



# The Recurrence Rate of Cervical Intraepithelial Neoplasia After Loop Electrosurgical Excision Versus Cold Knife Conization: A Cross-Sectional Study

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## Abstract

**Background:** Effective cervical intraepithelial neoplasia (CIN) treatment and detection of high-risk recurrence patients is very important.

**Objectives:** The present study aimed to compare the recurrence rate of CIN after loop electrosurgical excision procedure (LEEP) versus cold knife conization (CKC).

**Methods:** This cross-sectional study involved 329 patients who underwent either LEEP (294 cases) or CKC (35 cases) in the colposcopy clinic of referral hospitals between March 2016 and March 2021. The study population was followed up every six months for two years after their first conization to monitor for any recurrence of the disease.

**Results:** There was no significant difference between the two groups regards. Thirty-two patients experienced recurrence within two years after surgery. The rate of CIN recurrent was 30 (10.2%) cases in the LEEP group and 2(5.7%) cases in the CKC group, with no significant differences (P-value = 0.553, RR = 1.78; 95% CI = 0.44-7.15).

**Conclusions:** The present study compared the benefits and harms of LEEP and CKC. The recurrence rate and surgical complications associated with both methods appeared to be similar with no significant differences. However, further high-quality and comprehensive research with a long-term follow-up is necessary to confirm our findings.

**Keywords:** Recurrence, Human Papillomavirus, Cervical Cancer

## 1. Background

Cervical cancer places in the fourth rank of the most prevalent malignancies regarding incidence rate and mortality in women all over the world. Cervical intraepithelial neoplasia (CIN) is a well-known precursor lesion of invasive cervical cancer (1, 2).

The American Society for Colposcopy and Cervical Pathology (ASCCP) indicates precancerous cervical lesions such as CIN should be treated with conization (3). In this regard, the cold knife cone and loop electrosurgical excision procedure have been best known with the aim of performing cervical lesion treatment conization (4, 5).

Conization of the cervix or cold knife cone (CKC) is a surgical procedure used to diagnose and treat cervical dysplasia or even early-stage cervical cancer (6). It involves excising a cone-shaped portion of the cervix to remove a cervical lesion and the entire transformation zone (7).

A loop electrosurgical excision (LEEP) removes the cervical abnormal tissue using a loop of thin wire that is heated by electricity. The loop of wire acts like a scalpel to remove the tissue (6, 7). Unlike CKC, the LEEP procedure can be performed using local anesthesia and in an outpatient clinic at a significantly lower cost. This superior conservative approach of LEEP has led to a hot topic in treating CIN (5, 8).

However, there have been some limitations of LEEP that force some gynecologists to select the CKC. For example, in suspected patients with endo-cervical invasion and involvement, CKC is usually used instead of LEEP (9-11).

## 2. Objectives

Since about 15% of women who underwent conization experience different degrees of recurrence or residual after their treatment surgery (12), the present study was conducted to compare the recurrence rate of CIN after LEEP versus CKC, to report the recurrence rate separately for each conization method, and to improve the survival rate and prognosis of patients.

## 3. Methods

This cross-sectional study was conducted on 329 patients who underwent either LEEP or CKC in the gynecology-oncology clinics of Arash and Imam Khomeini hospitals affiliated with Tehran University of Medical Sciences between March 2016 and March 2021.

The women aged at least 18 years old with indications for conization were enrolled in the study. Indications for cone biopsy include CIN III, have been proven by biopsy sampling, the discrepancy between cytology and biopsy and colposcopy results, suspected cancer lesions with microscopic invasion, positive ECC, unsatisfactory colposcopy, or related persistent symptoms despite normal colposcopy. Patients with invasive cervical cancer or without dysplasia detection in cone sampling were excluded.

The first choice of conization in our department is LEEP; however, in some cases, CKC was done. The surgeries were all performed as an outpatient procedure under spinal anesthesia by an expert gynecology-oncology fellowship.

The study population was followed for an entire two-year period. The recurrence was considered as detecting high-grade CIN (CINII and CINIII) lesions in histopathological monitoring, which was done every six months.

The following data were recorded for all cases: Maternal age, Body Mass Index (BMI), menopausal status, contraception method, first intercourse age, sexual partner number, smoking, and underlying disease status.

Descriptive statistics including mean, standard deviation, and relative frequency were used to describe the data. For data analysis, the chi-square test (for correlation between qualitative variables) and the *t*-test (for correlation between quantitative variables) were

used. All analyses were performed using SPSS version 23 software at a significant level less than 0.05.

## 4. Results

The medical records of 329 women who underwent either LEEP or CKC enrolled in the study. The mean age of patients was  $36.9 \pm 8.5$  years. The age of first intercourse on average was  $22.2 \pm 4.2$  years. About 70% (223 cases) were married and about 25% (81 cases) were nulliparous.

The cases with high-risk HPV were 281 (95.6%) in the LEEP group and 32 (91.4%) in the CKC group, with no significant ( $P = 0.394$ ) differences between the groups regarding the prevalence of high-risk HPV. No significant differences were detected between the two study groups about demographic information (Table 1).

Thirty-two patients experienced recurrence within two years after surgery. High-grade CIN recurrence was detected in 30 (10.2%) cases in the LEEP group and 2 (5.7%) cases in the CKC group, with no significant differences ( $P$ -value = 0.553, RR = 1.78; 95% CI = 0.44-7.15). Recurrence with CINII was reported in 7 (25.9) women in the LEEP group and 2 (33.3%) cases in the CKC group. Recurrence with CINIII was detected in 20 (74.1%) women in the LEEP group and 4 (66.7) cases in the CKC group. Marginal involvement in the previous pathology was not reported in the cases with CIN recurrence.

None of the cases developed early hemorrhage within the first 24 hours after the conization. Delayed bleeding occurred in two patients in the LEEP group and no patient in the CKC group. Other complications were not reported.

## 5. Discussion

Cervical cancer progress is a multi-step process that is initiated with minimal changes in the cervical cells and without effective treatment; it can advance into invasive cervical cancer over time (13-15). Although, CKC and LEEP, as the local cervical treatments, have important roles in preventing invasive cervical cancer (16-18), all patients after conization should be followed up over 20 years to detect any treatment failure that causes residual or recurrence of cervical cancers (19, 20).

In line with our study, the recurrence rate of high-grade cervical lesions is reported at 6.6%, although it can vary as low as 2.1% in CKC and equal to 14% in LEEP (21). In some previous studies, the risk of  $\text{CIN}2^+$  recurrence at one next year is detected about twice-fold in women who underwent LEEP rather than in CKC (22, 23), this fact is also represented in our study.

**Table 1.** The Baseline Information of the Patients <sup>a</sup>

Variables	LEEP Group	CKC Group	P-Value
Mean women age (y)	37.2 ± 8.4	34.5 ± 8.7	0.089
Gravida (times)			0.057
0	68 (23.1)	13 (37.1)	
≥1	226 (76.9)	22 (62.9)	
Mean age of first intercourse (y)	22.1 ± 4.2	22.6 ± 4.2	0.508
Number of sexual partners			0.459
1	233 (79.2)	27 (77.1)	
≥1	61 (20.8)	8 (22.9)	
Smoking			0.574
Yes	42 (14.3)	4 (11.4)	
No	252 (85.7)	31 (88.6)	
Underlying disease			0.555
No	253 (86.1)	31 (88.6)	
Diabetes mellitus	8 (2.7)	0 (0.0)	
Hypertension	3 (1.1)	1 (2.8)	
HIV	7 (2.4)	0 (0.0)	
Multiple sclerosis	8 (2.7)	0 (0.0)	
SLE	3 (1.1)	0 (0.0)	
Others	12 (4.1)	3 (8.6)	
High-risk HPV			0.394
Positive	281 (95.6)	32 (91.4)	
Negative	13 (4.4)	3 (8.6)	

Abbreviations: LEEP, loop electrosurgical excision procedure; CKC, cold knife conization.

<sup>a</sup> Values are expressed as No. (%) or mean ± SD.

One study from multiple hospitals in China which includes 5050 women and another cohort study from the national population of Sweden which consists of 153632 women with CIN or carcinoma in situ who underwent CKC or LEEP conization, indicated that women who underwent CKC treatment had a significantly lower risk of recurrent cervical lesions compared to those who underwent LEEP treatment, which confirms our findings (24).

In contrast to our findings, in a retrospective study by Galli et al. the recurrence rate was 8.3% vs 11.1% in women undergoing LEEP vs. CKC group (25). Furthermore, in four trials involving 1,035 women with CIN, it was reported that women who underwent LEEP for CIN experienced significantly lower rates of disease persistence at a 6-month follow-up biopsy and significantly lower rates of recurrence at a 12-month follow-up biopsy compared to those who received cryotherapy. Additionally, the study found no increase in complication rates associated with the LEEP procedure (26).

In some others studies, there was no significant difference between CKC or LEEP groups regards the

overall proportion of positive surgical margins (27). In a study by Wang et al., 447 cases (259 with LEEP and 188 with CKC) were evaluated. The mean recurrence rate of high-grade cervical lesions had no significant differences in the two applied conization methods. Recurrence with CINII was reported in 7 women (25.9) in the LEEP group and 2 (33.3%) cases in the CKC group. While CIN3 detection was in 20 (74.1%) women in the LEEP group and 4 cases (66.7) in the CKC group (28).

Similar to our findings, some former studies (29, 30) showed that post-LEEP or cryotherapy surgery complications seem rare and the same. In contrast, in some studies, CKC was associated with higher complications such as preterm labor, premature rupture of membranes, and adverse neonatal outcomes. Higher biopsy specimen and risk of post-conization bleeding and stenosis (31, 32).

In addition, they concluded that women who received CKC are associated with a lower risk of HPV persistence and recurrent cervical lesions compared to women who received LEEP (25); otherwise, HPV persistence rate was not evaluated in our study. Close

follow-up is necessary for prompt detection and treatment of persistent or recurrent disease (30).

One of the major limitations of our study was incomplete data about HPV clearance in the follow-up visits. The other limitation was not evaluating reproductive outcomes such as the effect of treatment on future spontaneous abortion rate or infertility. Future well-designed multi-center research is needed to evaluate the time-to-event CIN2+ recurrence rate and its related factors, as well as high-quality follow-up studies.

### 5.1. Conclusions

The present study compared the benefits and harms of CKC and LEEP. The recurrence rate and surgery complications of the two methods seem similar with no significant differences, although more high-quality and comprehensive research with a long-term follow-up period is needed to confirm our findings.

### Footnotes

**Authors' Contribution:** Study concept and design: A. G.; Acquisition of data: E. R.; Analysis and interpretation of data: N. T.; Drafting of the manuscript: N. T. and E. F.; Critical revision of the manuscript for important intellectual content, statistical analysis: E. F.; Administrative, technical, and material support: A. T.; Study supervision: A. G.

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**Data Availability:** The dataset presented in the study is available on request from the corresponding author during submission or after publication.

**Ethical Approval:** Ethical approval of the study was obtained from the Institutional Review Board of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.1041) based on the Declaration of Helsinki.

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