PhD DISSERTATION

RARE CLINICAL EVENTS DURING LONG TERM INTRAUTERINE CONTRACEPTIVE DEVICE USE: ECTOPIC PREGNANCY AND CERVICAL MALIGNANCY

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ABBREVIATIONS

CCa	Cervical carcinoma
CRF	Case Report Form
CWMU	Cumulative Woman Month of Use
EP	Ectopic Pregnancy
FPC	Family Planning Center
HPV	Human Papilloma Virus
IUD	Intrauterine Contraceptive Device
LT	Life table
PI	Pearl Index
SE	Standard Error
USFDA	United States Food & Drug Administration

INTRODUCTION

The intrauterine contraception as a modern method of fertility control is the product of the twentieth century. Since the 1960s, the intrauterine contraceptive device has remained a generally safe, effective and useful form of contraception. The number of women using the device is growing slowly but steadily throughout the world.

Some of the original problems of IUD such as increased menstrual bleeding, expulsion of the device, pelvic infection as well as unwanted pregnancies have been reduced to a minimum, and promising new solutions are being tested.

In recent years, IUDs have been widely introduced all over the world. It is currently estimated that about 50-60 million women are wearing IUDs worldwide. They have been popular in the developing countries because most of them are inexpensive, easy to manufacture, ship and store, and can be inserted by trained medical staff members as well. In the early days of use, some of the side effects reported were the result of poor sterile techniques and insertion by not sufficiently trained individuals. This produced such backlash that a number of international programs that started off with great enthusiasm and wide acceptance had to be discontinued. However, IUDs continued to be used and, in fact, are receiving increased attention, particularly by older women in light of the new information on the increased risks of cardiovascular and other complications associated with the pill. Thus, while no device has been invented as yet that can be considered ideal, intrauterine contraception remains an important part of the contraceptive arsenal.

Large international comparisons continue to collect evidence that IUDs are both safe and effective for extended periods of time. In 1994, the USFDA approved the TCu-380A IUD for use of up to 10 years, recognizing it as the longest-lasting copper IUD. The TCu-380A is now the most widely available IUD, and one of the most effective methods of contraception ever developed. In large studies fewer than one women per 100 became pregnant in the first year of use and in the longest comparative study only 2.1 per 100 became pregnant in 10 years of use. [1]

Intrauterine devices have been used throughout the world for more than four decades. Millions of women have found them effective, safe and convenient. During the 1960s and 1970s, researchers developed the „second generation" copper-bearing IUDs, which were highly effective, long lasting and had fewer side effects than the earlier models. Now that these improved IUDs have been thoroughly tested, attention is shifting toward identifying appropriate IUD users and providing good-quality medical care and counseling to maximize effectiveness, safety, and acceptability [1].

The first modern IUDs – the Lippes Loop and the Margulies spiral – appeared in the early 1960s. They were made of polyethylene, a biologically inert plastic [2,3]. In the late 1960s, researchers discovered that adding copper to a plastic IUD frame increased effectiveness, thus allowing sizes smaller than the all plastic devices. The first copper IUDs – the Cu-7 and TCu-200 – proved to cause fewer side effects such as pain and bleeding and are just as effective in preventing pregnancy [4,5]. It was thought that time these IUDs would have to be replaced every few years. Therefore, the second generation of copper IUDs was developed further. The result was a new series of devices including the TCu-380A, the TCu-220C, the Nova T, the Multiload 250 and 375 (MLCu-250, MLCu-375), and others. These IUDs last longer, and are

even more effective. IUDs that release a hormone in the uterus also were developed in the 1970s [6,7]. The TCu-380A is now the most widely available IUD distributed in more than 70 countries [8].

Up to now countless publications provide substantial detail on IUD performance, types of devices and made comparisons among different IUDs, but relatively few evaluated rare events with IUDs as this could be studied only in large population samples. The aim of this twin study is to focus on mainly two rare clinical events: ectopic pregnancy and cervical carcinoma in women wearing intrauterine contraceptive device.

Ectopic Pregnancy. In 1965, Lippes [9] reported 4 (17.4%) ectopic pregnancies among women who had become pregnant with the Lippes Loop in situ. Researchers unanimously found an increased incidence of ectopic pregnancy during the next 20 years [10-16]. Although extensive research has been carried out on this topic, there are still some questions relating to the use of IUDs and the risk of ectopic pregnancy. The incidence of EP among users of non-medicated and medicated (copper-containing) IUD who become pregnant with their IUD in situ is still to be evaluated. In this study the incidence of ectopic pregnancy among these two groups was compared.

Cervical Carcinoma. According to official statistics, in the year 2000, malignant tumors accounted for 6.2 million (12 %) of the nearly 56 million deaths worldwide from all causes, and cervical cancer was among the 20 most common cancers worldwide [17]. HPV infection is reported to be the strongest risk factor for cervical intraepithelial neoplasia, however, contraceptive and reproductive risk factors have also been found to play a role in this disease [18].

It is now widely accepted that intrauterine contraceptive devices are not implicated in carcinogenesis [19-22]. This is further supported by results from over a 100 million users worldwide [23]. Even so, there are meager data from in situ human IUD use [19,24], moreover many of them are case reports and rather old observations.

The relatively low number of publications on the topic may indicate that the concept of no-correlation between the IUD and cervical carcinoma is now accepted, and no further investigations are necessary in this field. But in contradiction to this there still are conflicting opinions, including case studies [18,19,25], which suggest different effects of non-medicated and copper-containing devices on the development of cervical malignancy.

The controversies could be attributed to the different approaches used to address this question. Namely, most of the previously published reports are population based observations, meta-analysis or multi-center case control studies having relatively low number of cases and short follow-up periods. As cervical carcinoma is a relatively rare event, only a high number of directly observable cases with different type of IUDs and a long follow-up period would enable us to conclude on the role of IUD in cervical malignancy.

MATERIALS AND METHODS

Ectopic Pregnancy

Study period. Data collected between 1986 and 1999 at the Family Planning Center, Department of Obstetrics and Gynecology, University Medical School of Debrecen were analyzed in this study. Devices inserted at the request of patients in the routine daily practice and IUDs used by volunteers in different clinical trials were included in the evaluation of the pooled data. All studies involved in this work had had the approval of the local institutional ethics board before the recruitment of cases. The ectopic pregnancy rates of a non-medicated IUD were compared to that of some copper-containing devices.

Devices. During the early years of the observational period only one plastic device was available for intrauterine contraception in Hungary (Figure 1), and it was later withdrawn from the market. This constituted the group of the non-medicated devices. The loop like Hungarian *Szontágh IUD* was made of a simple nylon fishing line of 1 mm in diameter that had a tail of 0.1 mm in diameter. This design provided proper flexibility in two dimensions, and fitted all sizes of uteri well.

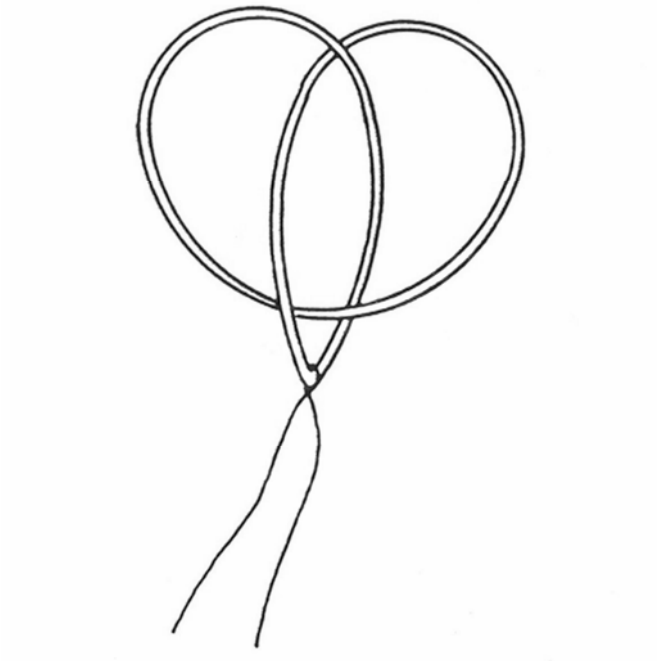

Figure 1. Szontágh IUD

Copper IUDs included the well-known Copper T series, the Nova T and MLCu devices (with 250 and 375 mm^2 of copper) as well as the SilverLily and GoldLily. The two latter Hungarian devices (Figure 2) are similar in format to the Nova T, but the wire wound around the vertical plastic stem of the IUD is made of copper-silver and copper-gold alloy, respectively. In the later phase of the study mostly these medicated devices were inserted.

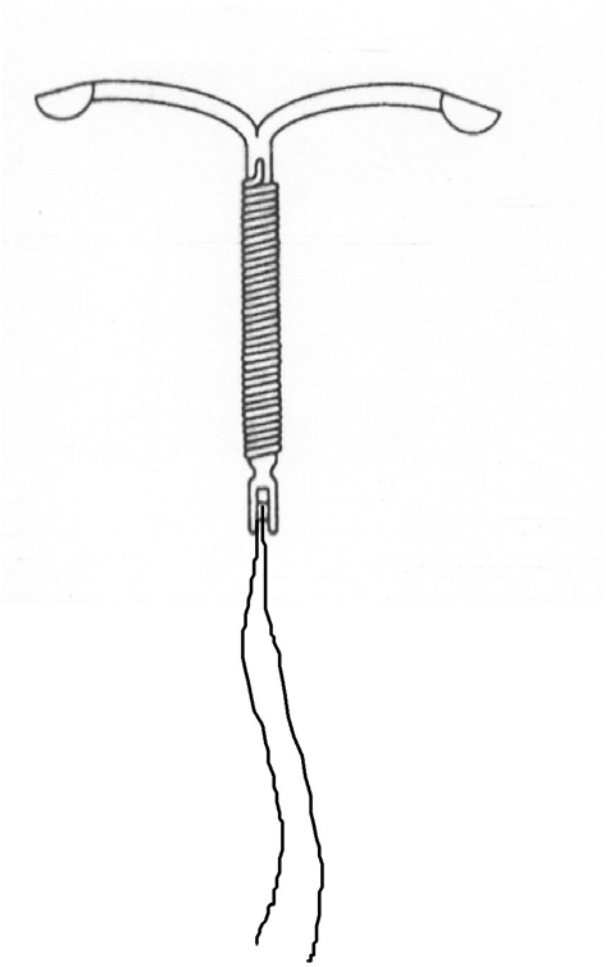

Figure 2. SilverLily/GoldLily IUD

Candidates were parous women requesting intrauterine contraception regardless of previous IUD use and having no contraindications. The main patient characteristics are shown in Table 1. There were no statistically significant differences between the two groups.

Table 1. Patient characteristics of the EP Study

Characteristics	Non-medicated IUDs	Medicated IUDs
Mean age (years)	30.7	31.8
Mean parity (n)	2.2	2.0
Mean induced abortion (n)	0.8	0.8
Mean spontaneous abortion (n)	0.2	0.2

Insertion and follow-up. Insertions in both the EP and the CCa study were carried out during the interval period. Neither immediate post-abortal nor post-partal insertions were included in the studies. Follow-ups were scheduled at 1, 6, and 12 months after insertion and annually thereafter. Unscheduled checkups were performed if problems arose.

The total number of insertions was 3,491 and 11,682 for non-medicated and medicated devices, respectively, and the devices were not changed routinely for time reason during the observation period. The study characteristics are shown in Table 2.

Table 2. Main characteristics of the EP study

Characteristics	Non-medicated (Szontagh) IUD	Medicated (Copper) IUDs
No. of insertions	3,491	11,682
No. of patients at risk (10 years)	550	569
CWMU (10 years)	180,151	463,890
CWMU (total)	191,678	473,533
Relevant terminations (10 years)*	70.4	60.2

* Gross cumulative lifetable termination rates per 100 users

Study design. Special CRFs designed by the FPC (Annex I) for insertion and follow-ups were filled in for each IUD user at the time of examination. Data collected on these forms were immediately stored in and later evaluated by computer using software partly developed by the Center.

Statistical evaluation. For comparing the two groups and the different follow-up periods (ordinal years), lifetable rates were calculated with the lifetable program of the International Fertility Research Program (now known as the Family Health International) [26] as suggested by Tietze and Lewit [27]. This study uses the gross cumulative rates. Pearl-index (PI) was also calculated in order to make the results comparable to literature data. Since EP occurs less frequently than other terminations characteristic for intrauterine devices, the rates were calculated for 1,000 users instead of 100 users. Statistical differences were measured by Chi-square test [28] and were regarded as significant at p value ≤ 0.05.

Besides ectopic pregnancy, we studied the occurrence of intrauterine pregnancy, the terminations for other competing risks (expulsion, removals for bleeding/pain, other medical and personal reasons) and non-competing risks (removal for investigator's choice, moved, died, lost to follow-up) as well, but this part of the work evaluates and discusses the rates of ectopic pregnancy only.

Cervical Carcinoma

Study period. Data collected between 1977 and 2003 at the FPC were analyzed in this evaluation. The composition of the pooled data of different devices was the same as described in the previous section of ectopic pregnancy.

The aim was to compare the incidence of premalignant and malignant cervical conditions during a period of ten years of use of non-medicated and medicated (copper-containing) IUDs.

Devices. The Szontágh IUD (see its description above) constituted the group of the non-medicated devices. As it was used in the first years of the study period, the number of the cases with this device was less.

The medicated IUDs included only the above-mentioned copper devices. Hormone containing devices (Progestasert, Mirena), due to their different entity, cannot be pooled with the copper-containing IUDs and were excluded from the observation. Another reason for not including them was the relatively small size of the user group: the total number of these cases was less than 1000, leaving them ineligible for reliable evaluation.

Candidates were also parous women requesting intrauterine contraception regardless of the previous IUD use and having no contraindications. Table 3 shows the patient characteristics. There were no statistically significant differences between the two groups.

Table 3. Patient characteristics of the CCa Study

Characteristics	Non-medicated IUDs (n = 3,536)	Copper-containing IUDs (n = 13,518)
Mean age (years)	32.75	32.56
Mean parity (n)	2.17	1.95
Mean induced abortion (n)	0.94	0.97
Mean spontaneous abortion (n)	0.23	0.19

The total number of insertions was 3,536 and 13,518 for non-medicated and medicated devices, respectively (Table 3-4).

All patients were followed by the same center as described earlier; and as such – according to our knowledge – this is the first study that has the highest number of patients addressing the question of cervical abnormalities in IUD users. (Previous results were derived either from smaller samples, or have been achieved using meta-analysis or population-based case-control observations.) The follow-up of 10 years means that the same user was followed for 10 years with the same device in place.

Screening for cervical pathology. Colposcopy and oncocytology was performed at insertion and at the yearly follow-ups. More frequent (six-monthly) screening was done in case of a colposcopic alteration if it was not combined with pathological cytology. Abnormal Pap smear (≥PIII) necessitated another sample taken and evaluated as soon as suggested by the cytologist. In case of a repeated positive result (with or without coploscopic alteration) biopsy was indicated and histopathology was performed. Although the Bethesda system has been used in the department for years, we applied the Papanicolaou method exclusively in this work, since in the 1970s and 1980s only this technique was available for oncocytological classification.

Study design. An earlier version of the CRFs developed by the FPC (Annex II) were used for the cases collected between 1977 and 1986. The two types of CRFs show no significant differences and they were filled in for each IUD user at the time of examination. The data collected on these forms were handled as already detailed above. This study is not randomized since only a small percentage of the users belonged to a randomized study pool and the remainder were routine out-patients who used a self chosen device.

Table 4 Main characteristics of the CCa Study

Ordinal Months	Non-medicated IUD users (n = 3,536)			Copper/containing IUD users (n = 13,518)		
	No. of patients at risk	CWMU	Terminations for all competing risks*	No. of patients at risk	CWMU	Terminations for all competing risks*
12	2,464	33,848	205.6	8,705	120,924	122.5
24	1,992	59,921	327.8	6,791	211,842	236.8
36	1,652	81,371	422.6	5,374	283,010	325.3
48	1,404	99,408	488.5	4,247	339,587	399.8
60	1,205	114,886	542.7	3,318	383,980	461.4
72	1,017	128,007	597.1	2,568	418,578	516.8
84	884	139,298	634.9	1,966	445,061	568.1
96	737	148,837	680.4	1,548	465,619	606.1
108	614	156,835	719.3	1,141	481,228	652.1
120	513	163,567	754.6	846	492,836	688.2

CWMU: Cumulative women month of use *calculated for 1000 users

Statistical evaluation. For comparing the two groups and the different follow-up periods (at the end of each ordinal year), net (multiple-decrement) and gross (single-decrement) cumulative lifetable rates were calculated [26,27]. Since IUD removals for cervical abnormalities occur less frequently than other terminations characteristic for intrauterine devices, the rates were also calculated for 1,000 users (instead of 100 users). Statistical differences were measured by Chi-square test [28] and were regarded as significant at p value ≤ 0.05.

On a routine basis here we also studied terminations for other competing risks (pregnancy, expulsion, removals for bleeding/pain, and other medical and personal reasons) and non-competing risks (removals due to investigator's choice, moved, death, lost to follow-up) as well, but the thesis evaluates and discusses the rates of pre-malignant and malignant cervical conditions only.

RESULTS

Results of this study were obtained after 10 years of clinical follow-up period from one center. The high number of cases (more than 15,000 in the EP and more than 17,000 in the CCa study) and the long follow-up period (10 years) yielded a very high number of woman-year of use: 53,670 and 54,700, respectively. The number of those at risk at ten years is more than 500 in either subgroup. This is eligible to draw a statistically valid conclusion for both ectopic pregnancy and cervical carcinoma of the uterus in IUD users.

Ectopic Pregnancy

The longest observation period was 169 months, but because the number of the cases eligible for statistical evaluation significantly dropped after the 120th month, we evaluated the first 10 years only.

The total number of the devices still in use at the end of the 10th year was 550 and 569 for the Szontágh and the copper devices, respectively (see Table 2). The maximum CWMU was 191,678 among the non-medicated IUD users, and 473,533 for the copper devices. At the end of the 10th year it was 180,151 and 463,890, respectively.

The total number of ectopic pregnancies during the follow-up period among the non-medicated IUD users was 13 and among those who used medicated IUDs was 40 (Table 5). The table shows other terminations as well but this paper evaluates the EP only. After the seventh year, there was no ectopic pregnancy in the non-medicated IUD group. Among the copper IUD users this type of conception occurred in the first six years and only in the ninth one thereafter.

Table 5. Type of terminations and cumulative woman-month of use (EP)

Period (years)	Non-medicated (Szontagh) IUD					Medicated (Copper) IUDs				
	Ectopic Pregnancy	Intrauterine Pregnancy	Other Competing Risks	Other Non-competing Risks	Annual WMU*	Ectopic Pregnancy	Intrauterine Pregnancy	Other Competing Risks	Other Non-competing Risks	Annual WMU*
	Number of terminations					Number of terminations				
1	4	138	503	243	35,924	9	136	956	2,135	118,970
2	2	98	261	94	28,302	8	126	758	1,169	88,930
3	2	54	209	85	23,604	12	80	480	858	67,968
4	2	31	146	76	20,016	3	44	360	665	52,736
5	1	22	112	65	17,329	2	23	265	586	41,224
6	1	12	124	60	14,950	4	21	202	538	31,523
7	1	4	85	68	12,918	0	13	151	386	23,467
8	0	6	94	70	10,821	0	3	96	323	17,804
9	0	1	73	68	8,978	2	5	90	311	12,805
10	0	9	55	85	7,309	0	3	48	274	8,463
11	0	4	42	110	5,378	0	4	19	218	4,829
12	0	1	34	117	3,567	0	0	15	112	2,722
13	0	1	21	93	1,974	0	0	13	64	1,561
14	0	0	6	93	603	0	0	7	78	524
14+	0	0	0	5	5	0	0	1	6	7
Total	13	381	1,765	1,332	191,678	40	458	3,461	7,723	473,533

* WMU = woman-month of use

The gross cumulative lifetable rates calculated for 1,000 users are shown in Table 6. These were 1.4 and 0.9 at the end of the first year, and 6.8 and 8.9 at ten years for the non-medicated and the copper IUDs, respectively. There were no statistically significant differences in the rates during the first 10 years of follow-up.

Table 6. Ectopic Pregnancy: cumulative gross lifetable rates per 1,000 users (EP)

Period (months)	Non-medicated (Szontagh) IUD	Medicated (Copper) IUDs	Chi-square	p
12	1.4	0.9	0.01	0.754
24	2.3	2.0	0.00	0.976
36	3.3	4.1	0.05	0.831
48	4.4	4.8	0.00	0.997
60	5.1	5.4	0.00	0.948
72	5.9	6.9	0.02	0.896
84	6.8	6.9	0.00	0.941
96	6.8	6.9	0.00	0.941
108	6.8	8.9	13 0.04	0.850
120	6.8	8.9	0.04	0.850

The PI calculated for the total follow-up period of 169 months was 0.8 and 1.0 per 1,000 non-medicated and medicated IUD users, respectively (Table 7). The annual figures are also shown in Table 7. Apart from some fluctuation the PI remained in the same range (1-2/1,000) in both groups without statistically significant difference.

Table 7. Annual and over-all ectopic pregnancy rates (Pearl Indices per 1,000 users)(EP)

Period (months)	Non-medicated (Szontagh) IUD	Medicated (Copper) IUDs	χ^2	p
1-12	1.3	0.9	0.442	>0.50
13-24	0.8	1.1	0.068	>0.50
25-36	1.0	2.1	0.845	>0.50
37-48	1.2	0.7	0.466	>0.50
49-60	0.7	0.6	0.037	>0.50
61-72	0.8	1.5	0.265	>0.50
73-84	0.9	0.0	1.989	0.5-0.1
85-96	0.0	0.0	n.a.	>0.50
97-108	0.0	1.9	1.268	0.5-0.1
109-120	0.0	0.0	0.442	0.5-0.1
121-132	0.0	0.0	n.a.	n.a.
132-144	0.0	0.0	n.a.	n.a.
145-156	0.0	0.0	n.a.	n.a.
157-168	0.0	0.0	n.a.	n.a.
1-169	0.8	1.0	0.069	>0.50

Based on these figures it can be concluded that there were no statistically significant differences in the rates of termination due to ectopic pregnancy between the two groups throughout the follow-up period of ten years. It is noteworthy that the devices, even the

copper IUDs, were not changed during the observation period. It means that the calculated rates relate to the same device, consequently, the copper loss did not increase the occurrence of ectopic pregnancy. On the contrary, the trend of the rates decreased parallel with the duration of use.

Cervical carcinoma

The basic study characteristics are mentioned in Table 4. The total number of devices still in use at the end of the 120th ordinal month was 513 and 846 for the non-medicated and the medicated devices, respectively. The CWMU was 180,989 and 514,464 in the two groups at the end of the longest observation period (199 months for the non-medicated and 204 for the medicated IUDs), and 163,567 and 492,836 at ten years. Since the number of observable cases beyond this point decreases below the level of a statistically credible evaluation [27], we studied only the first ten years of follow-up and did calculate life table rates for this period.

Table 8 shows the number of terminations due to the different types of cervical abnormalities and all other related terminations (pregnancy, expulsion, removal for personal and medical reasons other than suspected cervical pre-malignancy/malignancy) for the two groups. Cervical pathologies were divided into 5 categories, and their distribution is detailed by duration of follow-up in the table.

The total number of terminations due to suspected cervical abnormalities at the end of the 10th year of follow up was 33 in the group of the non-medicated IUDs (see Table 8). The gross cumulative life table rate calculated for 1,000 users was 26.1 (SE 10.8). The same number among the medicated IUD users was 138 terminations and the corresponding gross cumulative rate was 37.8 (SE 8.3).

Table 8 Number of terminations by time due to cervical abnormalities by type of IUD (CCa)

Follow-up period (months)	Terminations for suspected cervical pathology												Other related terminations	
	Histology not done		Negative histology		Cervical dysplasia		Carcinoma in situ		Invasive carcinoma		Total			
	Non-med IUD	Cu IUDs	Non-med IUD	Cu IUDs	Non-med IUD	Cu IUDs	Non-med IUD	Cu IUDs	Non-med IUD	Cu IUDs	Non-med IUD	Cu IUDs	Non-med IUD	Cu IUDs
1-12	1	6	3	5	1	5	1	4	0	0	6	20	645	1,267
13-24	1	3	1	7	1	15	0	7	0	1	3	33	360	1,014
25-36	2	2	0	3	2	6	0	2	0	1	4	14	267	712
37-48	1	0	3	4	1	5	0	4	0	0	5	13	177	535
49-60	0	1	2	5	2	12	0	2	1	1	5	21	139	375
61-72	0	0	0	6	1	2	1	3	0	2	2	13	136	297
73-84	0	2	0	2	1	2	0	2	0	1	1	9	91	237
85-96	1	0	0	2	2	3	0	0	0	0	3	5	103	151
97-108	1	2	0	1	1	2	0	1	0	0	2	6	84	154
109-120	0	0	0	3	0	1	0	0	2	0	2	4	72	101
Total	7	16	9	38	12	53	2	25	3	6	33	138	2,074	4,843

Since the first two termination types ('Histology not done' and 'Negative histology') seen in Table 8 did not prove any real oncopathological alterations of the cervix, they are not detailed here just the corresponding LT figures are shown in Table 9 and 10. Their terminology, however, needs to be clarified.

Histology not done. This pertains to those removals that took place for suspicion of cervical abnormality, but on later evaluation the repeated Pap smear examination reported no signs of malignancy and histology was not performed because of this.

Negative histology. This means those terminations where removals were made for suspicion of cervical abnormality upon colposcopy and/or oncocytology but the histolopathology showed no signs of malignancy.

Dysplasia.

It was coded as a type of termination when following an IUD removal biopsy was performed and the histopathology reported dysplasia. This category is used as a single entity in our work and was not sub-classified since staging of dysplasia was not available in the earlier periods of the study. Twelve cases were recorded among the non-medicated IUD users in ten years (Table 8); the cumulative net and gross life table termination rates (with SE) at the end of the observation period were 4.6 (1.3) and 10.1 (3.1), respectively. Table 9 and Figure 3 show rates also for the earlier years of follow-up. In the copper-containing IUD group there were 53 terminations for dysplasia (Table 8). The corresponding net and gross cumulative termination rates were 7.8 (1.1) and 13.8 (2.3), respectively (Table 10 and Figure 3). The differences between the two groups were not statistically significant ($\chi^2 = 1.322$, $p > 0.10$).

Table 9 Net cumulative termination rates (with SE) by duration of use among non-medicated IUD users calculated for 1000 women.(CCa)

Terminations	Duration of use (years)									
	1	2	3	4	5	6	7	8	9	10
Histology not done	0.3 (0.3)	0.7 (0.5)	1.4 (0.7)	1.7 (0.8)	1.7 (0.8)	1.7 (0.8)	1.7 (0.8)	2.2 (0.9)	2.6 (1.0)	2.6 (1.0)
Negative histology	0.9 (0.5)	1.3 (0.6)	1.3 (0.6)	2.4 (0.9)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)
Dysplasia	0.3 (0.3)	0.7 (0.5)	1.4 (0.7)	1.7 (0.8)	2.5 (0.9)	2.9 (1.0)	3.3 (1.1)	4.1 (1.2)	4.6 (1.3)	4.6 (1.3)
Carcinoma in situ	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.7 (0.3)	0.7 (0.5)	0.7 (0.5)	0.7 (0.5)	0.7 (0.5)
Invasive carcinoma	0	0	0	0	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	1.3 (0.8)
Other related terminations	203.7 (7.2)	324.9 (8.5)	418.2 (9.1)	482.4 (9.3)	534.6 (9.4)	588.3 (9.4)	625.7 (9.3)	669.9 (9.2)	707.9 (9.0)	742.2 (8.9)

Table 10 Net cumulative termination rates (with SE) by duration of use among copper-containing IUD users calculated for 1000 women.

Terminations	Duration of use (years)									
	1	2	3	4	5	6	7	8	9	10
Histology not done	0.6 (0.3)	0.9 (0.3)	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)	1.3 (0.4)	1.7 (0.5)	1.7 (0.5)	2.3 (0.6)	2.3 (0.6)
Negative histology	0.5 (0.2)	1.3 (0.4)	1.6 (0.4)	2.2 (0.5)	3 (0.6)	4.1 (0.8)	4.5 (0.8)	4.9 (0.9)	5.2 (0.9)	6.3 (1.1)
Dysplasia	0.5 (0.2)	2.1 (0.5)	2.8 (0.6)	3.5 (0.6)	5.4 (0.8)	5.8 (0.9)	6.2 (0.9)	6.9 (1.0)	7.5 (1.1)	7.8 (1.1)
Carcinoma in situ	0.4 (0.2)	1.1 (0.3)	1.4 (0.4)	1.9 (0.5)	2.3 (0.5)	2.8 (0.6)	3.2 (0.7)	3.2 (0.7)	3.5 (0.7)	3.5 (0.7)
Invasive carcinoma	0	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.4 (0.2)	0.7 (0.3)	0.9 (0.4)	0.9 (0.4)	0.9 (0.4)	0.9 (0.4)
Other related terminations	120.5 (3.2)	231.2 (4.3)	318 (4.9)	390.8 (5.3)	449.1 (5.6)	502.2 (5.8)	551.6 (6.1)	588.3 (6.3)	632.6 (6.6)	667.3 (6.8)

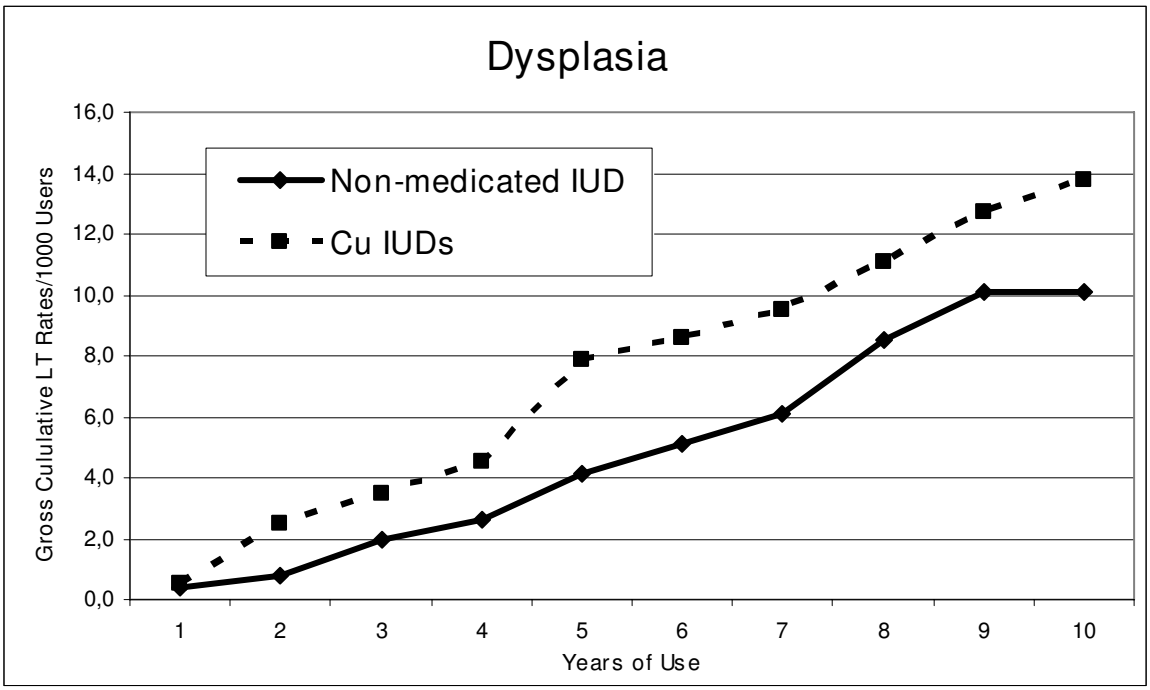

Figure 3

Carcinoma in situ.

These were the terminations that were histologically confirmed by biopsy as "Carcinoma cervicis uteri St 0" (CIS). Only two cases were recorded in the non-medicated group: one in the first and another in the sixth year (Table 8). The corresponding net and gross cumulative termination rates (with SE) were 0.3 (0.3) and 0.4 (0.4) in the first, and 0.7 (0.5) and 1.3 (1.1) in the sixth year remaining steady until the end of the study period (Table 9 and Figure 4). Twenty five medicated devices were removed for CIS (Table 8) giving a 3.5 (0.7) net and 5.9 (1.4) gross cumulative life table termination rate at the end of the study period Table 10 and Figure 4). Again, there were no statistically significant differences between the two groups (χ^2 = 3.494, p >0.10).

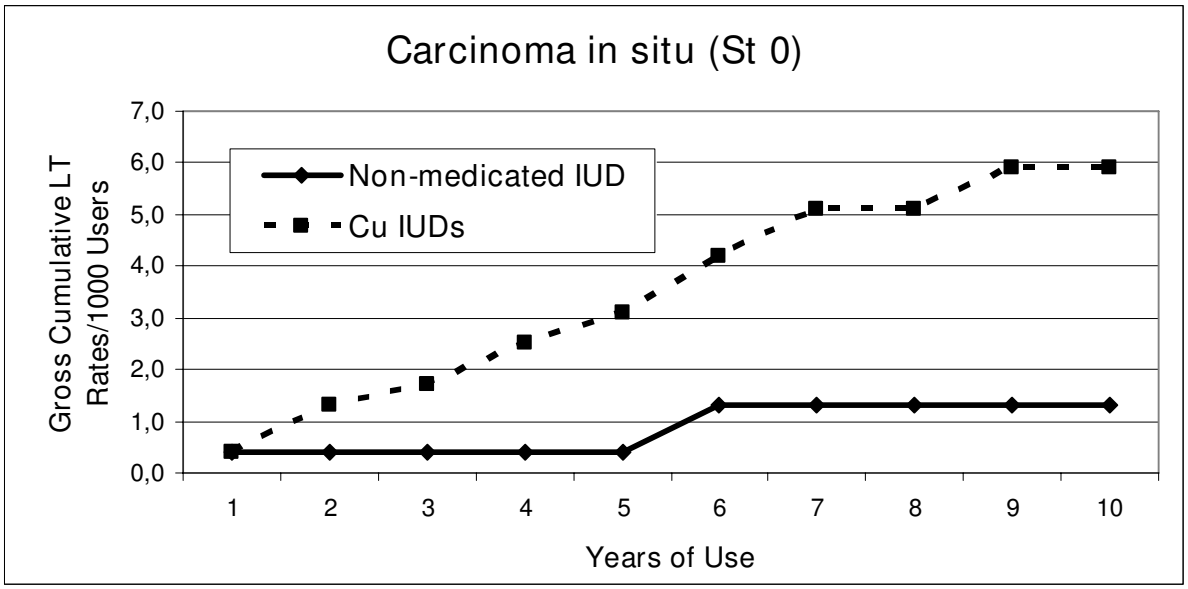

Figure 4

Invasive carcinoma.

Terminations for histologically confirmed invasive cervical malignancy were recorded in the non-medicated group only after the fourth year of the observation period. Three cases were reported: one in the fifth and two in the tenth year (Table 8). The net and gross cumulative termination rates (with SE) at the end of the study period were 1.3 (0.8) and 4.2 (2.5), respectively (Table 9 and Figure 5). Six cases of invasive carcinoma were found among the medicated IUD users (Table 8). The corresponding net and gross cumulative termination rates at seven years were 0.9 (0.4) and 1.7 (0.7), respectively, and remained at the same level up to the tenth year since no more cases were recorded in the last three years (Table 10 and Figure 5). Although these figures are lower than that of the non-medicated devices the difference was not statistically significant ($\chi^2 = 0.002$, $p>0.10$).

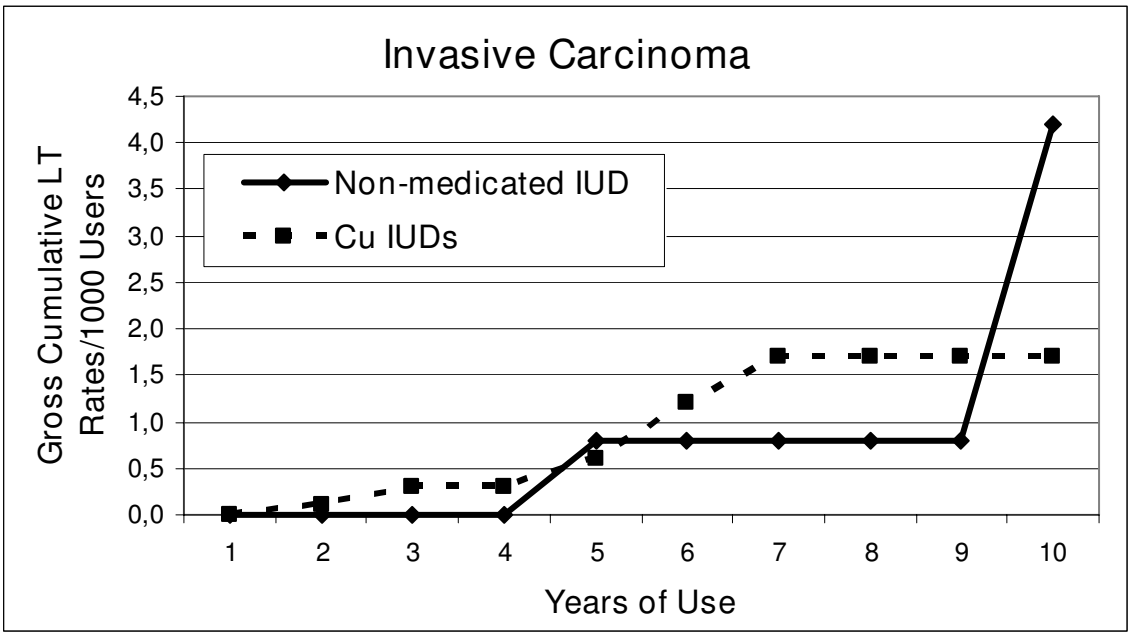

Figure 5

Not only were the end-study life table rates of terminations for suspected cervical malignancy similar in the two groups. We also could not find any statistically significant differences when the figures of each ordinal year were compared.

DISCUSSION

Ectopic Pregnancy. Snowden [29] was among the first who raised the question of the increased risk of ectopic pregnancy among IUD users. The USFDA held a special meeting in 1978 to evaluate the ectopic pregnancy rate associated with the use of different types of IUD [30]. These data showed that users of the Progestasert had the highest risk of ectopic pregnancy and users of copper-bearing IUDs had the lowest. The non-medicated IUD users fell in-between the two groups.

Ectopic pregnancy is a relatively rare event. To approximate its frequency a large number of studies on IUDs were reviewed by Edelman and Porter [31]. They pooled the data to give an overall estimate of ectopic pregnancy rates for users of different types of IUD. There was little difference between the rates for the copper bearing (0.08-0.09) and non-medicated IUDs (0.09 - 0.13) per 100 women-years, and both of these rates were lower than the rate of Progestasert (0.38 per 100 woman-years).

The present paper evaluates altogether more than 15,000 cases and 55,434 woman-years from one center which is eligible to draw a statistically valid conclusion. Although our database has hormone-containing devices (Progestasert and Levonorgestrel [LNG]-containing IUD) these were not included in this evaluation for the following reasons. The number of the Progestasert users is too few for making a reliable evaluation. Although the number of the LNG-IUD (Mirena) cases exceeds 500, these devices were changed routinely after 5 years, and in a 10-year observation period (2x5 years) no pregnancy (neither intrauterine nor ectopic) was recorded among the users. In this way the LNG-IUD group is also not suitable for studying the role of the device in a possible ectopic implantation. As such, both hormone-containing IUDs were excluded from this evaluation.

Our results show that the gross cumulative life table rates of ectopic pregnancy calculated for 1,000 users were similar in the two groups: 1.4 and 0.9 at the end of the first year, and 6.8 and 8.9 at ten years for the non-medicated and the copper IUDs, respectively. There were no statistically significant differences in the rates during the first 10 years of follow-up. The Pearl Index also calculated for 1,000 users per year was 0.8 and 1.0, respectively. Our findings are in agreement with those of Edelman and Porter [31] but in contrary to those published by the USFDA [30], which suggests that, the copper-containing IUDs may have a lower risk for ectopic pregnancy than the non-medicated ones.

Evaluating the role of IUDs in EP, Treiman and co-workers [32] refer to several studies in which different types of devices were used. The problem with these publications in general, even with the major and randomized clinical trials, is that the number of cases is relatively low and the duration of observation is relatively short. Meta-analysis would solve this problem, but potential publication biases in these cases may involve further difficulties in drawing definite conclusion. This has been disputed even in literature [33,34]. According to our knowledge, the present publication is unique since it is from a large data base (more than 15,000 cases), it comes from a single center (presumably with less biases), the evaluated follow-up period is long (ten years), and the calculated EP rates relate to the same IUD (devices were not changed during the observational period). Consequently, the results may stand the closest to reality.

In conclusion, based on the evaluation of this clinical study, there were no statistically significant differences in the ectopic pregnancy rates between the non-medicated (Szontágh) and the copper IUD users, although the gross cumulative lifetable rates for the Szontágh IUD were lower in the majority of the observations. Parallel with the duration of IUD use the

overall tendency in the occurrence of EP was decreasing which suggests that the duration of use may not be a risk factor for extrauterine implantation of the fertilized ova.

Cervical Carcinoma. Since most of the literature suggests that the incidence of cervical abnormalities among IUD users is not higher than non-users our aims were to find any difference in these pathologies between the medicated and the non-medicated device users.

Although there are reported incidences of epidermoid carcinoma and sarcoma from animal studies after IUD insertion by studies run 2-3 decades ago [35,36]. These results are not readily applicable to human cases [20], since Rhesus monkeys, closely related to humans, showed no increased incidence of uterine malignancies upon IUD use [37].

Lassise et al [25] in a case control study suggested that copper IUDs offer some protection against cervical cancer, their reduction in risk to about 60% was not statistically significant. Even in the very early period of the IUD use it has been demonstrated that inert devices have no influence in the genesis of cervical carcinoma [38].

In a retrospective study by Sandmire et al [39], no increased incidence of cervical carcinoma was reported in IUD users as compared to controls (non users), and there was no increase in incidence with duration of use. But their study was biased by methodological problems and they did not detail the types of IUDs studied. In another South American study [40], no increased incidence of cervical carcinoma among Lippes Loop IUD users was noted as compared to those using long acting progestogens. In a Chinese study [41], IUD use was associated with a decreased risk of cervical carcinoma attributed mainly to the frequent Pap smear examinations in this population. British authors [42] reported a higher prevalence of

cervical intraepithelial neoplasia among IUD users as compared to non users, and they too demanded further investigation. Some other surveys [43-45], have found no relationship between IUD use and dysplasia. No dysplasia was found in women using Lippes Loop from 4 [43] to 12 years [44] but the same authors [45] reported a small number of cases with cervical abnormalities among copper IUD users after 4-8 years of use. In another large study in Japan [46] no in situ or invasive carcinoma was found among IUD users as compared to non-users after 5-10 years of use. In a prospective 5-year follow up of IUD users in New Zealand [47], no difference in risk of cervical dysplasia was found between users of IUD, OC or depot medroxyprogesterone acetate.

The above results are derived either from smaller samples or have been achieved using meta-analysis. In our study all patients got the IUD and were followed up in the same center, and as to our knowledge this is the first study that has the highest number of patients addressing cervical abnormalities in non-medicated and medicated IUD users.

It is suggested that the development of cervical carcinoma usually takes several years [42], and continued assessment of women using IUDs for 10 years or more is required to confirm the safety of IUDs. In our study the same user was followed for 10 years with the same device in place, as such we can state that copper-containing devices cause no increase in the incidence of cervical carcinoma even upon prolonged use compared to plastic IUDs.

It needs mention that long term use of IUD is often associated with exfoliation of atypical cells [48-50]. These cells are commonly observed in gynecological preparations and can cause considerable difficulty in their correct interpretation, even having been mistaken to represent adenocarcinoma, epidermoid carcinoma and other serious lesions [48-50]. Acknowledging

these considerations, the incidence of cervical abnormalities among our IUD users is still very low and there is no difference between non-medicated and medicated IUDs. There are findings suggesting that in women with dysplasia a later diagnosis of carcinoma in situ is six times more common after five years of use of the oral contraceptive pill than that in a comparable group of patients using IUD for five years [51].

We were not in the position to compare our data to a nonuser population since there is no such database (with comparable group of women without IUD followed-up to ten years) that could be used for this purpose. The incidence among users may well be lower than that in nonusers since the users are regularly and stringently followed up. This was shown by an earlier report published from our department [52]. Although there may be demographic data showing the incidence of cervical abnormalities in the general population, they are usually biased and the mode of data collection not standardized. Apart from this any cervical abnormalities that may arise with IUD in place are not represented separately in such demographic data.

Based on this, it is concluded that the copper-containing intrauterine contraceptive devices do not have either an increased or a decreased risk of cervical cancer than the non-medicated (Szontágh) IUDs have.

SUMMARY

The Family Planning Centre of the Department of Obstetrics and Gynecology, University of Debrecen having more than 45,000 IUD cases provided a unique opportunity to study and evaluate the incidence of rare clinical events associated with long-term IUD use. Keeping in mind to get statistically valid results of such rare events, I have selected ectopic pregnancy and cervical carcinoma as the main focus of my Ph.D thesis. Since the incidence of these two rare events is in a minimum of magnitude of thousandth, statistical evaluations are valid provided with large number of cases and longer observation period. This becomes an absolute condition especially in terms of premalignant and malignant pathologies of the cervix. To the best of my knowledge, results based on a single centre's direct clinical observation with such a huge number of stringently followed-up cases for a long period of use has not been published yet. The number of patients at risk at the end of follow up period of 10 years (550-846) and the cumulative women months of use (180,000-492,000) was sufficient to conclude valid statistical results. On the sound basis of these fulfilled conditions, it is concluded that there is no statistically significant difference in the occurrence of ectopic pregnancy among medicated and non-medicated IUDs, in other words: duration of use of IUD does not play any role in generating ectopic pregnancy. Similar results have been concluded for cervical carcinoma as well: in case of premalignant and malignant cervical pathologies – also based on a long follow-up (10 years), a great number of cases (more then 17,000 IUD insertions) and a huge observation period (163,567-492,836) – there were no statistically significant differences between the non medicated and the copper containing devices. As such, it can be stated that on comparison to the non-medicated (Szontágh) IUDs, the copper-containing intrauterine contraceptive devices do not have either an increased or a decreased risk of cervical cancer.

The observation of the two rare clinical events during IUD use and the evaluation of the results with ectopic pregnancy and cervical premalignancies and malignancies further strengthen the opinion that intrauterine contraceptive devices still remain one of the most effective and safe method of contraception to avoid unwanted pregnancies.

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LIST OF PUBLICATIONS

Full length (related to the thesis)

1. Bhattoa HP, Ganacharya S, Batár I. A decade of experience with TCu200. *Advances in Contraception.* 1999;15(4):351-361 (IF: 0.509)
2. Ganacharya S, Bhattoa HP, Batár I. Ectopic pregnancy among non-medicated and copper containing intrauterine device users: a 10 year follow-up. *European Journal of Obstetrics and Gynaecology and Reproductive Biology.* 2003;111(1):78-82 (IF: 1.002)
3. Ganacharya S, Bhattoa HP, Batár I. Premalignant and malignant cervical pathologies among non-medicated and copper containing intrauterine contraceptive device users: a 10 year follow-up study. *European Journal of Contraception and Reproductive Health.* 2006 (In Press) (IF: 0.480)

Other publication

1. Bhattoa HP, Bettembuk P, Ganacharya S, Balogh Á. Prevalence and seasonal variation of hypovitaminosis D and its relationship to bone metabolism in community dwelling postmenopausal Hungrian women. *Osteoporosis International*. 2004;15(6):447-451 (IF: 2.954)