INTRAUTERINE CONTRACEPTION WITH COPPER AND WITH LEVONORGESTREL: A RANDOMIZED STUDY OF THE TCu 380Ag AND LEVONORGESTREL 20 mcg/DAY DEVICES

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ABSTRACT

First year results of a randomized study of 1509 users of the Copper T380Ag with a silver core or of an IUD releasing 20 mcg day of levonorgestrel are reported. The cumulative gross pregnancy rate for each device was 0.3 per 100 at one year, with more than 490 women having one year of use with each device. The levonorgestrel-releasing device was associated with significantly fewer bleeding days and significantly increased hemoglobin levels when compared with pre-admission values or the one year values observed among users of the TCu380Ag. Terminations attributable to amenorrhea were significantly more frequent among users of the levonorgestrel - releasing device. The TCu 380Ag was associated with increased frequency and severity of dysmenorrhea compared with pre-admission levels or with the steroid-releasing device. Hemoglobin levels were somewhat reduced among users of the TCu 380Ag device. Terminations attributable to pain were, however, not significantly different by device. Continuation rates at the end of the first year were not significantly different by device.

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INTRODUCTION

The first IUDs with copper wire wound on plastic platforms were smaller but not markedly more effective than plastic only devices. A major advance in effectiveness was first confirmed a decade ago when the Copper T, model TCu 380A, in a large randomized comparative study with the Copper T200, was found to have a gross cumulative pregnancy rate of only 1 per 100 at one year (1). This significantly improved anti-fertility effect was attributed to two design changes. Two sleeves of copper, positioned on the crossbar of the T, brought copper closer to the fundus and simultaneously to the tubal lumina. Second, the area of the wire on the vertical stem was increased to about 300mm^2, bringing the total copper surface to 380mm^2.

Several studies have since confirmed low annual pregnancy rates among users of the TCu380 devices (2-8). Developmental efforts have centered on extending the duration of effective action of the 380 device. Because copper wire with a silver core maintains its integrity after prolonged residence in utero, as observed in studies of the Nova T and the TCu200Ag in Scandinavia (9), the TCu 380Ag device used in the present study incorporates this feature.

Reports encouraging development of progesterone- and levonorgestrel-releasing IUDs were first presented a decade ago. IUDs releasing progesterone (10,11) or levonorgestrel (12) were associated with diminished menstrual blood loss. As anemia is endemic in developing countries, this feature of steroid intrauterine contraception is potentially of great importance. Preliminary estimates of effectiveness showed these steroid devices to be comparable to the standard devices then available.

A progesterone-releasing device quickly reached the stage of regulatory approval and marketing. A slower path was required for the synthetic steroid, levonorgestrel.

Finnish researchers undertook further safety studies and development (9,13). Their studies showed reductions in the volume of menstrual flow and low termination rates from bleeding, pain and infection. These advantages, ascribed to the levonorgestrel released by the IUD, warranted larger scale trials, as did a two-year Pearl pregnancy index of 0.4 per 100 (9).

D.N. Robertson and J. Braun developed a production model of a levonorgestrel-releasing device for the Population Council. This report concerns a large scale, randomized study of that device and of the copper-releasing TCu 380Ag. It focuses on the comparative effectiveness and comparative advantages and disadvantages of the two devices.

METHODS AND MATERIALS

Devices

The Copper T, model TCu 380Ag, has a polyethylene, T-shaped platform whose vertical and horizontal dimensions are 36 and 32 mm, respectively.

Two copper sleeves, swaged on the crossbar, provide approximately 70 mm^2 of copper surface in addition to 310 mm^2 of copper wire surface on the vertical stem of the T. The wire of 0.25 mm diameter weighs about 175 mg, of which 84 percent by weight is copper, and the remainder is silver in a core with a diameter of 0.095 mm. Polyethylene threads are tied through a 3 mm polyethylene ball at the bottom of the T. The TCu 380Ag devices were manufactured by Outokumpu Oy, Finland.

The levonorgestrel device (LNg 20) is designed to release 20 mcg of steroid daily for 2000 to 2300 days. Steroid is carried in a covered, homogeneous rod on the vertical stem of the polyethylene platform also used for the Nova T IUD (13). The rod is a mixture of 50 percent, by weight, of steroid and medical grade elastomer, silicone rubber (Dow Corning MDX4-4092). The levonorgestrel devices were manufactured by Leiras Pharmaceuticals, Finland.

Time Period

This report covers one year of experience of the first 1509 women, enrolled in study between September 1981 and 31 December 1982. The cut-off date of this report is 31 March 1984. Data were analyzed in July 1984.

Candidates and Contraindications

Candidates were parous women, 18-38 years old, regularly exposed to the risk of pregnancy and neither pregnant nor breast-feeding. Histories of ectopic pregnancy, cardio-vascular problems, copper allergy, persistent abnormal genital bleeding or cancer of any kind were contraindications, as was PID or salpingitis since the last pregnancy. Current clinical evidence of any of these conditions or of jaundice, diabetes, mental illness, anemia, pathological galactorrhea or severe hirsutism ruled a candidate ineligible for participation.

Informed consent was required. Participants agreed to random assignment. Use of a contraceptive other than the assigned IUD was considered as a termination from the study.

Randomization

Randomization of devices balanced in blocks of 50. Individually sterilized devices packed with inserter tubes were placed inside opaque, numbered envelopes in accordance with the random allocation and assembled in ascending sequence. Women were assigned study numbers in sequence of insertion, receiving the device contained in the corresponding numbered envelope. The study was single blind. Women did not know which device had been inserted.

Visits and Examinations

Insertions were performed within 7 days of the onset of menstruation. Revisits were scheduled at the end of months 1, 3, 6 and 12; breast and pelvic examinations were performed at 6-month intervals.

The first 100 acceptors at each clinic maintained daily menstrual records. All participants were asked, either at the one year visit or upon earlier termination, to characterize their menstrual experience subsequent to acceptance.

Subject Characteristics

Seven-hundred-and-fifty-five women received the LNg 20 device and 754 the Copper T 380Ag. Of 20 characteristics coded on the admission forms there were no statistically significant differences in distribution between users of either device.

Table I
Characteristics at Admission
Percentage Distribution

		LNg	380	
Age	18-24	41.7	40.8	
	25-29	34.3	36.1	P>.05
	30-38	24.0	23.1	
	Mean (SE)	26.0 (0.2)	26.0 (0.2)	
Parity	1	26.7	28.6	
	2	35.7	36.2	P>.05
	3+	37.7	35.1	
	Mean (SE)	2.44 (.05)	2.32 (.05)	
Desires additional children	Yes	34.7	36.2	
	No	57.9	54.6	P>.05
	Uncertain	7.4	9.2	
Number in Study		755	754	

Mean age at acceptance was 26.0 for women with each device. More than 40 percent of participants were under age 25 (Table I). Mean parity of LNg 20 device recipients was 2.4, not significantly different from the 2.3 mean parity of the Copper T 380Ag users. A majority in each group said, at admission, they wished to have no additional children (Table I).

On average, the last pregnancy of the acceptors had ended about 2 years before enrollment in this study. The last pregnancy had ended in spontaneous or induced abortion for 13 percent of the acceptors and in delivery for the remainder. One-fourth of the women enrolled had previously used IUDs; nine to ten percent reported having pelvic inflammatory disease (PID) prior to their most recent pregnancy. Mean duration of menstrual flow before admission was 4.1 days. Somewhat over 80 percent of the women were menstruating at insertion (Table II).

Table II
Menstrual Characteristics at Admission

Means (S.D.)	LNg 20	TCu 380Ag
Days since onset of last menses	3.2 (2.0)	3.4 (2.1)
Usual duration of flow (days)	4.1 (1.1)	4.1 (1.2)
Percentages		
Menstruating at admission	84.4	80.4
Has frequent dysmenorrhea	15.1	19.1
Has severe dysmenorrhea	3.8	5.6
Experiences intermenstrual bleeding or spotting	4.5	4.5

Analyses

Both multiple decrement (net) and single decrement (gross) event rates for the first segment of use are reported. By the cut-off date, 31 March 1984, more than one year had elapsed since the last insertion. One year results are presented. Many participants returned to the clinic for the one year visit in ordinal month 13, just after the conclusion of the year. Because this visit is functionally the end of the year (14) and coincides with an increased monthly removal rate, data are presented below as of the conclusion of ordinal month 13.

RESULTS

Insertion Ease and Pain

Physicians recorded whether insertion was easy or difficult. At least 88 percent of insertions with either device were "easy". Nevertheless, a significantly higher percentage of insertions of the LNg 20 device were recorded as difficult (Table III). Physicians ascribed the difficulty to the inserter tube. Concomitantly a higher percentage of women receiving the LNg 20 device (15.9%) felt moderate or severe pain at insertion than was the case with the TCu 380Ag device (9.3%) (Table III).

Table III
Insertion Characteristics
Percentages

		LNg	TCu 380Ag	X^2
Insertion (Physician's judgment)				
	Easy	88.7	97.0	35.8
	Difficult	11.3	3.0	P<.001
Pain at insertion (Woman's statement)				
	None	38.8	44.2	
	Mild	45.3	46.6	15.87
	Moderate	14.3	8.2	P<.01
	Severe	1.6	1.1	

There were 5 insertion failures with the LNg 20 device, all at a single clinic. No insertion failures were recorded for the TCu 380Ag.

A single fundal perforation was recorded after insertion of the LNg 20 device; no fundal perforations were recorded after insertion of the TCu 380Ag.

Pregnancy

Four women became pregnant in the first year while using study devices. Two had used the LNg 20 device and the other two the TCu 380Ag. Net and gross cumulative rates were both 0.3 per 100 for each device year (Tables IV and V).

One of the 2 pregnancies with the LNg 20 followed an unnoticed expulsion. The second pregnancy with the LNg 20 was carried to term with the device *in situ*. A normal, healthy male child was born. After confirmation of the pregnancies with the copper device *in situ*, neither of the two women returned to the clinic. Outcomes are unknown.

Table IV
Net Cumulative Termination Rates per 100
After One Year Visit - First Segment

Reason	LNg 20 Rate (S.E.)	TCu380 Ag Rate (S.E.)
Pregnancy	0.3 (0.2)	0.3 (0.2)
Expulsion	6.1 (0.9)	5.5 (0.9)
Menstrual/Pain	* 10.0 (1.1)	* 6.8 (1.0)
Other medical	4.0 (0.7)	4.8 (0.8)
Planning pregnancy	2.3 (0.6)	2.4 (0.6)
Other personal	2.6 (0.6)	1.9 (0.5)
Total Termination	25.3 (1.7)	21.8 (1.6)
Continuation	74.7 (1.7)	78.2 (1.6)
Numbers		
Total Terminations	174(23.0%)	150 (19.9%)
Lost to Follow-up	90(11.9%)	99 (13.1%)
Completed Year	491(65.0%)	505 (70.0%)
Number of Acceptors	755	754
Woman-Years of Use	640	645

*P < .05

Cut-off 31 March 1984

Expulsion

Net expulsion rates reached 5.5 to 6.1 per 100 at one year (Table IV). Differences in expulsion rates between devices were 1.2 per 100 or less at 4 of the 6 participating clinics. In the remaining clinics, one had somewhat more favorable experience with the LNg 20 device while the

other had a lower expulsion rate with the Copper T 380Ag. Women under age 25 experienced expulsion at the rate of 7 to 8 per 100 while those aged 30 and over had about half that rate. Decreased expulsion rates by age were observed with both devices.

Table V

Gross Termination Rates, Standard Errors & Events at the End of 1 Year by Device

	Rates		Standard Errors		Events	
Reason for Termination	LNg	380	LNg	380	LNg	380
Pregnancy	0.3	0.3	0.2	0.2	2	2
Expulsion	6.4	5.8	1.0	0.9	43	39
Menstrual/Pain	11.1 *	7.5	1.6	1.1	69	47
Other Medical	4.4	5.2	0.9	0.9	27	33
Planning Pregnancy	2.8	2.9	0.7	0.7	15	16
Other Personal	3.0	2.2	0.7	0.6	18	13
Detailed Reasons						
Menstrual/Pain						
Amenorrhea	5.6 ***	0.0	1.0	-	32	0
Other Menstrual	3.4	4.2	0.7	0.8	22	28
Pain	2.5	3.4	0.6	0.8	15	19
Other Medical						
PID	1.6	1.3	0.5	0.4	10	8
"Hormonal" changes	0.7	0.8	0.4	0.4	4	5
Other Medical	2.3	3.3	0.6	0.7	13	20

*P<.05 ***P<.001

Menstrual patterns and pain

The two IUDs evoked markedly different menstrual patterns (Table VI). A large majority (77.1 percent) of women using the LNg 20 IUD reported decreased menstrual flow and 58.9 percent reported decreased days of menstrual bleeding after insertion. Concomitantly, half (52.2 percent) reported the length of the menstrual cycle increased. In contrast, a majority of TCu 380Ag users reported increased menstrual flow and half (49.8 percent) reported increased days of bleeding. Cycle length was not greatly affected among users of the TCu380Ag. For the menstrual flow, days of bleeding and length of cycle variables, the probabilities that these divergent reports are attributable to chance were less than one in one million. For all menstrual variables in Table VI the probabilities were less than one in 10,000 (P<.0001).

Table VI
Menstrual Experience During IUD Use
(Compared to Own Pre-Insertion Experience)
Percentage Reporting Status by Device

Characteristic	Device	Increase	No Change	Decrease	X^2	P
Menstrual Flow	LNg	9.6	13.3	77.1	611.8	<.0001
	380	59.7	32.5	7.7		
Days of Bleeding	LNg	21.8	19.5	58.9	359.8	<.0001
	380	49.8	42.5	7.7		
Length of Cycle	LNg	52.2	20.3*	17.5	195.1	<.0001
	380	15.4	62.3*	22.2		
Intermenstrual Bleeding/Spotting	LNg	22.6	68.5	8.9	44.9	<.0001
	380	21.3	77.8	0.8		
Dysmenorrhea-Frequency	LNg	21.4	58.8	19.8	63.5	<.0001
	380	36.5	56.8	6.7		
Dysmenorrhea Severity	LNg	13.6	68.8	17.5	75.0	<.0001
	380	27.1	68.5	4.4		

*Includes <5 women stating change was variable.
Respondents: LNg20 616
380Ag 609

Increased frequency and increased severity of dysmenorrhea following insertion were reported by significantly larger percentages of women using the TCu 380Ag than by users of the LNg 20 device (Table VI). Decreased frequency and decreased severity of dysmenorrhea were more frequently reported by users of the steroid-releasing device. The majority using each device, however, reported no change in either frequency or severity of dysmenorrhea.

Perceptions of menstrual patterns reported at the end of the first year were substantiated by diaries maintained throughout the year by the first 100 acceptors at each clinic. After the initial month, 50 to 62 percent of LNg 20 IUD users recorded no bleeding days whatever in any selected month (30-day interval). In contrast, 15.6 was the highest percentage of Copper T 380 users who reported no bleeding days in any month during the first year (Table VII).

From the second month of use through the twelfth, the average number of bleeding days experienced by users of the copper device ranged narrowly between 3.8 and 4.3 days. There was no perceptible trend in the monthly averages. In contrast users of the LNg 20 device experienced on the average, far fewer days of bleeding each month. The mean declined from 2.2 days per woman in month 2 to an average of 1.3 days of bleeding per month in the tenth through 12th month. For all months after the first, the differences between devices in the associated average number of days of bleeding was significant at P<.001.

Table VII
Menstrual Diary Analysis
Percentage of Women with Characteristic
in Specified 30-Day Intervals from Admission
by Device

Period Days from Admission	No Bleeding or Spotting			No Bleeding			> 8 Days of Bleeding		
	LNg		380	LNg		380	LNg		380
1 - 30	4.2		3.5	19.1	*	9.3	19.5		21.7
31 - 60	21.0	**	10.4	49.3	***	15.6	4.9		7.6
61 - 90	26.5	***	5.4	56.6		8.4	3.1	*	9.4
91 - 120	27.5		7.8	55.0		11.5	4.4		3.1
121 - 150	29.8		6.6	57.3		8.2	2.2		4.9
151 - 180	34.5		4.5	61.5		6.2	4.6		6.8
181 - 210	37.5	P<.001	6.6	63.4	P<.001	9.5	4.6		8.9
211 - 240	31.0		3.1	60.3		6.8	5.5		5.5
241 - 270	32.1		1.9	56.0		5.7	2.9	*	8.8
271 - 300	32.8		9.3	56.2		11.9	2.3		4.6
301 - 330	38.2		2.7	60.0		6.8	1.6		4.8
331 - 360	30.5	***	5.0	62.5	***	8.6	0.0		2.9

* P < .05 **P<.01 *** P<.001

Records for 215 LNg users and 226 TCu 380Ag users in days 1-30
Records for 120 LNg users and 139 TCu 380Ag users in days 331-360

Spotting days were as, or slightly more, frequent than bleeding days among women using the LNg 20 IUD. Beginning with month three (day 61) the monthly mean number of bleeding and spotting days was significantly smaller for users of the LNg device than for users of the 380Ag to the end of the year (Table VII).

Over the first year hemoglobin levels of women using the steroid device rose slightly, 0.26g/dl, but statistically significantly. Women with the 380Ag experienced a small, 0.36g/dl, but statistically significant decline. On average however, women using either device who had initial hemoglobin levels below 12 g/dl were measured as having higher hemoglobin values after 1 year of use. Conversely, women using either device who had initial hemoglobin measurements at 14g/dl or above, tended to have somewhat lower measurements at one year (Table VIII). This regression to mean values is frequently observed in repetitive measurement processes.

Table VIII
Mean Changes in Hemoglobin by Value at Admission and Device

Initial Value	LNg 20			TCu 380 Ag		
g/dl	Mean Change	SE	Signif.	Mean Change	SE	Signif.
9	+3.1	0.6	NA	2.0	0.7	NA
10	+2.5	0.3	Yes	1.0	0.2	Yes
11	+1.1	0.2	Yes	0.1	0.2	No
12	+0.8	0.1	Yes	-0.1	0.2	No
13	+0.4	0.1	Yes	-0.4	0.1	Yes
14	-0.6	0.2	Yes	-0.9	0.1	Yes
15	-1.2	0.2	Yes	-1.5	0.1	Yes
16+	-1.4	0.4	NA	-1.6	0.6	NA
ALL	+0.26	0.09	Yes	-0.36	0.08	Yes

NA means N < 10, significance was not tested.

The contrasting menstrual experience of the users was accompanied by a significant difference between devices in the gross removal rate attributable to bleeding and pain. When analyzed in terms of 3 constituent factors, amenorrhea, other menstrual problems and pain, differences between devices center on the problem of amenorrhea. Thirty-two women had the LNg 20 device removed because of amenorrhea in the first 13 months; no one stopped use of the TCu 380AG for this reason, (P<.01) (Table V). Conversely, users of the TCu 380Ag terminated intrauterine contraception because of "other menstrual problems" at a marginally higher rate than did users of the the LNg 20 device (P>.05). Terminations ascribable to lower abdominal or back pain or to dysmenorrhea were also marginally higher among users of the TCu 380Ag (P>.05).

Removal rates attributable to bleeding and pain diminished significantly for users of the LNg 20 device as age and as parity increased. Similar but more modest diminutions in these removal rates were observed among users of the TCu 380Ag.

Pelvic Inflammatory Disease & Other Medical Reasons for Termination

The incidence of pelvic inflammatory disease (PID) was similar among users of the two kinds of devices (Table V). No consistent pattern of difference between devices emerged by age, parity, desire for additional children or by clinic. All cases of PID were considered to be terminations.

There were no significant differences between devices in termination rates ascribed to hormonal changes or to other medical reasons (Tables IV and V). When asked to describe their experience at the end of the first year or at termination, users of either device reported increases and decreases in nervousness, dizziness, depression, in acne and in other skin conditions with similar frequencies. Users of the levonorgestrel-releasing device, however, reported increases in headaches and in nausea significantly more frequently (P<.01 for each) than did users of the TCu 380Ag.

Continuation

At the end of month 13, 74.7 per 100 women continued in the study as a user of the LNg 20 device. Continuation was 78.2 per 100 among women assigned the TCu 380Ag. The continuation rate was somewhat, but not significantly lower for the steroid-releasing device than it was for the copper-releasing device (Table IV).

Continuation rates were positively correlated with age and with parity. Women who at admission desired to have additional children had significantly lower continuation rates at one year than did women who had said they wished no more children (Table IX).

Table IX
One Year Pregnancy and Continuation Rates per 100
by Age, Parity & Desire for Additional Children

	Pregnancy		Continuation	
	LNg	380	LNg	380
Age 18-24	0.0	0.4	70.3	75.2
25-29	0.4	0.4	73.3	79.6
30-38	0.6	0.0	84.6	81.8
Parity 1	0.0	0.5	68.1	77.1
2	0.4	0.0	75.5	76.3
3+	0.4	0.4	78.9	81.1
Desires additional children				
Yes	0.0	0.4	68.0	72.5
No	0.5	0.0	79.2	81.5
All groups	0.3	0.3	74.7	78.2

DISCUSSION

Both devices proved to be highly effective, with gross pregnancy rates of only 0.3 per 100 at 1 year. These pregnancy rates are of a magnitude usually associated with the theoretical effectiveness of oral contraceptives.

Several independent, randomized comparative studies involving the TCu 380, either with or without a silver core, have shown very low pregnancy rates. In multicentered studies, gross pregnancy rates have been 0.1, 0.3 and 0.9 at 1 year and in single clinic randomized studies the gross pregnancy rates were 0.0 and 0.5 at one year (7,8,2,5,3). The current study thus is at the median of these values.

In this study the LNg 20 device proved as effective as the TCu 380Ag. Insofar as pregnancy is concerned, the selected dosage of 20 mcg/day appears entirely adequate.

The first marketed steroid-releasing device, the Progestasert^{R}, is

associated with an ectopic pregnancy rate four to ten times that of copper IUDs (15). A second progesterone-releasing device had a seven-fold risk of ectopic gestation in randomized trials with copper IUDs (16). A prime concern in this study was the incidence of extrauterine pregnancies associated with the LNg 20. The point estimate in this study was zero; neither of the 2 pregnancies with the LNg 20 device was ectopic. This result coupled with the previously reported data of Nillson et al. (9), yields a point estimate of 1.1 ectopic pregnancies per 1,000 woman-years of LNg 20 use. This value is similar to the incidence of ectopic pregnancy observed with plastic and copper devices.

The LNg 20 device reduced the number of bleeding or bleeding and spotting days both in comparison with the TCu380Ag and with respect to the women's experience before IUD insertion. One consequence was that users of the LNg 20 IUD experienced a slight but significant, increase in hemoglobin. On the other hand, some women were sufficiently disturbed by prolonged absence of menstruation that they stopped use. Dissatisfaction with this feature appears to be the principal reason that the continuation rates of LNg IUD users were somewhat ($P>.05$) below those of women who used the 380A device.

Because combined oral contraceptives provide protection against PID, some investigators had thought it plausible that a levonorgestrel-releasing IUD would provide a similar protection. The current study does not support the hypothesis of protection, at least in comparison with the TCu 380Ag. There was no difference between devices in the incidence of PID.

Following the relatively poor experience in this study, the LNg 20 IUD inserter tube is being redesigned.

Overall, the two devices performed similarly with respect to pregnancy, expulsion, removals for medical reasons and total continuation. The very high effectiveness and good continuation rate associated with each device makes each useful for women seeking intrauterine protection against pregnancy. The determination of the effective life span of these devices is a principal goal of the continuing study.

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