Cervical Excision Procedure: A Trend of Decreasing Length of Excision Observed in a Multicenter Survey

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Objectives: The aim of the present study was to observe the trend of length of cone excisions in women treated with cervical excision procedure in five institutions of Central and Northern Italy.

Materials and Methods: A multicenter retrospective cohort study was conducted on women who underwent a cervical excision procedure between January 2006 and December 2014. The pertinent clinical, histopathological, and sociodemographic characteristics of each woman were collected. In particular, the length of the cone specimen was evaluated and all of the factors that potentially influenced the length of excision were considered.

Results: A total of 1482 women who underwent a cervical excision procedure from January 2006 to December 2014 were included. A mean (SD) cone length of 12.9 (5.0) mm was reported, and mostly, a significant decrease during the whole study period emerged. Age ($r = 0.1$, $p = .007$) and preoperative diagnosis of glandular lesions ($r = 0.1$, $p < .001$) were significantly related to the length of cone excision on multivariate analysis. Compared with the carbon dioxide laser excisional procedure, loop electrosurgical excision procedure showed a negative correlation with the length of excision ($r = -0.2$, $p < .001$).

Conclusions: During the study period, a significant decrease in the length of cone excision was observed, probably reflecting the gynecologists' acquired awareness of the increased risk of adverse obstetric outcomes for future pregnancies in the case of wide cone excisions.

Key Words: cervical conization, cervical excision, CIN, CO_2 laser conization, cone length, LEEP

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The peak incidence of high-grade intraepithelial lesions of the uterine cervix is observed in women aged 25 to 35 years,[1] and in these cases, a cervical excision procedure is recommended.[2,3] Childbearing age women can also develop microinvasive cervical cancer,[4] for which a "fertility-sparing" approach with cervical excision procedure is possible in selected cases.[5] Therefore, these women may undergo a cervical excision when their desire for future pregnancies is still present and, in some cases, before their first pregnancy.[6]

The procedures that are most commonly used for cervical excision are the loop electrosurgical excision procedure (LEEP) and carbon dioxide (CO_2) laser excisional procedure. However, to date, no method has proven to be superior considering the rate of treatment failure, the disease persistence on follow-up, the adequacy of the specimen for histopathological evaluation, and the risk of morbidity.[7]

Women who underwent a cervical excision procedure are generally considered at increased risk of preterm birth[8] because the surgical removal of a portion of the cervix, theoretically, leads to the loss of cervical integrity with an "anatomo-functional" cervical impairment in the subsequent pregnancies.[9,10] Interestingly, in the last decade, several studies have pointed out that the risk of preterm delivery in women with previous cervical excision procedure seem to be related to the dimensions of the excised specimen and, in particular, to the cone length.[1,8,9,11]

These studies have led to the awareness of the potential disadvantages of wide cone excision in terms of adverse obstetric outcomes for future pregnancies. Hence, in the last few years, gynecologists have tried to be as conservative as possible in treating cervical intraepithelial lesions.

Consequently, during the last decade, a trend of the reduction in the dimension of the cone specimen should have been expected; however, to our knowledge, no previous study has demonstrated this trend.

Therefore, the aim of the present study was to evaluate the cervical excision procedures performed in five institutions of Central and Northern Italy, with a particular interest in analyzing the trend of length of cone excisions, to observe whether the expected reduction is actually present.

MATERIALS AND METHODS

We conducted a retrospective cohort study of women who underwent a cervical excision procedure between January 2006 and December 2014 in five institutions of Central and Northern Italy.

We included in the present analysis only women who had undergone a cervical excision procedure for the first time, for whom the cytological, colposcopic, and histopathological documentation was fully available. We have extended the data collection retrospectively until 2006, because data about the previous years were not available in all of the participating institutions.

Abnormalities on referral cervical cytology were classified, according to the most recent Bethesda system terminology.[12] Cytology examinations performed before the introduction of the most recent Bethesda system terminology were revised accordingly, by the pathologists of each institution involved in the study.

The colposcopic examinations were recorded according to the 2011 revised colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy.[13] The colposcopies performed before the introduction of the 2011 International Federation for Cervical Pathology and Colposcopy nomenclature were revised accordingly by the gynecologists of each institution involved in the study, through the revision of colposcopic charts and images. Women with a concomitant diagnosis of high-grade vaginal intraepithelial lesions or vaginal cancer were excluded from the present analysis.

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We have defined a "two-step" strategy for those cases in which the cervical excision procedure was performed after a colposcopy-guided biopsy after an abnormal cytology, as usual. A "one-step" strategy (in which the excisional procedure was performed without a previous cervical biopsy) was adopted in some cases, taking into account the referral cervical smear, the colposcopic impression, the clinical history, and the patient's preference and adherence to recommendations, and after an informed discussion between the operator and the patient.

For the subsequent analysis, we have considered as "high-grade preoperative diagnosis" the following conditions: cytological report of atypical squamous cells - cannot exclude high grade squamous intraepithelial lesions (ASCH), high grade squamous intraepithelial lesion (HSIL), Atypical Glandular Cells, favor neoplastic (AGC-FN) and adenocarcinoma in situ (AIS), for women with one-step strategy, or histopathological diagnosis of cervical intraepithelial neoplasia 2, cervical intraepithelial neoplasia 3, AIS or invasive cancer (for women with a two-step strategy).

The histopathological characteristics of the cone specimen were collected for each patient. In particular, the status of ectocervical (external) margin and endocervical cone margin (apex of the cone) was reported. The dimensions of cone specimens were determined with a ruler by the pathologist after fixation in formalin, and the cone "length" was defined as the distance from the distal to the proximal margin of the cone specimen, as otherwise described.[13]

All of the cervical excision procedures were performed in an outpatient setting, under local anesthesia and strict colposcopic guidance, through LEEP or CO_2 laser. Loop electrosurgical excision procedures were performed with rounded loops of appropriate size, which were chosen according to the type of the transformation zone and the area of cervical tissue to remove. Laser excisional procedures were performed with a hand-directed CO_2 laser (Sharplan CO_2 Laser System, Laser Ventures Inc, Woodstock, GA) with a maximum power output of 40 W, used in continuous mode. The beam spot diameter ranged from 0.5 to 1 mm with an irradiance ranging from 2500 to 3500 W/cm^2, guided by a micromanipulator. All the excisional procedures were performed by one gynecologist with particular expertise in the management of lower genital tract lesions for each institution.

The primary aim of the present study was to analyze the trend of the cone length of cervical excisional procedures during the study period. As a secondary analysis, we investigated the factors related to the positivity of endocervical margins and their potential correlation with the cone length.

Statistical software SPSS 20 (SPSS Inc, Chicago, IL) was used for the data analysis. All of the continuous variables were tested for normality with the D'Agostino-Pearson test. Normally distributed variables were expressed as mean(SD), whereas skewed variables were reported as median and interquartile range. Either the *t* test or the Mann-Whitney test was used for comparison, as appropriate. Qualitative variables were expressed as proportions and were compared with χ^2 or Fisher exact test as appropriate. Correlation between continuous, normally distributed variables was determined with Pearson's correlation coefficient (*r*). A multivariate analysis was performed to identify the factors that are significantly associated with the length of cone excision and with the positivity of endocervical margin. A *p* value of less than .05 was considered as statistically significant. An informed consent for data collection was obtained from each patient at the time of procedure. Local ethic committee approval was obtained for the present study (CRO IRB-2014-08).

Role of the Funding Source

There is no funding source for this study.

RESULTS

From January 2006 to December 2014, 1795 women underwent a cervical excision procedure in the institutions involved in this study. Among these, 1482 fulfilled the study inclusion/exclusion criteria and were included in the present analysis. A total of 89 patients were excluded because of previous cervical treatments, 134 because of concomitant diagnosis of preinvasive or invasive vaginal lesions, and 90 because of incomplete or missing data.

The cervical excisional procedures were performed through LEEP in 908 cases (61.3%) and through CO_2 laser in the remaining 574 women (38.7%). A one-step strategy was adopted in 340 women (22.9%). The rate of one-step approach was similar in 2006–2009 compared with 2010–2014 (24.1% vs 22.3%, $p = .47$).

In the whole study cohort, the mean (SD) age was 38.2(9.2) years and 142 women (9.6%) were postmenopausal. Considering the mean age at the time of the procedure per year, no difference emerged during the whole study period ($p = .31$).

Table 1 reports the cytological findings or histopathological preoperative diagnosis, according to the two different therapeutic strategies (one-step or two-step). In particular, a "high-grade preoperative diagnosis" (as previously defined) was reported in 1343 women (90.6%) and a preoperative diagnosis of cytological or histological glandular abnormalities (AGC, AIS, or invasive glandular lesion) emerged in 66 women (4.5%).

The histopathological diagnosis on the final cone specimens is reported in Table 2.

In the whole study cohort, the mean (SD) cone length was 12.9 (5.0) mm. At the histopathological evaluation of the final cone specimens, the endocervical margin (apex of the cone) was positive in 189 women (12.8%), whereas the ectocervical margin was positive in 71 cases (4.8%). Among women with positive margins, only 20 (1.3% of the entire study population) required a re-excision.

Figure 1 shows the trend of cone length during the study period (i.e., 2006–2014). A significant decrease during the whole study period emerged ($p < .001$, one-way analysis of variance), and in particular, the mean (SD) cone length in 2006–2009

TABLE 1. Preoperative Diagnosis According to the Two Different Therapeutic Approaches (See-and-Treat and Two-Step)

Approach	Cytology or histology reports	*n* (%)
One-step (*n* = 340)	ASCUS	5 (1.5)
	ASCH	62 (18.2)
	LSIL	33 (9.7)
	HSIL	204 (60.0)
	AGC-NOS	30 (8.8)
	AGC-FN	5 (1.5)
	AIS	1 (0.3)
Two-step (*n* = 1142)	CIN 1	71 (6.2)
	CIN 2	509 (44.6)
	CIN 3	510 (44.7)
	AIS	18 (1.6)
	Invasive (squamous)	20 (1.8)
	Invasive (glandular)	14 (1.2)

ASCUS indicates atypical squamous cells of undetermined significance; ASCH, atypical squamous cells cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC-NOS, atypical glandular cells not otherwise specified; AGC-FN, atypical glandular cells favor neoplastic; AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia.

TABLE 2. Histopathological Diagnosis on Final Cone Specimens

Diagnosis	*n* (%)
Negative	105 (7.1)
CIN 1	163 (11.0)
CIN 2	460 (31.0)
CIN 3	667 (45.0)
AIS	23 (1.6)
Invasive squamous cells carcinoma	39 (2.6)
Invasive adenocarcinoma	25 (1.7)

CIN indicates cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ.

was significantly higher than 2010–2014 (14.0[5.0] vs 12.3 [5.0]mm, $p < .001$).

The univariate analysis of factors potentially related to the cone length (age, menopause, one- vs two-step approach, high-grade preoperative diagnosis, glandular preoperative diagnosis, and type of excisional procedure) is reported in Table 3. During the subsequent multivariate analysis, the association between the length of cone excision and the patients' age ($r = 0.1$, $p = .007$), the preoperative diagnosis of glandular lesions ($r = 0.1$, $p < .001$), and LEEP ($r = -0.2$, $p < .001$) was confirmed.

The factors potentially associated with positive endocervical margin status are reported in Table 4.

In particular, women with cone length of less than 15 mm showed a significantly higher positivity of endocervical margin with respect to women with cone length of 15 mm or greater (14.2% vs 10.5%, $p = .04$). On multivariate analysis, among the factors that resulted significant at the univariate, only age (odds ratio = 1.02, 95% confidence interval [CI] = 1.01–1.04, $p = .008$) and cone length (odds ratio = 0.96, 95% CI = 0.93–0.99, $p = .008$) were significantly related to the positivity of the endocervical margins.

DISCUSSION

Through our retrospective survey among the five institutions in Central and Northern Italy, we observed a significant reduction of the length of cone excision from 2006 to 2014 (see Figure 1).

On multivariate analysis, the patients' age at the time of the procedure was significantly related to the length of cone excision.

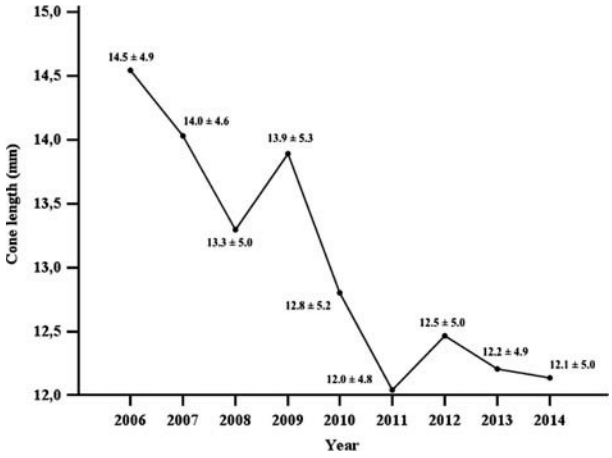

FIGURE 1. Length of cone excisions (expressed as mean[SD]) in the entire study cohort ($N = 1482$) considering the year of procedure.

TABLE 3. Univariate Analysis of Factors Associated With Cone Length in the Study Population

Outcome	*n*	Cone length, mm	*p*
Age < 25 y	87	12.3(5.0)	.02
Age 26–40 y	850	12.6(4.9)	
Age 41–55 y	476	13.4(5.2)	
Age ≥ 56 y	69	13.6(5.0)	
Menopause	142	13.3(4.6)	.26
Child-bearing age	1340	12.8(5.1)	
One step	340	13.3(4.7)	.06
Two step	1142	12.7(5.2)	
High-grade preoperative diagnosis	1343	12.9(5.1)	1.0
Low-grade preoperative diagnosis	139	12.9(4.6)	
Squamous preoperative diagnosis	1416	12.7(5.0)	<.001
Glandular preoperative diagnosis	66	15.6(5.4)	
LEEP	908	12.0(6.1)	<.001
LASER	574	14.3(1.8)	

Data are expressed as mean(SD), unless otherwise indicated.
LEEP indicates loop electrosurgical excision procedure.

This result was not unexpected because gynecologists tend to be more "conservative" (performing smaller excisional procedures) in younger patients, to minimize the potential risks for future pregnancies.

However, it should be considered that as recommended by the 2012 American Society of Colposcopy and Cervical Pathology guidelines, for young women diagnosed with high-grade squamous intraepithelial lesions of the uterine cervix, a careful observation (rather than intervention) could be taken into account, provided colposcopy is adequate.[2]

Furthermore, the correlation between the patients' age and the length of cone excision may be explained also by the fact that older women with an endocervical transformation zone could have lesions that reside deep in the endocervical canal; thus, deeper excisions are advisable in these cases.

Interestingly, the age distribution in women of the study cohort was similar in each year of the study period; thus, the observed trend of length of excision is not affected by the potential bias of the different age distribution.

Even the preoperative diagnosis of glandular lesions was significantly related to the length of cone excision on multivariate analysis. In addition, in this case, such a correlation was not unexpected, because in case of glandular lesions, the lesion itself can develop deep in the endocervical canal[14–16]; thus, deeper excisions are advisable.

Furthermore, a higher length of excisions was reported in women who underwent a CO_2 laser excisional procedure compared with LEEP. The reasons behind this correlation are unclear. It is possible to speculate that such a difference could be due to the procedure itself; with the LEEP, even by the use of "standard" round loops of different sizes, it is more difficult to "customize" the excisional procedure, and the depth of the excisions itself may depend on the superficial extent of the lesion, which influence the choice of the appropriate loop.

In a recent study by Kyrgiou et al,[11] with respect to the general population, the women treated with CO_2 laser excisional procedure showed a higher risk of preterm birth (relative risk = 2.11, 95% CI = 1.26–3.54) rather than those treated with LEEP (RR = 1.56, 95% CI = 1.36–1.79).

Based on our findings, it is possible to speculate that the higher risk of preterm birth observed in women treated with CO_2 laser compared with LEEP could be due to the higher length

TABLE 4. Univariate Analysis of Factors Associated with Positive Endocervical Margin in the Study Population

Outcome	Positive endocervical margin (n = 189)	Negative endocervical margin (n = 1293)	p
Age, mean (SD), y	40.2 (9.2)	37.9 (9.1)	<.01
Cone length, mean (SD), mm	12.1(4.8)	13.0 (5.1)	.02
Menopause	22 (11.6)	120 (9.3)	.38
One-step approach	47 (24.9)	293 (22.7)	.56
High-grade preoperative diagnosis	175 (92.6)	1168 (90.3)	.38
Glandular preoperative diagnosis	13 (6.9)	53 (4.2)	.14
LEEP	131 (69.3)	777 (60.1)	.02
LASER	58 (30.7)	516 (39.9)	.02

Data are expressed as n (%), unless otherwise indicated.
LEEP indicates loop electrosurgical excision procedure.

of cone excisions obtained by CO_2 laser technique. However, further studies assessing this specific topic are advisable.

As a secondary analysis, we investigated the factors potentially related to the positivity of endocervical margins and both age and cone length showed a significant correlation with the positivity of cone apex.

In particular, women with cone length of less than 15 mm showed a significantly higher rate of positive endocervical margin with respect to women with cone length of 15 mm or greater.

According to these data, we should state that an excision of at least 15 mm should be achieved to reduce the risk of positivity of endocervical margin of the cone. However, previous published studies reported a doubled risk of preterm birth in women with a previous cervical excision of greater than 15 mm.[17] Therefore, we think that an excision of at least 15 mm should be achieved in women without desire for future pregnancies or in women with glandular preoperative diagnosis. In the latter case, if a diagnosis of AIS with positive endocervical margin is made, a re-excision procedure is recommended.[2] In the other cases, smaller excisional procedures can be sufficient to reach a balance between the risk of preterm delivery in the subsequent pregnancies and the risk of positive endocervical margin of the cone. This is particularly true if we considered that only 1.3% of the women included in the study needed a re-excision for positive endocervical margin.

The main strength of the present study is the large number of cases, which were included through a multi-institutional data collection for almost 10 years. Moreover, the use of different techniques allowed a comparison between LEEP and the CO_2 laser that are currently the most commonly used cervical excision procedures.

Due to its retrospective nature, unavoidably, this study has potential limitations. For example, because different gynecologists and pathologists (one per each institution involved in the study) contributed to data collection and analysis (even through a revision of cytology and colposcopy reports), the interobserver variability could be considered a potential bias.

The main limitation of the present study is probably that because the data collected are limited to those already reported in the medical charts, it has not been possible to analyze the obstetric outcome in the patients included (e.g., the rate of preterm delivery after the cervical excision procedure). However, because in a prospective setting the operators may change their approach under observation (Hawthorne effect), the retrospective design allows us to observe the real trend of decreasing length of cervical excisions.

The potential correlation between cervical excision procedures (and especially the length of excision) and preterm delivery is widely discussed in the recent literature.[1,8,9,11] More precisely, a recent meta-analysis found a mean rate of preterm delivery in women with a history of conization of 8.8%.[18] The reduction of cone length excisions observed in our study, theoretically, should lead to at least a minimal reduction of such a burden of preterm deliveries. Therefore, this could have important clinical and public health implications, if we consider that preterm delivery is still one of the most important obstetric issues, and infants born prematurely have increased risks of mortality and morbidity throughout childhood.[19] However, in our opinion, further studies assessing the obstetric outcome in women treated with cervical excisional procedure are advisable. These studies could allow to evaluate whether the trend of the reduction in the dimension of the cone specimen observed in the last years actually determine a reduction in the rate of preterm delivery in such patients.

Furthermore, the introduction of human papillomavirus vaccination should determine, in the next years, a reduction of the incidence of human papillomavirus–related intraepithelial lesions of the uterine cervix, and thus a reduction of the need of cervical excisional procedures. However, even in this case, future studies assessing this specific topic are advisable.

CONCLUSIONS

In recent years, gynecologists have developed an increased sensitivity to the issues of adverse obstetric events related to previous cervical excision procedures; thus, they have tried to reduce the length of cone excisions in their daily clinical practice. This is the first study in which such a trend has been clearly demonstrated.

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