PROLONGED INTRAUTERINE CONTRACEPTION: A SEVEN-YEAR RANDOMIZED STUDY OF THE LEVONORGESTREL 20 mcg/DAY (LNg 20) AND THE COPPER T380 Ag IUDS

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ABSTRACT

A levonorgestrel-releasing IUD and the Copper T 380Ag IUD were in randomized comparison for seven years in five clinics. In two other clinics the randomized study was truncated at five years, but use of the Copper T continued. No pregnancies occurred to users of either device in years 6 and 7. Cumulative pregnancy rates were 1.1 per 100 at seven years for the steroid-releasing and 1.4 per 100 for the copper-releasing IUDs. Cumulative rates of PID did not differ between devices. Infection rates appeared to be lowest during the sixth and seventh years of the study. Termination attributable to amenorrhea was the principal contributor to differences in cumulative continuation rates between devices. At the five clinics that carried the comparative study to seven years, cumulative continuation rates were 24.9 per 100 for LNg20 IUD users and 29.4 per 100 for TCu 380Ag users. Women who used either method for periods of five to seven years experienced, on average, marked to mild increases in hemoglobin as compared with levels at admission. The Copper T380 family and the LNg20 IUDs represent the most effective reversible contraceptive methods yet studied in long-term randomized trials.

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INTRODUCTION

Long-acting contraceptive methods enhance user control of reproductive potential. By providing effective contraception for many years following a single insertion or placement, intrauterine devices or implants afford the convenience of a reversible method unrelated to coitus, and freedom from adverse effects associated with repeated insertion or implant placement. In theory at least, very long-acting methods are economical both to the couples that use them and to the societies that promote their use or provide them. This report covers events in the seven-year period following insertion of medicated IUDs releasing copper or levonorgestrel in a trial undertaken by the Population Council's International Committee for Contraception Research.

METHODS AND MATERIALS

The methods, trial design, schedule of visits and subject characteristics have been previously described.[1-3] Briefly, a levonorgestrel-releasing IUD containing approximately 60 mg of steroid was used in five clinics. A similar device containing 46 mg of levonorgestrel was used in two clinics. The rated release of each model was 20 mcg/day. Drug resides in a cylinder which, by weight, is 50 percent levonorgestrel. The cylinder is borne on a polyethylene frame also used for the Nova T IUD. The devices were manufactured by Leiras Pharmaceuticals, Turku, Finland. Continuing users of the 46 mg IUD were required to have it removed at or shortly after completion of five years.

For comparison, the Copper T, model TCu 380Ag, was studied. The copper surface area is approximately 380 mm^2 of which 310 mm^2 is copper wire, made with a silver core, placed on the vertical shaft of the IUD. The remaining copper is in the form of collars or sleeves swaged onto the crossbar of the T. Devices were manufactured by Outokumpu Oy, Finland.

Selection and Schedule of Visits: Parous women, aged 18-38, in good health, without contraindication to copper, contraceptive steroids or IUD use, were candidates for this study. Histories of PID after the last pregnancy or of ectopic pregnancy precluded entry. Informed consent was obtained for random assignment of devices, and for clinic visits 1, 3, 6 and 12 months after insertion, and semiannually thereafter. Gynecological examinations were provided immediately prior to admission and at semi-annual visits. Hemoglobin was measured semi-annually and at termination. Data on hemoglobin changes are presented for five clinics which measured levels for at least five years.

Design and Duration of Study: The original protocol called for a comparative trial of five years duration. Analysis of steroid release and of pregnancy rates performed as the trial reached five, and later, six years suggested that devices containing 60 mg of levonorgestrel could be used effectively for 6 and then for 7 years. Informed consent was sought and obtained for these extensions. At the conclusion of seven years, all remaining devices were removed. Women with the 46 mg levonorgestrel device had it removed at the end of 5 years. Copper IUD users gave informed consent for extensions of use through six, then seven and finally ten years.

Analysis: Actuarial life tables with the Jain-Sivin conventions[4] have been used. Women not known to have terminated and last seen seven or more months before a 31 December 1990 cut-off date are classified as lost to follow-up after their last clinic visit.

Characteristics of Subjects: Earlier publications have described the subjects.[1-3] Women were, on average, 26.6 to 26.7 years of age (last birthday) at admission, and had had an average of 2.4 children. One-third (32.8 to 33.6%) had prior experience with IUDs. Six to eight percent reported a history of PID, but none had had the disease after the most recent pregnancy preceding admission.

RESULTS

General: Average annual rates of termination because of adverse health events, expulsion or pregnancy tended to be lower in years six and seven than at earlier times (Table I). The single exception was the category "other medical problems," a category excluding terminations attributable to menstrual problems, pelvic pain and PID. The category includes terminations for change of method. Terminations attributable to personal reasons also occurred at a higher average annual rates in the later years than in the first two years.

Table I: Average Annual Gross Rates Per 100

Rate	Device	Years		
		1-2	3-5	6-7
Pregnancy	LNg 20	0.1	0.3	0.0
	TCu 380Ag	0.4	0.2	0.0
Expulsion	LNg 20	4.2	1.3	0.0
	TCu 380Ag	3.3	0.3	0.6
Amenorrhea	LNg 20	5.5	3.5	3.0
	TCu 380Ag	0.2	0.0	0.4
Other Menstrual	LNg 20	5.1	2.4	2.5
Or Pain	TCu 380Ag	6.2	4.7	4.2
PID/	LNg 20	0.9	0.5	0.2
Endometritis	TCU380Ag	0.8	0.4	0.3
Other Medical	LNg 20	3.4	2.6	5.6
	TCu 380Ag	2.5	3.4	3.6
Planned	LNg 20	3.9	7.2	2.2
Pregnancy	TCu 380Ag	3.2	6.5	7.0
Other Personal	LNg 20	1.6	2.0	3.6
	TCu 380Ag	1.4	2.5	2.5

Cumulative rates at seven years (Table II) highlight differences and similarity between the two IUDs. Demographic and family formation stages contributed significantly to variation in cumulative rates with respect to terminations for either medical or personal reasons, total termination and continuation rates. In Table III the termination rates significantly affected by demographic and family stage variables are indicated.

Pregnancy: No pregnancies were reported among users of either device in the sixth or seventh years. Seven-year cumulative rates were 1.1 and 1.4 per 100 for the steroid- and copper-releasing devices, respectively. The Pearl index associated with the LNg 20 IUD was 0.18±0.07 per 100; that associated with the TCu 380Ag IUD was 0.27±0.08 per 100. As stated in the 5-year report, there were no ectopic pregnancies among women with the LNg 20 IUD and two among women who had used the TCu 380Ag, corresponding to a rate of 0.53±0.38 per 1000 woman-years.[3]

Expulsion: No expulsions were experienced by women using the LNg 20 device in the sixth and seventh years. The cumulative expulsion rate among women with the TCu 380Ag increased to 8.4 per 100, but remained significantly below the rate associated with

the LNg 20 device, 11.7 per 100 (P<.05). Expulsion rates decreased significantly with age at insertion of the copper device.

Table II: Seven-Year Gross Cumulative Rates Per 100

Item	Rates				No. of Events	
	All Clinics		Clinics with Seven-Year LNg IUD		All Clinics	
	LNg 20 Rate S.E.	TCu Rate S.E.	LNg 20 Rate	TCu Rate	LNg 20	TCu 380Ag
Pregnancy	1.1±0.5	1.4±0.4	0.5	1.0	6	10
Expulsion	11.7±1.2*	8.4±1.0	11.7*	8.3	99	74
Amenorrhea	24.6±2.0***	1.1±0.6	21.9***	1.0	150	5
Other Menstrual/Pain	20.4±1.9**	30.0±1.9	18.2**	28.0	133	210
PID/Endometritis	3.6±0.8	3.6±0.8	3.6	3.4	24	24
Other Medical	23.3±2.2	20.4±1.9	22.6	19.4	121	116
Planning Pregnancy	29.4±2.0	33.8±2.1	29.5	33.5	169	195
Other Personal	15.5±2.0	14.2±1.7	15.6	12.2	71	72
End of Study[A]	15.6±2.2	4.1±1.2	3.6	4.4	47	14
Continuation	23.1±1.4*	27.2±1.5	24.9	29.4		
N., Enrolled			897	896	1125	1121
N.,Entered Month 84			172	189	172	211
Woman-Years			2831	3085	3371	3758
Users with <7 yrs			0	0	5	16
Percent LFU					11.5	16.2

A Includes women who stopped use before month 82; not counted as a relevant termination.
LFU = Lost to Follow-Up

*p < .05, **p < .01, ***p < .001

Amenorrhea: Terminations attributed to amenorrhea were at a markedly higher cumulative rate, 24.6 per 100, among women with the LNg 20 device than was found among women using the Copper T 380Ag device. Age at acceptance of the steroid-releasing device was significantly related to termination for this cause at two years (P<.05).

Other menstrual events and for pelvic pain: Copper T users had significantly higher termination rates for pain and menstrual events except amenorrhea than did women with the steroid-releasing device. In the initial two years, termination rates for this event differed significantly among users of the Copper T, by whether at admission additional children were desired. As the study continued, however, this variable was no longer significant among the copper T users (Table III). By five years, significant differences by initial (statement of) desire for more children developed among women with the LNg IUD. These differences in removal rates remained significant through the end of seven years. Women who had wanted more children had higher termination rates attributable to bleeding and pain than did women who had wanted no more children.

Effects on hemoglobin: In the first two study years, women with the steroid-releasing device experienced an increase in hemoglobin of 0.5-0.7 g/dl, while the users of the copper IUD experienced a slight loss. Thereafter, continuing users of either device experienced increments in hemoglobin which were statistically significant in comparison with their status at admission or at two years (Table IV). Women continuing

with the steroid-releasing IUD experienced a mean increase of 1.17 g/dl of hemoglobin at five years in comparison with their own admission levels, and an increment of 0.38 g/dl compared with their own hemoglobin levels at two years of use. Compared to their own admission levels, the increment at five years for continuing users of the Copper T was 0.28 g/dl (P<.01). Four of the five clinics that monitored hemoglobin reported increased mean hemoglobin among LNg 20 IUD users. A different four clinics reported increased mean values of hemoglobin among women with the TCU 380Ag, and one clinic reported a decrease. For women with the copper IUD, the mean hemoglobin increment from the two-year baseline was 0.31 g/dl at five years (P<.01).

The seven-year data show a further increase to 1.44 g/dl in hemoglobin among the users of the LNg 20 device in comparison with admission values. For women who used the Copper T continuously through 5.26-7.25 years, the increase over admission was modest, 0.26 g/dl (P<0.05) and not consistent by clinic.

Table III: Significant Effects of Demographic and Family Formation Variables on Performance at 5 and 7 Years; Values are Probabilities

	LNg		TCu 380Ag	
Event Category	5 Yrs	7 Yrs	5 Yrs	7 Yrs
		Age		
Expulsion	NS	NS	<.05	<.05
Amenorrhea	<.05	NS	NS	NS
Planned Pregnancy	<.001	<.001	<.001	<.001
Other Personal	<.05	<.05	NS	NS
Continuation	<.001	<.001	<.001	<.001
		Parity		
Planned Pregnancy	<.001	<.001	<.001	<.001
Other Personal	.005	.005	NS	NS
Continuation	<.001	<.001	<.001	<.001
		Desire for Additional Children		
Other Menstrual Problems	<.05	<.05	NS	NS
Planned Pregnancy	<.001	<.001	<.001	<.001
Other Personal	<.01	<.01	NS	NS
Continuation	<.001	<.001	<.001	<.001

NS means p>.05

Pelvic Inflammatory Disease and Endometritis: A diagnosis of probable or certain PID required device removal. Both the number of events ascribed to PID and endometritis and the corresponding termination rates were essentially identical for the two devices. This identity in rates persisted throughout the study (Tables I and II). Events during years 6 and 7 appeared to occur at lower rates than in earlier years.

Table IV: Hemoglobin Changes (g/dl) from Admission Levels and from Levels after Two Years of Use

Time Periods Compared (yrs)		LNg 20 IUD		TCu380Ag		No. of Women	
A	B[1]	Change	SE	Change	SE	LNg	TCu
Admission	< 2.26	+.53***	.06	-.13**	.05	640	634
Admission	1.76-2.25	+.67***	.08	-.04*	.07	317	316
Admission	2.26-5.25	+1.02***	.09	+.18**	.07	334	393
Admission	4.76-5.25	+1.17***	.12	+.28*	.10	156	188
Admission	5.26-7.25	+1.44	.14	+.26	.10	133	186
1.76-2.25	4.76-5.25	+.38***	.11	+.31**	.11	131	140
1.76-2.25	5.26-7.25	+.49	.12	+.16	.12	100	131

[1]Last reading in period; *P<.05 **P<.01 ***P<.001

Other Medical Conditions: For all clinics, cumulative seven-year rates of termination for "other" medical conditions ranged from 20.4 to 23.3 per 100, but did not differ by device (Table II). Skin and hair conditions and headaches, sometimes associated with steroidal contraception, led to termination at significantly higher rates among LNg 20 IUD users than among copper IUD users (P<.05). Lower reproductive tract problems culminated in device removal somewhat more frequently among women with the copper than with the steroid-releasing IUD, but this was not statistically significant.

Personal Reasons: After the first two study years, terminations for personal reasons occurred at higher rates than did terminations for medically related reasons (Table I). For each IUD model, the gross cumulative termination rate at seven years attributed to planned pregnancy was higher than any other cumulative rate (Table II). Younger women, those with only one child, and women who at admission wanted more children had higher termination rates attributed to planned pregnancy and to other personal reasons than did women who were older, had had more children or who, at admission, desired no more children.

Continuation: In the five clinics in which the 60 mg LNg 20 IUD was studied, the seven-year continuation rate was 24.9 per 100, somewhat below the rate of 29.4 per 100 for the TCu 380Ag (P=0.054). These rates exclude terminations for "end of study." Combined data for all seven clinics indicated that Copper T users had significantly higher continuation rates (P<0.05) when end of study terminations are excluded (Table II). High rates and numbers of women using the LNg 20 device who terminated because of "end of study" make the comparison at all clinics difficult to interpret.

DISCUSSION

The remarkable effectiveness of these two devices at shorter intervals in randomized trials has previously been noted[1-3,5,6]. This study represents an extension of effective use to seven years for the 60 mg LNg 20 device.

Two models of the Copper T380, the TCu 380Ag studied here, and the TCu 380A, studied by WHO[7], maintain effectiveness through at least seven years. Deposition of calcium salts on the frame, copper wire or collars, or wire fragmentation has not appeared to diminish the IUD's effectiveness. Indeed, there is an apparent decrease in pregnancy rates with prolonged use. Age may be an intervening factor. Mean age of continuing users increased by a greater amount than the study length, because younger women had lower continuation rates. Older age is associated with lower pregnancy rates. All long-term contraceptive methods are subject to the same apparent increase in effectiveness

associated with the aging of the study group. Nevertheless, the Copper T380 family of IUDs and the LNg20 IUD appear to be the most effective reversible contraceptive methods yet studied in long-term multicenter randomized trials.

The annual incidence of PID appeared to be lower in years six and seven than at earlier durations. Low rates of disease at extended durations may reflect a greater proportion of couples in mutually monogamous relationships. Be that as it may, these low rates of PID provide clear indications of the safety of prolonged IUD use as compared with risks of infection following an insertion or reinsertion. Speculations appear unfounded that deposits, building up on IUDs, would, by harboring colonies of microorganisms, eventuate either in higher rates of PID[8] or in more extensive infection[9]. Long-term, seven-year studies of the TCu 380 A and the TCu 220 C conducted by WHO also have not indicated either increased rates of infection or the existence of more extensive infection at later intervals. We did not find at seven years, or at any earlier annual evaluation, a significant difference in PID rates between devices. European observers have reported low PID rates with the LNg20 IUD in comparison with the copper-releasing Nova-T IUD[6].

Women who used the LNg 20 IUD unequivocally benefitted from it with respect to their hemoglobin levels. Hemoglobin increased during the first years of use and this increase became more marked with the passage of time. A contrast is presented by the collared Copper T IUD. Hemoglobin fell somewhat during the course of the first two years, and removals occasioned by bleeding and pain occurred at a higher rate than observed with the LNg 20 device. But after two years, hemoglobin levels of continuing users of the TCu 380Ag were maintained and appeared to increase to and above levels measured at insertion.

Earlier studies of menstrual blood loss have shown that by 24 months of use, menstrual blood loss among women using copper IUDs was not very different in amount from that experienced prior to insertion[10]. With normal blood loss, hemoglobin values would slowly tend to be restored. A second factor associated with the increase in hemoglobin levels among long-term users of the Copper T380Ag appears to be a regression to mean values; the most marked increases at 5-7 years occurred at clinics where the initial and/or two-year hemoglobin levels were the lowest. A third factor is likely to be continued selection favoring women with light or moderate bleeding.

Over the seven-year period, devices were removed at greater rates for planned pregnancy than for any other major reason or removal category. Conception rates following removals for planned pregnancy have been normal[11].

Approximately one-quarter of the original cohort (gross rate) continued to use the randomly allocated device seven years after entrance to the study. It is clear that with average annual continuation rates of 80 per 100 for each device, these IUDs have proved highly acceptable as well as highly effective over the entire seven-year study span.

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