



Yoichi Kobayashi

Abstract

Conization is the most important clinical procedure for patients with CIN3 and microinvasive carcinoma of the uterine cervix who need to preserve fertility. The main purposes of conization are confirmation of pathological diagnosis and treatment of CIN3 or early invasive cervical cancer. Preoperative evaluation should include cytology, colposcopy, and histology. Conization is performed with cold knife (CKC), laser, loop electrocautery (LEEP/LLETZ), and other devices. The treatment success of CKC, laser, and LEEP/LLETZ for CIN is reported to be about 90–98%, and there are no significant differences among these three procedures in treatment outcomes. The recurrence rate after conization has been reported to be approximately 5% regardless of surgical procedures, while age is a risk factor of recurrence. Human papilloma virus (HPV) testing is useful for detecting recurrence as well as cytology. Hemorrhage and cervical stenosis are the main complications after conization. Cone height is one of the risk factors for stenosis, while postmenopausal and postpuerperal amenorrheic women are also high risk for stenosis. Conization can also influence subsequent pregnancy. Treatment for CIN significantly increases the risk of preterm premature rupture of the membrane (pPROM) and preterm birth, and its risk is associated with cone height. CIN during pregnancy should be observed, and conization should be avoided except when invasive cancer cannot be excluded. Several trials have attempted to apply conization with pelvic lymphadenectomy for early invasive cervical cancer instead of radical trachelectomy. Further prospective studies should be conducted to establish these “less invasive” procedures to preserve fertility.

Y. Kobayashi (✉)

Department of Obstetrics and Gynecology, School of Medicine, Kyorin University,
Mitaka-City, Tokyo, Japan

e-mail: yoichi@ks.kyorin-u.ac.jp

Keywords

Cold knife · Laser · LEEP/LLETZ · Premature delivery · HPV · Bleeding Cervical

4.1 History

In the past, patients with cervical intraepithelial neoplasia 3 (CIN3) and microinvasive carcinoma of the uterine cervix had undergone hysterectomy. However, recently, conization has become the most important procedure for these patients especially when there is a need to preserve fertility. In Japan, among patients with carcinoma in situ (CIS), the proportions of those received hysterectomy and conization were 49.6% and 40.6%, respectively, in 1995, but the proportion of hysterectomy had decreased to 11.8% while that of conization had increased to 80.3% in 2013 [1, 2].

It is unclear when the first report of the “conization” procedure of the uterine cervix was published in the literature. A search for “cone biopsy and cervix” as keywords in PubMed shows a report from Crossen RJ to be the oldest publication on record; he described the history of conization in detail [3]. According to his manuscript, in 1815, Lisfranc reported the removal of a wedge-shaped block for presumed early cervical cancer, although later investigation demonstrated that these cases were not cancer but chronic inflammation [3]. Since then, many surgeons have attempted to improve the procedures and to reduce complications. In 1916, Sturmdorf devised his cold knife conization (CKC) technique with sutural coaptation of the vaginal cuff [3]. In 1935, Pendleton Tompkins compared trachelorrhaphy, amputation, and Sturmdorf operation, and he statistically demonstrated that the Sturmdorf operation was the most preferable in cure rate and had the lowest influence on subsequent pregnancies [3]. Thus, the Sturmdorf operation became the gold standard of conization performed by cold knife.

With the development of improved surgical devices, the cold knife has been replaced with other devices such as laser, electrical cautery (loop electrosurgical excisional procedure (LEEP)/large loop excision of the transformation zone (LLETZ)), and harmonic scalpel. Carbon dioxide (CO₂) laser for gynecology use was first described by Bellina [4]. Dorsey JH et al. reported on cone biopsy performed by CO₂ laser and demonstrated its advantages in both pathological diagnosis and low surgical complications [5]. But CO₂ laser technique is limited by the difficulties in setting instruments and its relatively longer surgical time for procedure. Kitsuki applied Nd:YAG laser for cervical conization and demonstrated satisfactory results compared to CO₂ laser [6]. Parallel to the development of laser, loop excisional technique was first introduced by Cartier et al. in the early 1980s, and then the LEEP technique was later developed. In 1992, another electrical cautery device, Shimodaira-Taniguchi cone biopsy probe, was developed to minimize the disadvantages of LEEP [7]. Konno et al. later reported conization using harmonic scalpel that could improve disadvantages of laser and LEEP [8]. As described, many new

procedures and instruments have been established in accordance with technological development. Every procedure has its own characteristics, and the advantages and disadvantages of these methods are described below.

4.2 Principle and Indication

The main purposes of cervical conization are to confirm diagnosis and to treat the lesion. As a treatment modality, conization is able to preserve fertility and allow for subsequent pregnancy; thus, surgeons should make every effort to reduce reproductive and obstetrical complications. Indications for conization are shown in Table 4.1. Diagnostic conization should be performed if invasive cancer is suspected by cytology, but a histological diagnosis cannot demonstrate invasion. Conization can also be applied to evaluate depth of invasion and lymphovascular space invasion (LVSI) for the determination of subsequent surgical procedure in early invasive cancer (stage 1A).

Indications for treatment of CIN differ with various patient populations. According to the 2012 updated consensus guidelines for the management of abnormal cervical cancer screening and cancer precursors, therapeutic conization is unacceptable for CIN3 in pregnant women, and diagnostic excisional procedure is recommended only if invasion is suspected [9]. Special attention should be also paid to postpuerperal and postmenopausal women in performing conization since the incidence of cervical stenosis or occlusion after conization is considered higher in postpuerperal amenorrhic women; additionally, diagnosis of hematometra due to cervical occlusion could possibly be delayed in this subpopulation of patients [10]. In postmenopausal women, Hasegawa et al. reported that incidence of cervical stenosis is significantly higher compared to premenopausal women (59.1 vs. 8.3%) [11]. Based upon these findings, although conization is a less invasive procedure for CIN, conization should be only prudently offered to postmenopausal women. Hysterectomy might be a more preferable treatment for postmenopausal cases.

Table 4.1 Indication of conization of the uterine cervix

Therapeutic
1. Histologically diagnosed CIN3 or stage Ia1
2. Recurrent CIN2~3
3. Adenocarcinoma in situ (AIS)
Diagnostic
1. Suspected CIN3 or more lesion with unsatisfactory colposcopy (entire squamocolumnar junction cannot be visualized)
2. Diagnosis for AIS
3. Suspected (early) invasive cancer in cytology but no correspondence histology/colposcopic finding
4. To devaluate depth of invasion and LVSI for determination of following surgical procedure in early invasive cancer
5. Insufficient cytology or histology to warrant procedure

CIN cervical intraepithelial neoplasia, *LVSI* lymphovascular space invasion

4.3 Preoperative Evaluation

Before conization, preoperative evaluation is very important. When an abnormal Papanicolaou smear is confirmed, colposcopy followed by biopsy should be performed by an experienced colposcopist. Songveeratham et al. reported that 15% of high-grade squamous intraepithelial lesion (HSIL) cases are underdiagnosed by cytology [12]. Although the value of endocervical curettage (ECC) at colposcopy has been controversial, and while ECC has not been routinely performed, Fine et al. reported that preoperative ECC is associated with grade of dysplasia and suggest that routine ECC should be included as part of the preoperative assessment [13]. Pretorius et al. also concluded that ECC should be performed for the patients with abnormal cytology even when colposcopy is satisfactory [14].

4.4 Technique

In performing conization, historically cold knife has been used. Recently, in accordance with the development of new technologies and equipments, electrocautery (LEEP/LLETZ), laser, and harmonic scalpel have been applied for conization. A randomized prospective study comparing CKC, laser, and LEEP and their respective characteristics as reported by Mathevet et al. is summarized in Table 4.2 [15]. They concluded that laser conization is relatively costly and time-consuming and that laser and LEEP may induce artifact so that histological evaluation of the surgical margin is difficult. In a meta-analysis, LEEP/LLETZ is as effective as CKC with regard to recurrence rate, positive margin, residual disease as well as secondary hemorrhage and cervical stenosis [16]. As described, every procedure has its advantages and disadvantages; thus, the procedures should be selected by the surgeon according to the institutional settings, size and depth of the lesion, and/or economic status of the patients.

The scheme of our procedure for laser conization is shown in Fig. 4.1. Briefly, the patient is set in lithotomy position, and the speculum is inserted in the vagina. Acetic acid or Schiller's solution is used in order to determine the range of surgical resection. Hemostatic sutures using No. 2-0 Vicryl are placed at 3 and 9 o'clock positions. Local injection of vasoconstrictor is not routinely used in our institute. Four to eight sutures by No. 3-0 Vicryl are made just inside of the margin to retract

Table 4.2 Characteristics of cold knife, laser, and LEEP (modified ref. 15)

	Mean operative time	Mean blood loss	Mean cone volume	Difficulty of technique	Cost	Evaluation of margin
Cold knife	○	○	◎	○	◎	◎
Laser	○	○	○	○	X	○
LEEP	◎	◎	○	◎	○	X

LEEP loop electrosurgical excision procedure

◎: superior, ○: acceptable, X: inferior

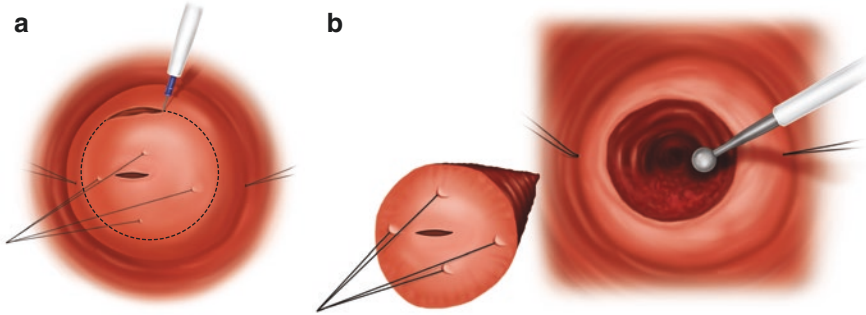


Fig. 4.1 Conization technique by laser. (a) After marking the line of incision 3–5 mm of outer margin with small spot by laser, cervix is cut by laser beam. (b) After removal of the specimen, hemostasis and vaporization are made by defocused laser spot or ball electrode

the lesion, and a knot is made on the thread at 12 o'clock to recognize orientation of the specimen [17]. Width and depth of conization could be determined individually according to the colposcopic findings. After marking the line of incision 3–5 mm of outer margin with small spots by laser, the cervix is cut by laser beam. During the procedure, if surgical mist or bleeding occurs, an aspirator is used during the procedure. After the desired depth is obtained, the upper margin is cut by scalpel so that the pathological diagnosis of the endocervical surgical margin is more readily possible. After removal of the specimen, hemostasis and vaporization are made by defocused laser spot or ball electrode. Additionally, the outer margin is vaporized to reduce recurrence of surgical margin-positive cases. We usually insert a 8 Fr Nelaton catheter into the uterine cavity to avoid stenosis; this will later be removed after about 1 week after conization, but insertion of catheter can be omitted. Absorbable hemostat such as oxidized cellulose is placed on the wound.

When using LEEP/LLETZ, excision in multiple fragments can complicate histopathological assessment, so surgeons should inform the pathologist on the precise orientation of the resected specimens. If CKC is performed, the surgeons should take care to minimize side effect such as hemorrhage and cervical stenosis [17].

Evidence to support use of antibiotics to reduce infectious complications after conization is insufficient, so routine use of antibiotics should be avoided [18].

4.5 Result and Outcome

According to a systematic review, the treatment success rates (no residual disease during follow-up) for CKC, laser conization, and LEEP/LLETZ for CIN are reported as 90–94%, 93–96%, and 91–98%, respectively, and there are no significant differences among these three procedures in treatment outcomes [19]. Even in unsatisfactory colposcopic examinations, there is no significant difference in the incidence of persistent or recurrent disease between LEEP and CKC for CIN [20]. For cervical adenocarcinoma in situ (AIS), there is no difference in residual

and recurrence rates between LEEP and CKC. Conization is acceptable as a definitive treatment for Ia1 squamous cell carcinoma of the cervix if the surgical margin is negative [21, 22].

4.6 Influence of Conization for Pregnancy

The safety of delaying treatment for CIN during pregnancy has been reported. The risk of progression of CIN3 in pregnancy is low, and the spontaneous regression rate is high [23, 24]. For CIN1 to CIN3 in pregnant women, regression rates and persistence rates were reported 16.7–77.4% and 22.6–70.0%, respectively, while progression rates were 0–13.3% [25]. CIN3 in pregnancy is usually observed and should be re-evaluated at 6 weeks postpartum [9], and diagnostic conization during pregnancy is recommended only if invasion is suspected [9].

Adverse obstetrical outcomes after conization have been shown in number of studies. Sadler et al. reported that LEEP and laser conization were associated with significantly increased risk of preterm premature rupture of the membrane (pPROM), and if cone height is ≥ 1.7 cm, pPROM risk increased threefold compared with untreated women [26]. A systematic review and meta-analysis by Kyrgiou et al. showed that treatment for CIN significantly increased the risk of preterm birth. Relative risks (RRs) of preterm delivery according to the conization procedures are 2.70 (2.14–3.40) for CKC, 2.11 (1.26–3.54) for laser conization, and 1.56 (1.36–1.79) for LEEP/LLETZ, respectively. Cone depth is also associated with preterm delivery, and if cone depth is ≥ 20.0 mm, the RR increased to 4.91 (2.06–11.68). Chorioamnionitis and low birth weight are also significantly increased after conization [27].

For young women, the indication and application of conization should be sufficiently discussed. Chevreau et al. reviewed the age at LEEP on obstetrical outcome, and they found that age younger than 25 years at the time of LEEP is associated with extremely early preterm delivery (before 26 weeks) if cone depth is ≥ 15 mm [28]. It can perhaps be surmised that the cervix is a growing organ, and its length is significantly shorter in young women [29]. In these patients, vaporization might better be considered as a treatment option instead of conization. Mariya et al. reported there were no significant differences in cure rate, human papilloma virus (HPV) clearance rate, or recurrent rates between conization and vaporization groups, and no adverse pregnancy outcome was observed in the vaporization group [30]. In order to reduce the height of cone, Kim et al. reported “coin-shaped” conization. In their report, mean cone height was reduced from 14.0 mm to 12.8 mm, and it improved reduction rate of uterine cervical length over the subsequent pregnancy [31], but whether it could contribute to improve obstetrical outcome is still controversial. In order to minimize the incidence of adverse events as well as positive margin, Kawano et al. showed the cutoff value of cone length was 15 mm

in single quadrant disease and 20 mm in two or more quadrant disease to avoid positive cone margin in women ≤ 40 years old [32].

4.7 Residual Disease/Recurrence

After treated for CIN, early detection of residual/recurrent disease is essential. Histology taken under colposcopy after conization has been reported to be highly negative, so colposcopy as the only postoperative test may not be suitable for follow-up after conization [33]. For follow-up after conization, cytology and screening of HPV can be useful for detecting recurrence. Nobbenhuis et al. reported sensitivity of HR-HPV test 6 months after treatment was higher than abnormal cervical cytology in posttreatment CIN2/CIN3 (90 vs. 62%) [34]. Additionally, co-testing with cytology and HPV testing at 12 and 24 months has been recommended as follow-up after conization [9].

The recurrence rate after conization has been reported to be approximately 5% regardless of surgical procedures [35]. Recognizing high-risk factors for recurrence after conization is important. It is well-known that a positive surgical margin is a risk factor for residual disease/recurrence after conization [36]. Age ≥ 50 , parity ≥ 5 , positive post-cone ECC, and multi-quadrant disease can also predict post-cone residual disease [37]. Tanaka et al. mentioned aged ≥ 46 was an independent risk factor for recurrent/persistent disease [35]. In multivariate analysis from Zhu et al., for patients with high-grade squamous intraepithelial lesion (HSIL) with positive margins after LEEP, age ≥ 35 was an independent risk factor [38]. Giannella et al. described HPV clearance after conization decreased with age; thus increasing age can be categorized as a risk for post-conization recurrence [39]. Park et al. reported positive margin and pre-cone HR-HPV load were the only significant factors predicting post-cone residual disease [36].

4.8 Complications

Several complications of conization have been reported. Intraoperative bleeding is a major complication but is rarely heavy and in most cases can be controlled by sutures and electrocoagulation. In our experience, most cases of bleeding can be controlled by ball electrode. Postoperative bleeding is a frequent complication. Usually, it takes 4–5 weeks for postoperative reepithelialization of the cervix. During this period, slight hemorrhage may occur, but in cases of massive hemorrhage, this will occur on the 8th to 12th day after conization because during this period the fibrino-leukocytic membrane covering the denuded cervix sloughs away [40]. Incidences of secondary hemorrhage of conization in LEEP, CKC, and laser were reported 5.3–10.1%, 0–9.4%, and 0.9–6.1%, respectively [15, 16, 41–45] (Table 4.3). Occasionally it requires hemostasis including suturing or packing and rarely requires blood transfusion, uterine artery embolization, or hysterectomy.

Table 4.3 Incidence of secondary hemorrhage and cervical stenosis after conization

	LEEP (%)	CKC (%)	Laser (%)
Secondary hemorrhage	5.3–10.1	0–9.4	0.9–6.1
Cervical stenosis	3.4–19	2.9–29	0–9

LEEP loop electrosurgical excision procedure, CKC cold knife conization

Cervical stenosis is another major problem after conization. Cone height is a risk of stenosis, but elderly age is another risk [35]. Incidences of postoperative cervical stenosis of CKC, LEEP, and laser conization were reported 3.4–19%, 2.9–29%, and 0–9%, respectively [15, 16, 41–45] (Table 4.3). As there is no standard definition of stenosis, these findings could not be simply compared. Special consideration for postmenopausal and postpuerperal amenorrhic women should be made because they are at high risk for cervical stenosis (see Chap. 4.2).

Although there is a possible risk of infection, major infection after conization in any procedures (CKC, LEEP, and laser) is approximately 0.1–2% [46, 47], but it will depend on the patients' status (history of pelvic inflammatory disease, etc.). Other uncommon complications of conization have been reported to include bladder perforation, peritonitis, intra-abdominal bleeding, pseudoaneurysm of uterine artery, and vaginal evisceration [45, 48–51].

4.9 Future Prospect

Although fertility-sparing surgery for International Federation of Gynecology and Obstetrics (FIGO) stage 1A1 with LVSI, 1A2, and small 1B1 cervical cancer patients is radical trachelectomy (RT) with pelvic lymphadenectomy, postoperative severe complications could occur as well as a high incidence of premature delivery in subsequent pregnancy. Thus, several trials have been performed to develop less invasive procedures for low-risk early-stage cervical cancer (histology; squamous cell carcinoma, adeno/adenosquamous cell carcinoma, tumor size <2 cm, stromal invasion <10 mm, no LVSI) [52]. Biliatis et al. performed loop biopsy with pelvic lymphadenectomy for 35 small-volume stage 1B1 cervical cancer patients, and there was no recurrence, and 7 full-term pregnancies have been achieved [53]. Fagotti et al. reported CKC and laparoscopic pelvic lymphadenectomy for early-stage cervical cancer. Four of 17 cases involved LVSI, and 2 patients received adjuvant chemotherapy, and no recurrence was observed after a median follow-up of 16 months. They concluded CKC and laparoscopic pelvic lymphadenectomy might be feasible as a fertility-sparing procedure instead of radical trachelectomy in selected and informed patients [54]. Literature review has demonstrated cone biopsy to be a feasible treatment of \geq stage 1A2 disease by Reade et al. including data from Fagotti et al. In this review, a total of 1163 cases received conization, and recurrence rate and death from disease were 2.0% and 0.7%, respectively [55]. Andikyan et al. reported cervical conization with sentinel lymph node (SLN) mapping could be acceptable for small-volume stage I cervical cancer [52]. Neoadjuvant chemotherapy followed by conization with lymphadenectomy for stage 1B2 disease case has also been attempted

[56]. In order to establish a less invasive procedure employing conization with warranted curative rate, further prospective studies should be conducted.

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