TWO YEARS OF INTRAUTERINE CONTRACEPTION WITH LEVONORGESTREL AND WITH COPPER: A RANDOMIZED COMPARISON OF THE TCu 380Ag AND LEVONORGESTREL 20 MCG/DAY DEVICE

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ABSTRACT

IUDs releasing 20 mcg/day of levonorgestrel (LNg20) were in randomized trial together with the Copper T, model TCu 380Ag, in seven centers involving 2244 women. Two-year (25 months) gross cumulative pregnancy rates were 0.2±0.2 and 0.9±0.3 for the levonorgestrel and copper releasing devices, respectively ($P>0.05$). There were no ectopic pregnancies in more than 1600 woman-years of use of each device. Removal rates for bleeding and/or pain or for medical reasons other than menstrual problems did not differ significantly between devices. Oligomenorrhea or amenorrhea prompted 10.7 per hundred (gross rate, 8.4 net rate) women using the LNg 20 IUD to request removal in the two-year period, significantly above the 0.2 per hundred rate among women with the Copper IUD ($P<0.001$). At the end of two years an estimated 59.4 per 100 women were continuing use of the LNg 20 IUD, and 67.5 per 100 ($P<0.001$) with the TCu 380Ag. This difference is almost wholly ascribable to a marked reduction in bleeding episodes and days among women using the LNg 20 device with concomitant removal of device. Hemoglobin rose an average of 0.5g/dl ($P<0.001$) for this group whereas women using the TCu 380Ag experienced a decline of 0.2g/dl compared with baseline values ($P<0.001$).

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INTRODUCTION

Some intrauterine devices bearing copper have been associated with low pregnancy and expulsion rates in comparison with widely used plastic devices, steel rings or other copper IUDs (1-4). T-shaped copper releasing devices with 380 mm^2 copper surface area have consistently exhibited failure rates at or below 1 per 100 per year in randomized comparative studies (2-8). Menstrual blood loss is generally less during use of copper IUDs than of effective plastic IUDs (9-11), but increased menstrual bleeding has remained an important reason for removal of copper devices. Progesterone-releasing devices reduce menstrual blood loss (11,12) but have a short effective life of 1-2 years (Alza Corporation Patient Information, 1986). Because of the potency of levonorgestrel, only a few tens of micrograms per day need be released into the uterus to have contraceptive effect (13-15). Such low daily release rates permit an IUD carrying levonorgestrel to have a long effective life (16). Data in this report derive from a seven-center, large-scale, comparative randomized trial undertaken by the International Committee for Contraception Research of the Population Council to examine the performance of a levonorgestrel IUD releasing 20 mcg/day and that of the Copper T, model TCu 380Ag. The trial sought to measure overall performance by continuation rates, effectiveness, bleeding patterns and their effect on hemoglobin levels and termination rates, rates of pelvic infection, and over the long term, rates of ectopic pregnancy and duration of contraceptive effect. Data pertain to the first two years of the comparative trial.

METHODS AND MATERIALS

The Copper T, model TCu 380Ag, releases copper from sleeves swaged on the 32-mm crossbar and from a 0.25-mm diameter wire wound tightly around the vertical bar of the T. The wire has a core of silver to maintain its integrity should elution of copper be complete at a single locus on a coil. Devices used in this study were manufactured by Outokumpu Oy, Finland. The second device carries levonorgestrel in a covered homogeneous rod resident on the vertical polyethylene stem. The covered rod releases a rated 20 mcg/day of levonorgestrel from a mixture which is 50 percent, by weight, levonorgestrel and 50 percent medical grade elastomer silicone rubber encased in a thin-walled tube. Devices used in 5 clinics contained 60 mg of the drug with an expected effective life of about 7 years. Devices used in the Los Angeles and Singapore clinics contained 46 mg of steroid and have an expected life of 5 years. The levonorgestrel-releasing IUDs were manufactured by Leiras Pharmaceuticals, Turku, Finland.

Candidates were parous women, 18-38 years old who sought intrauterine contraception. Current clinical evidence or histories of ectopic pregnancy, PID since last pregnancy, copper allergy, cardiovascular problems, persistent abnormal genital bleeding, or cancer made candidates ineligible. Similarly evidence of jaundice, diabetes, mental illness, anemia, pathological galactorrhea, severe hirsutism, pregnancy or breastfeeding precluded participation. The women, in giving informed consent, agreed to accept random assignment of devices and to clinic visits 1, 3, 6, and 12 months after insertion and semiannually thereafter. Pelvic examinations were performed at 6-month intervals.

Women agreed to maintain menstrual diaries.

A study of 2400 women, 1200 assigned randomly to each device was envisaged. This would permit an observed difference between an 80 per 100 and a 75 per 100 one year continuation rate to be deemed statistically significant at the five percent level with 80 percent power. From preliminary studies we assumed the efficacy of the levonorgestrel-releasing device would be similar to that of the copper device, with pregnancy rates at one per hundred per year or less. The overall study size would not permit a distinction to be drawn between devices at this level. Even with moderate attrition for loss to follow-up, however, the study size is sufficient to permit detection, again at 80 percent power, of a difference between a cumulative pregnancy rate of 3 per 100 for one device as against 1 per 100 for the other device. (Studies have shown the cumulative failure rate of a copper T 380 device to be around 3 per 100 at four years.) Differences in cumulative rates of pelvic infection between a device associated with a one per hundred and a device associated with a 3 per 100 rate could also be detected at the 5 percent significance level with 80 power. With regard to long-term effectiveness, annual continuation rates lying between 75 and 80 per 100 were expected to produce five-year continuation rates of the order of 30 per 100. The study size in the fifth year would thus suffice, again assuming moderate loss to follow-up, to distinguish with 80 percent power, whether each device, considered separately, had annual failure rates remaining at or near 1 per 100 or whether the failure rates mount to 3 per 100 or more per year as drug release rate decreases. External constraints halted enrollment at 1120 to 1124 women per device.

Randomization of devices was balanced in blocks of 50 at each clinic. Individually sterilized devices with inserter tubes were placed inside opaque, numbered envelopes in accordance with the random allocation and assembled in ascending sequence. The algorithm generating random numbers was the linear congruent method. Women were assigned study numbers in the sequence of insertion, receiving the device contained in the corresponding numbered, opaque envelope. The study was single blind. Women did not know which device they were using.

Enrollment was completed in 1982 in Santo Domingo, D.R., in Campinas and Salvador, Brazil; in 1983 in Cairo; in 1984 in Santiago and Singapore; and in 1986 in Los Angeles.

Life table actuarial analyses use the Tietze conventions. The cut-off date is 31 August 1986 with computer analysis in November, 1986. Analysis was open.

RESULTS

Randomization produced two groups with no numerically large nor statistically significant differences between them. Average age was 26.6 years and mean parity was 2.4 live births. One-third of the women desired to have additional children. Approximately one-third had previously used an IUD. Seven percent reported having had an episode of pelvic infection before their last pregnancy (Table I).

Table I

Characteristics at Admission (Means or Percent and Standard Error)

Characteristic	Device: LNg 20 Mean	(SE)	TCu 380 Ag Mean	(SE)
Age	26.6	0.1	26.7	0.1
Parity	2.44	0.04	2.40	0.04
Months since last pregnancy	23.7	0.7	24.1	0.8
Hemoglobin (g/dl)	12.7	0.05	12.6	0.04
Days of menstrual flow	4.2	0.04	4.3	0.04
% Prior IUD use	32.8	1.4	33.6	1.4
% PID before last pregnancy	7.7	0.8	6.4	0.7
% Desire additional children	33.1	1.4	32.4	1.4
No. of Subjects	1124		1120	

Table II

Insertion Problems

	LNg 20 %	N	TCu 380 %	N	
Uterine perforations	0.4	5	0	0	P>.05
Difficult insertions (physician's report)	14.7	165	3.0	33	P<.001
Moderate or severe pain at insertion (woman's report)	18.8	211	10.8	120	P<.001
Failed insertions	1.3	15	0.2	2	P<.001

Insertion Problems

Physicians reported difficulty in 14.7% of the LNg insertions, a significantly higher proportion than the 3.0 percent of TCu 380 Ag insertions judged difficult (Table II). Correspondingly, moderate or severe pain at insertion was felt by 18.8 percent of women assigned to the LNg 20, and by 10.8 percent of women during insertion of the T device ($p<.001$).

Five fundal perforations, 3 from a single center, occurred following insertion of the LNg 20 but none following TCu 380 Ag insertion. Insertion failures were reported significantly more frequently with the LNg device than with the Copper T 380. There were 15 insertion failures with the former and 2 with the latter. Failures clustered by clinic.

Terminations

Pregnancy

In 25 months (2 years) of exposure, two women using the LNg 20 IUD became pregnant; there were seven accidental pregnancies with the TCu 380 Ag. None of the pregnancies with either device was ectopic. Cumulative gross pregnancy rates at two years were 0.2 and 0.9 per 100 with the LNg 20 and TCu 380 Ag devices, respectively. Both pregnancies

ascribed to the steroid-releasing device occurred in the first year of use, one following an unnoticed expulsion. The cumulative gross pregnancy rate was significantly below 1 per 100 for the levonorgestrel device. The few pregnancies with this device did not exhibit relation with age. The distribution of pregnancies observed among women assigned the Copper IUD (Table III), however, is consistent with a decline in failure rates as age increases. The two-year gross rate among Copper T 380Ag users under age 25 at acceptance was 1.6 per 100 and for women over age 35, it was zero.

Table III

Selected Gross Termination and Continuation Rates
Per 100 at 25 Months by Age & Device

Age	Pregnancy		Amenorrhea		Planned Pregnancy	
	LNg	380	LNg	380	LNg	380
<25	0.0	1.9	16.2***	0.3	12.1	10.2
25-29	0.3	0.3	9.8**	0.0	10.4	7.8
30-34	0.4	0.6	7.5	0.6	3.0	4.9
35-38	0.0	0.0	1.6***	0.0	0.0	0.0
All Ages	0.2	0.9	10.7	0.2	8.3	7.4

Age	Expulsion		PID		Continuation	
	LNg	380	LNg	380	LNg	380
<25	7.2	7.5	2.2	3.3	50.6**	58.7
25-29	6.3	5.3	1.7	0.9	59.4	69.7
30-34	4.7	3.8	0.9	1.3	69.5	75.0
35-38	5.4	6.2	1.4	0.0	70.2***	77.6
All ages	6.3	5.7	1.6	1.7	59.4	67.5

** P<0.01; *** P<0.001

Expulsion

At one year net expulsion rates were 6.0 and 5.5 per 100 with the steroid and copper devices, respectively (Table IV). Through two years (25 months) these rates were 7.3 and 6.1, respectively (Table IV). The corresponding gross expulsion rates (Table III) did not significantly differ either at one or at two years. At one clinic, however, the two-year gross cumulative expulsion rate following insertion of the LNg 20 IUD was 16.0 per hundred, compared with a 3.7 per 100 rate for the TCu 380Ag (P<.01).

Menstrual Problems and Pain

By the end of two years menstrual problems and pain led 17.1 per 100 women assigned the LNg 20 IUD to terminate (net rate) (Table IV) and 11.5 per 100 assigned the TCu 380Ag. For the steroid-releasing device approximately half of these removals were ascribed by the women to reduced menstrual bleeding (oligomenorrhea or amenorrhea). These removals constituted the major difference in device performance not only with respect to menstrual problems and pain, but also with respect to overall removal and continuation rates (Table IV) as virtually no woman requested removal of the TCu 380Ag because of infrequent bleeding. No large nor statistically significant differences between device types

were found with respect to removal for other menstrual problems or for pain associated with IUD use.

Table IV

Levonorgestrel 20 mcg and Copper T 380 Ag
Net Cumulative Termination Rates at 13 and 25 months

	13 Months		25 Months	
	LNg 20	TCu 380 Ag	LNg 20	TCu 380 Ag
Pregnancy	0.2±0.1	0.3±0.2	0.2±0.1	0.7±0.3
Expulsion	6.0±0.7	5.5±0.7	7.3±0.8	6.1±0.7
Amenorrhea	4.9±0.7***	0.1±0.1	8.4±0.9***	0.2±0.1
Other Menstrual	3.4±0.6	4.3±0.6	4.6±0.6	6.6±0.8
Pain	2.6±0.5	2.6±0.5	4.0±0.6	4.7±0.7
PID	1.0±0.3	0.9±0.3	1.3±0.4	1.5±0.4
Hormonal	1.0±0.3	0.6±0.2	1.8±0.4	0.7±0.2
Other Medical	2.4±0.5	2.2±0.5	3.8±0.6	3.9±0.6
Planning Pregnancy	2.8±0.5	2.2±0.5	6.2±0.8	5.7±0.8
Other Personal	2.2±0.4	1.5±0.4	2.8±0.5***	2.4±0.5
Total Terminations	26.5±1.4**	20.2±1.3	40.6±1.6***	32.5±1.5
Continuation	73.5±1.4**	79.8±1.3	59.4±1.6***	67.5±1.5
No. Completed Period	743	791	548	605
No. of Woman-Years	991	1007	1637	1703
No. Lost to Follow-up	74	90	109	132
No. of Subjects	1124	1120	31 Aug. 1986 Cut Off	

**P < 0.01; ***P < 0.001

Diaries indicate the pervasive menstrual effects associated with use of the LNg IUDs. Prior to admission women reported normal menstrual patterns with an average of 4.2 days of flow per cycle. From Day 91 onward (after the first quarter year of use), at least 25 percent of women using the LNg 20 device reported no "bleeding" events ("menses") in each quarter year to the end of the eighth quarter year. This is the case when "spotting" is differentiated from bleeding and not considered a "bleeding" event. Ten percent or more of users of the LNg device recorded neither bleeding nor spotting events in each quarter year after the first. Twenty or more percent of the women recorded no bleeding or spotting in 4 of the 8 (90-day) quarter years. In contrast women randomly assigned the TCu 380 averaged between 3.0 and 3.2 "bleeding" events per quarter year, with little variation.

Termination rates among young women were most affected by the diminished bleeding and spotting accompanying use of the LNg 20 device. Sixteen per 100 users in the age group under 25 terminated because of amenorrhea during the first 2 years. In contrast, 2 per 100 women aged 35-38 at admission (Table III) terminated for this reason.

Hemoglobin levels were measured in 6 of the 7 centers. Average hemoglobin changes by clinic for users of the LNg IUD ranged from a decrease of 0.02 g/dl to an increase of 0.76 g/dl (Table V), overall increasing by a mean of 0.47 g/dl. Women assigned the Copper T 380 Ag

experienced an average decrease of 0.24 g/dl.

Table V

Levonorgestrel 20 mcg and TCu 380 Ag IUDs
Average Hemoglobin Change From Admission - 2 Years of Use
By Clinic

	LNg 20			380 Ag		
	Change	SE	Prob.	Change	SE	Prob.
Santiago, Chile	-0.02	0.10	NS	-0.34	0.10	***
Santo Domingo, D.R.	+0.76	0.12	***	-0.02	0.12	NS
Los Angeles, US	+0.38	0.12	**	-0.30	0.13	**
Campinas, Brazil	+0.17	0.13	NS	-0.63	0.12	***
Cairo, Egypt	+0.76	0.12	***	-0.03	0.10	NS
Singapore	+0.49	0.11	***	-0.38	0.15	**
All Clinics	+0.47	0.04	***	-0.24	0.05	***
N	721			730		

Prob. is measured in relation to change from baseline

**=P<0.01; ***=P<0.001

Other Medical Reasons for Removal

Pelvic inflammatory disease (PID) occurred at a rate of less than two per hundred users of either device in the two years. Investigators were requested to remove devices whenever there was evidence of PID. Thus the "termination" rate is identical with the rate of reports of evidence of the occurrence of PID.

A group of conditions--headaches, acne, nausea, dizziness, etc.--have been associated with contraceptive steroids. Women who had devices removed after complaining of these conditions were categorized as having terminated for "hormonal complaints", whether using the Copper T 380 or the LNg 20 IUD. Although the point estimate of this termination rate appeared to be higher among women using the steroid device (1.8 per 100), the difference in removal rates between devices was not significant either at one or at 2 years.

"Other medical" reasons for termination include device-associated reasons, such as accidental removal, discomfort to husband; medical reasons possibly associated with intrauterine devices, e.g. vaginitis, cervicitis, etc.; and reasons believed to be unrelated. Women who changed contraceptive method were categorized as having an "other medical" removal.

Terminations for Personal Reasons

Planned pregnancy. Women using either device requested removal to have planned pregnancies at rates which were somewhat higher in the second year than in the first. At two years the net cumulative termination rate for planned pregnancy was estimated to be 6.2 per 100 among women who used the LNg 20 IUD and was estimated as 4.6 per 100 for users of the Copper T 380 Ag.

Other personal reasons. Separation, widowhood and divorce were the principal personal reasons, other than planning pregnancy, that led women to seek removal. At the end of two years removals for "other personal" reasons cumulated to somewhat less than 3 per 100 for either device.

Continuation Rates

By one year (13 months), the continuation rate of women randomized to the LNg 20 IUD was 73.5 per 100. This was significantly below the 79.8 per 100 continuation rate estimated for women assigned the TCu 380Ag ($P<0.01$). At two years (25 months), the difference in continuation rates was more distinct. An estimated 59.4 per 100 women continued use of the LNg 20 IUD as did 67.5 per 100 with the TCu 380 Ag ($P<0.001$). Period continuation rates in the second year were higher than in the first, in part because expulsion rates for both devices were significantly lower in the second than in the first year.

Demographic correlates of continuation were manifest. Women aged 35 or more at admission had two-year continuation rates which were about 20 per 100 higher than those of women under age 25 at admission (Table III). Continuation rates increased monotonically by age-group for each device. A similar spread of 20 per 100 in continuation rates was observed between women of parity 1 and women who had several children.

DISCUSSION

The present study is the fifth multicenter randomized comparative study of a Copper T 380 device (2,6-8). As in the other studies, the TCu 380Ag device manifested a high degree of effectiveness, with a cumulative 25-month gross pregnancy rate below 1 per 100. Even for the youngest women, those under age 25, the two-year cumulative failure rate was less than two per hundred (gross rate). Women in this age group tend to have higher pregnancy rates than do other women of reproductive age, regardless of contraceptive method (17). None of the few pregnancies were ectopic. In 8,000 woman-years of experience in randomized multicenter trials there has been a total of only a single ectopic pregnancy reported with a TCu 380 device, a rate of 0.125 per 1000. This rate is about one-tenth the ectopic pregnancy rate associated with the Lippes loop, Saf-T-Coil or TCu 200 (18-20).

The levonorgestrel device with a Pearl index of 0.12 per 100 women appears as a most effective means of reversible contraception. Concerns that a device at this dosage level may be associated with unacceptable rates of ectopic pregnancy have not materialized. There have been no ectopics in this study in 1600 woman-years of use. Reduction in bleeding and spotting days, also observed in earlier studies (13,16), has been accompanied by significantly increased levels of hemoglobin, but also by increased termination rates ascribed to amenorrhea. Assurance to users that absence of bleeding is not a sign of pregnancy, poor health, or lack of femininity should, presumably, diminish the rate of terminations ascribable to amenorrhea in future studies or use of the device. Apart from removals attributed to oligo-amenorrhea the termination rates among users of the LNg 20 for each other major category of removal were quite similar to those estimated for the TCu 380Ag, as they

were in our first year report (21).

The higher rates of physician "difficulty" with insertion, of insertion failure, of moderate or severe pain experienced by woman at insertion, and 5 perforations all may bespeak of potential problems with this device or its inserter tube. Adequate training in insertion appears mandatory. One must note that this was the initial trial of the device in 6 of the 7 clinics. Three perforations at one clinic followed insertion by a clinician who, in another randomized trial, had, unhappily, another series of perforations. Because of these problems the fit of the device and inserter tube have been modified. The relative lack of problems with the TCu 380 Ag may indicate greater familiarity with insertion of the collared T device.

Each of the two devices provides highly effective intrauterine protection. The copper device had a significantly higher continuation rate, but simultaneously was associated with modest but significant declines in hemoglobin. The levonorgestrel device with its attendant scanty and infrequent bleeding was associated with increased hemoglobin levels. Thus the devices may be seen as complementary. The use-effectiveness of either of these devices begins to approach the theoretical effectiveness ascribed to combined oral contraceptives.

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REFERENCES

1. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Intrauterine Devices for Fertility Regulation. Interval IUD insertion in parous women: A randomized multicentre comparative trial of the Lippes loop D, the TCu 220 and the Copper 7. Contraception 26:1-22 (1982)

2. Sivin, I. and Stern, J. Long-acting, more effective Copper T IUDs: A summary of U.S. experience, 1970-1975. Stud. Fam. Plann. 10:263-281 (1979)

3. Diaz, J., Diaz, M., Pastene, L., Araki, R., and Faundes, A. Randomized clinical study of the TCu 380A and Lippes Loop C in Campinas, Brazil. Contraception 26:221-228 (1982)

4. Sung, S., Qian, L.-J., and Liu, X. Comparative clinical experience with 3 IUDs, TCu 380Ag, TCu 220C and Mahua ring in Tianjin, People's Republic of China. Contraception 29:229-239 (1984)

5. Roy, S., Casagrande, J., Cooper, D.L., and Mishell, D.R. Comparison of three different models of the Copper T intrauterine contraceptive device. Am. J. Obstet. Gynecol. 134:568-574 (1979)

6. Cole, L.P., Potts, D.M., Aranda, C., Behlilovic, B., Etman, E.-S., Moreno, J., and Randic, L. An evaluation of the TCu 380Ag and the Multiload Cu 375. Fertil. Steril. 43:214-217 (1985)

7. World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction. Intrauterine devices. 13th Annual Report, 52-57 (1984)

8. Sung, S., Qian, L.-J., and Liu, X. Two-year comparative clinical experience with three IUDs in China. In: Intrauterine Contraception: Advances and Future Prospects (G.J. Zatuchni, A. Goldsmith, and J.J. Sciarra, eds). Harper and Row, Philadelphia, pp 109-114 (1985)

9. Israel, R., Shaw, S.T., and Martin, M.A. Comparative quantitation of MBL with the Lippes Loop, Dalkon Shield and Copper-T IUDs. Contraception 10:63-71 (1974)

10. Guillebaud, J. and Bonnar, J. Longer though lighter menstrual and intermenstrual bleeding with copper as compared to inert intrauterine devices. Br. J. Obstet. Gynaecol. 85:707-712 (1978)

11. Gallegos, A., Aznar, R., Merino, G., and Guizer, E. Intrauterine devices and menstrual blood loss. A comparative study of eight devices during the first six months of use. Contraception 17:153-161 (1978)

12. Zador, G., Nilsson, B.A., Nilsson, B., Sjöberg, N.-O., Weström, L., and Wiese, J. Clinical experience with the uterine progesterone system (Progestasert®). Contraception 13:559-568 (1976)

13. Nilsson, C.G. and Luukkainen, T. Improvement of a d-norgestrel-releasing IUD. Contraception 15:295-306 (1977)

14. El-Mahgoub, S. d-Norgestrel slow releasing T device as an intrauterine contraceptive. In: Analysis of Intrauterine Contraception (F. Hefnawi and S.J. Segal, eds). American Elsevier Publishing Co., Inc., New York, pp 317-324 (1975)

15. Nilsson, C.G., Lähteenmäki, P., and Luukkainen, T. Patterns of ovulation and bleeding with a low levonorgestrel-releasing intrauterine device. Contraception 21:155-164 (1980)

16. Luukkainen, T., Allonen, H., Haukkamaa, M., Lähteenmäki, P., Nilsson, C.G., and Toivonen, J. Five years experience with levonorgestrel-releasing IUDs. Contraception 33:139-148 (1986)

17. Grady, W.R., Hayward, M.D., and Yagi, J. Contraceptive failure in the United States: Estimates from the 1982 national survey of family growth. Fam. Plann. Perspect 18:200-209 (1986)

18. Tietze, C. and Lewit, S. Evaluation of intrauterine devices: Ninth progress report of the Cooperative Statistical Program. Stud. Fam. Plann. 55:1-40 (1970)

19. Vessey, M., Yeates, D., and Flavel, R. Risk of ectopic pregnancy and duration of use of an intrauterine device. Lancet 2:501 (1979)

20. Sivin, I. IUD-associated ectopic pregnancies, 1974 to 1984. In: Intrauterine Contraception: Advances and Future Prospects (G.I. Zatuchni, A. Goldsmith, and J.J. Sciarra, eds). Harper and Row, Philadelphia, pp 340-353 (1985)

21. Sivin, I., Alvarez, F., Diaz, J., Diaz, S., Mahgoub, S. El, Coutinho, E., Brache, V., Diaz, M.M., Faundes, A., Pavez, M., Mattos, C.E.R., and Stern, J. Intrauterine contraception with copper and with levonorgestrel: A randomized study of the TCu 380Ag and levonorgestrel 20 mcg/day devices. Contraception 30:443-456 (1984)