项目报告

无支架含铜IUD（吉妮）与 TCu380A IUD：多中心随机比较性研究 8 年结果

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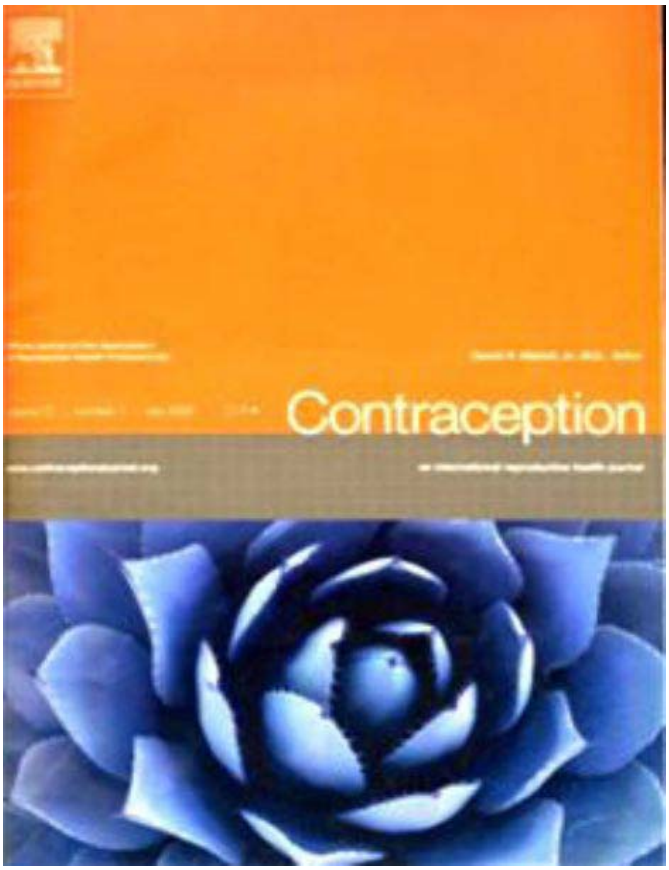

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Original research article

The frameless copper IUD (GyneFix) and the TCu380A IUD: results of an 8-year multicenter randomized comparative trial☆,☆☆,★

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Abstract

Background: Clinical performance of the frameless copper IUD (GyneFix), designed to reduce side effects related to the frame of conventional IUDs, and TCu380A was compared.

Study Design: Randomized Multicenter randomized comparative trial. Parous women requesting and eligible to use IUD were admitted in 21 centers in eight countries in 1989–1993 and followed-up for up to 8 years.

Results: Two thousand twenty-seven women were randomized to the frameless IUD and 2036 to TCu380A; 43 insertions of the frameless IUD failed and none for TCu380A. First-year expulsion rate of the frameless IUD was 5.3 (95% CI: 4.4–6.4) per 100 and 2.5 (95% CI: 1.9–3.3) for the TCu380A; second- through eighth-year expulsion rates were not different. First-year pregnancy rates for the frameless IUD and TCu380A were 1.3 (95% CI: 0.9–2.0) and 0.5 (95% CI: 0.3–0.9), respectively; second- through eighth-year cumulative pregnancy rates were 1.2 (95% CI: 0.7–1.9) and 2.5 (95% CI: 1.8–3.4), respectively. The 8-year cumulative rates of ectopic pregnancy and IUD removal for pain were lower for the frameless IUD than for TCu380A. Removals for other reasons were not different.

Conclusions: The frameless IUD had more insertion failures, expulsions and pregnancies in the first year than TCu380A, but fewer pregnancies from the second through the eighth year, and by 8 years had fewer ectopic pregnancies and removals for pain.

Keywords: Frameless copper IUD; GyneFix; TCu380A; Paragard; Randomized clinical trial

1. Introduction

Common reasons for discontinuation of use of intrauterine devices (IUDs) are bleeding or pain or both, and expulsion of the device [1]. It is thought that these conditions and events are associated with the frame and size of conventional IUDs; hence development of a frameless copper IUD began in the mid-1980s [2]. In 1989, the Special Program of Research, Development and Research Training in Human Reproduction (HRP) at the World Health Organization (WHO) in Geneva, Switzerland, initiated a multicenter randomized clinical trial of the frameless IUD (GyneFix) and the T-shaped CuT380A IUD to evaluate

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pregnancy, expulsion and removal rates for specific reasons of the two devices. The results of the first 3 years of the trial were reported in 1995 and demonstrated that the 3-year cumulative pregnancy rates were similar for the two devices, but the expulsion rate of the frameless device was higher than that of the TCu380A [3]. Incomplete results from 8 years of follow-up from the trial were reported by O'Brien and Marfleet [4]. We report the complete results of the 8-year follow-up from the trial.

2. Materials and methods

The study was conducted in 22 centers. One center failed adhering to the randomization scheme and was excluded. Data reported here are from 21 centers in Brazil, Chile, People's Republic of China (12 centers), Hungary, Mexico, The Philippines, Slovenia and Thailand (two centers). IUD insertions occurred between November 1988 and September 1993; the 8-year follow-up was completed in September 2001.

2.1. The IUDs

The frameless IUD consists of a length of nonbiodegradable 00-size monofilament surgical thread with six copper tubes each with a diameter of 2.2 mm mounted on the thread with the upper and the lower copper tubes crimped onto the thread to keep all six copper tubes in place. The surface area of the copper is 330 mm^2. A knot at the upper end of the thread is inserted into the myometrium of the uterine fundus by means of a special insertion instrument, thereby anchoring the device in the uterine cavity. Before starting the study, one or more investigators in each center were trained in insertion of it. When the trial started, the device was called CuFix; during the trial its name was changed to FlexiGard and later to GyneFix. The T-shaped copper IUD, TCu380A, is well known and studied [5,6]. Interval insertion was applied to both types of IUD.

2.2. The study

2.2.1. Women

To be eligible for enrolment, women had to be healthy; >16 years (>18 years from August 1989) and <40 years old; having had at least one previous pregnancy of at least 20 weeks' gestation or delivery of a fetus weighing more than 500 g; relying solely on the IUD for fertility regulation; exposed to risk of pregnancy; and be able to attend follow-up visits at the required intervals. Exclusion criteria were a history of recurrent pelvic inflammatory disease (PID) or pelvic abscess after the last viable pregnancy; an episode of PID in the 12 months preceding admission; sexually transmitted disease within the past 6 months; genital tract bleeding other than attributable to menses; congenital malformations of the vagina, cervix or uterus; multiple uterine fibroids associated with menstrual abnormalities; parturition or termination of pregnancy within the recent 6 weeks; clinical or laboratory evidence of anemia; history of ectopic pregnancy or hydatidiform mole; multiple sexual partners; uterine cavity length >9 cm; and known or suspected to be pregnant.

Women attending family planning clinics choosing IUD for contraception were informed about the study. Women consenting to participate were randomly allocated to insertion of either the frameless IUD or TCu380A. Blinding of the IUDs was not possible because of the differences in appearance and insertion technique of the devices, and the number of threads visible in the cervix.

2.2.2. Randomization procedure

The randomization sequence was computer generated by HRP/WHO and stratified by center. All centers received sets of opaque sealed envelopes containing the randomly allocated IUD code assigned to a given subject number. When a woman was assigned a subject number, the envelope with the corresponding subject number was opened giving information on which IUD was allocated to her.

2.2.3. Ethical approvals

The Scientific and Ethical Review Group of HRP/WHO and the WHO Secretariat Committee on Research Involving Human Subjects approved the study protocol. Each center obtained approval for the study by the ethics committee of the university it was affiliated with.

2.2.4. Pilot study

In a pilot study starting in November 1988, 40 women per center were randomly allocated to the frameless IUD or TCu380A and followed up at 2–6 weeks after the insertion and at 3, 6, 9 and 12 months.

2.2.5. The main study

After evaluation of the pilot study as described elsewhere [3], the main study started between January 1991 and May 1992. Each center enrolled another 160 women. Follow-up in the main study was at 3, 6 and 12 months after IUD insertion and annually thereafter. Women enrolled in the pilot study continued in the main study.

Women were instructed to return to the clinic if they had any problems or if they wanted to have the IUD removed. The device was removed if a woman wanted so, had side effects associated with the device or was recommended to have it removed for medical reasons. After removal of the IUD, there was no further follow-up.

2.2.6. Sample size

Assuming a pregnancy rate of 0.5 per 100 at 2 years with the TCu380A device, to detect as significantly different a rate of 2.0 per 100 for the frameless IUD device with a two-sided 5% level significance test, a total of 865 women completing 2 years would be required per study group for 80% power or 1159 women completing 2 years for 90% power [7]. With an annual discontinuation rate of 10 per 100, the required total recruitment to each device would be 1068 women or 1430 women for 80% and

90% power, respectively. For a discontinuation rate of 10 per 100 at 2 years (e.g., total medical removals) of the comparator IUD (TCu380A), a target of 1600 women recruited per device would allow detection of a significant difference from the discontinuation rate of the index IUD of 14 or 7 per 100 with about 85% power in a two-sided 5% level significance test.

2.2.7. Outcomes

The main outcomes were pregnancies; removal of the IUD for reasons of bleeding, pain or pain and bleeding; perforations; and expulsions. Secondary outcomes were IUD removal for other device-related medical reasons, incidental medical reasons unrelated to IUD use, nonmedical reasons (desire for pregnancy, no need for contraception, "other" personal reasons) and overall discontinuation of IUD use.

2.2.8. Changes in the conduct of the study

In 1996, the inserter and the insertion technique of the frameless IUD were modified. Thus, the inserter and insertion technique being investigated would not be what was to be marketed, although the IUD per se remained unchanged. Therefore, in November 1996, it was decided to end the follow-up of women still in the study. On 26 November 1996, the coordinating investigator informed the centers that there were no data on the contraceptive efficacy of the frameless IUD or side effects beyond 5 years of use, but the device should be adequate for at least 8 years of use. It was up to the clinical judgment of principal investigators in the centers to recommend removal of the frameless IUD or not; a woman deciding to continue using it should return annually to the clinic where the research was conducted or sooner if she experienced problems, rather than attend another clinic where the device was not known. The investigators got a specific code to distinguish between IUD removal for reason of "end of study" and removal for other reasons. The 1996 decision was modified in March 1997 in that follow-up of women with TCu380A would continue; the principal investigators were informed accordingly on 11 April 1997. Subsequent to these instructions, the centers continued to submit relevant study forms related to all women irrespectively of which IUD they used as the women were followed up, and data entry of the forms in HRP/WHO continued.

2.3. Data management and statistical analysis

Data were recorded on study-specific case report forms with carbon copies for centers. Completed forms were sent to HRP/WHO at regular intervals. Data quality was assured by manual and computer-generated queries that were sent to the investigators in the centers; confirmed corrections were entered into the database. The coordinating investigator and committees in HRP/WHO monitored the quality of conduct of the study from the data submitted to the coordinating center. There was no regular on-site monitoring at participating centers.

In a retrospective data review, 61 admitted women were found to have conditions potentially or truly violating admission criteria: 22 were aged above 40 years with one above 41 years; 38 gave information on conditions potentially of chronic nature of which seven were truly chronic (diabetes, epilepsy, hyperthyroidism, hypothyroidism); and one had a history of ectopic pregnancy. None of the 61 women were excluded from the analysis.

The data were analyzed in HRP/WHO using SAS software. To calculate annual rates, we considered daily steps to be a sufficiently accurate approximation to continuous time [8]. Discontinuation rates, their standard errors and 95% confidence intervals were computed using the Kaplan–Meier product-limit method for continuous time. We analyzed each reason for discontinuation of IUD use separately. In each analysis of a specific reason for IUD discontinuation, we censored for other reasons for discontinuations. No adjustments for baseline prognostic variables were done.

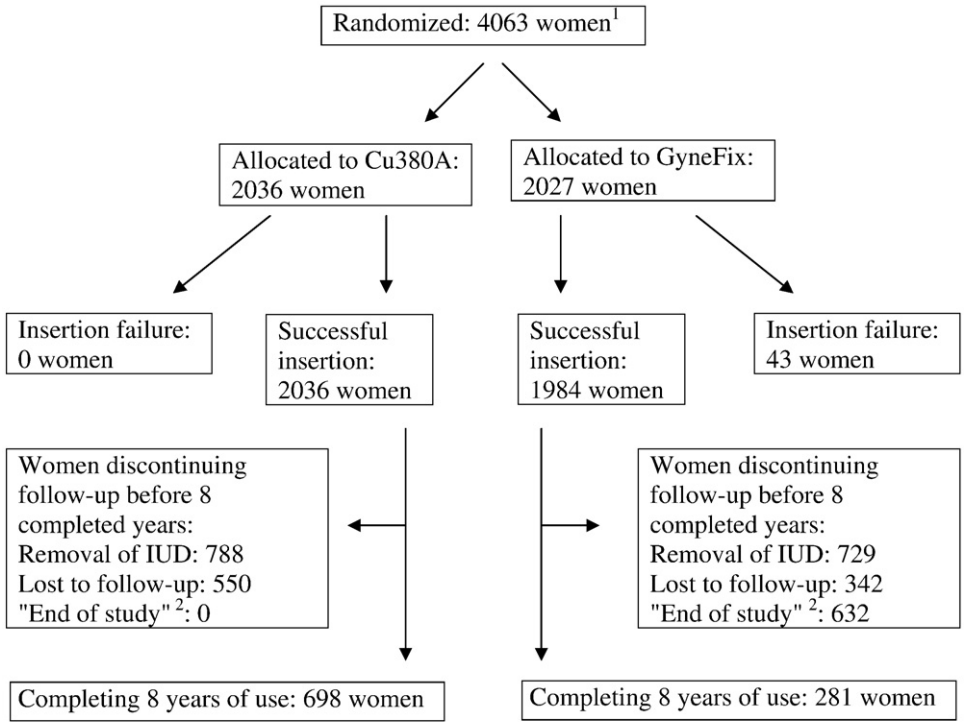
The number of women at risk on a particular day consists of all those with an observation time greater than or equal to the number of days since insertion. The interval-based estimates of discontinuation, both absolute for that interval and cumulative, were calculated conditional on those subjects observed at the start of interval.

To compare outcomes between the two IUDs, a test for the interaction of type of center (Chinese and non-Chinese) by type of IUD was conducted using Cox's proportional hazards regression model. A correction for nonproportional hazards was introduced when needed. If the interaction was significant at the 5% level, the two IUDs were compared separately for Chinese and non-Chinese centers. Otherwise, the comparison was made over all centers. In both cases, the log rank test was used. All outcome variables were standard outcomes for IUD trials; no adjustment was made for multiple inferences, therefore, the results reported here are comparable to those of other IUD studies coordinated by HRP/WHO.

Life tables and statistical tests were conducted for three populations: (1) Women with successful IUD insertion censored after 8 completed years if their follow-up time since insertion was more than 8 years. (2) Same as (1) but starting at time=366th day after insertion. This sensitivity analysis was done to investigate the effect of the high first-year expulsion rate of the frameless IUD. (3) In an additional sensitivity analysis, prompted by the changes in the conduct of the study referred to above, the date of censoring was 26 November 1996.

3. Results

Altogether, 4063 eligible women consented to participate in the study; 2027 women were assigned to the frameless IUD and 2036 to TCu380A (Fig. 1). Forty-three insertions of the frameless IUD failed, 35 in non-Chinese and eight in Chinese centers. No insertion of TCu380A failed. The main



[1] Information on numbers of women assessed for eligibility, not meeting inclusion criteria and refusal to participate was not collected.
[2] For "End of study" see section on Materials and methods of the article.

Fig. 1. Disposition of women consenting to randomization and admittance to the study by type of IUD.

reason for insertion failures was that when the inserter tube was withdrawn from the uterine cavity, the IUD was removed with it. Other failures were attributed to severe uterine anteflexion or retroflexion. Overall, there were no important differences in age, parity and outcome of last pregnancy between women with successful insertions of the frameless IUD or TCu380A (Table 1). Women in Chinese centers had lower parity and were older than women in non-Chinese centers.

3.1. Pregnancies

In the first year of use, the overall (intrauterine and ectopic) pregnancy rate was higher (p=.006) for the

Table 1
Demographic characteristics of women admitted to the study and having a successful IUD insertion by type of device for all centers, non-Chinese and Chinese centers

Variables	All centers		Non-Chinese centers		Chinese centers	
	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A
No. of women[a]	1984	2036	794	836	1190	1200
Age (years)						
Mean (SD)	29.9 (4.7)	29.9 (4.6)	28.9 (5.6)	28.9 (5.5)	30.6 (3.9)	30.6 (3.8)
Min–Max	17–40	16–41	17–40	16–41	21–40	21–40
Parity						
Mean (SD)	1.3 (0.7)	1.4 (0.7)	1.8 (0.8)	1.8 (0.9)	1.0 (0.1)	1.0 (0.1)
Min–Max	1–7	1–7	1–7	1–7	1–2	1–2
1	1511	1513	346	340	1165	1173
2	352	390	327	363	25	27
3+	121	133	121	133	0	0
Last pregnancy						
Live birth (%)	1190 (60.0)	1299 (63.8)	666 (83.9)	738 (88.3)	524 (44.0)	561 (46.8)
Stillbirth (%)	5 (0.3)	5 (0.2)	4 (0.5)	5 (0.6)	1 (0.1)	0
Miscarriage (%)	32 (1.6)	24 (1.2)	28 (3.5)	23 (2.8)	4 (0.3)	1 (0.1)
Induced abortion (%)	757 (38.2)	708 (34.8)	96 (12.1)	70 (8.4)	661 (55.5)	638 (53.2)

[a] enotes women admitted to the study and having a successful IUD insertion.

frameless IUD (1.3; 95% CI: 0.9–2.0) than for TCu380A (0.5; 95% CI: 0.3–0.9), but over time the overall cumulative pregnancy rate of the frameless IUD gradually declined to below the rate of users of TCu380A (Table 2). In the sensitivity analysis using data from the second through the eighth year of use, the overall cumulative pregnancy rates at completed 5 and 8 years and the intrauterine pregnancy rate at 8 years for the frameless IUD were significantly lower than for TCu380A (p=.015, p=.011 and p=.044, respectively) (Table 5).

Among users of the frameless and the TCu380A IUDs, one and seven ectopic pregnancies occurred, respectively, giving 8-year cumulative rates of ectopic pregnancy of 0.1 (95% CI: 0.0–0.4) and 0.5 (95% CI: 0.2–1.0) per 100

Table 2
All centers: cumulative rates (95% confidence limits in parenthesis) of pregnancies, expulsions, IUD removals for pain or bleeding or both, pelvic inflammatory disease, other medical and nonmedical reasons for removal, overall discontinuation, lost to follow-up and end of study

Variable	1st year		2nd year		3rd year		4th year	
	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A
No. of women[a]	1984	2036	1707	1802	1585	1638	1469	1492
Woman-years	1807	1893	3448	3609	4968	5163	6352	6581
Pregnancies								
All	1.3 (0.9–2.0)	0.5 (0.3–0.9)	1.7 (1.2–2.4)	1.2 (0.8–1.8)	2.1 (1.6–2.9)	1.7 (1.2–2.4)	2.2 (1.6–3.0)	2.0 (1.5–2.8)
Intrauterine	1.3 (0.9–2.0)	0.4 (0.2–0.9)	1.7 (1.2–2.4)	1.1 (0.7–1.7)	2.1 (1.5–2.9)	1.6 (1.1–2.3)	2.1 (1.6–3.0)	1.8 (1.3–2.6)
Ectopic	0	0.1 (0.0–0.4)	0.1 (0.0–0.4)	0.1 (0.0–0.5)	0.1 (0.0–0.4)	0.1 (0.0–0.5)	0.1 (0.0–0.4)	0.3 (0.1–0.7)
Expulsions								
All	5.3 (4.4–6.4)	2.5 (1.9–3.3)	6.2 (5.2–7.3)	3.3 (2.5–4.2)	7.0 (6.0–8.3)	4.1 (3.3–5.1)	7.5 (6.4–8.8)	4.3 (3.5–5.4)
Total	4.7 (3.9–5.8)	0.6 (0.4–1.1)	5.5 (4.6–6.6)	0.7 (0.4–1.2)	6.2 (5.2–7.4)	1.2 (0.8–1.8)	6.6 (5.6–7.9)	1.3 (0.8–1.9)
Partial	0.6 (0.3–1.1)	1.9 (1.4–2.6)	0.7 (0.4–1.2)	2.5 (1.9–3.4)	0.8 (0.5–1.4)	3.0 (2.3–3.9)	0.9 (0.6–1.5)	3.1 (2.4–4.0)
Removals								
All medical removals	9.0 (7.9–10)	6.5 (5.5–7.7)	12 (11–14)	10 (9.1–12)	15 (14–17)	13 (12–15)	18 (17–20)	16 (14–18)
All pain and/or bleeding	2.6 (1.9–3.4)	3.4 (2.7–4.3)	4.3 (3.4–5.3)	5.8 (4.8–7.0)	6.4 (5.3–7.6)	7.5 (6.4–8.9)	8.7 (7.4–10)	9.1 (7.9–11)
Pain	0.6 (0.3–1.1)	0.8 (0.5–1.3)	0.8 (0.5–1.4)	1.4 (1.0–2.0)	1.2 (0.8–1.9)	1.9 (1.3–2.6)	1.5 (1.0–2.2)	2.3 (1.7–3.1)
Bleeding	1.6 (1.1–2.3)	2.1 (1.5–2.8)	3.0 (2.3–3.9)	3.6 (2.9–4.6)	4.3 (3.5–5.4)	4.7 (3.8–5.8)	6.1 (5.1–7.4)	5.9 (4.9–7.1)
Pain and bleeding	0.4 (0.2–0.8)	0.6 (0.3–1.0)	0.5 (0.3–1.0)	0.9 (0.5–1.4)	0.9 (0.5–1.5)	1.1 (0.7–1.7)	1.2 (0.8–1.9)	1.2 (0.8–1.8)
Other medical removals	0.1 (0.0–0.5)	0	0.4 (0.2–0.8)	0.1 (0.0–0.4)	0.6 (0.3–1.2)	0.5 (0.2–0.9)	1.0 (0.6–1.6)	0.7 (0.4–1.2)
Nonmedical removals	1.5 (1.0–2.2)	1.2 (0.8–1.8)	3.8 (3.0–4.8)	3.8 (3.0–4.8)	5.6 (4.6–6.8)	6.7 (5.6–8.0)	9.1 (7.8–11)	9.4 (8.1–11)
PID	0	0.3 (0.1–0.6)	0.1 (0.0–0.4)	0.4 (0.2–0.8)	0.1 (0.0–0.5)	0.4 (0.2–0.8)	0.3 (0.1–0.7)	0.4 (0.2–0.8)
Overall discontinuation rate	11 (9.4–12)	7.8 (6.7–9.1)	16 (14–18)	14 (13–16)	21 (19–22)	20 (18–22)	26 (24–28)	24 (22–26)
Lost to follow-up	3.7 (2.9–4.6)	4.0 (3.2–4.9)	5.2 (4.3–6.3)	6.5 (5.4–7.7)	6.9 (5.8–8.2)	8.8 (7.6–10)]	9.1 (7.8–11)	11 (9.5–12)
End of study[b]	0	0	0	0	0	0	0	0

Variable	5th year		6th year		7th year		8th year	
	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A
No. of women[a]	1333	1380	1199	1237	913	1135	521	948
Woman-years	7628	7892	8684	9071	9326	10101	9696	10889
Pregnancies								
All	2.4 (1.7–3.2)	2.7 (2.0–3.6)	2.4 (1.7–3.2)	2.9 (2.1–3.8)	2.5 (1.8–3.4)	3.0 (2.2–4.0)	2.5 (1.8–3.4)	2.9 (2.2–3.9)
Intrauterine	2.3 (1.7–3.1)	2.2 (1.6–3.1)	2.3 (1.7–3.1)	2.4 (1.8–3.3)	2.4 (1.8–3.3)	2.5 (1.8–3.4)	2.4 (1.8–3.3)	2.5 (1.8–3.4)
Ectopic	0.1 (0.0–0.4)	0.5 (0.2–1.0)	0.1 (0.0–0.4)	0.5 (0.2–1.0)	0.1 (0.0–0.4)	0.5 (0.2–1.0)	0.1 (0.0–0.4)	0.5 (0.2–1.0)
Expulsions								
All	7.7 (6.6–9.0	4.5 (3.7–5.6)	8.1 (7.0–9.5)	4.7 (3.8–5.8)	8.8 (7.5–10)	5.1 (4.2–6.3)	9.0 (7.7–11)	6.1 (5.0–7.5)
Total	6.9 (5.8–8.1)	1.3 (0.9–2.0)	7.2 (6.1–8.5)	1.5 (1.0–2.2)	7.9 (6.7–9.4)	1.7 (1.1–2.4)	8.1 (6.8–9.7)	1.8 (1.2–2.6)
Partial	0.9 (0.6–1.5)	3.3 (2.5–4.2)	1.0 (0.6–1.6)	3.3 (2.5–4.1)	1.0 (0.6–1.6)	3.5 (2.8–4.5)	1.0 (0.6–1.6)	4.4 (3.4–5.6)
Removals								
All medical removals	20 (19–22)	18 (16–20)	23 (21–25)	20 (18–22)	26 (24–29)	23 (21–25)	29 (27–32)	27 (25–30)
Pain and/or bleeding	10 (8.8–12)	10 (9.1–12)	12 (11–14)	12 (10–13)	15 (13–17)	15 (13–16)	18 (15–20)	18 (16–20)
Pain	1.8 (1.3–2.6)	2.7 (2.0–3.6)	2.1 (1.5–3.0)	3.1 (2.3–4.1)	2.4 (1.7–3.4)	3.9 (3.0–5.1)	2.4 (1.7–3.4)	4.6 (3.6–5.9)
Bleeding	7.3 (6.1–8.7)	6.8 (5.7–8.1)	9.0 (7.7–11)	7.7 (6.5–9.1)	12 (9.8–14)	9.7 (8.3–11)	14 (12–16)	12 (10–14)
Pain and bleeding	1.4 (0.9–2.1)	1.3 (0.9–2.0)	1.6 (1.0–2.3)	1.4 (1.0–2.1)	1.7 (1.1–2.6)	1.6 (1.1–2.4)	2.3 (1.4–3.7)	1.9 (1.3–2.7)
Other medical removals	1.1 (0.7–1.8)	0.9 (0.5–1.5)	1.7 (1.1–2.6)	1.4 (0.9–2.1)	2.8 (1.4–5.5)	2.9 (1.6–5.1)	1.3 (0.8–2.3)	0.7 (0.4–1.5)
Nonmedical removals	12 (11–14)	15 (13–17)	16 (14–18)	18 (16–20)	19 (17–21)	20 (18–22)	20 (18–22)	22 (20–25)
PID	0.3 (0.1–0.7)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.6 (0.3–1.1)	0.4 (0.2–0.9)	0.7 (0.4–1.3)
Overall discontinuation rate	30 (28–33)	30 (28–33)	35 (33–38)	34 (32–36)	41 (38–37)	39 (37–41)	44 (41–47)	44 (42–46)
Lost to follow-up	11 (9.2–12	13 (11–14)	12 (11–14)	15 (14–17)	21 (19–24)	24 (22–26)	32 (29–36)	39 (36–41)
End of study[b]	2.9 (2.1–4.0)	0	19 (17–21)	0	44 (41–47)	0	63 (59–66)	0

[a] Number of women starting the interval with the IUD in utero.
[b] Number of women discontinued for reason of end of study; see Materials and Methods.

woman-years, respectively (p=.038) (Table 2). The ratio of ectopic to intrauterine pregnancies for the frameless IUD was 0.025 (1:40) and 0.180 (7:39) for TCu380A. In the second- through the eighth-year sensitivity analysis, the cumulative rates of ectopic pregnancy were largely similar for the frameless and the TCu380A IUDs (Table 5), and the ratios of ectopic to intrauterine pregnancies were 0.063 (1:16) and 0.162 (6:31), respectively.

3.2. Perforations and expulsions

There were no uterine perforations. In the first year, the rate of all (complete and partial) expulsions was approximately twofold higher among users of the frameless IUD than among users of TCu380A (p<.001) (Table 2). Complete expulsions were more frequent than partial expulsions for the frameless IUD, while the opposite held for the TCu380A. From the second through the eighth year of use there were no significant differences in the cumulative rates of all expulsions of the IUDs (p=.374).

3.3. IUD Removals

3.3.1. Bleeding, pain, pain and bleeding

In the first years of follow-up, the rates of removal for reasons of bleeding and/or pain were somewhat higher in users of TCu380A than in users of the frameless IUD, but the difference leveled out resulting in the same 8-year cumulative rate (p=.883) (Table 2). The rates of IUD removals because of bleeding and bleeding and pain were largely similar for the frameless IUD and TCu380A users over the 8 years. The 8-year cumulative rate for removal for reason of pain in users of the frameless IUD was almost half of that in TCu380A users (p=.015).

3.3.2. Other medical, incidental medical, nonmedical

The annual rates of IUD removal for "other medical reasons" were around or less than 1 per 100 with no important differences between the devices (Table 2). The rate of removal of the IUD for incidental medical reasons was half that of removal for other medical reasons with no important difference between the IUDs (not shown). There were no significant differences between the two IUDs in the overall rates (p=.189) (Table 2) or in the specific rates (not shown) of IUD removal for nonmedical reasons.

3.3.3. Pelvic inflammatory disease

Pelvic inflammatory disease (PID), defined as in previous HRP/WHO IUD studies [9], occurred in altogether 15 women, 12 in non-Chinese centers, without any significant differences between the two IUDs (p=.282) (Tables 2–4).

3.4. Overall discontinuation rates

The first-year overall discontinuation of use rate, which includes all reasons for stopping IUD use, was significantly higher among users of the frameless IUD (11; 95% CI: 9.4–12) than among TCu380A users (7.8; 95% CI: 6.7–9.1)

Table 3
Non-Chinese centers: number of women entering each year of follow-up, cumulative number of woman-years and rates (95% confidence limits in parenthesis) of pregnancy, expulsions, IUD removals for pain or bleeding or both, pelvic inflammatory disease, other medical and nonmedical reasons for removal, overall discontinuation, lost to follow-up and end of study

Variable	1st year		2nd year		5th year		8th year	
	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A
No. of women[a]	794	836	596	675	364	414	91	216
Woman-years	670	733	1222	1354	2423	2671	2820	3350
Pregnancies								
All	2.4 (1.5–3.8)	0.4 (0.1–1.3)	2.7 (1.7–4.3)	1.1 (0.5–2.1)	3.3 (2.2–5.1)	2.0 (1.1–3.7)	3.3 (2.2–5.1)	2.0 (1.1–3.7)
Intrauterine	2.4 (1.5–3.8)	0.4 (0.1–1.3)	2.7 (1.7–4.3)	1.1 (0.5–2.1)	3.3 (2.2–5.1)	1.8 (0.9–3.3)	3.3 (2.2–5.1)	1.8 (0.9–3.3)
Ectopic	0	0	0	0	0	0.3 (0.0–1.8)	0	0.3 (0.0–1.8)
Expulsions								
All	7.7 (6.0–9.9)	3.1 (2.1–4.6)	9.4 (7.4–12)	3.8 (2.6–5.4)	12 (9.6–15)	5.2 (3.8–7.3)	16 (12–21)	5.8 (4.0–8.1)
Total	6.7 (5.1–8.7)	0.4 (0.1–1.2)	8.0 (6.2–10)	0.7 (0.3–1.7)	10 (8.2–13)	1.3 (0.6–2.6)	15 (11–20)	1.3 (0.6–2.6)
Partial	1.1 (0.6–2.2)	2.8 (1.8–4.2)	1.5 (0.8–2.7)	3.1 (2.1–4.6)	1.7 (0.9–3.0)	4.0 (2.7–5.9)	1.7 (0.9–3.0)	4.5 (3.0–6.8)
Removals								
All medical removals	14 (12–17)	8.0 (6.3–10)	18 (15–21)	13 (11–15)	29 (26–33)	22 (19–25)	42 (36–47)	36 (32–41)
All pain and/or bleeding	4.3 (3.0–6.1)	4.1 (2.9–5.8)	6.3 (4.7–8.5)	7.5 (5.8–9.7)	15 (12–18)	13 (11–16)	25 (20–31)	28 (24–33)
Pain	1.4 (0.8–2.7)	1.1 (0.6–2.2)	2.1 (1.3–3.6)	2.9 (1.9–4.5)	5.0 (3.4–7.4)	6.0 (4.2–8.3)	6.6 (4.4–9.9)	11 (8.5–15)
Bleeding	2.3 (1.4–3.8)	2.3 (1.4–3.6)	3.6 (2.4–5.3)	3.7 (2.5–5.4)	8.7 (6.5–12)	6.2 (4.4–8.5)	16 (12–21)	16 (12–20)
Pain and bleeding	0.6 (0.2–1.6)	0.8 (0.4–1.8)	0.8 (0.3–1.8)	1.1 (0.6–2.2)	1.9 (1.0–3.6)	1.8 (1.0–3.4)	4.4 (1.9–10)	3.4 (1.8–6.2)
Other medical removals	0.3 (0.1–1.3)	0	0.5 (0.2–1.5)	0.2 (0.0–1.2)	1.4 (0.7–3.0)	1.9 (1.0–3.6)	2.8 (1.4–5.5)	2.9 (1.6–5.1)
Nonmedical removals	3.5 (2.4–5.3)	2.6 (1.7–4.1)	8.1 (6.2–11)	8.4 (6.5–11)	32 (28–36)	38 (34–42)	54 (48–60)	56 (52–60)
PID	0	0.5 (0.2–1.4)	0.2 (0.0–1.2)	0.8 (0.4–1.8)	0.6 (0.2–2.0)	1.1 (0.5–2.3)	1.0 (0.4–3.1)	1.6 (0.7–3.7)
Overall discontinuation rate	18 (15–21)	11 (8.9–13)	25 (22–29)	21 (18–24)	52 (49–56)	52 (48–56)	74 (69–78)	73 (69–76)
Lost to follow-up	8.9 (7.1–11)	9.4 (7.6–12)	12 (10–15)	14 (12–17)	20 (17–24)	23 (20–27)	29 (24–35)	31 (27–35)
End of study[b]	0	0	0	0	11 (8.6–15)	0	92 (90–93)	0

[a] Number of women starting the interval with the IUD in utero.
[b] Number of women discontinued for reason of end of study; see Materials and Methods.

(Table 2). The difference is largely attributable to the high first-year discontinuation rate in the non-Chinese centers (Table 3). From the second through the eighth year, the difference leveled out and the 8-year cumulative discontinuation rates were the same (p=.454) (Table 2).

In the sensitivity analysis with censoring on 26 November 1996, the rates of removal of the IUD for different reasons were very similar to those of the main analysis (not shown). In this analysis, 1124 GyneFix users and 1138 TCu380A users had used their IUD for at least 5 years, and 80 women used the frameless IUD and 91 the TCu380A IUD at the start of the eighth year.

3.5. Loss to follow-up

The rates of loss to follow-up through the sixth year were low, while in the last 2 years of follow-up the overall annual rates of loss to follow-up ranged between 10 and 20 per 100 (Table 2).

3.6. Discontinuations for end of study

Following the instructions from the coordinating investigator in 1996–1997, altogether 632 women using the frameless IUD and none using the TCu380A IUD discontinued from the study for reason of end of study from the fifth through the eighth year of follow-up (Tables 2–4). The rates of discontinuation from the study for this reason were higher in non-Chinese than in Chinese centers.

3.7. Non-Chinese and Chinese centers

Since the difference in pregnancy rates between devices tended to be higher in non-Chinese than in Chinese centers (p=.079 for the interaction type of device by type of center), we analyzed the two groups of centers separately (Tables 3 and 4). In the first year of IUD use, the difference between the pregnancy rates of the frameless IUD and CuT380A was smaller in Chinese (p=.569) than in non-Chinese centers (p=.002), and the rate of expulsions of the frameless IUD in the Chinese centers was half that in the non-Chinese centers (Tables 3 and 4). The 8-year cumulative pregnancy rate of CuT380A was numerically higher than that of the frameless IUD in Chinese centers (p=.051), while in non-Chinese centers it was the opposite (p=.042) (p=.015 for the interaction of IUD type by type of center). In the sensitivity analysis of the second through the eighth year of use, the pregnancy rates in the two groups of centers were similar (Table 5). Losses to follow-up up to 5 years were smaller in the Chinese than in the non-Chinese centers, but increased substantially thereafter in the Chinese centers (Tables 3 and 4).

4. Discussion

The long-term clinical performance of the frameless IUD was largely on par with that of TCu380A. In some aspects,

Table 4
Chinese centers: number of women entering each year of follow-up, cumulative number of woman-years and cumulative rates (95% confidence limits in parenthesis) of pregnancy, expulsions, IUD removals for pain or bleeding or both, pelvic inflammatory disease, other medical and nonmedical reasons for removal, overall discontinuation, lost to follow-up and end of study

Variable	1st year		2nd year		5th year		8th year	
	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A
No. of women[a]	1190	1200	1111	1127	969	966	430	742
Woman-years	1138	1160	2226	2255	5205	5221	6877	7539
Pregnancies								
All	0.7 (0.4–1.4)	0.5 (0.2–1.2)	1.2 (0.7–2.0)	1.3 (0.7–2.1)	1.8 (1.1–2.7)	3.0 (2.2–4.3)	1.9 (1.2–3.0)	3.4 (2.4–4.7)
Intrauterine	0.7 (0.4–1.4)	0.4 (0.2–0.9)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	1.7 (1.1–2.6)	2.5 (1.7–3.6)	1.8 (1.2–2.9)	2.8 (2.0–4.0)
Ectopic	0	0.1 (0.0,0.6)	0.1 (0.0–0.6)	0.2 (0.1–0.7)	0.1 (0.0–0.6)	0.6 (0.3–1.3)	0.1 (0.0–0.6)	0.6 (0.3–1.3)
Expulsions								
All	3.8 (2.9–5.1)	2.1 (1.4–3.1)	4.2 (3.2–5.6)	2.9 (2.1–4.1)	5.4 (4.2–6.9)	4.1 (3.1–5.5)	6.0 (4.7–7.6)	6.0 (4.7–7.7)
Total	3.6 (2.6–4.8)	0.8 (0.4–1.5)	4.0 (3.0–5.3)	0.8 (0.4–1.5)	4.9 (3.8–6.4)	1.4 (0.8–2.2)	5.5 (4.3–7.0)	2.0 (1.3–3.0)
Partial	0.3 (0.1–0.8)	1.4 (0.8–2.2)	0.3 (0.1–0.8)	2.2 (1.5–3.2)	0.5 (0.2–1.1)	2.8 (2.0–4.0)	0.6 (0.3–1.3)	4.2 (3.0–5.7)
Removals								
All medical removals	5.9 (4.7–7.4)	5.6 (4.4–7.1)	8.5 (7.0–10)	8.8 (7.3–11)	15 (13–17)	16 (14–18)	23 (20–26)	23 (21–26)
All pain and/or bleeding	1.5 (0.9–2.4)	3.0 (2.1–4.1)	3.0 (2.2–4.2)	4.8 (3.7–6.2)	7.9 (6.4–9.6)	9.0 (7.5–11)	15 (12–18)	14 (12–16)
Pain	0.1 (0.0–0.6)	0.6 (0.3–1.3)	0.1 (0.0–0.6)	0.6 (0.3–1.3)	0.3 (0.1–0.9)	1.0 (0.6–1.8)	0.6 (0.3–1.5)	1.8 (1.1–3.0)
Bleeding	1.1 (0.7–2.0)	2.0 (1.3–2.9)	2.6 (1.8–3.7)	3.6 (2.6–4.8)	6.6 (5.3–8.3)	7.1 (5.7–8.7)	13 (10–16)	11 (9.0–13)
Pain and bleeding	0.3 (0.1–0.8)	0.4 (0.2–1.0)	0.4 (0.1–1.0)	0.7 (0.4–1.4)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	1.6 (0.9–2.8)	1.3 (0.8–2.3)
Other medical removals	0	0	0.3 (0.1–0.9)	0	1.0 (0.5–1.8)	0.4 (0.2–1.1)	2.3 (1.3–3.8)	2.2 (1.3–3.5)
Nonmedical removals	0.4 (0.1–0.9)	0.3 (0.1–0.8)	1.4 (0.8–2.2)	1.1 (0.6–1.9)	2.3 (1.6–3.4)	2.1 (1.4–3.1)	4.6 (3.4–6.3)	4.0 (2.9–5.4)
PID	0	0.1 (0.0–0.6)	0	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.2 (0.1–0.9)
Overall discontinuation rate	6.3 (5.1–7.9)	5.8 (4.6–7.3)	9.9 (8.3–12)	9.8 (8.2–12)	18 (15–20)	18 (16–20)	28 (25–31)	27 (24–30)
Lost to follow-up	0.4 (0.1–0.9)	0.3 (0.1–0.8)	0.7 (0.4–1.4)	1.1 (0.6–1.9)	5.0 (3.8–6.5)	6.0 (4.7–7.7)	31 (27–35)	39 (36–42)
End of study[b]	0	0	0	0	0.1 (0.0–0.8)	0	64 (60–68)	0

[a] Number of women starting the interval with the IUD in utero.
[b] Number of women discontinued for reason of end of study; see Materials and Methods.

TCU380A performed better while in others it was the opposite. The pregnancy rate of the frameless IUD in the first year was more than double that of TCu380A (Table 2), but from the second through the eighth year the cumulative rate for each year was about half of that of TCu380A (Table 5). This shift of the rates was caused by the high expulsion rate of the frameless IUD in the first year of use. The 8-year cumulative rate of ectopic pregnancy and the ratio of ectopic to intrauterine pregnancies of the frameless IUD were low. The small ratio among women having had a frameless device inserted is likely to be exaggerated by the relatively large number of pregnancies caused by unnoticed device expulsions; most of the first-year pregnancies among these women occurred without the frameless IUD in utero. From the second through the eighth year of use the ratio of ectopic to intrauterine pregnancies was 0.063, similar to what has been reported for other copper IUDs [10].

While the expulsion rate of the frameless IUD was high in the first year, as reported previously [3,4], the rates of expulsions were not different between the two IUDs from the second through the eighth year (Table 2). Skills and experience of clinicians are determinants of early expulsion of IUDs [11,12]; the different first-year expulsion rates of the frameless device between non-Chinese and Chinese centers (Tables 3 and 4) may be due to greater experience in general of IUD insertion among the Chinese investigators. A new inserter and insertion technique for the frameless IUD, not used in our study, are reported to reduce the expulsion rate to levels similar to those of current copper IUDs [13], but independent trials need to confirm this.

The frameless IUD was designed to reduce removals for bleeding and/or pain. The 8-year cumulative removal rate for pain alone was significantly lower for the frameless IUD, but not so for bleeding or bleeding and pain. The cumulative 8-year removal rate for bleeding and/or pain was the same for the two IUDs.

Despite the 1996–1997 decisions to stop the follow-up of users of the frameless IUD and continue follow-up of TCu380A users, the centers continued the follow-up of users of both devices. A likely explanation for this is that centers were reimbursed by number of women followed up irrespective of which IUD they used. Nevertheless, from year 1997 it led to discontinuation from the study of 632 users of the frameless IUD for reason of end of study (Table 2). The end-of-study discontinuations may have influenced outcome variables. However, the sensitivity analysis with censoring on 26 November 1996 had results very similar to those of the main analysis, indicating that the results of the latter were not materially affected by these discontinuations.

The rates of losses to follow-up were low in the first 5 to 6 years of follow-up (Tables 2–4). The higher rates in the last 2 years with higher losses for TCu380A probably relate to the 1996–1997 instructions to stop the follow-up of users of the frameless IUD and the advice to them to attend the study clinics rather than other clinics.

As in previous multicenter IUD studies done by WHO, we found differences in outcomes between Chinese and non-Chinese centers [5,6]: a higher first-year pregnancy rate for the frameless IUD in non-Chinese centers, judged as a consequence of the higher expulsion rate of it; the magnitude

Table 5
Cumulative rates per 100 woman-years (95% confidence limits in parenthesis) of all pregnancies; intrauterine and ectopic pregnancies from the second through the eighth year in women using the IUD at the start of the second year after IUD insertion; by end of second, fifth and eighth year after insertion; and by type of device for all centers, non-Chinese and Chinese centers

Variable	2nd year		5th year		8th year	
	GyneFix	TCu380A	GyneFix	TCu380A	GyneFix	TCu380A
All centers						
No. of women[a]	1707	1802	1333	1380	521	948
Pregnancies						
All	0.4 (0.2–0.9)	0.7 (0.4–1.2)	1.0 (0.6–1.7)	2.2 (1.6–3.1)	1.2 (0.7–1.9)	2.5 (1.8–3.4)
Intrauterine	0.4 (0.2–0.8)	0.6 (0.4–1.2)	1.0 (0.6–1.6)	1.8 (1.3–2.6)	1.1 (0.7–1.8)	2.1 (1.5–3.0)
Ectopic	0.1 (0.0–0.4)	0.1 (0.0–0.4)	0.1 (0.0–0.4)	0.4 (0.2–1.0)	0.1 (0.0–0.4)	0.4 (0.2–1.0)
Non-Chinese centers						
No. of women[a]	596	675	364	414	91	206
Pregnancies						
All	0.4 (0.1–1.5)	0.7 (0.3–1.7)	1.0 (0.4–2.3)	1.6 (0.8–3.3)	1.0 (0.4–2.3)	1.6 (0.8–3.3)
Intrauterine	0.4 (0.1–1.5)	0.7 (0.3–1.7)	1.0 (0.4–2.3)	1.4 (0.6–2.9)	1.0 (0.4–2.3)	1.4 (0.6–2.9)
Ectopic	0	0	0	0.3 (0.0–1.8)	0	0.3 (0.0–1.8)
Chinese centers						
No. of women[a]	1111	1127	969	966	430	742
Pregnancies						
All	0.5 (0.2–1.1)	0.7 (0.4–1.5)	1.1 (0.6–1.9)	2.5 (1.7–3.7)	1.2 (0.7–2.1)	2.9 (2.0–4.1)
Intrauterine	0.4 (0.1–1.0)	0.6 (0.3–1.3)	1.0 (0.5–1.8)	2.0 (1.3–3.1)	1.1 (0.6–2.0)	2.4 (1.6–3.5)
Ectopic	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.1 (0.0–0.6)	0.5 (0.2–1.2)	0.1 (0.0–0.6)	0.5 (0.2–1.2)

[a] Number of women starting the interval with the IUD in utero.

of medical IUD removals rates were different but trends over time coincided; and, as noted, rates of follow-up and of stopping follow-up due to end of study differed. Notwithstanding these differences and the impact of the 1996–1997 decisions, we think the findings of this trial are generalizable because the trial was large and multicentric; the trends of the outcome rates were stable from the second through the eighth year of follow-up, and the findings are in concordance with other comparative studies of GyneFix [4].

5. Conclusions

With the inserter and insertion technique used in this trial, the frameless IUD had more insertion failures and higher rates of expulsion and pregnancy in the first year compared to TCu380A. For the other clinical variables, the frameless IUD exhibited similar or even better clinical performance than TCu380; the cumulative 8-year rates of discontinuation for pain and ectopic pregnancy, and the cumulative pregnancy rate from the second through the eighth year were significantly lower for the frameless than for the TCu380A IUD.

Appendix A

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无支架含铜 IUD（吉妮）与 TCu380AIUD：多中心随机比较性研究 8 年结果

联合国开发计划署/联合国人口基金/世界卫生组织/世界银行人类生殖研究与发展项目

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[摘要]

背景：为减少由支架引发相关副反应而设计的无支架铜 IUD（吉妮）与 TCu380A IUD 临床效果比较。

方法：多中心随机对照性临床试验。自 1989 年-1993 年接纳来自 8 个国家 21 个中心，符合条件、需要使用 IUD 避孕的经产妇女，随访 8 年。

结果：2027 例随机放置了吉妮 IUD，2036 例放置 TCu380AIUD，其中吉妮 43 人放置失败，TCu380A 无一例放置失败。第一年吉妮脱落率为 5.3%（95%，CI：4.4-6.4），TCu380A 为 2.5%（95%，CI：1.9-3.3）。统计 8 年的脱落率相同。第 1 年妊娠率，吉妮为 1.3%（95%，CI：0.9-2.0），TCu380A 为 0.5%（95%，CI：0.3-3.4），统计 8 年的累积妊娠率分别为 1.2%（95%，CI：0.7-1.9）和 2.5%（95%，CI：1.8-3.4）。8 年累积宫外孕和因疼痛取出率，吉妮低于 TCu380A，因其他原因取出率两组相同。

结论：吉妮 IUD 更容易发生放置失败，第一年脱落和妊娠比 TCu380A 宫内节育器高，但是 8 年统计结果显示，吉妮 IUD 妊娠率、宫外孕发生率和因疼痛取出率均低于 TCu380A。

关键词：无支架铜宫内节育器　吉妮　TCu380A　随机临床试验

1. 介绍

终止使用宫内节育器的常见原因是出血、疼痛或出血和疼痛并存，以及脱落[1]。这些情况可能与传统宫内节育器的支架及大小密切相关。因此 1980 年中旬开始研发无支架的含铜宫内节育器[2]。1989 年，世界卫生组织（WHO）人类生殖项目（HRP）组织了吉妮 IUD 与 TCu380A IUD 的多中心随机临床试验，评估两种宫内节育器的妊娠率，脱落率和与 IUD 使用有关的终止率。1995 年报告了两种宫内节育器 3 年累积妊娠率几近相同，但吉妮 IUD 比 TCu380A 脱落率高[3]，随后 Obrien 和 Marfleer 发表了 8 年不完全随访结果[4]。本文报道的是 8 年随访的完整结果。

参加研究单位中国中心：

国家人口计生委科研所
北京妇产医院
北京协和医院
北京宣武医院
四川省计划生育研究所
江苏省计划生育研究所
上海国际和平妇幼保健院
上海仁济医院
上海计划生育研究所
上海新华医院
天津计划生育研究所
湖北同济医科大学计划生育研究所

国外中心：

泰国 2 家医院
巴西
斯诺维尼亚
菲律宾
墨西哥 2 家医院
智利
匈牙利

2.材料和方法

这项研究在22个研究中心进行，其中1个中心没有秉承随机的方法，其数据被删除。现在收集的数据来源于巴西、利智、中国（12 个中心）、匈牙利、墨西哥、菲律宾、斯洛文尼亚和泰国（2 个中心）。宫内节育器放置于1988年10月和1993年9月；到2001年完成全部8年随访

2.1 宫内节育器

吉妮IUD由一条00非生物降解单丝外科手术线和6个直径为2.2mm的铜套组成，最上面和最下面的铜套压制固定在手术线上，以保持6个铜套不会滑落。吉妮IUD的铜表面积为330mm^2。手术线顶端有一线结，使用专用的放置器将线结植入子宫底肌层，使节育器固定在子宫腔。在此项研究之前，每个研究中心都有1名或多名研究人员接受了放置技术培训。这项研究开始后，这种叫做铜固定式的节育器经历两次更名，FlexiGard 以及现在的GyneFix(吉妮)。TCu380A宫内节育器已经众所周知[5、6]。于月经间期放置两种宫内节育器。

2.2 研究

2.2.1 研究对象

接收条件：健康，年龄18-40岁；至少有过一次大于20周妊娠分娩或分娩过体重超过500克的婴儿；仅使用宫内节育器避孕；夫妻同居；能按研究要求随访。拒绝条件：有复发性盆腔炎或盆腔肿瘤史；12个月内有盆腔炎发作；6个月内患有性病；不明原因的生殖道出血；先天性阴道、宫颈或子宫畸形；伴有月经异常的多发性子宫肌瘤；分娩不足6 周；临床或实验室诊断患有贫血症状；有宫外孕或葡萄胎史；无固定性伴侣；宫腔深度大于 9cm；已知或怀疑妊娠。

在计划生育门诊要求使用宫内节育器避孕的妇女都会被告知此项研究的内容。有意愿参加的妇女随机放置吉妮 IUD 或 TCu380A。由于两种宫内节育器外观和放置技术及尾丝不同，不可能达到全程完全双盲研究。

2.2.2 随机过程

随机表由HRP/WHO的电脑排列，发给各个研究中心。所有研究中心都会收到宫内节育不透明的随机信封，信封外面印有受试者序号，信封内的代码决定妇女放置哪种宫内节育器。

2.2.3 伦理审批

此项研究经过 HRP/WHO 的科学与伦理小组及WHO 人类课题研究委员会的认可。每个研究中心也经过了伦理委员会批准。

2.2.4 预试验

1988年11月开始,每个研究中心做了预实验。随机放置吉妮或TCu380A宫内节育器40例，并在放置后的2-6周，3，6，9和12月进行随访。

2.2.5 主试验

经过评估预试验后[3]，主试验于1991年1月至1992年5月进行。每个研究中心接收了另外160名受试者。并在放置后3,6和12月以及随后的每年都进行了随访。预试验中的受试者与主试验一样继续追踪随访。

如果妇女有不适或她们希望取出节育器都可以回到中心。妇女可以随时因与节育器使用相关的副反应要求取出，或者由于一些医学原因建议取出。取出节育器后不再进行随访。

2.2.6 样本量

假设使用TCu380A宫内节育器2年发生妊娠率为0.5%,采用5%双侧显著性检验,吉妮IUD为2.0%，每组完成865例2年的随访，把握度80%。如果把握度达到90%，需要1159例完成2年随访。在80%或者90%的把握度下[7],按每年平均终止率10%推算，每组需要接收1068例使用妇女。如TCu380A宫内节育器2年终止率为10%（医疗问题取出），随访率达到85%，每种节育器需要接收1600名使用妇女，与观察组终止率为14%或7%有显著差异。

2.2.7 结果

主要观察指标是妊娠、出血、疼痛或出血和疼痛、穿孔及脱落终止率。其它观察指标有，与宫内节育器使用相关的其他医疗原因终止，与宫内节育器使用无关的医疗原因，非医疗原因（希望怀孕，无需避孕，个人原因）和总终止率。

2.2.8 研究过程的变化

在1996年，吉妮IUD的放置器和放置技术都经过改进。然而，此项研究使用的放置器和放置技术

是改进前的。因此 1996 年 11 月决定对吉妮 IUD 停止随访。1996 年 10 月 26 日，课题协调员通知各研究中心尚没有吉妮 IUD 五年以上的有效性和副反应数据，然而，吉妮 IUD 可以使用 8 年以上。就这样，由临床研究负责人判断吉妮宫内节育器是否取出，如果妇女不取出，继续每年到研究中心随访，因为其他非研究单位不了解这个节育器。在这样情况下的研究结束，由研究人员标记专用代码以区分研究终止代码。1996 年的决定在 1997 年 3 月进行了修正，由于 TCu380A 使用者的继续随访，主要研究人员于 1997 年 4 月 11 日发布通知，要求各研究中心继续提交未取出吉妮研究对象使用妇女研究记录，由此，HRP/WHO 就连续此课题的数据。

2.3 数据管理和统计分析

所有收集到的数据均填写在为此研究设计的表格内，并在各研究中心留有备档。填写完成的表格会定期寄到 HRP/WHO。所有数据都会通过人工和电脑筛查鉴定后发送给研究中心课题负责人。纠错后输入数据库。HRP/WHO 的相关研究员和委员会成员监督从数据收集到各个中心的研究质量，并不是在各个研究中心设置定期现场监控。

回顾数据，61 例被发现可能或确实不符合接收条件：其中 22 例年龄超过 40 岁，并有 1 人超过 41 岁；其中 38 例可能有慢性疾病，且其中有 7 例确认为慢性疾病（糖尿病，癫痫，甲状腺功能亢进症，甲状腺功能低下）；1 例有宫外孕史。而这 61 例未从分析中删除。

HRP/WHO 收集的数据使用 SAS 软件进行统计年率，以天递进准确计算需用时间。终止率、标准误、95%可信限区间用 kaplan-meier 方法计算。我们分别做了与使用宫内节育器相关的终止原因分析，也分析其他终止原因。尊重对原始判断，不做更改。

妇女暴露于妊娠风险的次数大于或等于自放置宫内节育器的天数，所以，估算终止时段是从放置日开始进入观察计算的。

不同研究中心（中国研究中心和非中国研究中心）之间两种宫内节育器的结果比较采用 Cox 回归分析。当有必要的情况下校正了不对称风险。当两种宫内节育器观察项比较达到 5%的显著性时，将分组在中国研究中心和非中国研究中心进行比较，否则做整体数据比较。这两种情况都使用 log rank 检验法进行检验。所有结果的变量都按宫内节育试验的标准化分析，不做其他推断，因此，本报告与既往 HRP/WHO 组织的其他宫内节育器研究报告结果有可比性。

生命表和统计学检验三组人群数据：（1）成功放置宫内节育器并完成 8 年随访的妇女。（2）除上述条件外，且自第 366 天开始计算，敏感性分析由于吉妮第一年脱落率高对结果的影响。（3）敏感性分析由于 1996 年 11 月 26 日决定使研究变化，给结果带来的影响。

3.研究结果

所有 4063 人符合标准的妇女进入研究，2027 人被纳入到吉妮 IUD 组，2036 人被纳入到 TCu380A 组（图 1）。吉妮组 43 例放置失败。其中 35 例在非中国区，8 例为中国区。TCu380A 组没有放置失败发生。放置失败的主要发生在放置器撤出宫颈口时，宫内节育器随之脱出。放置失败的原因可能是子宫极度前屈或后屈。两组年龄，产次和末次妊娠结果无明显差异。（表 1）。中国区各中心妇女产次低于非中国区中心，年龄高于非中国区域研究中心。

图 1.

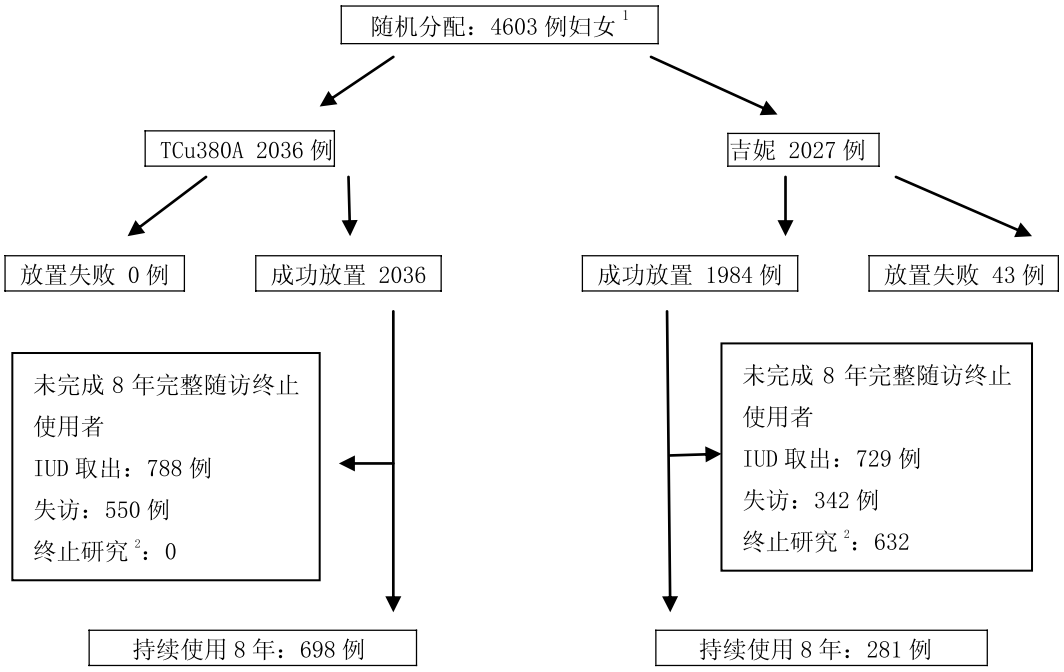

图 1 随机进入研究组的使用者分布

3.1 妊娠

第一年妊娠率(带器妊娠和宫外孕)，吉妮(1.3；95% CI：0.9-2.0）高于 TCu380A（0.5；95% CI：0.3-0.9）为（P=.006)。但是随后吉妮累积妊娠率逐年下降并低于 TCu380A（表 2)。敏感性分析使用的数据为第 8 年二次统计数据，其中，吉妮 5 年、8 年累积全部妊娠率和 8 年累积的带器妊娠率远低于使用 TCu380A(分别为 p=.015,p=.011andp=.044)（表 5)。在吉妮和 TCu380A 两组观察对象中，分别发生了 1 例和 7 例宫外孕，8 年累积的宫外孕发生率分别为 0.1%（95%CI:0.0－0.4）和 0.5%(95%CI:0.2－1.0)。(表 2)。

吉妮的宫外孕与宫内孕之比为 0.025(1:40)，TCu380A 为 0.180(7:39)。第二次的 8 年统计分析中，吉妮和 TCu380A 的累积宫外孕发生率基本相同（表 5），宫外孕比宫内孕分别为 0.063(1:16) 和 0.162(6:31)。

表 1.所有中心置器妇女一般情况

观察项目	所有中心		非中国中心		中国中心	
	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A
例数	1984	2036	794	836	1190	1200
年龄（周岁）						
平均年龄	29.9 (4.7)	29.9 (4.6)	28.9 (5.6)	28.9 (5.5)	30.6 (3.9)	30.6 (3.8)
年龄范围	17–40	16–41	17–40	16–41	21–40	21–40
产次						
平均产次	1.3 (0.7)	1.4 (0.7)	1.8 (0.8)	1.8 (0.9)	1.0 (0.1)	1.0 (0.1)
产次范围	1–7	1-7	1-7	1-7	1-2	1-2
1	1511	1513	346	340	1165	1173
2	352	390	327	363	25	27
3+	121	133	121	133	0	0
末次妊娠结局						
活产 (%)	1190 (60.0)	1299 (63.8)	666 (83.9)	738 (88.3)	524 (44.0)	561 (46.8)
死产 (%)	5 (0.3)	5 (0.2)	4 (0.5)	5 (0.6)	1 (0.1)	0
自然流产 (%)	32 (1.6)	24 (1.2)	8 (3.5)	23 (2.8)	4 (0.3)	1 (0.1)
人工流产 (%)	757 (38.2)	708 (34.8)	96 (12.1)	70 (8.4)	661 (55.5)	638 (53.2)

3.2 穿孔与脱落

研究对象无一例子宫穿孔发生。吉妮 IUD 第 1 年脱落率(完全脱落和部分脱落)是 TCu380A(p<.001)的两倍（表 2)。吉妮的完全脱落比部分脱落要高，而 TCu380A 则相反。在第二次 8 年统计中两种宫内节育器累积脱落率没有明显的差异。

3.3 宫内节育器的取出

3.3.1 出血，疼痛，疼痛和出血

第一年的随访，TCu380A 宫内节育器因出血或/和疼痛取出宫内节育器比吉妮高，但 8 年累积结果无显著差异。（表 2）

表2.所有中心累计妊娠率、脱落、因医疗或非医疗原因取出、盆腔炎、终止使用情况。

观察项目	第1年		第2年		第3年		第4年	
	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A
例数	1984	2036	1707	1802	1585	1638	1469	1492
妇女年	1807	1893	3448	3609	4968	5163	6352	6581
妊娠								
合计	1.3 (0.9–2.0)	0.5 (0.3–0.9)	1.7 (1.2–2.4)	1.2 (0.8–1.8)	2.1 (1.6–2.9)	1.7 (1.2–2.4)	2.2 (1.6–3.0)	2.0 (1.5–2.8)
宫内妊娠	1.3 (0.9–2.0)	0.4 (0.2–0.9)	1.7 (1.2–2.4)	1.1 (0.7–1.7)	2.1 (1.5–2.9)	1.6 (1.1–2.3)	2.1 (1.6–3.0)	1.8 (1.3–2.6)
异位妊娠	0	0.1 (0.0–0.4)	0.1 (0.0–0.4)	0.1 (0.0–0.5)	0.1 (0.0–0.4)	0.1 (0.0–0.5)	0.1 (0.0–0.4)	0.3 (0.1–0.7)
脱落								
合计	5.3 (4.4–6.4)	2.5 (1.9–3.3)	6.2 (5.2–7.3)	3.3 (2.5–4.2)	7.0 (6.0–8.3)	4.1 (3.3–5.1)	7.5 (6.4–8.8)	4.3 (3.5–5.4)
完全	4.7 (3.9–5.8)	0.6 (0.4–1.1)	5.5 (4.6–6.6)	0.7 (0.4–1.2)	6.2 (5.2–7.4)	1.2 (0.8–1.8)	6.6 (5.6–7.9)	1.3 (0.8–1.9)
部分	0.6 (0.3–1.1)	1.9 (1.4–2.6)	0.7 (0.4–1.2)	2.5 (1.9–3.4)	0.8 (0.5–1.4)	3.0 (2.3–3.9)	0.9 (0.6–1.5)	3.1 (2.4–4.0)
取出								
医疗原因	9.0 (7.9–10)	6.5 (5.5–7.7)	12 (11–14)	10 (9.1–12)	15 (14–17)	3 (12–15)	18 (17–20)	16 (14–18)
所有疼痛/出血	2.6 (1.9–3.4)	3.4 (2.7–4.3)	4.3 (3.4–5.3)	5.8 (4.8–7.0)	6.4 (5.3–7.6)	7.5 (6.4–8.9)	8.7 (7.4–10)	9.1 (7.9–11)
疼痛	0.6 (0.3–1.1)	0.8 (0.5–1.3)	0.8 (0.5–1.4)	1.4 (1.0–2.0)	1.2 (0.8–1.9)	1.9 (1.3–2.6)	1.5 (1.0–2.2)	2.3 (1.7–3.1)
出血	1.6 (1.1–2.3)	2.1 (1.5–2.8)	3.0 (2.3–3.9)	3.6 (2.9–4.6)	4.3 (3.5–5.4)	4.7 (3.8–5.8)	6.1 (5.1–7.4)	5.9 (4.9–7.1)
疼痛和出血	0.4 (0.2–0.8)	0.6 (0.3–1.0)	0.5 (0.3–1.0)	0.9 (0.5–1.4)	0.9 (0.5–1.5)	1.1 (0.7–1.7)	1.2 (0.8–1.9)	1.2 (0.8–1.8)
其他医疗原因	0.1 (0.0–0.5)	0	0.4 (0.2–0.8)	0.1 (0.0–0.4)	0.6 (0.3–1.2)	0.5 (0.2–0.9)	1.0 (0.6–1.6)	0.7 (0.4–1.2)
非医疗因素取出	1.5 (1.0–2.2)	1.2 (0.8–1.8)	3.8 (3.0–4.8)	3.8 (3.0–4.8)	5.6 (4.6–6.8)	6.7 (5.6–8.0)	9.1 (7.8–11)	9.4 (8.1–11)
盆腔炎	0	0.3 (0.1–0.6)	1 (0.0–0.4)	0.4 (0.2–0.8)	0.1 (0.0–0.5)	0.4 (0.2–0.8)	0.3 (0.1–0.7)	0.4 (0.2–0.8)
全部终止率	11 (9.4–12)	7.8 (6.7–9.1)	16 (14–18)	14 (13–16)	21 (19–22)	20 (18–22)	26 (24–28)	24 (22–26)
失访	3.7 (2.9–4.6)	4.0 (3.2–4.9)	5.2 (4.3–6.3)	6.5 (5.4–7.7)	6.9 (5.8–8.2)	8.8 (7.6–10)	9.1 (7.8–11)	11 (9.5–12)
研究结束	0	0	0	0	0	0	0	0

观察项目	第5年		第6年		第7年		第8年	
	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A
例数	1333	1380	1199	1237	913	1135	521	948
妇女年	7628	7892	8684	9071	9326	1010	1 9696	10889
妊娠率								
合计	2.4 (1.7–3.2).	2.7 (2.0–3.6)	2.4 (1.7–3.2)	2.9 (2.1–3.8)	2.5 (1.8–3.4)	3.0 (2.2–4.0)	2.5 (1.8–3.4)	9 (2.2–3.9)
宫内妊娠	2.3 (1.7–3.1)	2.2 (1.6–3.1)	2.3 (1.7–3.1)	2.4 (1.8–3.3)	2.4 (1.8–3.3)	2.5 (1.8–3.4)	2.4 (1.8–3.3)	2.5 (1.8–3.4)
异位妊娠	0.1 (0.0–0.4)	0.5 (0.2–1.0)	0.1 (0.0–0.4)	0.5 (0.2–1.0)	0.1 (0.0–0.4)	0.5 (0.2–1.0)	0.1 (0.0–0.4)	0.5 (0.2–1.0)
脱落率								
合计	7.7 (6.6–9.0)	4.5 (3.7–5.6)	8.1 (7.0–9.5)	4.7 (3.8–5.8)	8.8 (7.5–10)	5.1 (4.2–6.3)	9.0 (7.7–11)	6.1 (5.0–7.5)
完全	6.9 (5.8–8.1)	1.3 (0.9–2.0)	7.2 (6.1–8.5)	1.5 (1.0–2.2)	7.9 (6.7–9.4)	1.7 (1.1–2.4)	8.1 (6.8–9.7)	1.8 (1.2–2.6)
部分	0.9 (0.6–1.5)	3.3 (2.5–4.2)	1.0 (0.6–1.6)	3.3 (2.5–4.1)	1.0 (0.6–1.6)	3.5 (2.8–4.5)	1.0 (0.6–1.6)	4.4 (3.4–5.6)
取出率								
医疗原因	20 (19–22)	18 (16–20)	23 (21–25)	20 (18–22)	26 (24–29)	23 (21–25)	29 (27–32)	27 (25–30)
疼痛和/或出血	10 (8.8–12)	10 (9.1–12)	12 (11–14)	12 (10–13)	15 (13–17)	15 (13–16)	18 (15–20)	18 (16–20)
疼痛	1.8 (1.3–2.6)	2.7 (2.0–3.6)	2.1 (1.5–3.0)	3.1 (2.3–4.1)	2.4 (1.7–3.4)	3.9 (3.0–5.1)	2.4 (1.7–3.4)	4.6 (3.6–5.9)
出血	7.3 (6.1–8.7)	6.8 (5.7–8.1)	9.0 (7.7–11)	7.7 (6.5–9.1)	12 (9.8–14)	9.7 (8.3–11)	14 (12–16)	12 (10–14)
疼痛和出血	1.4 (0.9–2.1)	1.3 (0.9–2.0)	1.6 (1.0–2.3)	1.4 (1.0–2.1)	1.7 (1.1–2.6)	1.6 (1.1–2.4)	2.3 (1.4–3.7)	1.9 (1.3–2.7)
其它医疗原因	1.1 (0.7–1.8)	0.9 (0.5–1.5)	1.7 (1.1–2.6)	1.4 (0.9–2.1)	2.8 (1.4–5.5)	2.9 (1.6–5.1)	1.3 (0.8–2.3)	0.7 (0.4–1.5)
非医疗因素	12 (11–14)	15 (13–17)	16 (14–18)	18 (16–20)	19 (17–21)	20 (18–22)	20 (18–22)	22 (20–25)
盆腔炎	0.3 (0.1–0.7)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.6 (0.3–1.1)	0.4 (0.2–0.9)	0.7 (0.4–1.3)
总终止率	30 (28–33)	30 (28–33)	35 (33–38)	34 (32–36)	41 (38–37)	39 (37–41)	44 (41–47)	44 (42–46)
失访率	11 (9.2–12)	13 (11–14)	12 (11–14)	15 (14–17)	21 (19–24)	24 (22–26)	32 (29–36)	39 (36–41)
研究结束	2.9 (2.1–4.0)	0	19 (17–21)	0	44 (41–47)	0	63 (59–66)	0

8 年两种宫内节育器因出血、出血和疼痛取出率基本上相同。8 年累积的因疼痛取出率吉妮宫内节育器只有 TCu380A 的一半（p=.015）。

3.3.2 其他医疗原因，与医疗相关原因，和非医疗性的原因

两种宫内节育器因“其他医疗原因”取出率每年小于 1%，并无差异。（表 2）。“医疗相关原因”取出是其他医疗原因取出的一半，并且两组也无差异。因“非医学性原因”取出器两组也没有差异（表 2）。

3.3.3 盆腔炎

盆腔炎早在以前 HRP/WHO 宫内节育器研究项目明确定义[9]。其中一共发生 15 例，12 例在非中国区研究中心，并且两种节育器的发生率（P=.282）都没有明显差异（表 2-4）。

3.4 总终止率

吉妮 IUD 第一年包括所有取器终止使用率(11；95%CI:9.4－12)高于 TCu380A(7.8;95%CI:6.7－9.1)（表 2）。第一年的差异主要发生于非中国区研究中心。(表 3)。第二次 8 年的统计分析这项差异消失，并且两种节育器 8 年累积终止使用率基本相同（p=.454）（表 2）。

针对 1996 年 10 月 26 日决定的敏感分析中，因各种原因终止率与总体分析及其相同（未标示）。这项分析了 1124 例吉妮使用者和 1138 例 TCu380A 使用 5 年的结果，和 80 例吉妮使用者和 91 例 TCu380A 使用 8 年结果。

3.5 失访

在第 6 年时使用者失访率很低，而最后 2 年失访率增加，大约在 10-20%（表 2）。

3.6 因研究结束终止

根据 1996-1997 年的决定，632 名吉妮宫内节育器使用者在第 5 年末因研究结束终止，TCu380A 组没有。（表 2,4）。因该原因的终止例数在非中国区研究中心比中国研究中心高。

3.7 非中国研究中心与中国研究中心

我们将非中国区与中国区分组，两种节育器在非中国区妊娠率高于中国区(p=.079)，（英文表 3，4）。第一年中国区两种宫内节育器妊娠率低于非中国区，中国区吉妮宫内节育器脱落率是非中国区的一半。(表 3，4)。在中国区 8 年累积妊娠率，TCu380A 比吉妮宫内节育器明显高 (p=.051)，而在非中国组这一数字则相反(p=.042)。在第二次 8 年结果敏感分析中，两组的妊娠率几近相同（表 5）。中国区 5 年失访率比非中国区低，但在 5 年后中国区失访率增加（表 3，4）。

表3.非中国中心观察结果

观察项目	第1年		第2年		第5年		第8年	
	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A
例数	794	836	596	675	364	414	91	216
妇女年	670	733	1222	1354	2423	2671	2820	3350
妊娠率	2.4 (1.5–3.8)	0.4 (0.1–1.3)	2.7 (1.7–4.3)	1.1 (0.5–2.1)	3.3 (2.2–5.1)	2.0 (1.1–3.7)	3.3 (2.2–5.1)	2.0 (1.1–3.7)
合计								
宫内妊娠	2.4 (1.5–3.8)	0.4 (0.1–1.3)	2.7 (1.7–4.3)	1.1 (0.5–2.1)	3.3 (2.2–5.1)	1.8 (0.9–3.3)	3.3 (2.2–5.1)	1.8 (0.9–3.3)
宫外妊娠	0	0	0	0	0	0.3 (0.0–1.8)	0	0.3 (0.0–1.8)
脱落率								
合计	7.7 (6.0–9.9)	3.1 (2.1–4.6)	9.4 (7.4–12)	3.8 (2.6–5.4)	12 (9.6–15)	5.2 (3.8–7.3)	16 (12–21)	5.8 (4.0–8.1)
完全	6.7 (5.1–8.7)	0.4 (0.1–1.2)	8.0 (6.2–10)	0.7 (0.3–1.7)	10 (8.2–13)	1.3 (0.6–2.6)	15 (11–20)	1.3 (0.6–2.6)
部分	1.1 (0.6–2.2)	2.8 (1.8–4.2)	1.5 (0.8–2.7)	3.1 (2.1–4.6)	1.7 (0.9–3.0)	4.0 (2.7–5.9)	1.7 (0.9–3.0)	4.5 (3.0–6.8)
取出								
医疗原因	14 (12–17)	8.0 (6.3–10)	18 (15–21)	13 (11–15)	29 (26–33)	22 (19–25)	42 (36–47)	36 (32–41)
出血和/或疼痛	4.3 (3.0–6.1)	4.1 (2.9–5.8)	6.3 (4.7–8.5)	7.5 (5.8–9.7)	15 (12–18)	13 (11–16)	25 (20–31)	28 (24–33)
疼痛	1.4 (0.8–2.7)	1.1 (0.6–2.2)	2.1 (1.3–3.6)	2.9 (1.9–4.5)	5.0 (3.4–7.4)	6.0 (4.2–8.3)	6.6 (4.4–9.9)	11 (8.5–15)
出血	2.3 (1.4–3.8)	2.3 (1.4–3.6)	3.6 (2.4–5.3)	3.7 (2.5–5.4)	8.7 (6.5–12)	6.2 (4.4–8.5)	16 (12–21)	16 (12–20)
疼痛和出血	0.6 (0.2–1.6)	0.8 (0.4–1.8)	0.8 (0.3–1.8)	1.1 (0.6–2.2)	1.9 (1.0–3.6)	1.8 (1.0–3.4)	4.4 (1.9–10)	3.4 (1.8–6.2)
其它医疗原因	0.3 (0.1–1.3)	0	0.5 (0.2–1.5)	0.2 (0.0–1.2)	1.4 (0.7–3.0)	1.9 (1.0–3.6)	2.8 (1.4–5.5)	2.9 (1.6–5.1)
非医疗因素	3.5 (2.4–5.3)	2.6 (1.7–4.1)	8.1 (6.2–11)	8.4 (6.5–11)	32 (28–36)	38 (34–42)	54 (48–60)	56 (52–60)
盆腔炎	0	0.5 (0.2–1.4)	0.2 (0.0–1.2)	0.8 (0.4–1.8)	0.6 (0.2–2.0)	1.1 (0.5–2.3)	1.0 (0.4–3.1)	1.6 (0.7–3.7)
总终止率	18 (15–21)	11 (8.9–13)	25 (22–29)	21 (18–24)	52 (49–56)	52 (48–56)	74 (69–78)	73 (69–76)
失访	8.9 (7.1–11)	9.4 (7.6–12)	12 (10–15)	14 (12–17)	20 (17–24)	23 (20–27)	29 (24–35)	31 (27–35)
研究结束	0	0	0	0	11 (8.6–15)	0	92 (90–93)	0

表4.中国中心观察结果

观察项目	第1年		第2年		第5年		第8年	
	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A
例数	1190	1200	1111	1127	969	966	430	742
妇女年	1138	1160	2226	2255	5205	5221	6877	7539
妊娠率								
合计	0.7 (0.4–1.4)	0.5 (0.2–1.2)	1.2 (0.7–2.0)	1.3 (0.7–2.1)	1.8 (1.1–2.7)	3.0 (2.2–4.3)	1.9 (1.2–3.0)	3.4 (2.4–4.7)
宫内妊娠	0.7 (0.4–1.4)	0.4 (0.2–0.9)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	1.7 (1.1–2.6)	2.5 (1.7–3.6)	1.8 (1.2–2.9)	2.8 (2.0–4.0)
宫外妊娠	0	0.1 (0.0,0.6)	0.1 (0.0–0.6)	0.2 (0.1–0.7)	0.1 (0.0–0.6)	0.6 (0.3–1.3)	0.1 (0.0–0.6)	0.6 (0.3–1.3)
脱落率								
合计	3.8 (2.9–5.1)	2.1 (1.4–3.1)	4.2 (3.2–5.6)	2.9 (2.1–4.1)	5.4 (4.2–6.9)	4.1 (3.1–5.5)	6.0 (4.7–7.6)	6.0 (4.7–7.7)
完全	l3.6 (2.6–4.8)	0.8 (0.4–1.5)	4.0 (3.0–5.3)	0.8 (0.4–1.5)	4.9 (3.8–6.4)	1.4 (0.8–2.2)	5.5 (4.3–7.0)	2.0 (1.3–3.0)
部分	0.3 (0.1–0.8)	1.4 (0.8–2.2)	0.3 (0.1–0.8)	2.2 (1.5–3.2)	0.5 (0.2–1.1)	2.8 (2.0–4.0)	0.6 (0.3–1.3)	4.2 (3.0–5.7)
取出								
医学原因	5.9 (4.7–7.4)	5.6 (4.4–7.1)	8.5 (7.0–10)	8.8 (7.3–11)	15 (13–17)	16 (14–18)	23 (20–26)	23 (21–26)
疼痛和/或出血	1.5 (0.9–2.4)	3.0 (2.1–4.1)	3.0 (2.2–4.2)	4.8 (3.7–6.2)	7.9 (6.4–9.6)	9.0 (7.5–11)	15 (12–18)	14 (12–16)
疼痛	0.1 (0.0–0.6)	0.6 (0.3–1.3)	0.1 (0.0–0.6)	0.6 (0.3–1.3)	0.3 (0.1–0.9)	1.0 (0.6–1.8)	0.6 (0.3–1.5)	1.8 (1.1–3.0)
出血	1.1 (0.7–2.0)	2.0 (1.3–2.9)	2.6 (1.8–3.7)	3.6 (2.6–4.8)	6.6 (5.3–8.3)	7.1 (5.7–8.7)	13 (10–16)	11 (9.0–13)
疼痛和出血	0.3 (0.1–0.8)	0.4 (0.2–1.0)	0.4 (0.1–1.0)	0.7 (0.4–1.4)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	1.6 (0.9–2.8)	1.3 (0.8–2.3)
其他医疗原因	0	0	0.3 (0.1–0.9)	0	1.0 (0.5–1.8)	0.4 (0.2–1.1)	2.3 (1.3–3.8)	2.2 (1.3–3.5)
非医疗原因	0.4 (0.1–0.9)	0.3 (0.1–0.8)	1.4 (0.8–2.2)	1.1 (0.6–1.9)	2.3 (1.6–3.4)	2.1 (1.4–3.1)	4.6 (3.4–6.3)	4.0 (2.9–5.4)
盆腔炎	0	0.1 (0.0–0.6)	0	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.2 (0.1–0.9)
总终止率	6.3 (5.1–7.9)	5.8 (4.6–7.3)	9.9 (8.3–12)	9.8 (8.2–12)	18 (15–20)	18 (16–20)	8 (25–31)	27 (24–30)
失访	0.4 (0.1–0.9)	0.3 (0.1–0.8)	0.7 (0.4–1.4)	1.1 (0.6–1.9)	5.0 (3.8–6.5)	6.0 (4.7–7.7)	31 (27–35)	39 (36–42)
研究结束	0	0	0	0	0.1 (0.0–0.8)	0	64 (60–68)	0

4. 讨论

吉妮宫内节育器与 TCu380A 长期大样本观察，在一些观察指标 TCu380A 表现好于吉妮，而另一些指标吉妮优于 TCu380A。吉妮宫内节育器第一年的妊娠率是 TCu380A 的两倍之多（表 2），在二次统计的 8 年累积妊娠率吉妮只有 TCu380A 一半（表 5）。这样的结果是由于第一年吉妮 IUD 的脱落率高引起的。吉妮 8 年累积的宫外孕发生和宫外孕与宫内孕比值比较低。吉妮 IUD 妊娠率高是由于部分未知的脱落导致妊娠率似乎被夸大了，吉妮使用者第一年妊娠大部分节育器未在宫内。8 年累积宫外孕与宫内孕之比是 0.063，与其他含铜宫内节育器的报道结果相似。

如前所述，吉妮 IUD 的第一年脱落率比较高，而二次统计分析 8 年结果显示，两种宫内节育器的脱落率无明显差异（表 5）。医生的放置技术和经验是吉妮早期脱落的主要性因素。非中国区与中国区比较（表 3，4）第一年吉妮脱落率有明显差异，这可能是中国医生有丰富的放置宫内节育器经验。据报道吉妮 IUD 的新放置器能够减少脱落率，脱落率与其他含铜宫内节育器相似，但是新放置器未在本次研究中使用。我们需要专门的试验来验证上述观点。

吉妮 IUD 设计旨在减少因出血和/或疼痛取器。8 年累积因疼痛终止率明显减低。但是因出血、出血和疼痛取出与 TCu380A 无明显差异。

尽管 1996-1997 曾经一度中途终止了吉妮宫内节育器组随访，只继续随访 TCu380A，但是各个研究中心还是继续随访了两种节育器的使用者。对此各研究中的解释是他们担心遭到由于受试号选择了放置宫内节育器的种类，提前终止可能被要求索赔。尽管如此，632 例使用者自 1997 年因此研究结束终止。（表 2）考虑到研究结束终止可能影响整个研究结果，然而，敏感性分析 1996 年 10 月 26 日决定导致的结果与总体研究结果相似，这表明研究结果并没有受到前期“研究结束”事件的影响。

使用者失访率在前 5-6 年间非常低（表 2-4）。TCu380A 在最后两年的失访率增加，可能也因为 1996-1997 年决定终止吉妮宫内节育器随访有关，而吉妮使用者因为她们所使用的特殊节育器让他们坚持去研究中心随访，而不去其他医疗单位。

作为 WHO 的一项前瞻性多研究中心的宫内节育器研究，我们发现中国区和非中国区在结果上的差异：非中国研究中心脱落率高，导致第一年吉妮 IUD 的妊娠率比较高；因医疗原因终止也有很大差异，但长期观察结果差异无显著性；如已经知道的一样，还有随访率和因“研究结束”终止率也大不相同。尽管这些差异有 1996-1997 的决定的影响，我们仍然认为这项研究的结果是具有普遍性的，因为这项研究样本量大且是多中心研究；第二次统计分析，研究结果的趋势是平稳的，并且研究的发现与其他吉妮 IUD 的研究结果一致。

表5.所有中心、中国中心和非中国中心2、5、8年妊娠发生率

观察项目	第2年		第5年		第8年	
	吉妮	TCu380A	吉妮	TCu380A	吉妮	TCu380A
所有中心						
例数	1707	1802	1333	1380	521	948
妊娠率						
合计	0.4 (0.2–0.9)	0.7 (0.4–1.2)	1.0 (0.6–1.7)	2.2 (1.6–3.1)	1.2 (0.7–1.9)	2.5 (1.8–3.4)
宫内妊娠	0.4 (0.2–0.8)	0.6 (0.4–1.2)	1.0 (0.6–1.6)	1.8 (1.3–2.6)	1.1 (0.7–1.8)	2.1 (1.5–3.0)
宫外妊娠	0.1 (0.0–0.4)	0.1 (0.0–0.4)	0.1 (0.0–0.4)	0.4 (0.2–1.0)	0.1 (0.0–0.4)	0.4 (0.2–1.0)
非中国中心						
例数	596	675	364	414	91	206
妊娠率						
合计	0.4 (0.1–1.5)	0.7 (0.3–1.7)	1.0 (0.4–2.3)	1.6 (0.8–3.3)	1.0 (0.4–2.3)	1.6 (0.8–3.3)
宫内妊娠	0.4 (0.1–1.5)	0.7 (0.3–1.7)	1.0 (0.4–2.3)	1.4 (0.6–2.9)	1.0 (0.4–2.3)	1.4 (0.6–2.9)
宫外妊娠	0	0	0	0.3 (0.0–1.8)	0	0.3 (0.0–1.8)
中国中心						
例数	1111	1127	969	966	430	742
妊娠率						
合计	0.5 (0.2–1.1)	0.7 (0.4–1.5)	1.1 (0.6–1.9)	2.5 (1.7–3.7)	1.2 (0.7–2.1)	2.9 (2.0–4.1)
宫内妊娠	0.4 (0.1–1.0)	0.6 (0.3–1.3)	1.0 (0.5–1.8)	2.0 (1.3–3.1)	1.1 (0.6–2.0)	2.4 (1.6–3.5)
宫外妊娠	0.1 (0.0–0.6)	0.1 (0.0–0.7)	0.1 (0.0–0.6)	0.5 (0.2–1.2)	0.1 (0.0–0.6)	0.5 (0.2–1.2)

5. 结论

由于放置器和放置技术的原因使得吉妮 IUD 第一年放置失败率高，脱落率、妊娠率也高于 TCu80A。从另外角度分析，吉妮 IUD 显示了与 TCu380A 一样或更好的结果，累积 8 年因疼痛、宫外孕及妊娠终止使用率吉妮宫内节育器明显低于 TCu380A 宫内节育器。

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吉妮年鉴

- 1990年世界卫生组织（WHO）引进吉妮IUD，在中国做了多中心临床试验；
- 1995年国家人口计生委科研所牵头组织上市前临床试验；
- 1997年-2004年吉妮I、吉娜、柔适、致美先后被中国SFDA批准上市；
- 2008年吉妮IUD上市十年，国内专家达成“吉妮临床共识”成为应用指南（在中国计划生育学杂志发表）；
- 2009年UNPD/UNFPA/WHO报告：经过8年临床研究观察，吉妮IUD避孕效果可靠。

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