

# The MLCu375 intrauterine contraceptive device

M. THIERY, H. VAN DER PAS and H. VAN KETS

*Department of Obstetrics, University of Ghent, Ghent, Belgium*

## Abstract

Reports in the contraceptive literature and our own data concerning the MLCu375 intrauterine device indicate that the high-load ML model is effective, safe, and well tolerated. It is more effective than the MLCu250 without increase in the other cardinal event rates. Consequently, we consider the MLCu375 an improved ML model.

## Introduction

The standard Multiload (ML) IUD (MLCu250) is one of the most widely used medicated IUDs. Over the years this device has been adapted to fit large and small uterine cavities (MLCu250 short, mini, and maxi) and a model with higher copper load (MLCu375) has been tested. The latter was designed to enhance the antifertility effect and to extend the effective life span of the MLCu250 without affecting other parameters of performance, especially the risk of expulsion.

The purpose of this presentation is to analyze the reports in the contraceptive literature and our own data and assess the extent to which the objectives of the designer of the high-load ML IUD have been realized.

## Materials and methods

Table 1 shows the characteristics of the standard and the high-load ML models. Both have the same skeleton but the copper wire used in the experimental model is stronger. Due to this modification the MLCu375 has a 50% greater nominal surface area of exposed copper and carries an 82% greater weight of metal than does the MLCu250.

The two models are inserted according to the same technique: they are pushed in after sounding of the uterus and while the cervix is steadied with a volsellum.

**Table 1 Characteristics of MLCu250 and MLCu375 IUDs**

	MLCu250	MLCu375	Increment
<i>Skeleton*</i>			
Length (mm)	35	35	—
Maximum width (mm)	19	19	—
<i>Copper filament</i>			
Length (cm)	±29	±31	—
Diameter (mm)	0.30	0.40	0.10
Surface area (mm <sup>2</sup> )	250	375	125
Weight (mg)	176	320	144

\* Polyethylene without barium sulfate. The tail of both models is of monofilament nylon

## Clinical performance

### Straight study

We have inserted the MLCu375 at interval in 2422 women (Table 2). At 5 years a total experience of 84 411 woman-months had accumulated, with a lost to follow-up (LFU) rate of 9.0%. The results indicate that the high-load ML device is effective and safe, well retained by the uterus, and well tolerated by the recipient. Tables 3 and 4, which look at the same data arranged according to parity and age of the women, show that these variables had some effect on the overall performance of the MLCu375.

### Comparative trials

The relative performance of the MLCu375 was evaluated on the basis of the handful of multicenter trials in which the experimental device was compared either with the standard ML or with other IUD models (Table 5). Three of the studies were randomized trials and the remaining two were retrospective, due to sequential availability of the experimental ML models. With the exception of the first of these studies (Thiery *et al.*, unpublished), data on the randomized trials are available for the first year of use only.

### Randomized trials

In two hospitals in Belgium the MLCu375, MLCu250, and TCU200 were inserted and the patients followed for 3 years (Thiery *et al.*, unpublished). Cardinal event rates at 1 year are given in Table 6, and at that time the LFU rates ranged from 0.0 to 2.4. It is evident that the MLCu375 was more effective than the two other IUD models investigated, and at 3 years the difference was even more pronounced.

Family Health International (FHI) computerized the first-year results of a multicenter study comparing the MLCu375 with the TCU380Ag [1] (Table 7). The LFU

Table 2 Interval insertion of the MLCu375. Gross cumulative life-table rates per 100 women at yearly intervals. Values in parentheses give upper and lower confidence limits at 95% level (Thiery *et al.*, unpublished)

	1 year	2 years	3 years	4 years	5 years
Number	1979	1559	1233	893	521
Woman-months	26 423	47 114	63 448	75 772	84 411
Events					
Pregnancy	0.4 (0.2-0.8)	1.5 (0.9-2.0)	1.9 (1.2-2.5)	2.5 (1.7-3.3)	2.9 (2.0-3.7)
Expulsion	2.4 (1.8-3.1)	3.2 (2.4-3.9)	3.8 (3.0-4.6)	5.0 (4.0-6.0)	5.4 (4.3-6.5)
Removal for:					
Bleeding/pain	5.1 (4.2-6.0)	9.6 (8.3-10.8)	12.9 (11.4-14.4)	17.4 (15.5-19.2)	20.8 (18.8-22.8)
Other medical reasons	1.0 (0.5-1.4)	2.4 (1.7-3.1)	3.4 (2.5-4.3)	4.4 (3.4-5.4)	6.1 (4.8-7.4)
Planned pregnancy	4.9 (4.0-5.8)	10.6 (9.2-11.9)	14.5 (12.9-16.2)	18.3 (16.4-20.1)	21.0 (19.0-23.0)
Personal reasons	2.2 (1.6-2.8)	5.3 (4.3-6.3)	9.6 (8.2-11.0)	13.4 (11.7-15.1)	19.3 (17.1-21.4)
Investigator's choice	0.0 (0.0-0.2)	0.3 (0.1-0.7)	2.2 (1.4-3.0)	10.2 (8.5-12.0)	32.0 (28.9-35.1)
Continuation rate	85.6	72.0	61.7	52.6	43.9
Lost to follow-up	3.0 (2.2-3.7)	4.3 (3.4-5.2)	5.4 (4.4-6.4)	6.9 (5.7-8.1)	9.0 (7.5-10.5)
Released from study	1.0 (0.6-1.4)	1.5 (1.0-2.0)	2.7 (2.0-3.5)	4.2 (3.2-5.2)	5.8 (4.5-7.1)

**Table 3 Interval insertion of the MLCu375. Gross cumulative life-table rates per 100 women at yearly intervals, according to parity (NP=nulliparas; P=parous women)**

	1 year		2 years		3 years		4 years		5 years	
	NP	P	NP	P	NP	P	NP	P	NP	P
Number enrolled	585	1,837								
Woman-months	6399	20 024	11 489	35 625	15 639	47 809	18 889	56 883	21 310	63 101
Events										
Pregnancy	0.4	0.4	2.2	1.2	2.8	1.6	3.9	2.0	3.9	2.5
Expulsion	2.0	2.6	2.7	3.3	3.6	3.9	4.2	5.3	4.8	5.6
Removal for:										
Bleeding/pain	5.8	4.9	9.3	9.6	12.3	13.1	17.3	17.4	19.7	21.2
Other medical reasons	1.9	0.7	3.7	1.9	5.6	2.7	6.6	3.4	7.1	5.9

**Table 4 Interval insertion of the MLCu375. Gross cumulative life-table rates per 100 women at yearly intervals, according to age**

	1 year		2 years		3 years		4 years		5 years	
	<31 years	>30 years	<31 years	>30 years	<31 years	>30 years	<31 years	>30 years	<31 years	>30 years
Number enrolled	1297	1125								
Woman-months	13 955	12 469	24 466	22 649	32 342	31 107	38 210	37 562	42 313	42 098
Events										
Pregnancy	0.1	0.2	1.9	1.0	2.4	1.3	3.5	1.5	3.8	2.0
Expulsion	3.5	1.2	4.2	2.0	4.9	2.6	5.6	4.2	6.0	4.7
Removal for:										
Bleeding/pain	5.7	4.4	10.4	8.7	14.2	11.6	19.2	15.5	22.4	19.2
Other medical reasons	1.0	0.9	3.0	1.7	4.3	2.5	5.4	3.4	6.4	5.8

rates lay close to 14%. The two IUD models showed excellent and comparable profiles of performance.

**Table 5 MLCu375: comparative multicenter trials**

<i>Study design</i>	<i>Models compared with the MLCu375</i>	<i>Reference</i>
Randomized	MLCu250, TCu200 TCu380Ag Fincoïd, Nova-T	Thiery <i>et al.</i> (unpublished) Cole <i>et al.</i> , 1985 [1] Timonen <i>et al.</i> , 1982 [2]
Non-randomized	MLCu250 (case-controlled study) MLCu250, MLCu250 mini, MLCu250 short	Thiery <i>et al.</i> (unpublished) van Os [3]

**Table 6 Random comparison of MLCu375 with MLCu250 and TCu200. Gross cumulative life-table rates per 100 women at 1 year (Thiery *et al.*, unpublished)**

<i>Event</i>	<i>MLCu375 (n=134)</i>	<i>MLCu250 (n=136)</i>	<i>TCu200 (n=134)</i>
Pregnancy	0	1.8	3.6
Expulsion	4.7	3.1	5.3
Removal for:			
Bleeding/pain	4.9	2.4	5.9
Other medical reasons	0.8	0	0

**Table 7 Random comparison of MLCu375 with TCu380Ag. Gross cumulative life-table rates per 100 women at 1 year [1]**

<i>Event</i>	<i>MLCu375 (n=740)</i>	<i>TCu380Ag (n=737)</i>
Pregnancy	0.8	0.3
Expulsion	4.1	3.3
Removal for:		
Bleeding/pain	3.8	3.8
Other medical reasons	0.8	0.1

Seven hospitals in Finland have published the results of a randomized trial of the MLCu375, the Fincoïd, and the Nova-T[2] (Table 8). At 1 year, cardinal event rates showed only small differences, except for the pregnancy rate, which was lowest for the high-load ML IUD model.

From these randomized comparative trials we conclude that first-year pregnancy rates were lowest for the MLCu375 and the TCu380Ag. Although expulsion rates for the MLCu375 vary between studies, random comparison of the MLCu250 and

**Table 8 Random comparison of MLCu375 with Fincoind and Nova-T. Gross cumulative life-table rates per 100 women at 1 year [2]**

<i>Event</i>	<i>MLCu375</i> ( <i>n</i> =324)	<i>Fincoind</i> ( <i>n</i> =333)	<i>Nova-T</i> ( <i>n</i> =346)
Pregnancy	0.4	1.1	2.0
Expulsion	9.2	8.1	6.7
Removal for:			
Bleeding/pain	9.9	11.9	9.3
Other medical reasons	0.8	1.3	2.0

the MLCu375 failed to indicate the greater likelihood of the latter to be expelled. Since the removal rates for bleeding/pain and other medical reasons found for the MLCu375 are similar to those for other devices, all the IUD models investigated are comparable in this respect.

#### Non-randomized trials

Van Os [3] analyzed data collected at different periods from a multicenter assessment of four ML models and found no conspicuous difference in performance between the MLCu375 and the MLCu250. To overcome the methodological bias inherent in this study, we applied the case-controlled approach. Each of the 455 recipients of an MLCu375 was matched for age, gravidity, and parity with a woman who had previously had an MLCu250 inserted by the same group of investigators at the same hospital (Thiery *et al.*, unpublished). In these matched pairs, the device had been inserted during the same month as the standard model, exactly 2 years

**Table 9 MLCu375. Case-controlled comparison with MLCu250. Gross cumulative life-table rates per 100 users at 1 and 2 years (Thiery *et al.*, unpublished)**

<i>Event</i>	<i>1 year</i>		<i>2 years</i>	
	<i>MLCu375</i> ( <i>n</i> =455)	<i>MLCu250</i> ( <i>n</i> =455)	<i>MLCu375</i>	<i>MLCu250</i>
Pregnancy	0.0	2.3	0.6	3.2
Expulsion	0.5	0.8	1.0	1.1
Removal for:				
Bleeding/pain	4.1	5.7	10.6	9.7
Other medical reasons	0.0	3.4	1.6	4.0

earlier. The results (Table 9) indicate that the lower failure rate of the MLCu375 persisted through the second year and that the other event rates were comparable for the two models, except that the MLCu375 was removed less often for medical reasons.

## Discussion

The high-load ML was designed primarily to enhance the effectiveness of the MLCu250 but also to improve the overall clinical performance and extend the intrauterine life expectancy of the standard ML model.

The results of the case-controlled and the randomized studies show that at 1 year the MLCu375 was more effective than the standard ML IUD and a variety of currently used T-devices (TCu200, Nova-T, and Fincoïd).

The randomized trial for which data beyond this 1-year period were available and our case-controlled study indicate that the lower failure rate of the MLCu375 (compared with the MLCu250) persists. However, the effectiveness of the two ML models shows a divergent time relationship. Whereas cumulative pregnancy rates for the MLCu250 show a rise already during the first year, this phenomenon is apparently delayed for the MLCu375. Van der Pas [4] drew attention to the similarity in the behavior of low-load (MLCu250, TCu200) and high-load (MLCu375, TCu220C) copper-bearing models and hypothesized that the contrasting temporal pattern shown by the two classes might be related to the mass rather than to the surface area of the copper. A greater copper mass would from the very beginning enhance leukotaxis and increase the copper-dissolution rate, which in turn would increase the clinical effectiveness of the device at both the uterine and the cervical levels. Although fascinating, this hypothesis has not been completely validated by recent findings, including the lack of evidence of divergent corrosion patterns for the MLCu250 and the MLCu375 [5,6] and the fact that the mean daily copper-dissolution rate of the MLCu375 is lower than that of the MLCu250 [7]. In contrast, we found a higher mean concentration of copper in the midcycle cervical mucus of women wearing the high-load ML IUD than in patients carrying the low-load model (Thiery *et al.*, unpublished).

Van Os's second objective in designing the MLCu375 was to extend the life span of the standard ML by using thicker copper wire. Whether this goal has been met is still unknown, and the answer will have to await the results of long-term clinical studies.

The available data do not indicate that the high-load ML is less well retained by the uterus than the standard model, nor is there any indication that the rate of specific side effects is higher in MLCu375 wearers. Admittedly the termination rates for this indication vary widely in randomized studies, but within a given trial they are similar for the devices assessed. Comparative studies show that removal rates for medical reasons, which include PID, do not vary widely for the IUD models assessed, and no cases of uterine perforation were mentioned in any of the reports or studies we analyzed.

## Conclusions

Our conclusions can be summarized in three points:

1. The MLCu375 may unequivocally be called an effective, safe, and well-tolerated IUD.

2. The MLCu375 is more effective than the standard ML model, without any change in the other cardinal event rates. For this reason we consider the high-load device to be an improved ML IUD.
3. There is a need for further studies to assess long-term performance and establish the effective life span of the MLCu375.

## References

1. Cole, L. P., Potts, D. M., Aranda, C., Behlilovic, B., Etman, S., Moreno, J. and Randic, L. (1985). An evaluation of the TCu380Ag and the MLCu375. *Fertil. Steril.* (in press)
2. Timonen, H., Nylander, P., Kivijarvi, A., Hirvonen, E., Kajanoja, P., Kaivola, S., Kotilainen, A., Savia, E., Saure, A., Lonnblad, R., Tevava, M., Venhola, M., Mannikko, H., Kaar, K. and Vierola, H. (1982). Comparative performance of three copper IUDs (MLCu375, Fincoid, and Nova-T) after one year's follow-up in randomized multicenter trial. *Contracept. Deliv. Syst.*, 3(3/4), abstr. 226
3. van Os, W. A. A. (1983). Experience with four different models of the ML intra-uterine device. *Contracept. Deliv. Syst.*, 4(4), abstr. 16
4. Van der Pas, H., Thiery, M. and van Os, W. A. A. (1984). Observations on the MLCu375. In: *Research in Family Planning*, V. Bonnar, ed., MTP Press Ltd., Lancaster, p. 129
5. Kosonen, A. and Thiery, M. (1982). Corrosion of filamentous intrauterine copper. The MLCu250 and the MLCu375. *Contraception*, 27, 85
6. Thiery, M. (1984). Metallic corrosion characteristics of IUDs. International Workshop on Intrauterine Contraception, Program for Applied Research on Fertility Regulation, Chicago, May 29-June 1
7. Drost, R. H., Maes, R. A. A. and Thiery, M. (1983). Copper release from the MLCu375 IUD. *IRCS Med. Sci.*, 11, 895

*MS received 4 Jan. 85.*

*Accepted for publication 18 Feb. 85.*

## Resumé

D'après les publications spécialisées de la littérature et d'après nos propres résultats concernant le stérilet MLCu375, le modèle ML fortement chargé est efficace, sûr et bien toléré. Il est plus efficace que le modèle MLCu250, tout en ne provoquant pas plus d'incidents. Nous considérons donc le modèle MLCu375 comme un progrès par rapport au modèle précédent.

## Resumen

Los informes en la literatura sobre anticonceptivos y nuestros propios datos concernientes al dispositivo intrauterino MLCu375, indican que este modelo de alta carga, es efectivo, seguro y bien tolerado. Este dispositivo es más efectivo que el MLCu250, sin aumento de los efectos colaterales más importantes. En consecuencia consideramos que el MLCu375 es un modelo ML mejorado.