Cytopathological Hazards in Human Cervix and Endometrium Associated with Copper Intrauterine Contraception

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Summary: Since copper IUDs have been functioning as major component in family spacing activities in our country, it becomes mandatory to ascertain cytopathological changes in the female genital tract associated with their prolonged usage. The present study embodies cytological findings obtained on follow up of 2026 women using 6 different types of copper IUDs (CuT 200, CuT 220, CuT 380, CuT 380 Ag, CuY and Multiload) for periods ranging from 1 to 20 years. A high incidence of cervical dysplasia was found with devices containing high copper content (CuT 380 and Multiload) and also high persistence and recurrence rate of dysplasia with their continued contraception. The dysplasia rate as well as endometrial hyperplasia displayed significant rise following change of original cuT200 device and there was also a positive correlation between high copper loss and genital cytopathologies.

The accumulated data reveals some relationship between copper released from the device and cytopathological hazards in the cervix and endometrium. Consequently a constraint is advocated on the prolonged use of copper IUDs for period not exceeding 5 years.

Introduction

Copper intrauterine contraceptive device have been universally acclaimed as major achievement in contraceptive technology in view of their tremendous acceptance by fertile women for family spacing especially in developing countries. In India, copper T200 devices were launched in Family Welfare programme in 1978 after ascertaining safety and efficacy of their long term application through extensive multicentric clinical trials carried out by Indian Council of Medical Research (ICMR) in 1971. Since then it has contributed as major component of family spacing activities in this country.

It is hypotheticated that the contraceptive mechanism of copper clad IUDs is directly related with the amount of copper released from the device in the uterine milieu (Hagenfeldt, 1972). The depletion of copper occurs from the device in situ due to corrosion and subsequent dissolution of the metal from the device (Edelman et al 1990). It thus becomes mandatory to study effect of the slow and constant release of copper on the cervical epithelium and endometrium. The present study had been undertaken during multicentric clinical trial with different types of copper IUDs to find out relation between copper release and cellular abnormalities in the upper genital tract. A total of 2026 women have been followed from April 1971 till July 1997 wearing CuT200, CuT220, CuT380, CuT380 Ag, CuY, and Multiload for periods varing from 6 months to 20 years. Cytological findings obtained in cervical smears and endometrial aspirates of this cohort has been analysed in detail in the present paper to ascertain their bearing on the copper release from the device.

Materials and Methods

The study comprises of 2026 women using 6 different types of copper IUDs inserted at Family planning Clinic Queen Mary's Hospital, Lucknow. India from April 1971. The age of the subjects ranged from 18 to 45 years. The split of different copper IUDs in 2026 women was as follows: CuT200-1238, CuT220-305, CuT380-134 CuT380 Ap-188, CuY-115 and Multiload-46 cases.

Prior to insertion of device, careful bimanual and perspeculum examination was carried to see that there were no contraindications for IUD insertion. A scrape smear was taken from the two sites: (a) Squamocolumnar junction of cervix and (b) Endocervical canal. Endometrial aspirates were also collected at the time of insertion in women who were inserted with CuT 200 device. All women were called for follow up at six monthly interval for cervical smear evaluation and a total of 5711 smears have been examined. Endometrial aspirates were collected only when the patients had any symptom necessitating removal or when the devices were changed after 3-6 years

for maintaining contraceptive efficacy. This was because it was not considered advisable to disturb the IUD in asymptomatic women. Post-IUD endometrial aspirates were examined in 362 CuT 200 wearers in 71, when devices were changed after 3-6 years while in remaining 291 cases at the end of 1-20 years when IUD was removed because of complications such as pain or bleeding or because women desired another child. For making an endometrial smear, uterine fluid was aspirated from the endometrial cavity through an endometrial cannula with syringe attached and the smears were made by spreading the fluid on a glass slide.

All the collected smears (exocervical, endocervical and endometrial) were immediately fixed in absolute alcohol and later stained according to the Papinocalaou's technique. The cytopathological changes in the cervical smears were graded according to the WHO classification of 1973, while those in the endometrial cells were classified as normal, inflammatory and hyperplasia (mild, moderate and severe). As routine, cervical biopsy was performed in all cases of moderate dysplasia onwards. Endometrial biopsy was also taken in all women showing abnormal endometrial smears.

Quantitative estimation of copper loss from the removed devices have also been undertaken in 176 copper T 200 wearers. The used copper IUDs were dipped in water and cleaned with a brush to remove the adherent mucus. The devices were then dried and the quantitative estimation of copper loss was performed by substracting the weight of the device after removal from that of an unused device. The new device weighted 2.2 mg, the polyethylene part of the device weighing 1.0 mg and copper wire 1.2 mg.

The pretreatment cytological findings in the total 2504 contraceptive users (both IUD and hormone) registered at this centre have been taken as controls to compare dysplasia rate obtained with different copper IUDs of the study group. All the cytological data were subjected to a thorough statistical analysis applying the large sample 'Z' test for precentages.

Results

The analysis of cervical and endometrial cytological finding are presented below under different parameters.

I. Cervical Dysplasia

a) Incidence with different types of Copper IUDs

The incidence of cervical dysplasia obtained with 6 types of Copper IUDs have been shown in Table I which revealed a highly significant increase from the control value of 1.3% with CuT380 device (6.7%-9/134) and Multiload (6.5%-3/46-$p<0.01$). It should be emphasized here that both these devices contain maximum amount of Copper (380 mm and 250 mm respectively) among the 6 types evaluated. The rise in the dysplasia rate from the control value was only significant ($p<0.05$) with Copper T 200 (4.9%-61/1238) while with the remaining 3 types of copper IUDs, the difference was insignificant ($p<0.05$-CuT 220-2.1%-7/305, CuY - 2.1% - 3/115 and Cut 380 Ag 2.2% - 3/188). The copper carried out by the CuT 200, CuT 220 and CuY devices was comparatively small ranging from 200 mm to 220 mm surface area of the device. As CuT 380 and multiload contain high amount of copper, high dysplasia rate obtained on their follow up may be associated comparatively higher amount of copper released from these devices into the endometrium. This assumption gains support when the dysplasia rate in CuT 380 plain devices were compared with findings obtained with silver coated devices (CuT 380 Ag). The CuT 380 Ag device has been designed to prevent disintegration of copper by applying coating of silver on the copper wire. The release of copper from such devices would obviously be lower due to silver coating than the amount released from the plain device at the same period of time. Interestingly enough, dysplasia rate was found to be three times lower with CuT 380 Ag devices (2.2% - 3/188) when compared with figure of 6.7% obtained with plain CuT 380.

b) Follow up of cervical dysplasia cases

Incidence of persistence and recurrence of dysplasia was also analysed with continued contraception to find out if they had any relation with devices containing low or high content of copper. The findings are presented in Table I which reveals higher persistence rate of dysplasia with Multiload (33.3%) and was lowest with (CuT 200-13.2%). These findings also suggest a relation between high copper release from the device with persistence and recurrence of dysplastic lesions.

c) Incidence of cervical dysplasia in CuT 200 wearers after change of device

Out of 1238 women using CuT 200 devices, 1102 have

worn a single device uninterruptedly for periods ranging from 1 to 10 years while in remaining 136, the old CuTs were replaced by a new one after 3-6 years. The total period of contraception was almost identical (20 years) in both the groups as changed devices were worn for periods ranging from 1 to 15 years. A total of 61 dysplastic smears were detected, 39 of these were seen in 1102 women wearing single device (3.5%) while the remaining 22 were detected after the change was effected (16.1%). The dysplasia rate thus showed five fold increase when the second CuT was inserted in place of original device. This may be in all probability due to fresh exposure of cervical epithelium to the copper released from the new device. This is also corroborated from the analysis of the dysplasia rate yearwise when the original devices are worn and after the replacement (Table II). The incidence of dysplasia was higher at all stages of contraception in the corresponding years after the change than with the original device.

II Endometrial cytology in CuT 200 IUD wearers

Post – IUD endometrial aspirates were examined in 363

Table-I

Incidence of Dysplasia and Percentage of Persistence and Recurrence with Different Types of Copper Devices.

Type of Device	No of Dysp. detected (Incidence)	No. followed	No. regressed	No. persisted	No. showing recurrence (regressed cases)
Copper T_{200}	61 (4.7%)	38	35 (91.2%)	3 (7.8%)	5 (13.2%)
Copper T_{220}	7 (2.1%)	7	6 (85.8%)	1 (14.2%)	-
Copper T_{380} (Plain)	9 (6.7%)	6	5 (83.4%)	1 (16.6%)	1 (25.0%)
Copper T_{380}Ag	3 (2.2%)	3	3 (100%)	-	-
Copper Y	3 (2.1%)	3	3 (100%)	-	-
Multiload	3 (6.5%)	3	3 (66.6%)	1	1 (50.0%)

Table-II

Incidence of dysplasia in relation to period of IUD use with original and changed devices

Period of IUD use	Original device: No. examined	Original device: No. and Incidence of dysplasia	Changed devices: No. examined	Changed devices: No. and Incidence of dysplasia
1 Year	951	8 (1.4 %)	136	4 (7.1 %)
2 Year	339	9 (2.3 %)	96	4 (4.1 %)
3 Year	267	4 (1.5 %)	52	4 (6.8 %)
4 Year	189	4 (2.1 %)	47	3 (6.6 %)
5 Year	115	3 (2.6 %)	35	3 (8.5 %)
6 Year	66	4 (6.1 %)	25	2 (8.0 %)
7 Year	43	- - -	15	- -
8 Year	20	1 (5.0 %)	12	- -
9 Year	17	- - -	9	-
10 Year	11	- - -	8	1 (12.5 %)
11-12 Year	30	1 (3.3 %)	5	- -
13-14 Year	9	- - -	9	- -
15-16 Year	23	3 (13.1 %)	2	1 (50 %)
17-18 Year	13	2 (15.3 %)	-	- -
Total -		39		22

women, 292 of these have worn only single device for periods ranging from 1 to 8 years while in remaining 71 women, the devices have been changed after 3-6 years. A total of 19 cases of hyperplasia was encountered in 363 women, 7 in whom device had been changed (9.9%) while remaining 12 were detected with single device (4.4%). The incidence of hyperplasia was thus more than double when the original device was replaced by a new one. Twenty one inflammatory smears were also observed, 7 in whom devices had been changed (9.9%) and 14 in the group with original device (4.7%). The inflammatory changes were also thus more than double higher following change of device. The most plausible explanation for an enhanced rate of inflammation and hyperplasia after the change may be the fresh bombardment of genital epithelium from the copper in the new device.

The incidence of endometrial hyperplasia and inflammation in relation to period of IUD use with original and changed device is given in Table III. In women wearing original devices, both inflammation and hyperplasia was seen as early as 1 year after insertion and while the inflammation rate declined from 8.8% at 1 year to 1.4% at 4 years, the hyperplasia rate showed rise from 4.4% at 1 year to 13.3% at 3 years. It may be related with continuous increasing release of copper from the device upto 3 years. Further inflammatory changes were seen upto 6 years of insertion while hyperplasia upto 8 years indicating that copper in the uterine millieu first of all induces inflammatory changes in the endometrial cells which with prolonged reaction with copper transforms into hyperplasia. However, we do not have any followup of women with inflammatory smears developing into hyperplasia with continuous CuT use.

Further as evident from the Table II, in 71 women in whom devices have been changed, inflammatory and hyperplastic changes noticed in the endometrium after the change was affected, cellular were much higher in years following the change than with corresponding period of use of original device. This may be attributed to the fresh release of copper from the new device.

III Relationship between copper loss and abnormal cytology of cervix and endometrium.

The weight loss in 176 CuT 200 devices removed after 1-16 years of insertion revealed variable amount of copper loss in different subjects at different period of IUD use. The copper loss was divided into low (0.1 to 0.2 mg), moderate (0.3-0.6 mg) and high (0.7 to 1.1 mg). As stated earlier, the copper part of the device weighed 1.2 mg.

Table – III

Endometrial findings in relation to period of IUD use with original and changed devices

Period of IUD use	Original device			Changed devices		
	No. examined	No. and Incidence		No. examined	No. and Incidence	
		Inflammation	Hyperplasia		Inflammation	Hyperplasia
1 Year	24	2 (8.8 %)	1 (4.4 %)	5	1 (20 %)	-
2 Year	29	2 (6.8 %)	1 (3.6 %)	8	- - -	-
3 Year	23	- -	4 (13.3 %)	13	1 (7.6 %)	1 (7.6 %)
4 Year	67	1 (1.4 %)	- - -	14	2 (14.3 %)	2 (14.3 %)
5 Year	52	4 (5.2 %)	1 (1.8 %)	9	- - -	1 (11.1 %)
6 Year	19	1 (5.2 %)	2 (10.4 %)	9	- - -	-
7 Year	19	- - -	- - -	3	- - -	1 (33.3 %)
8 Year	15	- - -	1 (1.66 %)	2	- - -	-
9 Year	—	- - -	- - -	5	2 (40 %)	1 (20 %)
10 Year	4	1 (25 %)	- - -	2	- - -	1 (50 %)
11-12 Year	17	- - -	- - -	2	- - -	-
13-14 Year	4	- - -	- - -	1	- - -	-
15-16 Year	15	3 (20 %)	2 (13.3 %)	1	1 (50 %)	-
17-18 Year	1	- - -	- - -	-	- -	-
Total -		14	12		7	7

Seventeen cases of dysplasia (13 mild and 4 moderate) were detected from the cervical smears of 176 women. Distribution of these 17 dysplasia cases in three categories of copper loss was found to be as follows:

Copper Loss	No of Cases	No. and incidence of dysplasia.
Low	61	5
		>12 (7.7%)
Moderate	93	7
High	22	5 (22.7%)

A positive relationship was found between high loss of copper from the device into uterine milieu and production of cervical dysplasia as dysplasia rate was found to be 22.7% with high copper loss in contrast to 7.7% seen with low to moderate loss.

Post-IUD endometrial aspirates have been examined in 96 of the 176 women in whom copper loss was estimated from the removed devices. The copper loss was high in 19, moderate in 49 and low in the remaining 28 women. The inflammatory smears were seen in 7 cases while evidence of mild hyperplasia was seen in 3 cases. The distribution of these 10 abnormal endometrial smears in three categories of copper loss was as follows:

Copper Loss	No of cases	No. and incidence of abnormal smears
Low	28	1 Hyperplasia
		(> 2 (7.1%)
		1 Inflammation
Moderate	49	4 Inflammation (8.1%)
High	19	2 Hyperplasia
		(>4 (21.1%)
		2 Inflammation

The incidence of abnormal smears was maximum with high copper loss (21.1%) than those showing moderate and low loss (7.1% to 8.1%). The hazards of developing cytopathological lesions in the endometrium were thus also significantly higher when the loss of copper from the device was high.

Discussion

Different types of copper IUDs contain varying amount of copper on their surface area which is released slowly and progressively in the endometrium with increasing contraceptive use. Zipper et al (1971) in their preliminary studies have found copper ions to react with variety of aminoacid and proteins forming chelates in a property which allows the incorporation of the metal into the cell metabolism which enhances the biological activity of copper ions. Hagenfeldt (1972) has estimated a CuT 200 mm device releasing copper into the uterine cavity at the rate of 50 ug per day for period of a least one year. She has also demonstrated decrease in alkaline phosphatase activity and also delaying of synthetic phase of mitotic cycle in the endometrial cells. As DNA ultimately governs the whole cellular function, any abnormality in DNA synthesis associated with IUD contraception should be viewed with caution and raises need to study in detail the cytopathological changes in the uterine cervix and endometrium with prolonged use of copper IUD. A necessity is also felt to find out whether these cellular alterations in the female genital tract have any relation with amount of copper released from the device. This aspect has been critically evaluated in course of the cytological studies undertaken in 2026 wearers of 6 different varieties of copper device. It was very satisfying to find from the present cytological follow up study extending upto 20 years that no case of either cervical or endometrial carcinoma developed in any case. Also it was reassuring to note that none of the dysplasia, either pre or post, progressed to a higher grade or frank malignancy with continued contraception. These findings though suggest innocuousness of copper devices over their long term application as far as their oncogenic culpability is concerned, the accumulated follow up data does reveal some relationship between development of cytopathological hazards towards precancerous manifestations in the epithelia of cervix and endometrium and copper on the device which is slowly released and diminished steadily in the uterine milieu. This is relevant from following findings.

1. The incidence of cervical dysplasia showed highly significant difference form the control value with devices containing high copper content (CuT 380 and multiload) than bearing low amount of copper (Cut 200, CuT 220 and CuY). Follow up of postinsertional dysplasias revealed higher rate of persistence or recurrence with continued contraception with devices bearing high copper content (CuT 380 and multiload) than with devices carrying low copper content.

2. The incidence of dysplasia showed threefold decline when silver coating was effected on CuT 380 device (2.2% with CuT 380 Ag devices as against 6.7% with plain CuT 380).
3. The cervical dysplasia rate showed five fold rise when change of the original device with a new one was effected in 136 of the 1238 copper T_{380} wearers (16.1% against 3.5%). This may, in all probability, be attributed to the fresh bombardment of copper from the new device in the endometrial cavity. Our earlier studies have also pointed out similar conclusions (Misra et al., 1990).
4. Endometrial cytological findings in 363 wearers also lend support to the conclusion derived from the cervical cytology. The incidence of abnormal endometrial smears (inflammation and hyperplasia) displayed three fold rise in women in whom devices were replaced with a new one. This again reflects the fresh exposure of endometrium to copper from the new device may be the factor in inducing inflammatory and hyperplastic changes in the uterine epithelium.
5. The most substantial support to our proposition comes from quantitative estimation of copper loss from the removed devices. Interestingly enough, the incidence of cervical dysplasia and endometrial hyperplasia was quite high in women showing high copper loss than those displaying mild to moderate loss.

All these parameters studies, therefore, indicate to one single conclusion that there is some relation between copper released from the device and cytopathological changes noticed in epithelia of cervix and endometrium. It may be that copper released in the uterine milieu induces constant irritation in the upper genital tract paving way to the inflammatory changes in the epithelia which lead to precancerous manifestations because of continued exposure to the copper. It is, therefore, suggested that any type of copper device should not be worn for more than 5 years after which an IUD free interval is required. Further replacement of the original device with a new one for maintaining contraceptive efficacy is found absolutely redundant and probably deleterious as there was a marked increase in incidence of cervical dysplasia and endometrial hyperplasia following change of device.

Conclusions

Since copper IUDs have been functioning as major component in family spacing activities in our country, it becomes mandatory to ascertain cytopathological changes in the female genital tract associated with their prolonged usage. The present study was undertaken with this aim in 2026 women using 6 different types of copper IUDs (CuT 220, CuT 380, CuT 380 Ag, CuY and Multiload) for periods ranging from 1 to 20 years. The study revealed high incidence of cervical dysplasia with devices containing high copper content (CuT 380 and Multiload) and also high persistence and recurrence rate of dysplasia with their continued contraception. The dysplasia rate as well as endometrial hyperplasia displayed significant rise following change of the original CuT 200 device and there was also a positive correlation between high copper loss and genital cytopathologies.

The accumulated data reveals some relationship between copper released form the device and cytopathological hazards in the cervix and endometrium. Consequently a constraint is advocated on the prolonged use of copper IUDs for period not exceeding 5 years.

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