few data on the long-term efficacy of intrauterine devices (IUD) are available, and this article reports on the final 12-year experience with the TCu220C and TCu380A devices from two randomized, multicenter trials conducted in 24 centers. A total of 3,277 and 1,396 women, respectively, were recruited for use of each device between 1981 and 1986 and followed at 3, 6, and 12 months after insertion and yearly thereafter. At the end of 12 years, a total of 17,098 women-years of experience had been accumulated for the TCu220C and 7,159 women-years for the TCu380A. The cumulative 12-year intrauterine pregnancy rates were 7.0 (standard error [SE] 0.6) per 100 women for the TCu220C and 1.9 (SE 0.5) for the TCu380A ($p < 0.001$). Pregnancy rates were highest in the first years after insertion; the TCu220C had a consistently higher annual pregnancy rate than did the TCu380A at all intervals since insertion. No pregnancies were reported with the TCu380A after 8 years of use. Total medical removals were approximately 6% in the first year and dropped to approximately 4% per year for each device for up to 12 years of use (cumulative 12 year rates were 37.3 [SE 1.3] and 40.2 [SE 2.1] per 100 women for the TCu220C and TCu380A devices, respectively). The overall continuation rate at all intervals since insertion was higher with the TCu220C device, mainly due to higher removal rates for nonmedical reasons with the TCu380A. The cumulative ectopic pregnancy rates were 0.7 and 0.4 for the TCu220C and TCu380A, respectively. Pregnancy rates were higher in the Chinese compared with the non-Chinese centers for both devices, though the greater efficacy of the TCu380A was apparent in both groups of centers. The total medical and nonmedical removal rates were lower in the Chinese compared with the non-Chinese centers, and did not show any substantial differences between the devices. We conclude that both devices are safe and effective for at least 12 years of use and the low pregnancy rate with the TCu380A is comparable with that reported in the United States among women who had undergone tubal sterilization. The very high efficacy of the TCu380A makes it the IUD of choice, and it can be considered as a potentially reversible, nonsurgical alternative to sterilization for women requiring very long-term pregnancy protection. CONTRACEPTION 1997;56:341–352 © *1997 Elsevier Science Inc. All rights reserved.*

KEY WORDS: TCu380A intrauterine device, TCu220C intrauterine device, life table rates, eight, ten, twelve years' experience, geographical differences

Introduction

The intrauterine device (IUD), since its introduction in the 1920s and 1930s, has had a checkered career. Initially, the device was unpopular with the medical profession because of the risk of severe pelvic infection, which was often fatal in the preantibiotic era. Attitudes changed with the introduction of "second generation" IUD and, in particular, the Lippes Loop (Ortho Pharmaceuticals, Raritan, NJ). The copper-bearing IUD introduced in the 1970s were shown to have lower pregnancy rates, as well as removals due to side effects.[1]

Much of the literature on the safety and efficacy of the copper IUD has been confined to studies of 1 to 3 years,[2–4] and occasionally 5 to 7 years.[5–7] In many national family planning programs there is a need for a nonhormonal method of fertility regulation that is effective for >5 to 7 years and that does not require repeated clinical attendance. World Health Organization (WHO)-sponsored clinical research in multicenter, randomized studies has shown the TCu220C

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to be more effective than the Copper 7[1] and the TCu380A superior to the TCu220C.[8] The TCu380A has a significantly lower pregnancy rate at 3 years of use than the Nova T (Outokumpu Oy, Pori, Finland), Multiload 250 (Organon, Oss, Netherlands), and Multiload 375 IUD.[8,9]

This article describes the combined 12-year data from two randomized, multicenter clinical trials, which originally compared in the first study the interval insertion among parous women of the TCu220C and the TCu380A. The second study, which started in 1982 in 19 centers, involved a randomized comparison of interval insertion among parous women of the TCu220C and Nova T copper devices and the 2 μg levonorgestrel-releasing IUD developed by the WHO. The levonorgestrel device was withdrawn from the study in 1984 because of an excessive number of ectopic pregnancies,[10] and the Nova T was discontinued from the study in 1989 because of a statistically significantly higher pregnancy rate at both 3 and 5 years of use compared with that of the TCu220C.[8]

Regular yearly follow-up has continued for those subjects in each of the two trials who originally had either a TCu220C or a TCu380A IUD inserted.

The 5-year data on the Nova T versus the TCu380A,[8] the 3-year data on the Multiload 375 and the TCu380A,[9] and the combined 5- and 7-year data on the TCu220C and TCu380A[8] have been published previously. This report describes the final results on the long-term performance of the TCu380A and TCu220C at 8, 10, and 12 years.

Materials and Methods

The purpose of the two trials was to compare a variety of IUD following interval insertion in parous women. The main endpoints were major complications associated with insertion; expulsions; perforation and pregnancy rates; and rates of removal for complaints of pain, bleeding, or other medical or personal reasons.

A total of 24 centers participated in the two studies. In each institute the approval of the human experimentation or ethics committee was obtained and, where required, that of the appropriate governmental authority. The clinical protocols were also reviewed and approved by the Special Programme's Toxicology Group, Scientific and Ethical Review Group, and the World Health Organization's (WHO) Secretariat Committee on Research Involving Human Subjects.

Admission Procedure and Randomization

All women volunteering for the studies were screened for their clinical suitability for an IUD and for compliance with the eligibility criteria. The following were excluded: nulliparous women, women with a history of pelvic inflammatory disease (PID) or pelvic abscess since their last pregnancy, <6 weeks since parturition or abortion, a history of ectopic pregnancy, recent sexually transmitted disease, undiagnosed genital tract bleeding, congenital genital tract malformations, known or suspected genital tract malignancy, multiple uterine fibromyomas associated with menstrual disorders, clinical or laboratory evidence of anemia, or a history of hydatidiform mole in the last pregnancy. A medical, obstetric and gynecological history was obtained from each subject after she had given fully informed consent for participation in the study.

A subject number was assigned to eligible subjects from a register kept in each center. Each center was issued a series of sealed envelopes on which were printed the trial and subject numbers. Once the subject number had been allocated, the envelope was opened and the device to be inserted was read from a slip of paper inside the envelope. The devices were allocated at random from a computer generated list, and balanced in blocks of ten. Because the devices were different in appearance and required different insertion techniques, it was not possible for the physicians to be blinded as to which device was inserted.

Follow-Up Procedures

The subjects were requested to return to the clinic for scheduled follow-up visits at 3, 6, and 12 months after insertion and yearly thereafter. They were instructed to return to the clinic at any other time if they experienced any problems with the device, and were free to return to the clinic at any time and request removal.

Data Collection, Monitoring, and Analysis

Data were recorded on standard precoded forms in duplicate at admission, at each scheduled and unscheduled follow-up visit, and upon discontinuation from the study. All data were sent to the data coordinating center at the WHO in Geneva where they were managed according to standard procedures. Clarifications were sought from the individual centers where necessary and regular monitoring reports were reviewed by the study coordinator and the relevant task force steering committee. The rates of discontinuation for individual reasons and the groups of reasons were computed following the standard definitions used for WHO contraceptive and IUD clinical trials.[11,12] The most common medical reasons for removal were complaints of pain or bleeding; other medical reasons included pelvic inflammatory disease (PID), perforations, abnormal vaginal discharge,

Table 1. Number of insertions, patient age, and parity by device and study

	Number of Insertions	Age (years)			Parity		
		Mean	SD	Range	Mean	SD	Range
Study 1							
TCu380A	1,396	28.7	4.9	16–40	1.9	1.1	1–9
TCu220C	1,396	28.7	5.0	16–40	1.9	1.0	1–8
Study 2							
TCu220C	1,881	29.0	4.5	16–40	1.6	0.9	1–10

SD, standard deviation.

or other gynecological complaints. The most common nonmedical reasons for discontinuation were a desire for another pregnancy or no further need for contraception.

The data were analyzed using the SAS statistical software package (version 6)[13] and the cumulative discontinuation rates were computed using the daily life table method.[11] These rates are equivalent to Chiang's cumulative net rates[14] and to Tietze-Lewit's gross cumulative rates.[12] Comparisons among discontinuation rates were made using the χ^2 test.[15]

Results

Subjects Recruited

A total of 3,277 women were recruited for use of the TCu220C device and 1,396 for the TCu380A between January 1981 and July 1986.

Events at Insertion and Perforations

There were a total of three insertion failures with the TCu220C and none with the TCu380A. The results that follow refer to the successful insertions only.

Table 2. Cumulative net probabilities of discontinuation, standard error (SE) per 100 women, and significance of differences between devices (all centers)

	Study 1					Study 2		Studies 1 & 2*	
	TCu380A		TCu220C			TCu220C		TCu220C	
	Rate	SE	Rate	SE	p	Rate	SE	Rate	SE
Total pregnancies	2.2	(0.6)	5.1	(0.8)	0.002	7.8	(0.8)	6.7	(0.6)
Intrauterine	1.9	(0.5)	4.9	(0.8)	0.001	7.1	(0.8)	6.2	(0.5)
Ectopic	0.4	(0.3)	0.2	(0.2)	0.69	0.8	(0.3)	0.6	(0.2)
Expulsions	10.6	(1.1)	11.3	(1.1)	0.60	9.0	(0.8)	9.9	(0.6)
Perforations	0.0	(0.0)	0.2	(0.2)	0.18	0.1	(0.1)	0.1	(0.1)
Total medical removals	29.1	(1.6)	25.7	(1.5)	0.12	28.0	(1.3)	27.0	(1.0)
Total pain or bleeding	25.3	(1.5)	22.4	(1.5)	0.16	23.4	(1.3)	23.0	(1.0)
Pain	11.0	(1.1)	8.4	(1.0)	0.07	8.2	(0.8)	8.3	(0.6)
Bleeding	13.2	(1.3)	12.9	(1.2)	0.86	12.5	(1.0)	12.6	(0.8)
Pain and bleeding	3.3	(0.6)	2.6	(0.6)	0.46	4.7	(0.7)	3.9	(0.5)
Pelvic inflammatory disease	0.8	(0.4)	0.6	(0.3)	0.73	0.3	(0.2)	0.5	(0.1)
Other medical removals	4.3	(0.7)	3.7	(0.8)	0.61	5.6	(0.8)	4.8	(0.5)
Total use-related discontinuations	38.0	(1.6)	37.7	(1.6)	0.89	39.6	(1.3)	38.8	(1.0)
Total nonmedical removals	40.8	(1.7)	39.1	(1.7)	0.49	33.4	(1.4)	35.9	(1.1)
Wish to become pregnant	24.4	(1.5)	22.4	(1.5)	0.35	20.4	(1.2)	21.2	(1.0)
No further need	14.3	(1.4)	14.8	(1.4)	0.77	10.9	(1.1)	12.6	(0.9)
Other nonmedical removals	8.6	(1.2)	7.9	(1.1)	0.63	6.2	(0.8)	6.9	(0.6)
Loss to follow-up	21.8	(1.5)	23.9	(1.5)	0.32	22.9	(1.3)	23.3	(1.0)
Other discontinuations (devices not removed)	11.2	(1.4)	13.7	(1.6)	0.24	1.9	(0.4)	6.9	(0.7)
Continuation rate	25.5	(1.2)	24.9	(1.2)	0.73	30.4	(1.1)	28.1	(0.8)
Number of insertions	1,396		1,396			1,881		3,277	
Number of women completing the interval	356		349			560		909	
Woman-years experience	6,186		6,059			8,470		14,529	

* Data are for 8 years (2,940 days).

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Table 3. Cumulative net probabilities of discontinuation, standard error (SE) per 100 women, and significance of differences between devices (all centers)

	Study 1					Study 2		Studies 1 & 2*	
	TCu380A		TCu220C			TCu220C		TCu220C	
	Rate	SE	Rate	SE	p	Rate	SE	Rate	SE
Total pregnancies	2.2	(0.6)	5.8	(0.9)	0.001	8.2	(0.8)	7.2	(0.6)
Intrauterine	1.9	(0.5)	5.6	(0.9)	<0.001	7.4	(0.8)	6.6	(0.6)
Ectopic	0.4	(0.3)	0.2	(0.2)	0.69	0.8	(0.3)	0.6	(0.2)
Expulsions	11.2	(1.1)	11.9	(1.1)	0.64	10.1	(0.9)	10.9	(0.7)
Perforations	0.0	(0.0)	0.2	(0.2)	0.18	0.1	(0.1)	0.1	(0.1)
Total medical removals	35.2	(1.8)	31.5	(1.8)	0.15	31.4	(1.4)	31.3	(1.1)
Total pain or bleeding	30.9	(1.8)	27.2	(1.7)	0.14	25.9	(1.4)	26.3	(1.1)
Pain	12.2	(1.2)	9.9	(1.2)	0.16	8.8	(0.9)	9.2	(0.7)
Bleeding	17.2	(1.6)	16.5	(1.6)	0.75	14.1	(1.1)	15.0	(0.9)
Pain and bleeding	4.9	(1.0)	3.3	(0.7)	0.17	5.5	(0.8)	4.6	(0.6)
Pelvic inflammatory disease	1.1	(0.5)	0.9	(0.4)	0.70	0.3	(0.2)	0.6	(0.2)
Other medical removals	5.1	(0.9)	5.1	(1.0)	0.99	7.1	(0.9)	6.2	(0.7)
Total use-related discontinuations	43.7	(1.8)	43.3	(1.8)	0.88	43.4	(1.4)	43.2	(1.1)
Total nonmedical removals	47.7	(1.9)	47.3	(1.9)	0.89	39.9	(1.5)	43.0	(1.2)
Wish to become pregnant	25.6	(1.6)	23.9	(1.6)	0.46	22.2	(1.3)	23.0	(1.0)
No further need	19.3	(1.8)	21.5	(1.8)	0.39	14.9	(1.3)	17.6	(1.1)
Other nonmedical removals	12.9	(1.6)	11.8	(1.5)	0.62	9.2	(1.0)	10.2	(0.9)
Loss to follow-up	31.1	(1.9)	32.5	(2.0)	0.62	26.7	(1.4)	28.9	(1.2)
Other discontinuations (devices not removed)	13.4	(1.6)	13.9	(1.6)	0.81	2.3	(0.5)	7.2	(0.7)
Continuation rate	17.6	(1.0)	17.3	(1.0)	0.88	24.4	(1.0)	21.4	(0.7)
Number of insertions	1,396		1,396			1,881		3,277	
Number of women completing the interval	245		242			447		689	
Woman-years experience	6,767		6,637			9,449		16,086	

* Data are for 10 years (3,360 days).

Three uterine perforations were reported with the TCu220C and none with the TCu380A.

Age and Parity

The number of insertions, age, and parity distributions at admission to the studies are shown in Table 1.

Cumulative Life Table Rates

Tables 2 to 4 give the cumulative net probabilities for discontinuation for both the TCu220C and the TCu380A, along with standard errors (SE) per 100 women at 8, 10, and 12 years of use for all subjects in all participating centers and p values for the differences among devices.

In randomized Study 1, which involved the copper T devices only, the TCu380A had a significantly lower pregnancy rate at 8, 10, and 12 years than did the TCu220C. There were no other statistically significant differences in termination rates in this randomized trial. The higher pregnancy and continuation rates for women with the TCu220C in Study 2 and in the two studies combined are discussed later under the heading Geographical Differences.

Table 5 gives the cumulative number of events by device at each interval. Seven pregnancies occurred with the TCu220C between the 8th and 12th years of use and none with the TCu380A. Fourteen expulsions were reported with the TCu220C compared with five reported with the TCu380A (ratio 2.8), which is similar to the ratio of the number of women entering the 8th year of use using each device (1036/430 = 2.4). Similar ratios of the number of events are seen in the other use-related discontinuations.

Annual Life Table Rates

The annual life table intrauterine pregnancy rates are shown in Figure 1. The TCu220C had a consistently higher pregnancy rate than did the TCu380A. No pregnancies were reported with the TCu380A after 8 years of use.

Figure 2 shows the annual life table rates for total medical removals. Both devices had similar annual removal rates for this reason, and after the second

Table 4. Cumulative net probabilities of discontinuation, standard error (SE) per 100 women, and significance of differences between devices (all centers)

	Study 1					Study 2		Studies 1 & 2*	
	TCu380A		TCu220C			TCu220C		TCu220C	
	Rate	SE	Rate	SE	p	Rate	SE	Rate	SE
Total pregnancies	2.2	(0.6)	5.8	(0.9)	0.001	8.9	(0.9)	7.6	(0.7)
Intrauterine	1.9	(0.5)	5.6	(0.9)	<0.001	7.9	(0.9)	7.0	(0.6)
Ectopic	0.4	(0.3)	0.2	(0.2)	0.69	1.1	(0.4)	0.7	(0.3)
Expulsions	12.5	(1.4)	12.8	(1.3)	0.87	11.1	(1.1)	11.8	(0.8)
Perforations	0.0	(0.0)	0.2	(0.2)	0.18	0.1	(0.1)	0.1	(0.1)
Total medical removals	40.2	(2.1)	39.0	(2.2)	0.69	36.8	(1.7)	37.3	(1.3)
Total pain or bleeding	35.5	(2.1)	34.3	(2.2)	0.67	30.2	(1.7)	31.6	(1.3)
Pain	13.0	(1.3)	11.3	(1.4)	0.37	10.5	(1.2)	10.7	(0.9)
Bleeding	22.0	(2.0)	22.6	(2.1)	0.85	17.2	(1.5)	19.1	(1.2)
Pain and bleeding	4.9	(1.0)	4.3	(1.0)	0.66	5.9	(0.8)	5.3	(0.7)
Pelvic inflammatory disease	1.1	(0.5)	0.9	(0.4)	0.70	0.3	(0.2)	0.6	(0.2)
Other medical removals	6.1	(1.1)	6.3	(1.2)	0.91	9.1	(1.2)	7.9	(0.9)
Total use-related discontinuations	48.8	(2.0)	50.0	(2.0)	0.67	48.8	(1.6)	49.0	(1.2)
Total nonmedical removals	53.9	(2.0)	54.0	(2.0)	0.99	43.6	(1.6)	47.8	(1.3)
Wish to become pregnant	27.0	(1.7)	24.3	(1.7)	0.26	22.4	(1.3)	23.2	(1.0)
No further need	24.4	(2.1)	29.1	(2.3)	0.14	18.2	(1.6)	22.5	(1.3)
Other nonmedical removals	16.5	(1.9)	14.3	(1.8)	0.38	11.0	(1.2)	12.3	(1.0)
Loss to follow-up	38.4	(2.3)	38.8	(2.2)	0.91	33.2	(1.7)	35.4	(1.4)
Other discontinuations (devices not removed)	15.2	(1.8)	15.2	(1.7)	0.99	2.5	(0.5)	7.9	(0.8)
Continuation rate	12.3	(0.9)	12.0	(0.9)	0.77	18.8	(0.9)	15.9	(0.7)
Number of insertions	1,396		1,396			1,881		3,277	
Number of women completing the interval	172		167			174		341	
Woman-years experience	7,159		7,018			10,080		17,098	

Data are for 12 years (4,380) days.

Table 5. Cumulative number of events by device type at 8, 10, and 12 years of use (all centers)

	Study 1						Study 2		
	TCu380A			TCu220C			TCu220C		
	Year 8	Year 10	Year 12	Year 8	Year 10	Year 12	Year 8	Year 10	Year 12
Total pregnancies	18	18	18	47	49	49	96	98	101
Intrauterine	16	16	16	45	47	47	89	91	93
Ectopic	2	2	2	2	2	2	7	7	8
Expulsions	108	110	113	118	120	122	134	140	144
Perforations	0	0	0	2	2	2	1	1	1
Total medical removals	282	309	325	247	271	294	367	391	416
Total pain or bleeding	242	265	279	214	233	253	303	319	337
Pain	104	108	110	73	78	81	100	103	108
Bleeding	109	123	135	116	128	143	148	157	168
Pain and bleeding	29	34	34	25	27	29	55	59	61
Pelvic inflammatory disease	4	5	5	6	7	7	5	5	5
Other medical removals	36	39	41	27	31	34	59	67	74
Total use-related discontinuations	408	437	456	414	442	467	598	630	662
Total nonmedical removals	366	403	430	347	390	418	413	465	486
Wish to become pregnant	210	215	219	184	190	191	244	256	257
No further need	99	117	131	107	131	152	104	127	139
Other nonmedical removals	57	71	80	56	69	75	65	82	90
Loss to follow-up	207	244	267	219	253	272	267	292	324
Other discontinuations (devices not removed)	59	67	71	68	69	72	24	26	27
All discontinuations	1040	1151	1224	1048	1154	1229	1302	1413	1499

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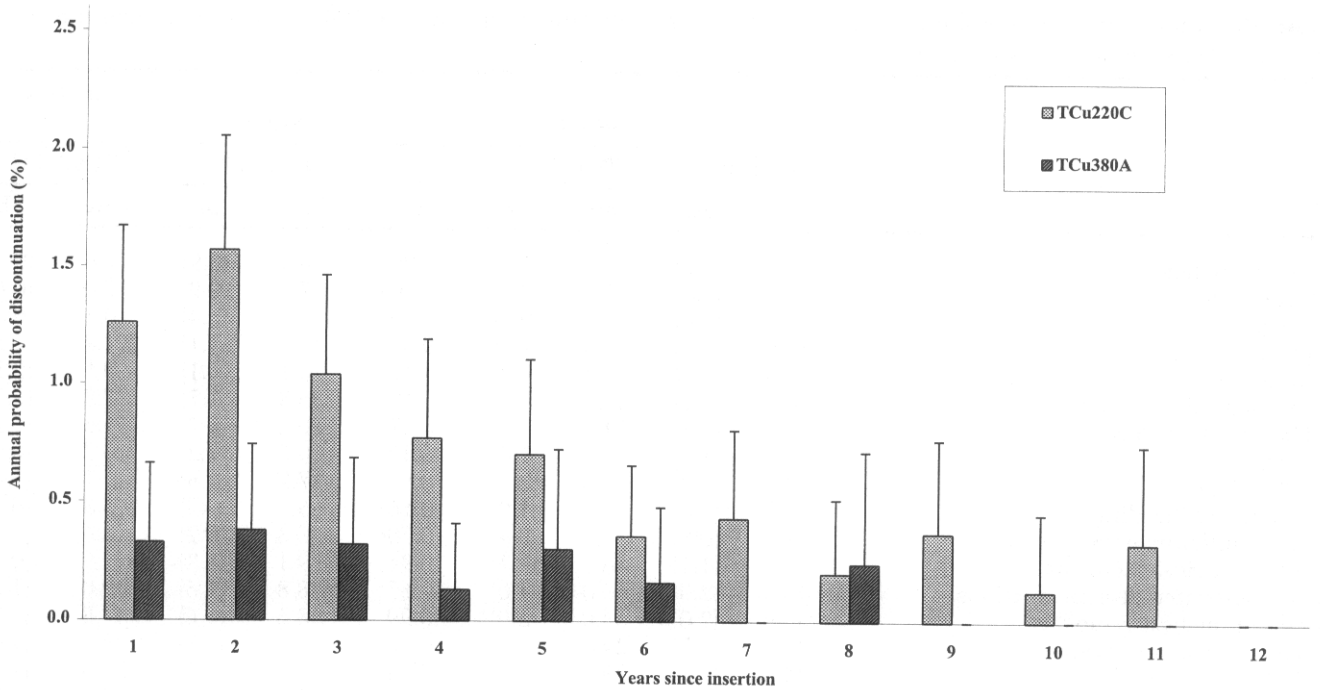

Figure 1. Annual net life table rates for intrauterine pregnancies (upper 95% confidence limit) by device—all centers.

year of use up to the 12th year the rates were approximately 4% for each device per year.

The majority of the removals for medical reasons were for pain or bleeding and, as with removals for total medical reasons, the annual rates were similar for both devices—approximately 3% per year from years 3 to 8—but with the TCu380A having consistently higher rates than the TCu220C (Figure 3).

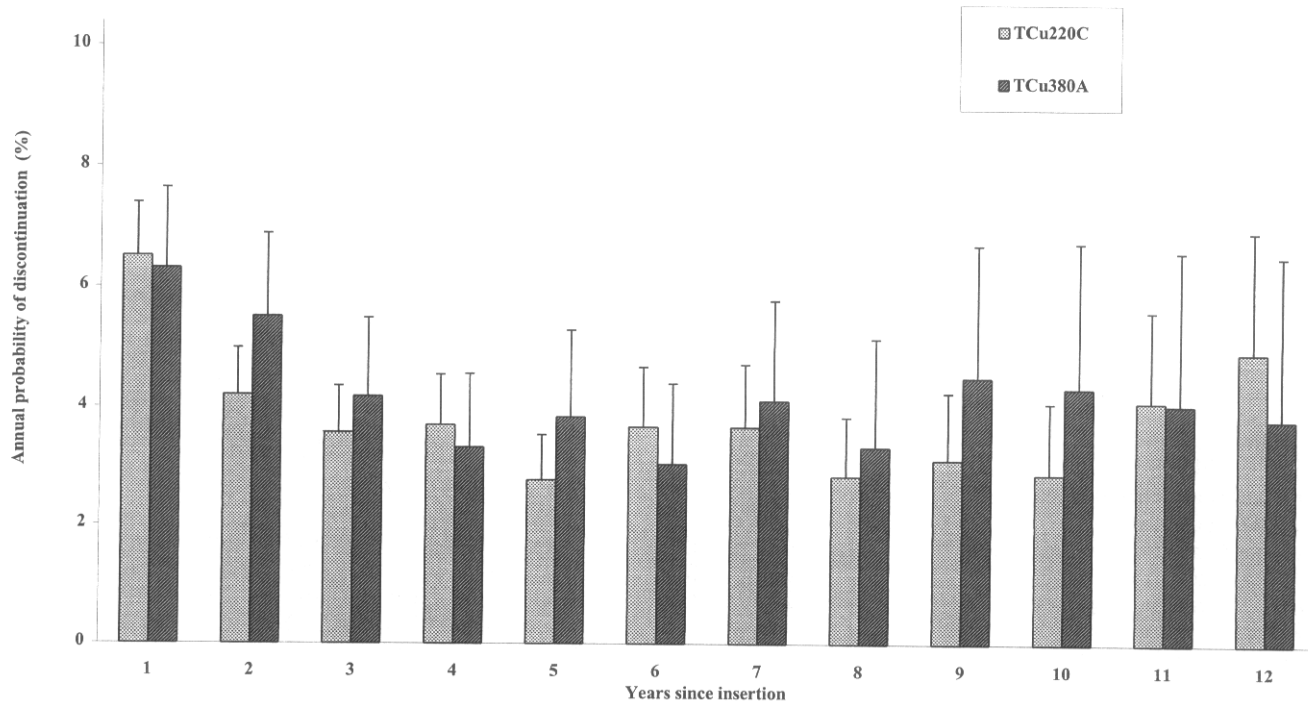

Figure 2. Annual net life table rates for total medical removals (upper 95% confidence limit) by device—all centers.

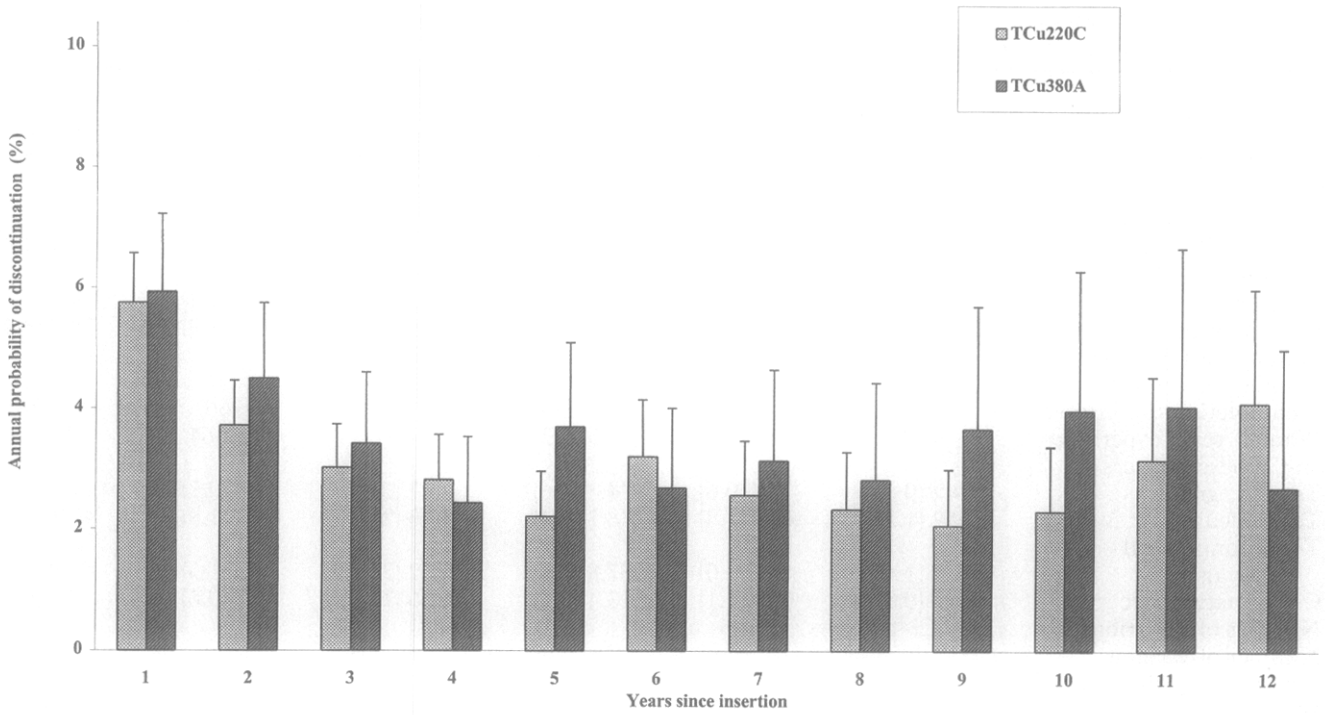

Figure 3. Annual net life table rates for removals for pain or bleeding (upper 95% confidence limit) by device—all centers.

Geographical Differences

Two centers in China participated in Study 1 and five in Study 2. The age and parity distributions by device are shown in Table 6. In the first study, these two centers contributed 14.3% of the admissions to the TCu220C and TCu380A groups and in Study 2, the five centers accounted for 28.7% of the 1,881 insertions of the TCu220C. Overall, the Chinese centers contributed 737 (22.5%) of the total TCu220C insertions and 14.4% of the total TCu380A insertions. However, the Chinese centers contributed 56.3% and 44.4% of the pregnancies occurring with the TCu220C and TCu380A, respectively.

Table 7 shows selected cumulative life table rates for the two devices for Chinese and non-Chinese centers. In both groups of centers, the pregnancy rate was significantly higher with the TCu220C device. The pregnancy rates for each device were significantly higher at all intervals in the Chinese compared with the non-Chinese centers, whereas the total medical and total nonmedical removal rates were significantly lower. The overall continuation rates were very much lower in non-Chinese centers. The number of subjects lost to follow-up in the Chinese centers was very low, with a cumulative rate of 18.0% for the TCu220C and 18.2% for the TCu380A 12 years after insertion, compared with 43.4% and 45.0%, respectively, in the non-Chinese centers. When data for women lost to follow-up were considered as censored observations in the calculation of the

Table 6. Age and parity percentage distributions by center and device

	Chinese Centers		Non-Chinese Centers	
	TCu220C (n = 737)	TCu380A (n = 201)	TCu220C (n = 2,540)	TCu380A (n = 1,195)
Age at insertion				
16–24 years	0.4	0.5	24.3	23.8
25–29 years	45.7	32.8	33.4	36.0
30–34 years	41.3	44.8	28.8	27.4
35–40 years	12.6	21.9	13.4	12.8
Parity at insertion				
Parity 1	90.9	78.6	38.2	35.8
Parity 2	9.1	20.9	41.2	41.8
Parity 3+	0.0	0.5	20.6	22.3

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Table 7. Selected cumulative net probabilities of discontinuation (standard errors) per 100 women by device at 8, 10, and 12 years of use—Chinese and non-Chinese centers

	8 Years (2,940 days)		10 Years (3,660 days)		12 Years (4,380 days)	
	TCu220C	TCu380A	TCu220C	TCu380A	TCu220C	TCu380A
Chinese Centers						
Total pregnancies	12.7 (1.4)†	4.8 (1.7)	13.4 (1.4)†	4.8 (1.7)	13.9 (1.4)†	4.8 (1.7)
Total medical removals	21.8 (1.7)	22.7 (3.1)	25.9 (1.8)	28.3 (3.5)	31.3 (2.1)	36.9 (3.9)
Total nonmedical removals	3.8 (0.8)	2.7 (1.3)	5.8 (1.1)	7.0 (2.3)	8.1 (1.4)	9.2 (2.7)
Continuation rate	57.0 (1.8)	62.7 (3.4)	48.3 (1.8)	46.8 (3.5)	40.3 (1.9)	38.8 (3.4)
Number of insertions	737	201				
Number of women completing the interval	420	126	356	94	166	78
Woman-years experience	4,367	1,239	5,132	1,454	5,664	1,622
Non-Chinese Centers						
Total pregnancies	4.2 (0.6)*	1.7 (0.6)	4.4 (0.6)*	1.7 (0.6)	4.8 (0.7)†	1.7 (0.6)
Total medical removals	29.2 (1.2)	30.9 (1.8)	33.7 (1.4)	37.5 (2.2)	40.7 (1.8)	40.1 (2.4)
Total nonmedical removals	47.8 (1.4)	49.1 (2.0)	57.8 (1.5)	57.2 (2.1)	64.0 (1.5)	64.9 (2.2)
Continuation rate	19.6 (0.8)	19.3 (1.1)	13.4 (0.7)	12.6 (1.0)	8.7 (0.6)	7.9 (0.8)
Number of insertions	2,540	1,195				
Number of women completing the interval	489	230	333	151	175	94
Woman-years experience	10,162	4,947	10,954	5,313	11,435	5,537

Significance of differences between devices within region: *$p < 0.01$; †$p < 0.001$.

overall continuation rate, the rates at 8, 10, and 12 years in the Chinese centers were 60.8%, 55.2%, and 49.1%, respectively, for the TCu220C, versus 64.9%, 56.6%, and 47.5%, respectively, for the TCu380A. Corresponding figures in the non-Chinese centers were 28,0%, 20.9%, and 15.4%, respectively, for the TCu220C, versus 26.0%, 19.1%, and 14.3%, respectively for the TCu380A.

Within the medical removals, there were more removals in the non-Chinese centers for pain or bleeding for both devices and for pain alone, but fewer for bleeding only. These differences at 12 years of use are summarized in Table 8.

Within the non-Chinese centers, five centers contributed 69.0% of the removals for pain alone but only 42.8% of the insertion of the TCu380A. Similarly, five centers had a total of 88 removals (45.8%) for the TCu220C but inserted 693 devices (21.1%). Less pronounced differences were also seen with removals for bleeding alone and for the combination of pain and bleeding.

At 12 years of use, the removal rates for desired further pregnancy were 33.1% (SE 1.5) for the TCu220C and 33.4% (SE 2.1) for the TCu380A in the non-Chinese centers, compared with 0.5% (SE 0.3) and 1.2% (SE 1.2), respectively, for the Chinese centers.

Age and Geographical Differences

There were insufficient numbers of subjects in the Chinese centers in the age groups 16 to 24 years and 35 to 40 years at insertion to make meaningful comparisons with the non-Chinese centers.

Figures 4 and 5 show the cumulative net pregnancy and total medical removal rates by age groups 25 to 29 and 30 to 34 years on entry to the study by device in the Chinese and non-Chinese

Table 8. Cumulative net removal probabilities (standard errors) per 100 women for pain or bleeding at 12 years of use by device in Chinese and non-Chinese centers

	Chinese Centers		Non-Chinese Centers	
	TCu220C	TCu380A	TCu220C	TCu380A
Pain alone	3.9 (0.9)	5.2 (1.9)	14.3 (1.4)	15.3 (1.7)
Bleeding alone	20.7 (1.8)	28.0 (3.8)	18.6 (18.6)	19.1 (2.3)
Pain and bleeding	5.4 (1.1)	3.9 (1.6)	5.0 (0.8)	5.5 (1.3)
Total pain or bleeding	27.9 (2.0)	34.4 (3.8)	33.7 (1.8)	35.3 (2.4)

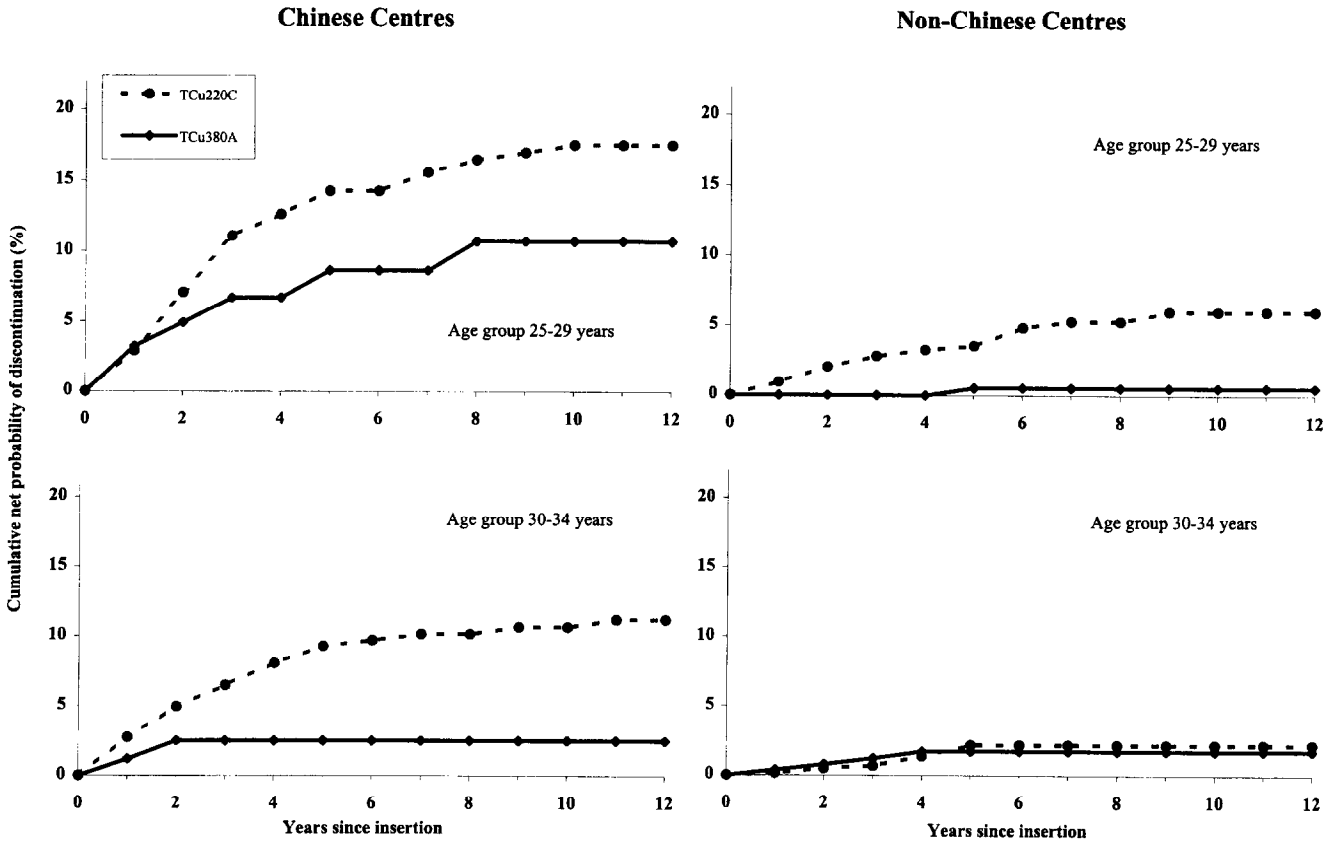

Figure 4. Cumulative net pregnancy rates by age at insertion and device in Chinese and non-Chinese centers.

centers. The removal rates for total medical reasons were lower in the 25 to 29 year old group for the Chinese centers for both the TCu220C and the TCu380A for the first 10 years of use.

Also, in the 30 to 34 year old group, both devices had lower total medical removal rates in the Chinese centers. The differences between the two age groups in total medical removals for the TCu220C in the non-Chinese centers did not show a consistent pattern.

Pelvic Inflammatory Disease

In Study 1, by year 12 there had been five removals for pelvic inflammatory disease (PID) with the TCu380A and seven with the TCu220C, with cumulative rates of 1.1 and 0.9 per 100 ($p = 0.70$), respectively. There were no removals for PID in the Chinese centers in either study. In Study 2, the 12-year cumulative rate of PID among users of the TCu220C was 0.3 (total of five cases) and, for the combined studies, the 12-year rate was 0.6 per 100 women with the TCu220C.

Ectopic Pregnancy

There were a total of eight histologically confirmed ectopic pregnancies (six for TCu220C, two for TCu380A), and an additional four ectopic pregnancies were reported with the TCu220C in which histological confirmation was not available. Both types of pregnancies are included in the life table analysis.

Discussion

This article presents the results from the largest international multicenter trial of two copper IUD. The pregnancy rates for both devices are low when compared with rates for other reversible methods of contraception. Sivin et al quote first year probabilities of pregnancy per 100 women of 0 to 2.1 for injectable contraceptives and of 2.8 to >10 for oral contraceptives.[16] Recent data suggest that even "irreversible" methods such as female sterilization are not as effective in preventing pregnancy as previously assumed. Peterson et al reported on a prospective, multicenter cohort study in which women who had undergone one of a variety of surgical methods of sterilization were followed for 8 to 14 years.[17] The cumulative 10-year probability of pregnancy for all methods combined was 1.8 per 100 procedures (range 0.8 to 3.7), which is comparable to the 2.2 pregnancies per 100 women observed at 12 years in this study with the TCu380A.

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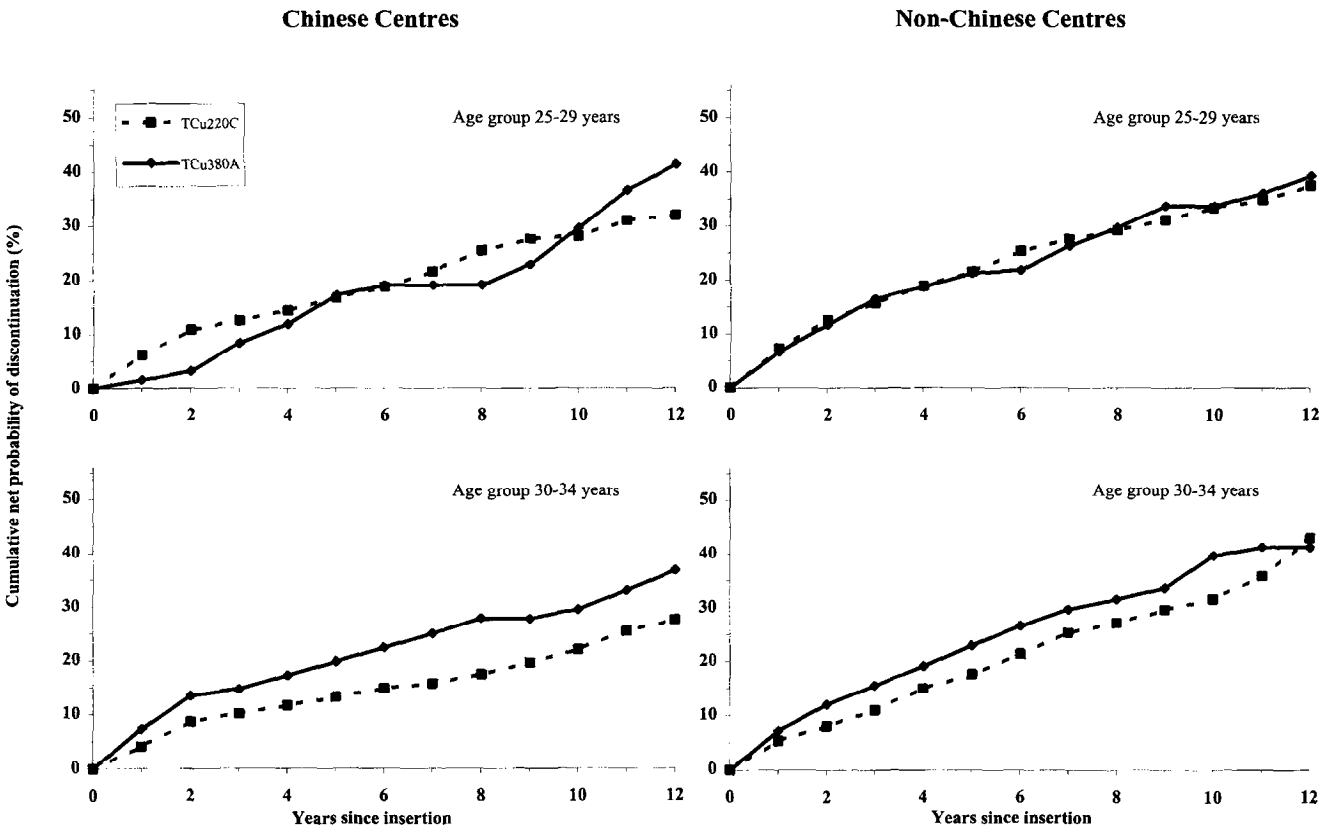

Figure 5. Cumulative net removal rates for total medical reasons by age at insertion and device in Chinese and non-Chinese centers.

The literature contains little information on the long-term efficacy of copper-releasing IUD beyond 6 years of use. Sivin et al have reported on a randomized study of the 20 μg levonorgestrel-releasing IUD and the TCu380A that was conducted in five centers including 1,121 women with the copper device.[5] The 7-year cumulative pregnancy rate was 1.4 (SE 0.4), which is similar to the 7-year rate of 1.6 (SE 0.4) per 100 women as previously reported by the WHO.[8]

A single-center study from Belgium was reported by Thiery et al in 1985. A total of 906 women with the TCu220C were followed for up to 10 years. The gross cumulative event rates per 100 women were 7.5 for pregnancy, 9.1 for expulsion, and 21.9 for removals for pain or bleeding.[18] The rates observed at 10 years in this WHO study were comparable for pregnancy (7.2 [SE 0.6]) and slightly higher for expulsion (10.9 [SE 0.7]) and removals for pain or bleeding (26.2 [SE 1.1]).

In this study, in the first 5 years of use, the TCu220C annual pregnancy rates ranged from 1.6 at 2 years to 0.7 at 5 years. Thereafter, the annual rate was consistently less than 0.5 per 100 women. On the other hand, the annual pregnancy rates for the TCu380A were always 0.4 or less per 100 women, and no pregnancies were reported after the eighth year of use.

Apart from the first year of use when the annual removal rate for total medical reasons for the TCu380A was approximately 6%, the annual rate for years 2 to 12 inclusive remained at approximately four per 100 women.

Although the majority of the expulsions occurred in the first few years following insertion, some were still recorded between the years 8 and 12. The expulsion rate rose from 9.9% at 8 years of use to 11.8% at 12 years for the TCu220C, and from 10.6% to 12.5% for the TCu380A. The 7-year expulsion rate previously reported[8] for the TCu380A of 8.6% in this trial is similar to that of 8.4% as reported by Sivin et al at 7 years of use.[5]

The higher pregnancy rates throughout the study in the Chinese centers remain unexplained. The Chinese women, as a group, were older at admission, which mitigates towards a lower expulsion rate,[5] but these women had a lower mean parity than did those at the non-Chinese centers. There were no differences observed in the number of pregnancies associated with either complete or partial expulsion between the

two groups with either the TCu220C or the TCu380A. A more detailed publication of the data from the Chinese centers is in preparation (Wu Shangchun, personal communication, 1997).

The overall rates for removal of the device for PID are very low. The 12-year rates of 0.56% (TCu220C) and 1.14% (TCu380A) are not significantly different, but are probably lower than those reported by Sivin et al. for the TCu380A at 7 years of use.

The removals for nonmedical reasons reflect the clinical practices in the Chinese and non-Chinese centers. In China, the IUD is used when the family size has been completed and the number of removals for desired further pregnancy are very much lower than in non-Chinese centers, where the IUD is viewed more as a method for spacing pregnancies.

The Chinese rates for loss to follow-up are very much lower than those seen in the non-Chinese centers, which are almost three times higher.

The cumulative pregnancy rate for the TCu220C at 10 years of use (7.6%) is low and compares favorably with the only other report on the long-term use of the TCu220C. However, this device is currently only used in China.

Because pregnancy rates with the TCu380A are so low, and are similar to those for depot injectable methods without the major disruptions in the menstrual cycle, any improvement in IUD technology must be directed towards reduction in the expulsion and removal rates for pain or bleeding. If the same magnitude of reduction in pregnancy rates from 3% to 5% with the first-generation plastic IUDs to <1% with the TCu380A could be achieved with medical removal rates, ie, to <5% at 8 years of use, the overall continuation rate would increase by up to 25% to 30%.

It can be concluded that the TCu380A and the TCu220C are safe and effective for at least 12 years of use. The TCu380A is significantly more effective and is an acceptable alternative to female sterilization or depot hormonal methods for very long-term pregnancy prevention.

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