Trend of decreasing length of cervical cone excision during the last 20 years

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Abstract. – OBJECTIVE: The aim of the present investigation was to evaluate the cervical conizations performed in the last 20 years in a single institution, with a particular interest in analyzing the trend of the length of cone excisions.

PATIENTS AND METHODS: A retrospective cohort study of women who underwent a CO_2-laser cervical conization between January 1996 and December 2015. Cytological abnormalities on referral pap smear, colposcopic findings and pertinent clinical and socio-demographic characteristics of each woman were collected. In particular, the length of cone specimen was evaluated, taking into account all the factors potentially influencing the length of excision.

RESULTS: A total of 1270 women who underwent cervical conization from January 1996 to December 2015 were included in the analysis. A mean cone length of 15.1 ± 5.7 mm was reported, and we observed a significant decrease in the length of cone excisions over the whole study period. Age ($r_{partial}$ = 0.1543, $p < 0.0001$), *see & treat* procedure ($r_{partial}$ = -0.1945, $p < 0.0001$) and grade II colposcopic findings ($r_{partial}$ = 0.1540, $p < 0.0001$) were significantly associated with the length of cone excision on multivariate analysis.

CONCLUSIONS: In the last 20 years, a significant decrease in the length of cone excision was observed. In our opinion, this can be due to the acquired awareness by the gynecologists of the potential disadvantages of wide cone excision in term of adverse obstetric outcomes in future pregnancies.

Key Words:
Cervical conization, CO_2 laser conization, CIN, Cervical excision.

Introduction

High-grade cervical intraepithelial neoplasia (CIN) and usual type adenocarcinoma *in situ* (AIS) are precancerous lesions of the uterine cervix, induced by persistent infection by high-risk human papilloma virus (HR-HPV)[1-3].

In the last decades, the ability of the cervical cancer screening test (Pap test and HPV DNA test) to identify women at risk of precancerous lesions, and the availability of effective and relatively non-invasive treatment for these lesions has led to a reduction of incidence and mortality for cervical cancer in most industrialized countries[4].

Cervical precancers can occur at any age, but the peak incidence is in women aged 25-35 years[5]; therefore, most of these lesions are diagnosed and treated in childbearing age women[6,7]. Moreover, in the last decades, we have seen a continuous trend of delayed childbearing, which has resulted in an increased proportion of women being diagnosed with high-grade CIN or AIS (and subsequently treated) before their first pregnancy[8].

As reported in the 2012 ASCCP guidelines for the management of abnormal cervical cancer screening tests and cancer precursors[9], and in the 2009 European guidelines for clinical management of abnormal cervical cytology[10], in the case of high-grade CIN, an excisional procedure is recommended. In the case of AIS, a total hysterectomy remains the treatment of choice; however, for women who wish to maintain fertility, a conservative approach with cervical conization

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can be proposed[9]. Similarly, a "fertility sparing" approach with cervical conization can be safely proposed (in selected cases) even for women with microinvasive cervical cancer[11].

Cervical conization can be performed with different techniques: cold knife, loop electrosurgical excision procedure (LEEP) and carbon dioxide laser (CO_2 laser). Regardless the technique used, the surgical removal of a portion of the cervix leads to a higher risk for obstetric complications due to the loss of cervical integrity[1,12]. Indeed, in women with a history of excisional cervical surgery, an increased risk of adverse obstetric events, such as premature rupture of the membranes and preterm birth has been reported[13,14]. In particular, the risk of preterm birth appears to be related to the length of cone excision[1,5,15]. It is indeed reported that a cone length > 15 mm is associated with a doubled risk of preterm birth[16]. For these reasons, in the last years, gynecologists have tried to be as more conservative as possible in treating cervical dysplasia. Thus, a trend of reduction in the dimension of the cone specimen should have been expected.

The aim of the present work was therefore to analyze the cervical conizations performed in the last 20 years in a single institution, evaluating the trend of the length of cone excisions.

Patients and Methods

This was a retrospective cohort study of women who underwent a cervical excision procedure for CIN, AIS or micro-invasive cervical cancer between January 1996 and December 2015 at the Gynecological Oncology Unit, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, Italy.

For the present analysis, we considered only women who had undergone a cervical conization for the first time. Women with a concomitant diagnosis of vaginal dysplasia or vaginal cancer were excluded, as well as women with previous ablative treatments on the uterine cervix.

Age, menopausal status, referral cytology, colposcopic findings and histological diagnosis (on colposcopy-guided biopsy) were collected for each patient.

Referral cytological abnormalities were classified according to the most recent Bethesda system terminology[17]. Cytology examinations performed before the introduction of the most recent Bethesda system terminology were revised accordingly.

The colposcopic characteristics of each woman (visibility of the squamocolumnar junction, normal/abnormal colposcopic findings and, in particular, the definition of grade I and grade II findings) were recorded according to the 2011 revised colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy (IFCPC)[18]. The colposcopies performed before the introduction of the 2011 IFCPC nomenclature were revised accordingly.

We have defined a "*two-step"* strategy for those cases in which the cervical conization was performed after a colposcopy-guided biopsy following an abnormal cytology. A "*see & treat"* strategy (in which the conization was performed without a prior cervical biopsy) was sometimes adopted in cases of high-grade referral cervical smear with a high-grade colposcopic impression. This approach was sometimes adopted also in the case of persistent low-grade cervical smear with a high-grade colposcopic impression or in case of high-grade cytology (or persistent low-grade cytology) in women in whom the squamocolumnar junction was not visible on colposcopy. However, the choice between the two strategies (*two-step* or *see & treat*) was made case by case, after an informed discussion between the operator and the patient, taking into account the referral cervical smear, the colposcopic impression, the clinical history and patient's preference.

We have considered as "high-grade preoperative diagnosis" the following conditions:

- Cytological diagnosis of atypical squamous cells – cannot exclude HSIL (ASCH), high grade squamous intraepithelial lesion (HSIL), Atypical Glandular Cells, favor neoplastic (AGC-FN) and adenocarcinoma *in situ* (AIS) for women with the *see & treat* strategy
- Histopathological diagnosis of CIN 2, CIN 3, AIS or invasive cancer, for women with a *two-step* strategy.

At the histopathological examination of the cone specimen, the status of ectocervical (external margins) and endocervical (apex) cone margins and the length of the cone specimen was analyzed.

The histopathological cone specimens were classified as negative, low-grade cervical intraepithelial neoplasia (CIN 1), high-grade cervical intraepithelial neoplasia (CIN 2 and CIN 3), squamous cell carcinoma (microinvasive or invasive), adenocarcinoma *in situ*, or adenocarcinoma (microinvasive or invasive)[19]. In the cases in which

different grades of dysplasia coexisted, the worse histopathological diagnosis was considered for the subsequent analyses.

The dimensions of cone specimens were determined with a ruler by the pathologist after fixation in formalin and are expressed in millimeters. In particular, the cone "length" was defined as the distance from the distal to the proximal margin of the cone specimen, as otherwise described[18].

All the data previously described were obtained by a review of the medical records of all the patients included in the analysis. Women with incomplete or missing data were excluded.

All the procedures were performed by the same experienced operator in an outpatient setting, under local anesthesia and strict colposcopic guidance, with a hand-directed CO_2 laser (Sharplan CO_2 Laser System, Laser Ventures Inc., Woodstock, GA, USA) with a maximum power output of 40 Watts. 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.

The primary aim of the present investigation was to analyze the cervical conizations performed during the study period, with a particular interest in evaluating the trend of the length of cone excisions.

As a secondary analysis, we investigated the factors related to the positivity of endocervical margins, even considering the cone length.

According to a previous studies[20], we identified the following categories of cone length for the analysis: 1-9 mm, 10-14 mm, 15-19 mm and ≥ 20 mm.

Statistical Analysis

Statistical software SPSS 20 (IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data analysis. All continuous variables were tested for normality with the D'Agostino-Pearson test; normally distributed variables were expressed as mean ± SD, while skewed variables were reported as median and interquartile range (IQR). The *t*-test or the Mann-Whitney test were used for comparison as appropriate. Qualitative variables were expressed as proportions and were compared with Chi-square or Fisher's exact test as appropriate. Correlation between continuous, normally distributed variables was determined with Pearson's correlation coefficient (r). We analyzed the trend of age and cone length as a function of the year of the procedure and the one-way ANOVA test, along with the Tukey-Kramer test as post-hoc test, was used for comparison between mean age and mean cone length during the study period. A univariate analysis was performed with the aim of identifying factors that were significantly associated with the length of cone excision. A stepwise multivariate linear regression analysis was, then, performed including factors that were significantly associated with cone length at the univariate analysis. A similar approach (univariate – stepwise multivariate logistic regression) was used to identify factors associated with positivity of endocervical margins.

Local Ethic Committee approval was properly obtained for this investigation.

Results

From January 1996 to December 2015, 1521 women underwent a CO_2-laser cervical conization at our institute. Among these, 103 patients with concomitant diagnosis of pre-invasive or invasive vaginal lesions, 73 women with previous cervical treatments and 75 women with incomplete or missing data on their medical charts were excluded. Therefore, 1270 patients were included in the final analysis and constituted the study population.

In the entire study cohort, the mean (± SD) age was 38.7 ± 9.3 years and 123 women (9.7%) were post-menopausal.

On colposcopy, the squamocolumnar junction was visible in 1235 women (97.2%). More precisely, 33 of them (2.7%) had a normal colposcopic finding; 458 (37.1%) showed grade I abnormal colposcopic findings and 744 women (60.2%) had grade II abnormal colposcopic findings.

Table I shows the preoperative diagnosis (before cervical conization) according to the two different therapeutic approaches (*see & treat vs. two-step*). The *see & treat* strategy was adopted in 270 women (21.2%). A "high-grade pre-operative diagnosis" (as previously defined) was found in 1204 (94.8%) patients and, in particular, a pre-operative diagnosis of glandular abnormalities (cytological or histological) emerged in 82 women (6.5%).

Table II reports the histopathological diagnosis on final cone specimens.

The mean (± SD) cone length in the entire study population was 15.1 ± 5.7 mm. The endocervical margin was positive in 145 (11.4%) patients, while the ectocervical margin in 23 cases (1.8%).

Table I. Pre-operative diagnosis according to the two different therapeutic approaches (*see & treat* and *two-step*).

Approach	Diagnosis	No. (%)
See & treat (no. = 270)	ASCUS	2 (0.7)
	ASC-H	48 (17.8)
	LSIL	8 (3.0)
	HSIL	168 (62.2)
	AGC-NOS	32 (11.9)
	AGC-FN	10 (3.7)
	AIS	2 (0.7)
Two-step (no. = 1000)	CIN 1	24 (2.4)
	CIN 2	398 (39.8)
	CIN 3	505 (50.5)
	AIS	16 (1.6)
	Invasive SCC	18 (1.8)
	Invasive AC	39 (3.9)

ASCUS: atypical squamous cells of undetermined significance; ASC-H: 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; SCC: squamous cell carcinoma; AC: adenocarcinoma.

Figure 1 presents the trend of cone length in the period 1996-2015. A significant decrease over the whole study period emerged ($p < 0.001$, *one-way ANOVA*) and, in particular, the mean (± SD) cone length in the period 2006-2015 was significantly lower than the period 1996-2005 (17.2 ± 6.0 *vs.* 13.3 ± 4.8 mm, $p < 0.0001$). Moreover, comparing the cervical conizations performed in 2015 with those performed in 1996, a reduction in the mean cone length of 30% was observed.

Analyzing the factors potentially related to the length of the cone excision, we found a significant positive correlation with women's age (r = 0.1110, $p = 0.0001$). Furthermore, patients with a "high-grade pre-operative diagnosis" on cytology or cervical biopsy had a significantly higher length of cone excision, compared to patients with a low-grade pre-operative diagnosis (15.2 ± 5.8 *vs.* 13.0 ± 5.0 mm, $p = 0.0026$). Similarly, a higher length of cone excision was observed in women with grade II colposcopic findings, compared to women with grade I colposcopy (15.9 ± 6.0 *vs.* 14.1 ± 5.2 mm, $p < 0.0001$). The women who underwent a *see & treat* procedure presented instead a significantly lower length of cone excision, compared to those who underwent the "two-step" approach (13.0 ± 4.6 *vs.* 15.6 ± 5.9, $p < 0.0001$).

No significant correlation emerged between the length of cone excision and the menopausal status, visibility of SCJ on colposcopy or pre-operative diagnosis of glandular lesion.

Therefore, we performed a multivariate logistic regression including the following variables: age, *see & treat* procedure, high-grade preoperative diagnosis and grade II colposcopic appearance. On multivariate analysis, age ($r_{partial} = 0.1543$, $p < 0.0001$), *see & treat* ($r_{partial} = -0.1945$, $p < 0.0001$) and high-grade colposcopic appearance ($r_{partial} = 0.1540$, $p < 0.0001$) were confirmed to be significantly and independently associated with the length of the cone excision.

As a secondary analysis, we investigated the factors related to the positivity of endocervical margins, even considering the cone length, in the whole study population.

The mean (± SD) cone length in women with a positive endocervical margin was significantly shorter than women with a negative endocervical margin (14.2 ± 6.0 *vs.* 15.3 ± 5.7 mm, $p = 0.0299$) and a significantly decrease in the positivity of the endocervical margin with respect to the categories of cone length emerged (Table III). More precisely, the women with 1-9 mm cone length showed a higher positivity of the endocervical margin than women with cone length

Table II. Histopathological diagnosis on final cone specimens.

Diagnosis	Whole study cohort no. = 1270	See and treat no. = 270	"two-step" no. = 1000	p
Negative	75 (5.9)	17 (6.3)	58 (5.8)	0.87
CIN 1	161 (12.7)	41 (15.2)	120 (12.0)	0.19
CIN 2	411 (32.4)	78 (28.9)	333 (33.3)	0.19
CIN 3	503 (39.6)	116 (42.9)	387 (38.7)	0.24
AIS	16 (1.2)	4 (1.5)	12 (1.2)	0.93
Invasive SCC	69 (5.4)	9 (3.3)	60 (6.0)	0.11
Invasive AC	35 (2.8)	5 (1.9)	30 (3.0)	0.44

CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ; SCC: squamous cell carcinoma; AC: adenocarcinoma. Data are expressed as n (%)

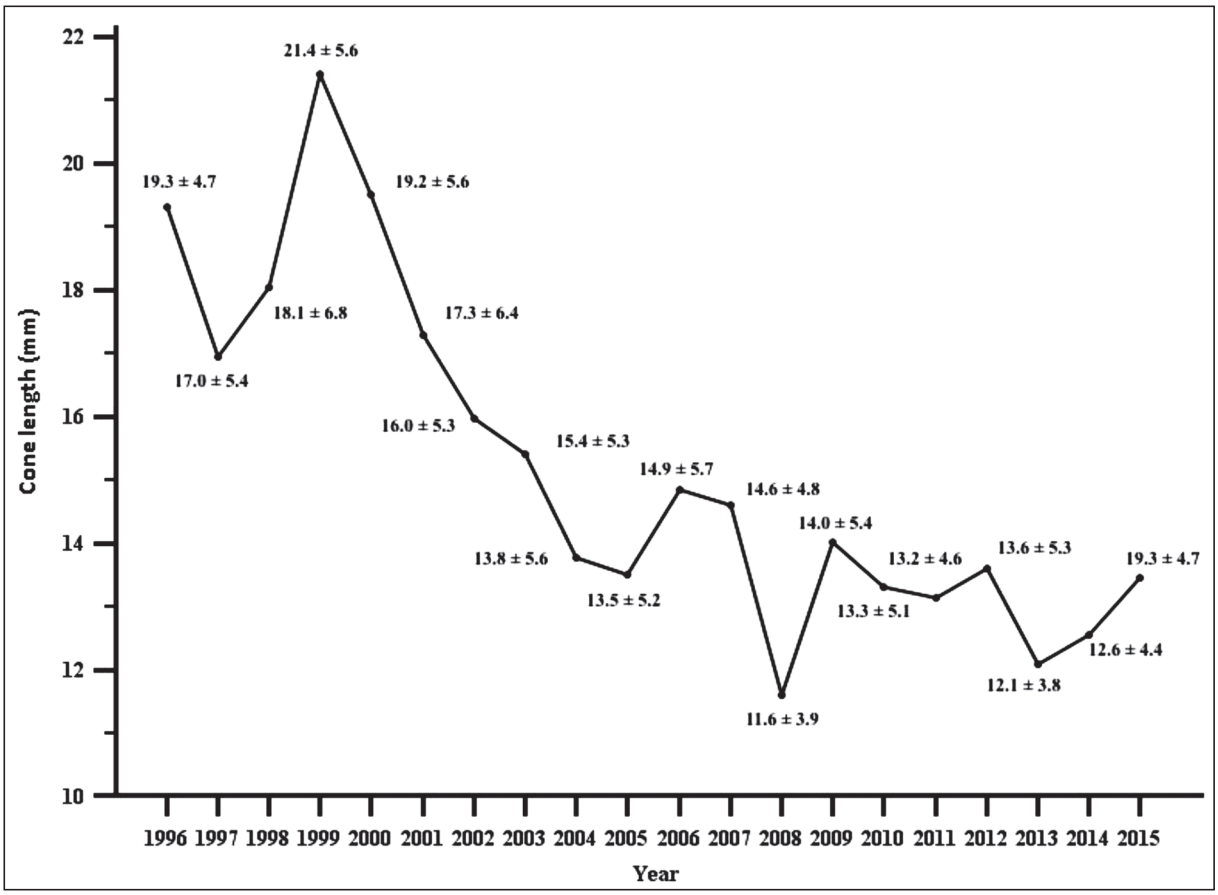

Figure 1. Length of cone excisions (expressed as mean ± SD) in the entire study cohort (n = 1270) considering the year of the procedure.

≥ 10 mm (17.9 *vs.* 10.7%, $p = 0.0185$), while no difference between women with a cone length of 10-14 mm *vs.* ≥ 15 mm was noted (12.0 *vs.* 9.9%, $p = 0.3145$). Patients with a positive endocervical margin presented a significantly higher age at the procedure than patients with a negative endocervical margin (41.8 ± 9.6 *vs.* 38.3 ± 9.2 years, $p < 0.0001$). None of the other considered factors (menopausal status, visibility of SCJ, *see & treat* strategy, "high-grade preoperative diagnosis", pre-operative diagnosis of glandular lesions or grade II colposcopic findings) was significantly associated with the positivity of the endocervical margin (Table IV). On multivariable logistic regression, age and cone length were both significantly and independently associated with the positivity of endocervical margins (age: OR = 1.0400, 95% CI 1.0222-1.0582, $p < 0.0001$ and cone length: OR = 0.9577, 95% CI 0.9272-0.9892, $p = 0.0089$).

Table III. Positivity of endocervical margin according to cone length in the entire study population.

Cone length	No.	Positive endocervical margin no. (%)	*p*
1-9 mm	134	24 (17.9)	0.05
10-14 mm	418	50 (12.0)	
15-19 mm	357	38 (10.6)	
≥ 20 mm	361	33 (9.1)	
Total	**1270**	**145 (11.4)**	

CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ; SCC: squamous cell carcinoma; AC: adenocarcinoma. Data are expressed as n (%)

Table IV. Univariate analysis of factors potentially related to positivity of endocervical margin in the entire study population.

Characteristics	Positive endocervical margin (no. = 145)	Negative endocervical margin (no. = 1125)	*p*
Age (yrs)	41.8 ± 9.6	38.3 ± 9.2	< 0.0001
Menopause	21 (14.5)	102 (9.1)	0.06
Visible SCJ	137 (94.5)	1098 (97.6)	0.06
See & treat	34 (23.4)	236 (21.0)	0.58
High-grade preoperative diagnosis	136 (93.8)	1068 (94.9)	0.72
Glandular preoperative diagnosis	14 (9.7)	67 (6.0)	0.13
Abnormal grade II colposcopy	86 (59.3)	667 (59.3)	0.93
Cone length	14.2 ± 6.0	15.3 ± 5.7	0.03

Data are expressed as mean ± SD or no. (%) as appropriate.

Discussion

CIN is currently considered the precursor of invasive carcinoma of the uterine cervix, and HPV is the most important pathogenetic factor[21]. Considering the growing incidence of HPV-related lesions in women of reproductive age[8], in the last few years, cervical excision procedures for treatment of high-grade cervical dysplasia have become increasingly common[9]. The peak incidence of such lesions is in women aged 25-35 years[5], thus, even considering the continuous trend of delayed childbearing observed over the last decades, many women with high-grade dysplasia are treated before their first pregnancy[8].

For this reason, the potential impact of cervical conization on future pregnancies is a matter of increasing relevance in the literature. In the last few years, several articles have been published on this topic, and there is currently a widespread evidence suggesting an increasing occurence of adverse obstetric events in women treated with cervical conization. In particular, a high rate of miscarriage and, mostly, a significant risk of preterm delivery have been reported[1,8,13,14,22,23].

The risk of preterm delivery in pregnancies following cervical conization seems to be related to the length of the cone excision[1,15,22], and a cone length > 15 mm has been found to be associated with a doubled risk of preterm birth[16]. Interestingly, such a risk is not restricted to the first pregnancy post-treatment[23].

Moreover, the need for a deep cone excision has been questioned by some authors who demonstrated that the average depth of the squamocolumnar junction is less than 12 mm in women in whom the upper limit of the transformation zone was not visible on colposcopy[24]. Hence, considering that the cervical dysplasia usually spreads on the transformation zone, a cone excision of 12 mm or less could be considered a safe option even for women in whom the squamocolumnar junction is not visible on colposcopy.

On these bases, in recent years, gynecologists have shown an increased sensitivity to the issues of "conization-related" adverse obstetric events, and have tried to reduce the length of cone excisions in their daily clinical practice.

Through this retrospective analysis, we observed a significant decrease in the length of cone excision over the whole study period, with a 30% reduction in the length of cone specimens, from 1996 to 2015. In the multivariate analysis, age and high-grade colposcopic appearance were associated with a deeper excision on cervical conization. This was expected since in older women, with a high-grade colposcopic appearance, the attitude of the gynecologist is to obtain a complete excision of the lesion, regardless of the potential problems for future pregnancies. On the contrary, in younger women, gynecologists try to be as "conservative" as possible, in order to minimize the risks of adverse obstetric outcomes in future pregnancies.

Women with a cone length < 10 mm showed a higher rate of positive endocervical margin compared to women with a cone length ≥ 10 mm. Furthermore, it is interesting to observe that no significant differences in the positivity of the endocervical margin of the specimen emerged in women with a cone length of 10-15 mm compared to women with a cone excision of 15 mm or more.

This datum is of particular clinical relevance since it demonstrates that a reduction in cone length does not influence the "radicality" of the surgical procedure (even if a length of excision of at least 10 mm should be reached in order to minimize the risk of positivity of the endocervical margin). This is a matter of relevance mostly

in women of childbearing age with glandular lesions and positive endocervical margin, in which a re-excision is recommended[9].

Thus, it should be advisable that the length of cone excision in women with high-grade cervical dysplasia ranges from 10 to 15 mm (except for women in whom a deeper progression of the lesion in the endocervical canal is documented), even if it is not always easy to control precisely the length of excision during the procedure of conization.

The main strength of the present study is the large number of cases, included through an over 20-years clinical practice. Moreover, all the excisions were performed in the same institution, with the same techniques (CO_2 laser excision), by the same gynecologist (FS) with particular expertise in the management of cervical preinvasive lesions and cancers.

As already described in previous studies, cervical conization can be performed with different techniques: LEEP and CO_2 laser are the most commonly used. No method has proved to be superior in terms of the rate of treatment failure, the disease persistence on follow-up, the adequacy of the specimen for histopathological evaluation and the risk of morbidity[25]. However, in a recent systematic review and meta-analysis, Kyrgiou et al[22] reported a slightly higher relative risk for preterm birth in women treated with CO_2 laser conization compared to LEEP (2.11 *vs.* 1.56).

Obviously, each technique of conization has strengths and weaknesses. For example, LEEP is less expensive and easy to use, with a faster learning curve for the operator, while CO_2 laser conization is more difficult technique that requires a greater expertise by the operator, and is more expensive. However, CO_2 laser conization has a great advantage: it allows the operator to "customize" the procedure, tailoring the extension and the depth of the excision to the characteristics of each woman (localization of the lesion, colposcopic appearance, cervical dimensions). For this reason, in our opinion, it is interesting to observe the trend of conization performed with this technique over the years, since it can be considered a real and reliable expression of the operator's tendency to reduce the depth of excision.

Due to its retrospective nature, unavoidably, this work has potential limitations. Since the data collected are limited to those already reported in the medical charts, it has not been possible to analyze the obstetric outcome in these patients (e.g., the rate of preterm delivery post conization).

Conclusions

In the last few years, gynecologists have shown an increased sensitivity to the problems related to cervical conization and have tried to reduce the length of cone excisions in their daily clinical practice. In this study, such a trend has been demonstrated in detail, reporting a significant decrease in the length of cone excision in the last 20 years.

Acknowledgements

The Authors thank Anna Vallerugo, MA, for the editing.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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