



Original research article

Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A^{☆,☆☆}

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Abstract

Objectives: To compare rates of unintended pregnancy, method continuation and reasons for removal among women using the 52-mg levonorgestrel (daily release 20 microg) levonorgestrel IUD (LNG-IUD) or the copper T 380 A (TCu380A) intrauterine device.

Study design: This was an open-label 7-year randomized controlled trial in 20 centres, 11 of which in China. Data on 1884 women with interval insertion of the LNG-IUD and 1871 of the TCu380A were analysed using life tables with 30-day intervals and Cox proportional hazards models.

Results: The cumulative 7-year pregnancy rate of the LNG-IUD was 0.5 (standard error 0.2) per 100, significantly lower than 2.5 (0.4) per 100 of the TCu380A, cumulative method discontinuation rates at 7 years were 70.6 (1.2) and 40.8 (1.3) per 100, respectively. Dominant reasons for discontinuing the LNG-IUD were amenorrhoea (26.1 [1.3] per 100) and reduced bleeding (12.5 [1.1] per 100), particularly in Chinese women and, for the TCu380A, increased bleeding (9.9 [0.9] per 100), especially among non-Chinese women. Removal rates for pain were similar for the two intrauterine devices (IUDs). Cumulative rates of removal for symptoms compatible with hormonal side effects were 5.7 (0.7) and 0.4 (0.2) per 100 for the LNG-IUD and TCu380A, respectively, and cumulative losses to follow-up at 7 years were 26.0 (1.4) and 36.9 (1.3) per 100, respectively.

Conclusion: The LNG-IUD and the TCu380A have very high contraceptive efficacy, with the LNG-IUD significantly higher than the TCu380A. Overall rates of IUD removals were higher among LNG-IUD users than TCu380A users. Removals for amenorrhoea appeared culturally associated.

[☆] The authors declare no conflicts of interest.

^{☆☆} The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the World Health Organization.

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Implications: The 52-mg LNG-IUD and the TCU380A have very high contraceptive efficacy through 7 years. As an IUD, the unique side effects of the LNG-IUD are reduced bleeding, amenorrhea and symptoms compatible with hormonal contraceptives.

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Keywords: Levonorgestrel IUD; Mirena®; TCU380A; Paragard®; Randomized trial; Seven years

1. Introduction

The copper-bearing intrauterine devices (IUDs) and the levonorgestrel (LNG)-medicated IUD are efficacious reversible contraceptive methods. The copper IUDs were developed during the 1960s and 1970s, and the copper T CU380A (TCU380A) was first approved by the US Food and Drug Administration (FDA) in 1984 for 4 years of use, subsequently extended to 10 years in 1994 [1–4]. Development of progestogen-mediated IUDs started in the 1970s and resulted *inter alia* in drug regulatory approval in Finland in 1990 of an IUD with a 52-mg LNG load initially releasing 20 microg daily (Levonova®) with a 5-year effective lifespan [Wahlbom A, Bayer AB, Sweden, Personal communication 2014]. The trials preceding approval in Finland studied LNG devices loaded with 46 and 60 mg of the hormone, both releasing 20-microg LNG per day [5–7]. The US FDA approved the 5-year 52-mg LNG-medicated IUD (Mirena®) in 2000. In 2013, FDA approved an IUD with 13.5-mg LNG (Skyla® or Jaydess®) [8] and, in 2015, a new 52-mg LNG-IUD (Liletta®) [9]. At present, these two new 13.5- and 52-mg LNG-IUDs both have an approved lifespan of 3 years.

While the TCU380A device had undergone extensive clinical evaluation, the clinical experience of the LNG-releasing IUD was limited in the 1990s. Hence, the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) in 1993 initiated a randomized multi-centre comparative trial in principally developing countries, of the 52-mg LNG-IUD and the TCU380A to examine the longer term efficacy and reasons for device removal, particularly removals for amenorrhea, pain and bleeding, of the two devices. Interim results from the trial were published previously [10]. This article gives data on contraceptive efficacy and reasons for discontinuation of use.

2. Material and methods

The study took place in 20 centres in nine countries, 11 of the centres were in China. The protocol was reviewed by the Toxicology Panel and the Scientific and Ethical Review Group of HRP and the World Health Organization (WHO) Secretariat Committee on Research involving Human Subjects. The ethics committee of participating centres reviewed and approved the study and where required the appropriate governmental authority. The trial was planned and initiated before registration of clinical trials became mandatory.

2.1. Devices and training of providers

The LNG-IUD (Mirena™) contains 52-mg LNG and initially releases 20-microg LNG/day. The device was manufactured by Leiras Pharmaceutical, Turku, Finland.

The TCU380A (Paragard™) device is T-shaped with a copper surface area of approximately 380 mm². The device was manufactured by Finishing Enterprises, Niagara, NY, USA.

The LNG-IUD was new to the family planning providers in the participating centres; hence, an experienced provider of the LNG-IUD (T. Luukkainen) visited centres to train physicians and nurses in insertion of the LNG-IUD and client counselling.

2.2. Admission and randomization

Eligible for the study were healthy informed women, over 16 and under 40 years old, with at least one pregnancy of ≥ 20 weeks gestation or a foetus delivered weighing ≥ 500 g, willing to participate and rely solely on the IUD for contraception, currently cohabiting and able to attend for follow up at the required intervals. Exclusion criteria were a history of pelvic inflammatory disease (PID) or pelvic abscess since last pregnancy, less than 6 weeks since parturition or abortion, past ectopic pregnancy, recent sexually transmitted disease, undiagnosed genital tract bleeding, genital tract malformations, known or suspected genital tract malignancy, uterine fibromyoma associated with menstrual disorders, evidence of anaemia and history of hydatidiform mole in the last pregnancy. After giving informed consent, each subject provided her medical, obstetric and gynaecological history.

Each centre received a list of unique trial- and centre-specific subject numbers consecutively assigned as each woman was enrolled and a series of sealed envelopes each labelled with the trial- and centre-specific subject numbers containing information about the randomly assigned IUD. When device insertion was due, the envelope with the corresponding subject number was opened revealing the assigned IUD. Randomization lists were computer-generated by HRP and balanced in blocks of 10. Since the IUDs were different in appearance and required different insertion techniques, providers inserting the device were not masked.

2.3. Follow-up

Scheduled follow-up visits were at 3, 6 and 12 months after insertion and yearly thereafter. Women were instructed to return to the clinic at any other time if they experienced any problem and were free to request IUD removal at any time.

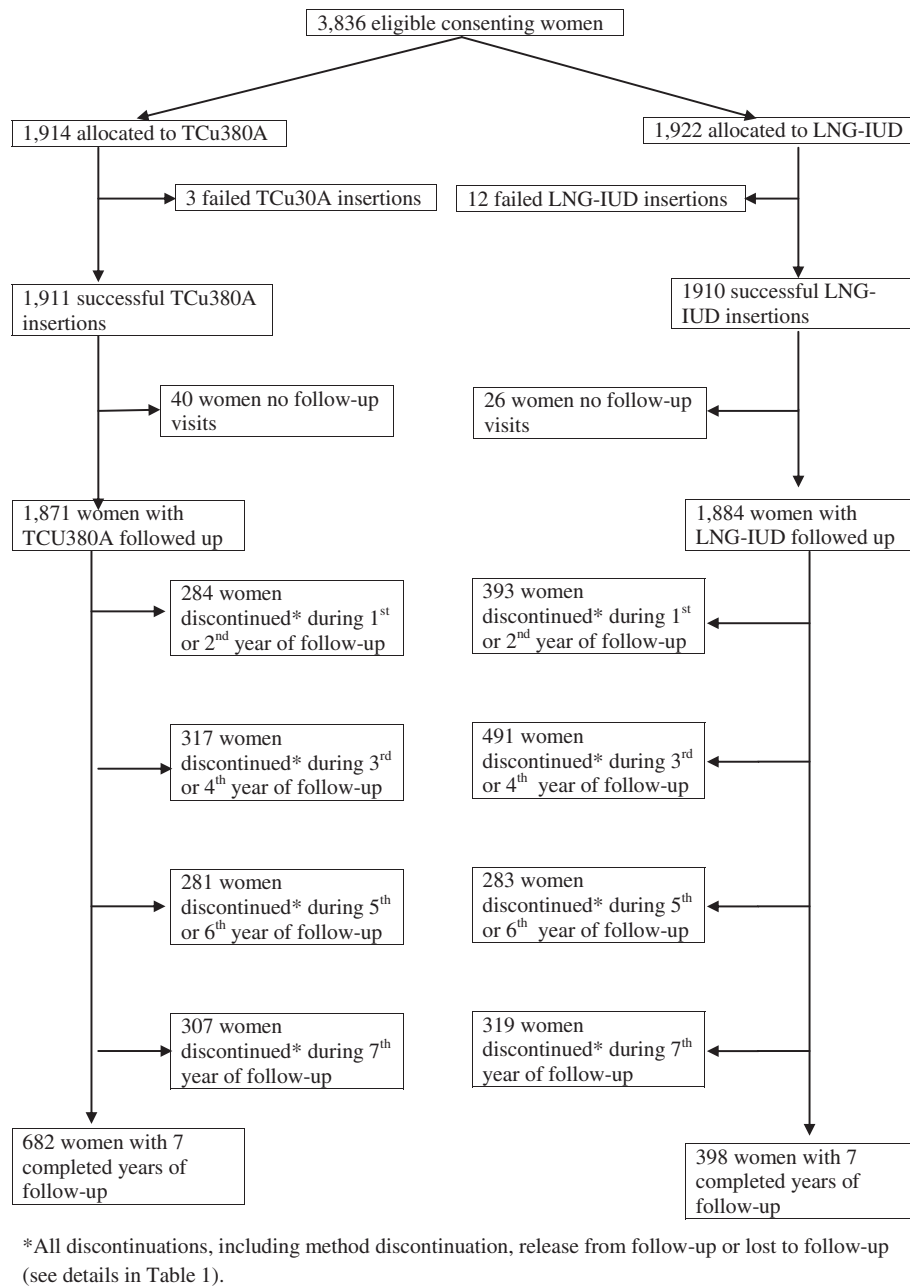


Fig. 1. Number of women eligible, randomized and followed up in the trial of the 52-mg LNG 20 micro-releasing IUD and the TCU380A IUD.

The trial was initially planned for a minimum of 8 years of use of the LNG-IUD. However, in the course of the trial, the manufacturer informed that the LNG drug load in the device might be insufficient for effective contraception after 7 years of use. The women were informed accordingly, although when the decision was taken, some women had already completed 8 years. This article is concerned with 7 years follow-up.

2.4. Sample size

Assuming a pregnancy rate of 0.5% at 2 years with the LNG-IUD, a rate of 2.0% for the TCU380A and a two-sided 95% significance test, a total of 865 subjects completing 2

years are required per study group for 80% power or 1159 subjects completing 2 years for 90% power. With an assumed annual discontinuation rate of 10%, the required total recruitment to each device was 1430 women for 90% power.

2.5. Data collection, monitoring, outcomes and analysis

Data were recorded on standard precoded forms in duplicate at admission, at each follow-up visit and at discontinuation from the study. Forms were sent to the data coordination centre at WHO in Geneva for data entry. Clarifications were sought from the individual centres where necessary. The classification of discontinuation for individual reasons and groups of reasons

Table 1

Cumulative numbers and rates per 100 of individual and grouped reasons for IUD discontinuation and loss to follow-up at 1, 3, 5 and 7 years of use by LNG-IUD and TCu380A IUD in all centres.

| Reason for discontinuation/variable | Year 1 | | | | | | Year 3 | | | | | | 3-year rate difference, 95% CI (TCu380A – LNG-IUD) | |
|--|------------------------------|-------|------|------------------------------|-------|------|------------------------------|-------|------|------------------------------|-------|------|--|--------------------|
| | LNG-IUD n. 1884 ¹ | | | TCu380A n. 1871 ¹ | | | LNG-IUD n. 1491 ¹ | | | TCu380A n. 1587 ¹ | | | | |
| | Events | Rate | SE | Events | Rate | SE | Events | Rate | SE | Events | Rate | SE | | |
| Pregnancies | | | | | | | | | | | | | | |
| All | 2 | 0.12 | 0.08 | 11 | 0.64 | 0.19 | 6 | 0.43 | 0.18 | 24 | 1.53 | 0.31 | 1.10 | (0.39 to 1.80) |
| Intrauterine | 2 | 0.12 | 0.08 | 11 | 0.64 | 0.19 | 6 | 0.43 | 0.18 | 22 | 1.39 | 0.30 | 0.96 | (0.28 to 1.64) |
| Ectopic | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 2 | 0.14 | 0.10 | 0.14 | (–0.05 to 0.33) |
| Expulsions | | | | | | | | | | | | | | |
| All | 53 | 2.94 | 0.40 | 63 | 3.49 | 0.43 | 82 | 5.21 | 0.57 | 95 | 5.64 | 0.57 | 0.43 | (–1.15 to 2.01) |
| Complete | 30 | 1.66 | 0.30 | 14 | 0.78 | 0.21 | 41 | 2.50 | 0.39 | 22 | 1.34 | 0.29 | –1.16 | (–2.11 to –0.21) |
| Partial | 23 | 1.29 | 0.27 | 49 | 2.73 | 0.38 | 41 | 2.79 | 0.44 | 73 | 4.36 | 0.50 | 1.58 | (0.27 to 2.89) |
| Medical | | | | | | | | | | | | | | |
| Bleeding problems, all ² | 160 | 9.02 | 0.68 | 54 | 3.04 | 0.41 | 363 | 22.81 | 1.07 | 96 | 5.84 | 0.58 | –16.97 | (–19.35 to –14.58) |
| Amenorrhoea | 72 | 4.31 | 0.50 | 1 | 0.06 | 0.06 | 212 | 14.49 | 0.93 | 1 | 0.06 | 0.06 | –14.43 | (–16.26 to –12.60) |
| Reduced bleeding ³ | 38 | 2.23 | 0.36 | 10 | 0.57 | 0.18 | 89 | 6.28 | 0.66 | 20 | 1.25 | 0.28 | –5.03 | (–6.43 to –3.63) |
| Increased bleeding ⁴ | 50 | 2.75 | 0.38 | 43 | 2.42 | 0.37 | 62 | 3.68 | 0.47 | 75 | 4.59 | 0.52 | –0.92 | (–0.45 to 2.29) |
| Pain | 35 | 2.07 | 0.35 | 30 | 1.72 | 0.31 | 59 | 3.95 | 0.51 | 58 | 3.60 | 0.47 | –0.35 | (–1.71 to 1.01) |
| PID | 5 | 0.29 | 0.13 | 0 | 0.00 | 0.00 | 5 | 0.29 | 0.13 | 0 | 0.00 | 0.00 | –0.29 | – |
| “Hormonal” reasons ⁵ | 21 | 1.25 | 0.27 | 1 | 0.06 | 0.06 | 53 | 3.64 | 0.50 | 2 | 0.12 | 0.09 | –3.52 | (–4.51 to –2.53) |
| End of IUD lifespan | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 0.00 | – |
| Other device-related | 4 | 0.24 | 0.12 | 2 | 0.12 | 0.08 | 13 | 1.02 | 0.29 | 9 | 0.61 | 0.20 | –0.41 | (–1.10 to 0.28) |
| Nondevice-related reasons ⁶ | 27 | 1.59 | 0.30 | 22 | 1.28 | 0.27 | 97 | 7.17 | 0.71 | 77 | 5.01 | 0.56 | –2.16 | (–3.94 to –0.39) |
| All IUD discontinuations | 307 | 16.49 | 0.86 | 183 | 9.94 | 0.70 | 678 | 38.23 | 1.16 | 361 | 20.48 | 0.97 | –17.75 | (–20.72 to 14.79) |
| Released from follow-up | 11 | 0.66 | 0.20 | 11 | 0.63 | 0.19 | 24 | 1.66 | 0.34 | 22 | 1.40 | 0.30 | –0.26 | (–1.15 to 0.63) |
| Lost to follow-up | 75 | 4.60 | 0.52 | 90 | 5.22 | 0.54 | 182 | 12.61 | 0.88 | 218 | 13.42 | 0.85 | 0.81 | (–1.59 to 3.21) |
| Year 5 | | | | | | | | | | | | | | |
| Year 7 | | | | | | | | | | | | | | |
| 7 year rate difference | | | | | | | | | | | | | | |
| Pregnancies | | | | | | | | | | | | | | |
| All | 7 | 0.53 | 0.21 | 28 | 1.85 | 0.35 | 7 | 0.53 | 0.21 | 33 | 2.45 | 0.44 | 1.91 | (0.97 to 2.86) |
| Intrauterine | 7 | 0.53 | 0.21 | 26 | 1.72 | 0.34 | 7 | 0.53 | 0.21 | 30 | 2.20 | 0.41 | 1.67 | (0.76 to 2.57) |
| Ectopic | 0 | 0.00 | 0.00 | 2 | 0.14 | 0.10 | 0 | 0.00 | 0.00 | 3 | 0.25 | 0.15 | 0.25 | (–0.04 to 0.55) |
| Expulsions | | | | | | | | | | | | | | |
| All | 92 | 6.30 | 0.66 | 115 | 7.30 | 0.67 | 104 | 8.18 | 0.84 | 129 | 8.84 | 0.77 | 0.67 | (–1.58 to 2.91) |
| Complete | 43 | 2.73 | 0.42 | 24 | 1.52 | 0.31 | 45 | 3.01 | 0.47 | 26 | 1.74 | 0.35 | –1.27 | (–2.42 to –0.13) |
| Partial | 49 | 3.67 | 0.54 | 91 | 5.87 | 0.61 | 59 | 5.32 | 0.74 | 103 | 7.23 | 0.72 | 1.91 | (–0.11 to 3.93) |
| Medical | | | | | | | | | | | | | | |
| Bleeding problems, all ² | 479 | 32.40 | 1.25 | 143 | 9.65 | 0.78 | 540 | 39.21 | 1.41 | 181 | 13.76 | 0.99 | –25.45 | (–28.83 to –22.08) |
| Amenorrhoea | 293 | 22.00 | 1.17 | 1 | 0.06 | 0.06 | 323 | 26.10 | 1.33 | 5 | 0.52 | 0.24 | –25.59 | (–28.24 to –22.94) |
| Reduced bleeding ³ | 118 | 9.41 | 0.86 | 33 | 2.34 | 0.41 | 139 | 12.53 | 1.07 | 44 | 3.65 | 0.56 | –8.88 | (–11.25 to –6.51) |
| Increased bleeding ⁴ | 68 | 4.33 | 0.53 | 109 | 7.42 | 0.70 | 78 | 5.96 | 0.73 | 131 | 9.91 | 0.86 | 3.95 | (1.74 to 6.17) |
| Pain | 71 | 5.28 | 0.63 | 75 | 5.01 | 0.57 | 76 | 6.09 | 0.73 | 96 | 7.37 | 0.76 | 1.28 | (–0.78 to 3.33) |
| PID | 5 | 0.29 | 0.13 | 1 | 0.10 | 0.10 | 5 | 0.29 | 0.13 | 2 | 0.21 | 0.15 | –0.08 | (–0.46 to 0.31) |
| Hormonal reasons ⁵ | 62 | 4.71 | 0.61 | 2 | 0.12 | 0.09 | 68 | 5.68 | 0.72 | 4 | 0.36 | 0.19 | –5.32 | (–6.78 to –3.86) |
| End of IUD lifespan | 0 | 0.00 | 0.00 | 0 | 0.00 | 0.00 | 113 | 20.38 | 1.72 | 0 | 0.00 | 0.00 | –20.38 | (–23.75 to –17.01) |
| Other device-related | 19 | 1.73 | 0.41 | 16 | 1.24 | 0.31 | 28 | 3.29 | 0.66 | 21 | 1.82 | 0.40 | –1.48 | (–2.99 to 0.04) |
| Nondevice-related reasons ⁶ | 168 | 14.68 | 1.08 | 141 | 10.13 | 0.82 | 222 | 22.17 | 1.39 | 184 | 14.64 | 1.03 | –7.54 | (–10.93 to –4.14) |
| All IUD discontinuations | 903 | 52.45 | 1.22 | 521 | 30.84 | 1.14 | 1163 | 70.62 | 1.17 | 650 | 40.81 | 1.27 | –29.81 | (–33.19 to –26.43) |
| Released from follow-up | 30 | 2.36 | 0.44 | 32 | 2.27 | 0.40 | 33 | 2.80 | 0.51 | 34 | 2.48 | 0.43 | –0.32 | (–1.63 to 0.99) |
| Lost to follow-up | 234 | 18.02 | 1.10 | 329 | 21.79 | 1.08 | 290 | 26.02 | 1.44 | 505 | 36.85 | 1.34 | 10.83 | (6.97 to 14.69) |

¹ Number of women starting the interval.

² Including 1 woman with “unclassified bleeding” problems.

³ Reduced bleeding includes reduced, light, infrequent bleeding, spotting, and irregular bleeding.

⁴ Increased bleeding includes heavy and prolonged bleeding.

⁵ Hormonal reasons for stopping use is defined in the Methods section.

⁶ Not device-related reasons include wish for pregnancy, no further need, menopause, and premature removal initiated by investigators for medical conditions unrelated to use of the IUD.

followed the standard definitions used for IUD and contraceptive clinical trials, and used in previous IUD trials by HRP/WHO [1,11–13]. An additional class of “hormonal reasons” for

discontinuation similar to that reported previously [14], was created to capture signs and symptoms potentially associated with hormonal contraception (reasons mentioned by at least one

Table 2

Cumulative numbers and rates per 100 of selected reasons for IUD removal at 1, 3, 5 and 7 years of use by LNG-IUD and TCu380A IUD in Chinese and non-Chinese centres.

| Year Reason for discontinuation | Chinese centres | | | | | | Non-Chinese centres | | | | | | p-value ¹ |
|------------------------------------|-----------------|-------|------|---------|-------|------|---------------------|-------|------|---------|-------|------|----------------------|
| | LNG-IUD | | | TCu380A | | | LNG-IUD | | | TCu380A | | | |
| | Events | Rate | SE | Events | Rate | SE | Events | Rate | SE | Events | Rate | SE | |
| Year 1 | | | | | | | | | | | | | |
| Pregnancies, all | 2 | 0.20 | 0.14 | 9 | 0.89 | 0.29 | 0 | 0.00 | 0.00 | 2 | 0.27 | 0.19 | 0.9921 |
| Expulsions, all | 30 | 0.03 | 0.01 | 34 | 0.03 | 0.01 | 23 | 0.03 | 0.01 | 29 | 0.04 | 0.01 | 0.6780 |
| Bleeding problems | 104 | 10.24 | 0.95 | 16 | 1.56 | 0.39 | 56 | 7.39 | 0.95 | 38 | 5.06 | 0.80 | <0.0001 |
| Amenorrhoea | 46 | 4.81 | 0.69 | 1 | 0.10 | 0.10 | 26 | 3.64 | 0.70 | 0 | 0.00 | 0.00 | 0.9839 |
| Reduced bleeding | 24 | 2.48 | 0.50 | 2 | 0.20 | 0.14 | 14 | 1.91 | 0.51 | 8 | 1.09 | 0.38 | 0.0206 |
| Increased bleeding | 34 | 3.31 | 0.56 | 13 | 1.27 | 0.35 | 16 | 2.02 | 0.50 | 30 | 4.02 | 0.72 | 0.0003 |
| Pain | 10 | 1.02 | 0.32 | 11 | 1.08 | 0.32 | 25 | 3.45 | 0.68 | 19 | 2.63 | 0.60 | 0.5672 |
| Nondevice-related reasons | 3 | 0.31 | 0.18 | 1 | 0.10 | 0.10 | 24 | 3.28 | 0.66 | 21 | 2.96 | 0.64 | 0.3857 |
| Year 3 | | | | | | | | | | | | | |
| Pregnancies, all | 6 | 0.72 | 0.30 | 20 | 2.05 | 0.45 | 0 | 0.00 | 0.00 | 4 | 0.66 | 0.34 | 0.9876 |
| Expulsions, all | 52 | 0.06 | 0.01 | 55 | 0.05 | 0.01 | 30 | 0.04 | 0.01 | 40 | 0.06 | 0.01 | 0.2786 |
| Bleeding problems | 253 | 26.25 | 1.43 | 37 | 3.75 | 0.61 | 110 | 17.42 | 1.56 | 59 | 9.03 | 1.15 | <0.0001 |
| Amenorrhoea | 149 | 16.88 | 1.27 | 1 | 0.10 | 0.10 | 63 | 10.70 | 1.31 | 0 | 0.00 | 0.00 | 0.9777 |
| Reduced bleeding | 61 | 7.15 | 0.89 | 10 | 1.04 | 0.33 | 28 | 5.03 | 0.96 | 10 | 1.44 | 0.46 | 0.0669 |
| Increased bleeding | 43 | 4.45 | 0.67 | 26 | 2.63 | 0.51 | 19 | 2.62 | 0.61 | 49 | 7.70 | 1.09 | <0.0001 |
| Pain | 20 | 2.33 | 0.52 | 15 | 1.51 | 0.39 | 39 | 6.19 | 0.99 | 43 | 7.07 | 1.06 | 0.2105 |
| Nondevice-related reasons | 11 | 1.39 | 0.42 | 6 | 0.63 | 0.26 | 86 | 15.49 | 1.57 | 71 | 12.33 | 1.40 | 0.2735 |
| Year 5 | | | | | | | | | | | | | |
| Pregnancies, all | 6 | 0.72 | 0.30 | 23 | 2.39 | 0.49 | 1 | 0.29 | 0.29 | 5 | 0.98 | 0.47 | 0.6700 |
| Expulsions, all | 58 | 0.07 | 0.01 | 69 | 0.07 | 0.01 | 34 | 0.06 | 0.01 | 46 | 0.08 | 0.01 | 0.3458 |
| Bleeding problems | 346 | 37.20 | 1.60 | 61 | 6.51 | 0.81 | 133 | 23.73 | 1.92 | 82 | 15.48 | 1.69 | <0.0001 |
| Amenorrhoea | 217 | 26.07 | 1.54 | 1 | 0.10 | 0.10 | 76 | 14.48 | 1.62 | 0 | 0.00 | 0.00 | 0.9765 |
| Reduced bleeding | 84 | 10.80 | 1.14 | 19 | 2.09 | 0.48 | 34 | 7.13 | 1.27 | 14 | 2.73 | 0.78 | 0.0479 |
| Increased bleeding | 45 | 4.76 | 0.70 | 41 | 4.42 | 0.68 | 23 | 3.98 | 0.91 | 68 | 13.11 | 1.59 | <0.0001 |
| Pain | 26 | 3.35 | 0.66 | 20 | 2.08 | 0.46 | 45 | 8.10 | 1.24 | 55 | 10.63 | 1.44 | 0.0746 |
| Nondevice-related reasons | 20 | 2.98 | 0.67 | 15 | 1.72 | 0.44 | 148 | 32.07 | 2.28 | 126 | 26.29 | 2.10 | 0.2896 |
| Year 7 | | | | | | | | | | | | | |
| Pregnancies, all | 6 | 0.72 | 0.30 | 27 | 3.01 | 0.58 | 1 | 0.29 | 0.29 | 6 | 1.44 | 0.65 | 0.6232 |
| Expulsions, all | 69 | 0.09 | 0.01 | 80 | 0.09 | 0.01 | 35 | 0.06 | 0.01 | 49 | 0.09 | 0.01 | 0.1934 |
| Bleeding problems | 396 | 44.41 | 1.72 | 87 | 10.17 | 1.05 | 144 | 28.34 | 2.27 | 94 | 21.60 | 2.33 | <0.0001 |
| Amenorrhoea | 245 | 31.02 | 1.70 | 5 | 0.70 | 0.31 | 78 | 15.56 | 1.78 | 0 | 0.00 | 0.00 | 0.9723 |
| Reduced bleeding | 98 | 13.74 | 1.35 | 27 | 3.28 | 0.63 | 41 | 10.56 | 1.78 | 17 | 4.64 | 1.34 | 0.0753 |
| Increased bleeding | 53 | 6.57 | 0.94 | 55 | 6.47 | 0.86 | 25 | 5.12 | 1.21 | 76 | 17.31 | 2.11 | <0.0001 |
| Pain | 28 | 3.78 | 0.73 | 29 | 3.48 | 0.65 | 48 | 9.98 | 1.64 | 67 | 15.80 | 2.00 | 0.1179 |
| Nondevice-related reasons | 27 | 4.58 | 0.89 | 23 | 2.94 | 0.61 | 195 | 49.07 | 2.81 | 161 | 38.82 | 2.62 | 0.4171 |

¹ p-value for interaction between Chinese and non-Chinese centres by IUD type.

participant included: abdominal pain, nausea, weight loss or gain, liver dysfunction, eczema/dermatitis, acne, chloasma, hirsutism, flushing, dizziness, anxiety/nervousness, depression, fatigue, decreased libido, headaches, adnexal mass, ovarian cyst, breast swelling, tenderness, breast pain and malignant tumour of the breast).

The cumulative discontinuation rates for each reason and groups of reasons and their 95% confidence intervals were computed using the life table method with 30-day intervals, which approximates the daily Kaplan–Meier method [15]. Tests of interaction of IUD by type of centre (Chinese/non-Chinese) were made using a Cox proportional hazards regression model with the exact date of discontinuation [16]. All analyses were performed using SAS Version 9.3 [SAS Institute. SAS/STAT Software, Version 9.3, <http://www.sas.com>]. Previous trials of IUDs by HRP that included populations of Chinese and non-Chinese women showed

that event rates differed between the two populations; hence, stratified analyses by Chinese and non-Chinese centres were done. Five centres had cumulative loss to follow-up rates at 7 years above 30%, and a sensitivity analysis explored whether exclusion of these five centres affected the overall results of the study.

3. Results

Recruitment took place from May 1993 to October 1998. Altogether, 1914 women were randomized to the TCu380A and 1922 to the LNG-IUD (Fig. 1). After excluding IUD-insertion failures and women who never returned to the clinic, 1871 women with TCu380A (1060 in 11 Chinese centres, 811 in nine non-Chinese centres) and 1884 with LNG-IUD (1062 in Chinese centres, 822 in non-Chinese

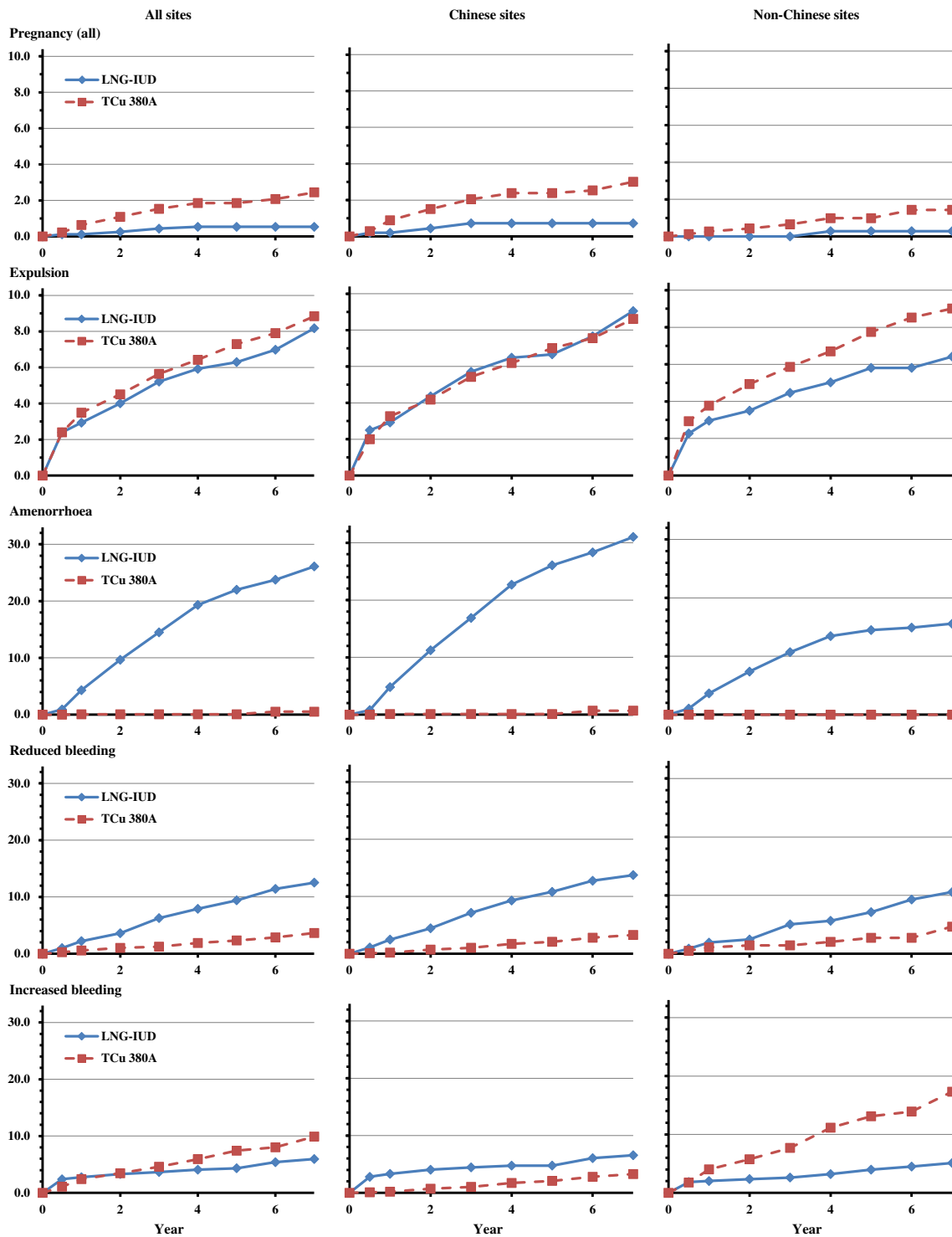


Fig. 2. Cumulative rates (per 100) of selected reasons for IUD removal by device in all Chinese and non-Chinese centres.

centres) are included in the analyses (Fig. 1), providing a total of 10,088 and 7903 woman–years of observation, respectively.

The mean ages of the women were 29.9 [standard deviation (*SD*) = 4.95] and 29.8 (*SD* = 5.12) years for women randomized to TCu380A and LNG-IUD, respectively. The median parity was 1 for both groups with ranges 0–7 and 0–

10, respectively. The median age of Chinese women was 30 years and that of non-Chinese women 29 years. Chinese women had lower parity (Median 1) than non-Chinese women (Median 2). Contrary to protocol requirements, a total of nine women (0.24%, 5 assigned to TCu380A and 4 to LNG-IUD) were found on review to be nulliparous (prior

abortion [5] or ectopic pregnancy [1], no history of pregnancy [2], and information missing [1]). These women have been retained in the analysis.

Table 1 shows cumulative pregnancy and method discontinuation rates at 1, 3, 5 and 7 years of use for both devices in all participating centres, overall continuation and loss to follow-up rates and differences in cumulative rates at 3 and 7 years.

The overall pregnancy rate of the TCu380A was significantly higher than that of the LNG-IUD, at the end of the seventh year the cumulative rate was 2.45 [standard error (SE) = 0.44] per 100 for the TCu380A and 0.53 (SE = 0.21) per 100 for the LNG-IUD (Table 1). Thirty-three pregnancies occurred among TCu380A users of which three were ectopic. Seven pregnancies occurred among LNG-IUD users, all intrauterine. No pregnancy occurred in the 1342 woman–years of observation of the TCu380A and 681 of the LNG-IUD from 8 to 11 years, based on 682 TCu380A and 398 LNG-IUD users starting the eighth year of use, respectively (Annex 1A).

The overall cumulative rate of method discontinuations was higher in the LNG-IUD group than in the TCu380A group throughout the 7 years (Table 1, Annex 1 A). There were 129 expulsions of the TCu380A and 104 of the LNG-IUD, with cumulative 7-year rates of 8.84 (0.77) and 8.18 (0.84) per 100, respectively (Table 1). Twenty-six (20%) expulsions in the TCu380A group and 45 (43%) in the LNG-IUD group were complete. One uterine perforation happened with the LNG-IUD and none with the TCu380A. Five LNG-IUD removals were due to diagnosis of PID, three in the first 6 months of use. Two TCu380A IUD removals occurred due to PID in the fifth and sixth year of use.

For each of the 7 years, the cumulative rate of method discontinuation due to bleeding problems was higher in the LNG-IUD than the TCu380A group (Table 1, Annex 1 A). Amenorrhea and reduced bleeding were the main causes for stopping use of the LNG-IUD while for the TCu380A it was increased bleeding (Table 1). The rate of removal of the IUD for reasons of pain was similar in both IUDs.

By seventh year of use, 68 women in the LNG-IUD group and four in the TCu380A group had stopped the use of the IUD for signs and symptoms compatible with those reported to be associated with use of hormonal contraception (Table 1). The most common reasons reported among LNG-IUD users were weight gain (24 women) and ovarian cysts (12 women). Other less frequent reasons were dizziness/faintness and headaches. Six TCu380A and 107 LNG-IUDs were removed for reason of “end of IUD lifespan” in the sixth and seventh year. The rates of “other device-related reasons” for IUD discontinuation were similar for the two devices, the most frequent included wish to change to another contraceptive method and complaints by the husband.

Nondevice-related reasons for method discontinuation were higher in the LNG-IUD than in the TCu380A group from year three to year seven (Table 1). The majority of these 406 IUD removals were for wish to become pregnant (245, 60%) and for no further need (65, 16%).

Losses to follow-up were higher among women using TCu380A than women with LNG-IUD, becoming statistically significantly different from the fifth year onwards (Table 1).

Selected results of the analysis stratifying by Chinese and non-Chinese centres are shown in Table 2 and Fig. 2 with details in Annexes 1B and 1C. The analysis indicates some important differences between the devices in the two groups of centres. The rate of discontinuation due to increased bleeding is higher for the LNG-IUD than for the TCu380A in Chinese centres, while in non-Chinese centres, this pattern is reversed. The cumulative pregnancy rates were generally higher in Chinese than in non-Chinese centres. In both groups of centres, the cumulative removal rates for amenorrhea were higher for the LNG-IUD and were consistently higher in Chinese compared to non-Chinese centres. For both types of IUDs, non-Chinese centres had higher cumulative removal rates for pain and for nondevice-related reasons than Chinese centres through each year of the study. In non-Chinese compared to Chinese centres, the overall discontinuation rates in users of the TCu380A were higher from the first year and among users of LNG-IUD from the second year of use. For both IUDs, the losses of follow-up were higher in non-Chinese than in Chinese centres throughout the duration of the study.

The results of the sensitivity analysis excluding the five centres with the highest losses to follow-up showed very similar results to those obtained when these five centres were included in the analysis.

There were 15 diagnoses of ovarian cysts and four of “adnexal mass”, 16 of which were in LNG-IUD users. One woman was diagnosed with malignant breast tumour and two with ovarian teratoma. Five women died during participation in the study, two from traffic accidents and one each from pulmonary and rectal carcinoma, and one woman died from systemic lupus erythematosus.

4. Discussion

This study found the 52-mg LNG-IUD provided by interval insertion to parous women to be highly efficacious with very low cumulative pregnancy rates through 7 years (Table 1, Annex 1 A), similar to the 3- and 5-year pregnancy rates reported in other studies of IUDs with 46-mg, 52-mg and 60-mg LNG [7,9,17]. Sivin et al. [18] reported a 7-year cumulative rate of 0.5 (1.0) for a 60-mg LNG-IUD. Three smaller studies have reported no pregnancies during use of the LNG-IUD in the sixth through the seventh year [19–21]. The TCu380A IUD, also a very efficacious contraceptive, had a 7-year cumulative pregnancy rate of 2.45 (0.44) per 100. The pregnancy rates for the TCu380A are significantly higher than those of the LNG-IUD in this study, albeit that in a large multicentre study coordinated by WHO, the pregnancy rates of the TCu380A were somewhat lower than in the current study, 1.0 (0.3), 1.4 (0.4) and 1.6 (0.4) per 100 at 3, 5 and 7 years of use, respectively [1]. A systematic

review by French et al. [22] reported no significant difference in annual pregnancy rates through 5 years between LNG-IUDs with initial release of 20 microg and copper IUDs with $>250\text{-mm}^2$ copper surface. In a European 1-year follow-up survey, the pregnancy rate was significantly lower for the 52-mg LNG-IUD compared to different copper-IUDs of which $>71\%$ had copper surface areas of $>300\text{ mm}^2$ [23].

Overall, the LNG-IUD had consistently higher rates of method discontinuation than the TCu380A IUD (Table 1). In the multicentre randomized studies by Sivin et al. [7] and by Andersson et al. [17], the overall 5-year continuation of LNG-IUDs and the copper-IUDs were 33.0 and 40.6 and 46.9 and 44.5 per 100, respectively. An observational study in the US reported a 4-year continuation rate of 62.3 for LNG-IUD and 64.2 per 100 for copper IUDs [24]. Amenorrhea and reduced bleeding accounted for most of the difference of method discontinuation in our study. The cumulative removal rates for amenorrhea rose from 4.3 at 1 year to 26.1 per 100 women after 7 years of use, the latter rate being similar to the 24.6 (2.0) per 100 in the Population Council study [18]. However, the 5-year removal rate for amenorrhea in the multicentre European study was 6.0 per 100 women [17], and Backman et al. [25] reported from a survey in Finland that amenorrhea was not associated with premature removal of the LNG-IUD. In a US study, bleeding problems were not among the main reasons for discontinuing the LNG-IUD [24].

In this study, the 7-year removal rate for amenorrhea in the Chinese centres was nearly twice that of the non-Chinese centres (31.0 compared with 15.6 per 100), these geographical dissimilarities point to cultural differences in the acceptability of amenorrhea but may also be associated with counselling before starting and during use of the device. Moreover, attitudes toward amenorrhea and reduced bleeding may change over time.

The 7-year rates of IUD removals for pain were similar for the two devices; other studies had inconsistent findings for removal rates for pain among users of LNG and copper IUDs [5–7,17,24,26–27]. In this WHO study and the European studies of the LNG-IUD, the removal rate for hormonal reasons was higher than that of the comparator copper device [14,17]. This finding is not unexpected as it is known that there is systemic absorption of LNG from the LNG-IUD [28]. Nondevice-related reasons for IUD removal accounted for a substantial proportion of the discontinuations.

Sivin et al. [7,18] reported higher cumulative expulsion rates for the 46-mg and 60-mg LNG-IUDs combined at 5 and 7 years of use, compared to the TCu380 Ag IUD. Overall, we found similar expulsion rates for the two IUDs, which is in agreement with findings of Andersson et al. [17] and the 3-year cumulative expulsion rates for LNG-IUD and copper IUDs recently reported by Madden et al. [29].

Differences between Chinese and non-Chinese centres have been noted in previous studies of different copper IUDs coordinated of by WHO; in Chinese centres, the pregnancy

rates have generally been higher while removal rates for medical reasons have been lower compared to non-Chinese centres [2,13], patterns also seen in the present study. However, this comparison between a copper and a hormonal IUD showed a substantial different pattern in the reasons for IUD removal for bleeding problems. The cumulative discontinuation rate at 7 years of the LNG-IUD for amenorrhoea was almost double in Chinese centres compared with non-Chinese centres. For the TCu380A IUD, these rates were negligible in both types of centres. The 7-year cumulative discontinuation rate for increased bleeding in the TCu380A group in non-Chinese centres was almost three times that in the Chinese centres, while for the LNG-IUD the rates were similar in the two types of centres.

As expected the cumulative loss to follow-up was lower with the new, experimental LNG-IUD than the standard TCu380A. The sensitivity analysis excluding the five centres with the highest losses to follow-up showed similar results and patterns of discontinuation as the analysis including all centres. A limitation of the current study is that it is concerned with parous women. In addition, during the time elapsed from the study, its completion and publication, women's attitudes to amenorrhea and reduced bleeding associated with the LNG-IUD may have changed.

Our data indicate that the 52-mg LNG-IUD and the TCu380A are safe with very high contraceptive efficacy through 7 years of use. The LNG-IUD is associated with hormonal side effects and reduced bleeding including amenorrhea. The reduced blood loss can be an advantage, although it may not be acceptable in certain cultural settings and can result in high removal rates.

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Appendix A. Supplementary data

Supplementary data to this article (Annexes 1A, 1B, 1C) can be found online at <http://dx.doi.org/10.1016/j.contraception.2016.02.024>.

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