

# Evaluation of cervical length and optimal timing for pregnancy after cervical conization in patients with cervical intraepithelial neoplasia

## A retrospective study

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### Abstract

**Purpose:** To evaluate the change of cervical length and the best timing for pregnancy after cervical conization in patients with cervical intraepithelial neoplasia (CIN).

**Methods:** This was a retrospective study including patients under 40 years with fertility desire treated by cervical conization for CIN. To assess the cervical length, the patients were divided into 2 groups according to different surgery procedure: loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC). Patients with cervical length < 2.5 cm in CKC group were divided into 2 groups according to whether receiving cervical cerclage. Trans-vaginal ultrasound examination was used to measure cervical length by fixed professional sonographers.

**Results:** In LEEP group, the cervical length preoperative was significantly longer than 3 months postoperatively ( $3.03 \pm 0.45$  cm vs  $2.84 \pm 0.44$  cm,  $P = .000$ ). In CKC group, the cervical length preoperative was significantly longer than 3 and 6 months postoperatively ( $2.90 \pm 0.41$  cm vs  $2.43 \pm 0.43$  cm and  $2.68 \pm 0.41$  cm, respectively,  $P = .000$ ). Cervical length was significantly longer at 12 and 9 months after cerclage compared to that without cerclage. Eighteen patients got pregnant in LEEP group, among which one was pregnant at 5 months postoperatively and had premature delivery. There was 1 inevitable abortion and 1 preterm birth among 39 pregnant patients from CKC group.

**Conclusions:** Patients who have fertility desire with CIN were recommended for pregnancy at 6 and 9 months after LEEP and CKC, respectively. Cerclage effectively prolonged cervical length in patients with that less than 2.5 cm to prevent cervical incompetence.

**Abbreviations:** CIN = cervical intraepithelial neoplasia, CKC = cold knife conization, LEEP = loop electrosurgical excision procedure.

**Keywords:** cervical cerclage, cervical conization, cervical intraepithelial neoplasia, cervical length

## 1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion closely related to invasive cervical cancer. With the popularization of cervical cancer screening program, an increasing CIN was

detected in women of childbearing age. The choice of treatment for CIN depends on histological grade and patient age. Cervical conization is the primary treatment for CIN, carcinoma in situ and microinvasive carcinoma in young patients with fertility

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desire, including loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC).

Cervical incompetence induced by cervical conization is a main factor for premature delivery and abortion when used for cervical squamous intraepithelial lesions.<sup>[1,2]</sup> In a population-based cohort study including 15,108 patients treated with cervical conization (CKC, LEEP, and laser conization), 216,406 patients never treated and 57,136 patients treated after delivery,<sup>[3]</sup> Albrechtsen S et al found that women who received cervical conization had a significantly higher rate of preterm delivery in subsequent pregnancies before 24 weeks' gestation than those who underwent treatment after delivery or those who were never treated (1.5% vs 0.4%). The Norwegian study including 9554 women with singleton births showed that cervical conization was significantly associated with increased risks of spontaneous abortion (0.5% vs 0.2%; hazard ratio 2.5, 95% CI 1.7–3.7).<sup>[4]</sup> Several other studies investigating the association between depth of the excised cone and risk of preterm delivery showed that the depth more than 10 mm was an independent risk factor for preterm delivery and preterm premature rupture of membranes.<sup>[5,6]</sup> However, few studies have assessed cervical length and the best timing for pregnancy after cervical conization. The present study measured the cervical length in patients with CIN to explore the effect of cervical conization on cervical length.

## 2. Materials and methods

### 2.1. Study population

Patients treated in gynaecological department of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine between January 2015 and December 2016 were collected who received cervical biopsy and needed further cervical conization. Patients should meet the inclusion criteria: less than 40 years old; no history of CIN, cervical carcinoma or other tumors; without cervical incompetence or related surgery history; with fertility desire and not pregnant; histologically confirmed grade I-III CIN (including carcinoma in situ). The ethics committee of Sir Run Run Shaw Hospital reviewed and approved the study.

### 2.2. Procedures and outcome measures

Cervical conization included LEEP and CKC; the former was performed for cervical squamous atypical hyperplasia and grade I-II CIN and the latter was performed for grade III CIN. A non-absorbable suture was used in cerclage to sew cervix into about 0.5 to 1.0 cm up the bladder peritoneal reflection, just above the level of internal orifice of the uterus.

Trans-vaginal ultrasound examination was used to measure cervical length by fixed professional sonographers. All patients were checked preoperatively and at 2 months after surgery for cervical length. Patients were followed up at 3, 6, 9, 12 months postoperatively to make sure no lesions remained and to assess cervical length.

### 2.3. Statistical analysis

Measurement data was in accordance with normal distribution by using Kolmogorov–Smirnov test and presented as mean  $\pm$  standard deviation. The Student *t*-test was used to compare continuous data. Count data was analyzed with  $\chi^2$  test and

present as absolute value or proportions. *P* value  $< .05$  was regarded as significant. All statistical analyses were carried out in SPSS statistical software (version 20.0 for Windows, SPSS, Inc.).

## 3. Results

A total of 190 patients were included in this retrospective study, including 95 patients with grade I-II CIN and 95 patients with grade III CIN. Average age was  $30.34 \pm 2.73$  and  $30.17 \pm 4.35$ , respectively.

### 3.1. Pre- and postoperative evaluation of cervical length in LEEP group

In LEEP group, the length of cervix at 3 months after surgery was significantly shorter than pre-operation ( $P = .000$ ). Also, a statistic difference was seen in cervical length at 6 months and 3 months postoperatively ( $2.97 \pm 0.51$  and  $2.84 \pm 0.44$ ,  $P = .000$ ). Comparison of cervical length between pre-operation and 6 or 9 months post-operation demonstrated no significant difference, neither did 9 and 6 months post-operation (Table 1).

### 3.2. Pre- and postoperative evaluation of cervical length in CKC group

Analysis of 95 patients in CKC groups showed that cervical length preoperative was  $2.90 \pm 0.41$  cm, which was significantly longer than that at 3 and 6 months after surgery ( $P = .000$ ). The comparison of cervical length between 6 and 3 months as well as 9 and 6 months showed significant difference ( $P = .000$ ). Cervical length at 12 and 15 months post-CKC were also measured, but other comparisons demonstrated no significant difference ( $P > .05$ ) (Table 2).

### 3.3. Comparison of the cervical length between cerclage and no cerclage group (cervical length $< 2.5$ cm)

In CKC group, 19 patients had their cervical length less than 2.5 cm. They were assessed to investigate the effect of cerclage on cervical length in patients who were willing to get pregnancy in 2 years. In this subgroup, cervical length was significantly longer at 12 and 9 months postoperatively compared to that without cerclage (Table 3).

**Table 1**

**Comparison of the length of cervix after coning with loop electrosurgical excision procedure (N=95).**

	Cervical length ( $\bar{x} \pm s$ , cm)	T	P
Preoperative	$3.03 \pm 0.45$		
Three mo after surgery	$2.84 \pm 0.44$	7.629	.000*
Preoperative	$3.03 \pm 0.45$		
Six mo after surgery	$2.97 \pm 0.51$	1.970	.052
Preoperative	$3.03 \pm 0.45$		
Nine mo after surgery	$3.01 \pm 0.41$	1.461	.147
Three mo after surgery	$2.84 \pm 0.44$		
Six mo after surgery	$2.97 \pm 0.51$	-3.979	.000*
Six mo after surgery	$2.97 \pm 0.51$		
Nine mo after surgery	$3.01 \pm 0.41$	-1.255	.213

LEEP = loop electrosurgical excision procedure.

\*  $P < .05$ .

**Table 2****Comparison of the length of cervix after coning with cold knife (N = 95).**

	Cervical length ( $\bar{x} \pm s$ , cm)	T	P
Preoperative	2.90 ± 0.41		
Three mo after surgery	2.43 ± 0.43	17.633	.000*
Preoperative	2.90 ± 0.41		
Six mo after surgery	2.68 ± 0.41	9.893	.000*
Preoperative	2.90 ± 0.41		
Nine mo after surgery	2.90 ± 0.39	-0.094	.925
Preoperative	2.90 ± 0.41		
Twelve mo after surgery	2.90 ± 0.39	-0.286	.776
Preoperative	2.90 ± 0.41		
Fifteen mo after surgery	2.90 ± 0.64	0.373	.710
Preoperative	2.43 ± 0.43		
Three mo after surgery	2.43 ± 0.43	-15.904	.000*
Preoperative	2.68 ± 0.41		
Six mo after surgery	2.68 ± 0.41	-14.276	.000*
Preoperative	2.90 ± 0.39		
Nine mo after surgery	2.90 ± 0.39		
Preoperative	2.90 ± 0.39		
Twelve mo after surgery	2.90 ± 0.39	-1.626	.107
Preoperative	2.90 ± 0.39		
Twelve mo after surgery	2.90 ± 0.39		
Preoperative	2.90 ± 0.64		
Fifteen mo after surgery	2.90 ± 0.64	0.577	.566

\*  $P < .05$ .**Table 3****Comparison the length of cervix after cerclage with no cerclage.**

	Cervical cerclage	N	Cervical length ( $\bar{x} \pm s$ , cm)	T	P
Preoperative	cerclage	10	2.33 ± 0.25		
	No cerclage	9	2.35 ± 0.17	-0.264	.795
Three mo after surgery	cerclage	10	2.11 ± 0.28		
	No cerclage	9	1.87 ± 0.29	1.783	.092
Six mo after surgery	cerclage	10	2.36 ± 0.24		
	No cerclage	9	2.13 ± 0.26	2.009	.061
Nine mo after surgery	cerclage	10	2.61 ± 0.28		
	No cerclage	9	2.28 ± 0.25	2.678	.016*
Twelve mo after surgery	cerclage	10	2.61 ± 0.28		
	No cerclage	9	2.32 ± 0.21	2.531	.022*
Fifteen mo after surgery	cerclage	10	2.46 ± 0.88		
	No cerclage	9	2.38 ± 0.15	0.214	.834

\*  $P < .05$ .**3.4. Pregnancy outcomes**

In LEEP group, 18 patients got pregnant, among which one was pregnant at 5 months postoperatively and had premature delivery (at 30 weeks of gestation), one was in the second trimester and the rest had full-term pregnancy. In CKC group, 39 patients got pregnant, among which 10 patients received cerclage, 35 patients had full-term pregnancy, 1 suffered premature rupture of membrane (at 36 weeks of gestation), 2 were in the second trimester and 1 was in test tube programme (Table 4).

**Table 4****Pregnancy outcome after loop electrosurgical excision procedure and cold knife conization.**

Pregnancy outcomes	LEEP	CKC
Inevitable abortion	0	1
In pregnancy	1	2
Premature delivery	1	1
Full-term pregnancy	16	35

LEEP = loop electrosurgical excision procedure, CKC = cold knife conization.

**4. Discussion and conclusions**

There is an increasing number of young CIN patients with fertility desire. American Society for Colposcopy and Cervical Pathology recommended cervical conization as the primary therapeutic strategy for grade II-III CIN. Cervical tissue loss after cervical conization could result in cervical incompetence, a primary reason for habitual abortion in the second trimester of pregnancy. Few studies have reported the change of cervical length after conization. It was reported that cervical canal could return to normal length at 6 months postoperatively.<sup>[7,8]</sup> Therefore, regeneration of cervical tissue occurred generally at 3 to 12 months after conization.

Previous studies have indicated that the shortened cervix at 3 months after LEEP or CKC would elongate with the wound healing. A retrospective study conducted by Dannie J<sup>[9]</sup> and his colleagues showed that cervix would recover at 3 months after LEEP and stop shortening. The results in Konno R' study<sup>[10]</sup> revealed that immediate pregnancy after LEEP increased the risk of premature delivery and pregnancy was recommended at 3 to 6 months postoperatively. In the present study, cervical length shortened remarkably at 3 months after LEEP ( $P < .05$ ). However, it returned to normal length at 6 months and had no difference with 9 months which indicated that cervix would stop growing at 6 months postoperatively. Therefore, it was suggested that cervix was during regeneration period at 3 to 6 months after LEEP, and 6 months postoperative was suitable for pregnancy in case of complications. In CKC group, because of the wider excision range, our results showed no difference was seen in cervical length between pre-operation and 9 months after surgery. No significant increase was found in cervix between the periods of 9 to 15 months postoperatively. Therefore, it took 9 months for cervix to recover completely, which was a recommended timing for pregnancy.

Cervical cerclage is the primary treatment for cervical incompetence. Prophylactic cerclage was used to prevent cervical incompetence caused by CKC.<sup>[11]</sup> In the present study, CKC increased the risk of postoperative cervical incompetence in patients with cervical length less than 2.5 cm. Therefore, a preoperative communication was necessary and CKC plus prophylactic cerclage was performed based on the patient's wishes. Interestingly, cervical length in cerclage group (10 cases) was longer in patients without cerclage (9 cases) after 1-and-a-half-year follow-up ( $P < .05$ ). A non-absorbable suture was used in cerclage which could constantly stimulate tissue proliferative response, resulting in fibrous tissue proliferation and cervical fibrosis. It accelerated cervical growth in favor of cervical function recovery.

The adverse pregnancy outcomes post-conization were associated with internal orifice damage, cervix stenosis, and destroyed cervical gland that secreted mucus. A study has reported that gestational age at birth presented a linear inverse correlation with depth not volume or transverse diameter of excised specimen. The rate of preterm delivery and abortion in the second trimester of pregnancy was significantly higher in patients with deeper excision specimen.<sup>[12]</sup> Some studies thought that cervical conization increased 4 to 7-fold the risk of preterm delivery, abortion and premature rupture of membranes.<sup>[13,14]</sup> The disagreement might be caused by different sample sizes, depth and diameter of the cone and gestation time. In the present study, 18 patients got pregnant in LEEP group, among which one was pregnant at 5 months postoperatively and had premature delivery (at 30 weeks of gestation), and the rest had full-term

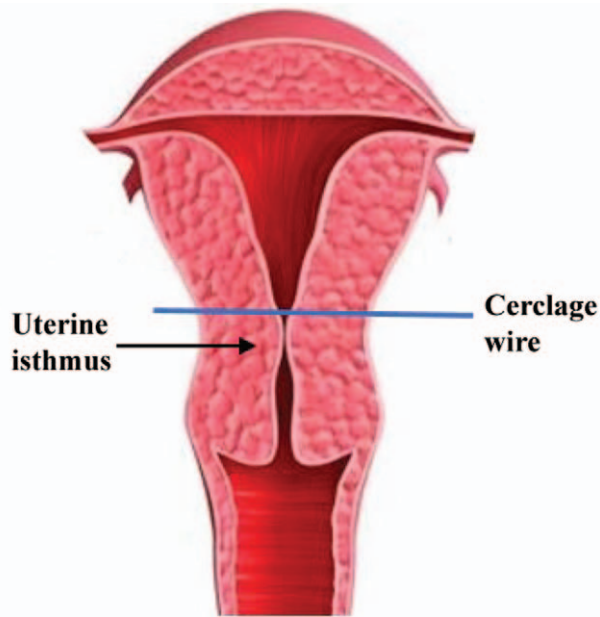


Figure 1. Cerclage position.

pregnancy. In CKC group, all 39 patients got pregnant 1 year after surgery, among which one suffered inevitable abortion due to chromosome abnormality.

Currently, the efficiency of cervical cerclage post-conization remained controversial. Shin MY et al<sup>[15]</sup> analyzed the data from 19 patients (12 with cerclage and 7 without cerclage) with cervical length less than 2.5 cm. The results showed the pregnancy outcomes and fetal conditions between 2 groups presented no significant difference. Althuisius et al<sup>[16]</sup> randomized patients with cervical length of < 25 mm into 2 groups: therapeutic cerclage (cerclage group) and bed rest alone (bed rest group). No spontaneous preterm delivery was found in 19 patients in cerclage group, yet the rate of preterm delivery before 34 weeks of gestation was up to 44% in bed rest group ( $P=.02$ ). It was reported that cerclage could reduce preterm delivery by 30% and reduce morbidity and mortality of perinatal infant by 36% in patients with cervical length < 25 mm.<sup>[17]</sup> A study of Kindinger including 725 patients at 3 London university Hospitals over a 10-year period (2004–2014) has shown that cerclage could significantly reduce preterm delivery rate in patients with shortened cervix post-conization.<sup>[18]</sup> CKC is a risk factor for cervical incompetence in pregnancy. It was wide accepted that cerclage should be performed in patients with short cervix measured preoperatively. In the present study, 10 patients with cervical length < 2.5 cm received cerclage, among which 5 had full-term pregnancy, 1 suffered premature rupture of membrane (at 36 weeks of gestation) and 2 were in the second trimester of pregnancy. Patients without cerclage have not been willing to get pregnancy until now. It was suggested that the contradiction between the 2 points was caused by the fact that we chose the position above isthmus of uterus for cerclage (Fig. 1) instead of the level of internal orifice of the uterus, which maintained a uniform pressure in uterine cavity during pregnancy in case of cervical expansion (Fig. 2). One-stage operation of cervical conization plus cerclage was technically easier with less pain and injury. If cerclage was performed after conization, surgery would become more difficult due to shortened cervix or postoperative

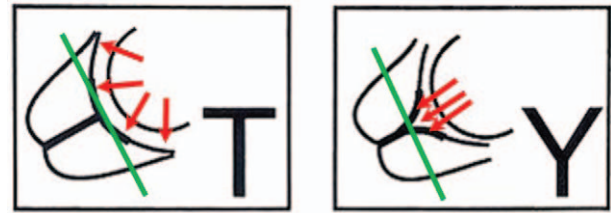


Figure 2. Cerclage position and pressure in the uterine cavity during pregnancy. The shape of cervical internal orifice was T-shaped and Y-shaped, respectively.

adhesions even a laparoscopic cervical cerclage was necessary. This would increase surgery cost and injury. A limitation for 1-stage operation was a secondary surgery to take out cerclage stitches if postoperative pathology showed positive lesion margin or lesion was adjacent to margin. Therefore, in our study cerclage was selected according to patients' fertility desire. The results lacked verification from randomized controlled trial and needed more cases for further study.

In conclusion, the depth and range of excised specimen might affect pregnancy outcome post-conization. A deeper and wider wound postoperative took longer for cervix to heal. Therefore, the range of conization depended on several factors including times of conization, degree of the lesion and fertility desire. According to our research result, 6 months was recommended for pregnancy after LEEP, while 9 months recommended after CKC. Prophylactic cerclage was considered for patients with cervical length less than 2.5 cm to stimulate cervical growth. Cervical length and uterine contraction supervision should be enhanced during pregnancy. It was suggested that experienced surgeons took the operation on patients with fertility desire to prevent not only the residual lesions but also the excessive resection particularly deeper excised specimen and subsequent cervical incompetence.

### Author contributions

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