

# Clinical significance of a negative loop electrosurgical excision procedure, conization and hysterectomy for cervical intraepithelial neoplasia

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## Summary

**Purpose of Investigation:** The absence of cervical intraepithelial neoplasia (CIN) in a loop electrosurgical excision procedure (LEEP), cold-knife conization and hysterectomy for treatment of CIN is an occasional finding of uncertain clinical significance. The aim of this study was to estimate the frequency of a negative procedure and its relationship to disease recurrence.

**Methods:** A retrospective study was conducted on 263 specimens from women submitted to the LEEP (n = 142), conization (n = 101) or hysterectomy (n = 20) due to CIN.

**Results:** The frequency of negative conization, LEEP and hysterectomy were, respectively, 15.5%, 19.8% and 25%. Recurrence occurred from 16 to 44 (median = 42) months in women with negative surgical specimens (LEEP or cold knife conization), and after five to 31 (median = 20) months after histological findings of CIN in surgical specimens, respectively, 7.1% and 11.2%.

**Conclusion:** The absence of CIN in those procedures of biopsy-confirmed CIN is a not an uncommon finding. Patients with positive or negative specimens should be carefully followed.

**Key words:** Cervical intraepithelial neoplasia; Conization; Loop electrosurgical excision procedure; Hysterectomy; Negative specimens, Recurrence.

## Introduction

Conization and a loop electrosurgical excision procedure (LEEP) are the most frequently used treatments for cervical intraepithelial neoplasia (CIN). The first procedure is a relatively safe and easy technique to perform and can be undertaken in an outpatient setting [1]. Cold-knife conization is an older procedure than LEEP, and the main indication is for women with CIN and a non visible squamocolumnar junction, but the procedure is more expensive and requires hospitalization [2, 3]. In the past, CIN and microinvasive carcinoma were treated by hysterectomy, especially for women who did not desire future pregnancy. Nonetheless, morbidity and mortality is considerable [4]. Today, hysterectomy is used for the treatment of CIN, but the main indication is in case of recurrence in the small uterine cervix and when there is no technical condition for LEEP or conization [5].

Reported success rates for the treatment of CIN range from 60% to 90% [6-10]. Women who have received treatment for CIN should be followed up for five years with cytology every six months for two years and after annually. Recurrent disease is the main problem in that period. Surgical margins, endocervical gland involvement, number of mitoses and extension of CIN have been shown to be associated with higher rates of recurrent disease in both LEEP and cold-knife conization [2, 3, 5, 11, 12]. Compromised margins are associated with a higher recurrence rate for CIN [3]. Residual neoplasia in hysterectomy specimens after compromised margins in

conization is frequent [5]. Compromised margins allow for follow-up since patients are submitted to rigorous cytological and colposcopic surveillance. Indications for hysterectomy prior to the appearance of vaginal intraepithelial neoplasia (VAIN) have frequently been associated with a previous history of CIN or invasive neoplasia [13].

Although recurrence after CIN treatment has been reported, the absence of CIN in a LEEP, cold-knife conization and hysterectomy for treatment of CIN I, II or III is an occasional finding of uncertain clinical significance. The aim of this study was to estimate the frequency of a negative LEEP, cold-knife conization, and hysterectomy and the relationship to disease recurrence.

## Material and Methods

### Patients

A retrospective study was conducted on surgical specimens of women submitted to LEEP, conization or hysterectomy due to CIN, from 1 January 1981 to 31 November 2003, in the Gynecologic and Obstetrics Outpatient Service of our Institution. The project was approved by the Research Ethics Committee of FMTM.

Two hundred and sixty-three patients had been referred because of presence of CIN I-III in biopsy specimens. All patients were previously submitted to both triple collection of material for cytological examination and colposcopically directed biopsies. Cold-knife conization, LEEP and hysterectomies were performed in 142 (54%), 101 (38.4%) and 20 (7.6%) women, respectively. Median age (range) and unsatisfactory colposcopy rate were, respectively, 35 (21-57) and 12 (8.4%), 29 (18-64) and nine (8.9%), and 58 (18-68) and one (5%).

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LEEP, conization and hysterectomy management, and follow-up criteria for LEEP, conization and hysterectomy were performed by residents supervised by board-certified attending obstetrician-gynecologists. A LEEP was performed in women with the LEEP WEM machine, with the power set at 50 watts. After application of Lugol's iodine, cervical anesthesia was performed with 2% lidocaine containing a solution of 1:1000 epinephrine (4-6 ml, approximately 1 ml per cervical quadrant). Loop size was 10 mm x 10 mm and current was blended to cut and coagulate. After the procedure, all cases were submitted to roller ball coagulation (50 watts) with the aim of hemostasis. The main criteria for a LEEP in the majority of cases were small lesions, a visible squamocolumnar junction (SCJ), and desire of future gestation.

Cold-knife conization was performed on women in the operating room after spinal anesthesia. After a Schiller test, a surgical margin of 2 mm was made by bistury and the cone specimen was extirpated. Sturmdorf points were performed. Hysterectomy was performed via the abdominal route on women in the operating room after spinal or general anesthesia.

Follow-up criteria after the above procedures consisted of cytology and colposcopy every six months for five years and after annually. The minimum time of follow-up was 16 months. Presence of CIN I-III confirmed by colposcopically directed biopsies was considered as recurrence.

*Cytohistological techniques and colposcopy*

The cytological material was processed by the Papanicolaou technique and reading was performed by trained cytologists. Biopsies were guided by colposcopic exams carried out by residents under teaching supervision, and the material was fixed in 4% formaldehyde. Colposcopy was considered unsatisfactory when the squamocolumnar junction was not visible. There was no standard number of histological cuts for each biopsy which varied from one to ten successive cuts as judged necessary by the pathologist for each case.

The cone biopsy specimens were marked with sewing thread at the 12 o'clock position. Hysterectomy and cone biopsy specimens were fixed in 4% formaldehyde. The cone biopsies of the uterine cervix were cut into pieces of about 1 mm in thickness, perpendicular to the surface of the endocervical mucosa, and the material was processed for inclusion in paraffin. One histological cut of each block was stained with hematoxylin-eosin. Additional cuts were made when necessary.

*Statistical analysis*

Comparisons between groups were made with the chi-square test with Yates' correction or the Fisher's exact test, depending on the conditions of validity of the chi-square test. The differences were considered significant with  $p < 0.05$ .

**Results**

The frequency of negative conization, LEEP and hysterectomy was, respectively, 15.5%, 19.8% and 25%, and recurrence after a negative surgical specimen was more frequent in women submitted to a LEEP than cold knife conization (Table 1).

Recurrence occurred from 16 to 44 (median = 42) months in women with negative surgical specimens (LEEP or cold-knife conization), and after five to 31 (median = 20) months after histological findings of CIN in surgical specimens, respectively, 7.1% and 11.2%. Treatment of recurrence in women submitted to cold-knife conization and a LEEP were, respectively, two reconizations and 12 hysterectomies, and seven cold-knife conizations and four hysterectomies.

**Discussion**

A number of studies have analyzed the follow-up of women who were treated for CIN, but to our knowledge this is one of the rare studies that compares the follow-up of women who had negative histology in a conization, LEEP or hysterectomy specimen.

Although the ages were different among the groups of treated women, mainly in patients submitted to conization, we would have expected a major number of negative specimens in the conization group because of the number of unsatisfactory colposcopies. One possible explanation for the high number of negative LEEPs in comparison to conization is the high frequency of CIN I and small lesions that probably were entirely excised by punch biopsy [1, 14].

Our results showed negative rates of negative conization, LEEP and hysterectomy specimens, respectively, 15.5%, 19.8% and 25%. Other studies have shown a variable frequency from 14% [14] to 41% [1, 15]. There are several reasons for a negative specimen. First, previously punch biopsy removed the CIN; second, spontaneous regression may occur after the biopsy; third, the pathologist failed to sample the area containing CIN, and forth, the CIN was missed by the surgical procedure [1].

This study found that eight (2.9%) of 273 women submitted to biopsy under colposcopy who underwent conization or hysterectomy had microinvasive lesions identified in histological specimens. This is consistent with data found in the literature [13, 16]. We observed that for women who underwent a LEEP, the microinva-

Table 1. — *Distribution of women according to surgical procedures, histopathological findings in surgical specimens and recurrence.*

Histopathological findings	Cold-knife conization				LEEP				Hysterectomy			
	Total		Recurrence		Total		Recurrence		Total		Recurrence	
	n	%	n	%	n	%	n	%	n	%	n	%
Without CIN	22	15.5	1	6.7 (4.5)	20	19.8	2	18.2 (10)	5	25	—	— (-)
CIN I	3	2.2	—	— (-)	32	31.7	4	36.4 (12.5)	—	—	—	— (-)
CIN II – III	111	78.2	13	86.6 (11.7)	49	48.5	5	45.4 (10.2)	13	65	3	75 (23)
Microinvasive cancer	6	4.2	1	6.7 (16.6)	-	-	-	- (-)	2	10	1	25 (50)
Total	142		15		101		11		20		4	

( ) percentage of recurrences according to histopathological findings; p = not significant.

sion rate was zero and the percentage of patients treated with hysterectomy was 10%. Nonetheless, it should be emphasized that both groups submitted to a hysterectomy, conization or LEEP were heterogeneous with respect to the clinical data and indications for each procedure, as aforementioned. This explains the different findings of invasive lesions among the groups. The results of our study showed that colposcopically directed biopsies are limited in accurately diagnosing CIN or invasive cervical lesions. Unsatisfactory colposcopy and menopause were more common in patients submitted to hysterectomy and conization, and explain the discrepancy in relation to the LEEP group.

LEEP, conization and hysterectomy can cure CIN when the excision is complete. Nevertheless, recurrence may occur and therefore follow-up is essential. CIN may also be managed with incomplete excision, especially if the compromised margin is the ectocervical margin. Follow-up via cytology and colposcopy may give indications for possible reconization or hysterectomy [17]. Conization is a method that has good accuracy and also little invasiveness, which leaves no diagnostic doubts and, for CIN, reduces the risk of invasive carcinoma [18]. Nonetheless, careful patient follow-up is essential.

This is especially the case for women whose squamocolumnar junction is not visible and those over 35 years old, when generally there is no preoccupation about fertility. In these cases the cone needs to be long and should reach the internal orifice or the region close to it. With this care, we believe that the rate of residual disease will diminish.

Vaginal intraepithelial neoplasia (VAIN) may occur after hysterectomy for benign or malignant conditions. A study conducted on VAIN showed that 23 of 33 women had undergone prior hysterectomy. The main surgical indications were CIN and cervical invasive carcinoma [13]. Other authors showed similar results [16]. With regard to the relationship between tumors of the uterine cervix, vagina and vulva, neoplasia of the uterine cervix is an important risk factor for VAIN as shown in our findings. Thus, hysterectomy does not assure absence of recurrence.

The absence of CIN in conization, a LEEP and hysterectomy performed for biopsy-confirmed CIN is a not an uncommon finding. Patients with positive or negative specimens should be carefully followed.

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