

Minimally Invasive Therapy of Cervical Intraepithelial Neoplasia for Fertility Preservation

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Abstract The aim of this study was to determine the extension of cervical intraepithelial neoplasia grade III (CIN III) into endocervical canal and depth of endocervical crypts involvement by CIN with the regard to patients' age and parity. Correlation between the area of CIN involvement and the extension into endocervical canal was estimated. A total of 218 cervical cone specimens with histologically proven CIN III were included in this study. Extension of CIN into the endocervical canal, depth of involved crypts and ectocervical area affected by CIN were histologically analyzed. The average endocervical crypt involvement was at 1.2 mm of depth. The excision of >4 mm (1.2 mm × 3S.D.) in depth removes >99% of CIN. With the cone length of 15 mm (nulliparous patients) and 18 mm (multiparous patients), no endocervical cone margins were affected with CIN. Since the cone length is the most important determining factor for fertility preservation, the measurement of cervical cone could be essential for future pregnancies.

Keywords CIN III · Conization · Fertility preservation

Introduction

Cervical intraepithelial neoplasia (CIN) is controversial clinical problem while diagnostic tools are still unable to predict which CIN will evolve to cancer. Positive correlation between grade of CIN and risk of progressing to cervical cancer has been globally accepted [1]. Therefore, early detection, follow-up and removal of lesion is obligatory. Hopefully, only about 12% of highest grade of intraepithelial neoplasia (CIN III) will progress to cervical cancer. Conization of the uterine cervix is the most frequently used method of treatment for CIN.

New attempts for minimally invasive treatment occurred in order to prevent the propagation of the CIN III and in the meanwhile to preserve the function of the cervix, especially in fertile and pregnant women [2]. The endocervical epithelium and crypts produce mucus which is required for sperm transportation and very important for protecting the pregnancy from the exogenous influences. Epidemiologic data suggest that the incidence among the nulliparous affected with CIN III undergoing conization is permanently increasing.

Macroscopic changes of CIN III are unspecific and appear as leukoplakia, erosion and cervicitis. The majority of incidents develop within the transformation zone and extend further to endocervical canal and crypts [3]. Histology is required in determining the stage of the disease [4–7]. Moreover, dysplasia might progress into the endocervix, become even worse in the endocervical canal or develop *de novo* in the endocervix [5]. Conization is the only diagnostic and therapeutic procedure which should remove the whole transformation zone with the part of

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cervical canal and therefore eliminate the entire lesion [6, 7]. On the other hand, conization may cause various complications such as cervical stenosis, infertility, infections and cervical insufficiency in pregnancy. Therefore maximal preservation of uterine cervix is essential for future pregnancies. Dimensions of the cervical cone depend upon the colposcopic finding and expected depth of lesion in the endocervix [8]. The spread of CIN III within the endocervical canal and crypts can be objectively determined only by histological analysis, after conization [9, 10]. Nowadays, loop excision of the transformation zone (LETZ) seems to be less invasive treatment than cold-knife conization, but there are serious problems with interpretation of cone margins after thermal damage with electric loop.

The primary objectives of this clinical trial were:

1. to determine the extension of CIN III into endocervical canal;
2. to determine the depth of endocervical crypt involvement by CIN III;
3. to estimate the relation between patients' age and parity with the extension of CIN III into crypts and cervical canal;
4. to correlate the area of ectocervical CIN III involvement with the depth of CIN III extension into the crypts.

Materials and Methods

This is a retrospective cohort study on 296 cervical cones of patients in reproductive age that underwent conization for CIN III confirmed by pathohistologic findings. The study was performed at the Department of Obstetrics&Gynecology, School of Medicine, University of Zagreb and at the Department of Obstetrics&Gynecology, Gospić General Hospital, Croatia. Patients with the diagnosis of CIN III ($N = 218$) after conization were included in the study. The extension of intraepithelial neoplasia into the endocervical canal and endocervical crypt involvement is the most excessive in CIN III, therefore lower grade of intraepithelial neoplasia were excluded from the study ($N = 78$). We estimated age, parity and type of surgical treatment. All patients underwent cold knife conization due to the most precise interpretation of resected margins after this surgical option. Analyzed data included age, parity, biopsy finding and endocervical curettage (ECC) finding before conization. Each cone was cut on 14 paraffin cubes in average, with two slices per cube, which amounted approximately 30 slices per cone. Besides the routine pathohistological analysis (diagnosis, dimensions of cone, ECC) the depth of the endocervical crypts, depth of the endocervical canal involvement by CIN III and depth of the endocervical crypts involved by CIN III were analysed. The largest depth of cervical crypts and the largest depth of crypt affected with CIN III on each

cone were measured by PC program ISSA 3.6. Chi-square and Mann-Whitney test were used for statistical analysis. P value less than 0.05 indicated statistical significance.

Results

Two-hundred and eighteen women with the mean age of 31.6 ± 6 years underwent cold knife conization for CIN III. Sixty-four out of 218 patients were nulliparous (29.4%) and were younger (28.6 ± 7.2) than multiparous (32.6 ± 5 years, $p < 0.001$) with one delivery in average. Mean values of cone dimensions were $28.8 \times 24.8 \times 15.9$ mm.

Significant differences were detected in all three dimensions of the cone between nulliparous and multiparous. The most significant difference was detected according to cone length (Table 1).

CIN III was found in 6.4 out of 14 slices on average, which indicated that 46% of cone circumference was affected with CIN III. Mean depth of endocervical crypts was 4.5 mm, without significant difference between nulliparous and multiparous women ($p = 0.28$).

We detected endocervical crypts involvement by CIN III in 173 of 218 (79%) cones, with the mean depth at 1.4 mm. When uninvolved crypts were included, the average depth of CIN III in crypts was 1.2 mm. The extension of CIN III to the apex of endocervical canal was noticed in 31 of 218 (14.2%) cones. Twenty-one percent of nulliparous and 11% of multiparous had apex of the cone affected with CIN III. Furthermore the relationship between cone circumference and endocervical crypts affected with CIN III was observed. Ectocervical circumference was divided in four segments (each containing 25% of ectocervical area) and the extent of CIN III lesion on cone circumference was examined (Table 2).

We observed that in 32% of patients more than a half of cone circumference was affected with CIN III. The relationship between cone circumference affected with CIN III and depth of endocervical crypts involved by CIN III is shown in Table 3.

The depth of crypts involvement by CIN III increases with the cone circumference affected with CIN III. There is a significant difference in depth of crypts affected with CIN III between involved circumference of $<1/4$ and $<1/2$ in

Table 1 Dimensions of cervical cones according to parity

Cone dimension (mm)	Nulliparous ($n=64$)	Multiparous ($n=154$)	p
Width 1	$26,4 \pm 7,6$	$29,8 \pm 5,8$	$<0,01$
Width 2	$22,1 \pm 4,9$	$25,9 \pm 5,1$	$<0,001$
Length	$11,0 \pm 2,5$	$17,9 \pm 5,3$	$<0,0001$

Table 2 Cone circumference affected with CIN III

Cone circumference	n	%
<1/4	44	20,2
1/4–2/4	103	47,2
2/4–3/4	42	19,3
>3/4	29	13,3

correlation with affected circumference of $>1/2$ ($p < 0.001$). No significant difference was found if more than a half of the circumference was affected with CIN III (1/2–3/4 : $>3/4$; $p = 0.29$). The area of circumference affected with CIN III between nulliparous and multiparous was not significantly different although nulliparous had greater segment of CIN III lesion on circumference.

Furthermore we wanted to establish the required depth of incision into cervical stroma to prevent residual CIN III in cervical crypts. Maximal extension of CIN III into crypts was 4 mm (Table 4). Further results were observed: 13/64 nulliparous (20.3%) had extension of CIN III into crypts deeper than 2 mm. More than a half of the circumference area affected with CIN III was found in 12 out of 13 patients (92.3%) with invasion of crypts >2 mm. Forty out of 154 (26%) of multiparous patients had extension into crypts more than 2 mm. The extension of CIN III deeper than 3 mm into crypts was more frequent in multiparous than in nulliparous patients (7/154: 1/64, $p = 0.267$)

We also evaluated CIN III extension into endocervical canal and determined the obligatory length of cone to exclude residual lesion on the cone apex (Fig. 1). The risk for residual neoplasia obviously decreases with the depth of endocervical canal. No residual CIN III was observed at the cone apex if cone length was 15 mm for nulliparous and 18 mm for multiparous patients.

Discussion

Although hysterectomy might be the optimal route of treating CIN III, the management should be accommodated for preserving the fertility in generative age [11]. Epidemiologic data revealed that the majority of women affected with CIN III were those in reproductive age [12, 13]. Our results, similar to other investigators, confirmed the mean age of 30–35 year for patients with CIN III. In our study 29.4% were nulliparous and others had in average one or two childbirth. We attempted to treat the fertile patients with minimal invasiveness. Multivariate analysis revealed that endocervical extension of CIN III and cone margins affected with CIN III were the strongest predictors for residual neoplasia [14]. Therefore, the imperative was to determine the dimensions of the cone in order to remove the

whole lesion and to preserve the function of the remaining cervix [15]. The average cone dimensions were $28.8 \times 24.8 \times 15.9$ mm, similarly to current reports [14, 16, 17]. The maximal preservation of the cervix was confirmed at nulliparous patients since their cones were significantly shorter than from multiparous (11 ± 2.5 cm vs 17.9 ± 5.3 cm).

The length of the preserved cervical canal after conization is the strongest predictor for the pregnancy outcome. Besides the prevention of cervical stenosis and insufficiency, production of endocervical mucus has predominant effect on cervical efficiency. Previous data suggest that at least one half of the residual endocervical canal after conization is related with favourable pregnancy outcome [17]. Lack of cervical gland and mucus after amputation of the endocervical canal is often followed by infection, miscarriage or preterm delivery. Data from literature indicate the positive correlation between the grade of CIN and the linear extension to the endocervical canal (CIN I : 4.10 ± 2.84 , CIN II : 5.84 ± 4.13 , and CIN III: 7.60 ± 4.32 mm) [12, 14, 18]. In addition, the endocervical crypts involvement by CIN was proportional with the grade of CIN (CIN I, II, III : 0.42 ± 0.28 , 0.93 ± 0.71 , 1.35 ± 1.15 mm, respectively). Previous reports suggested that 26–88% of crypts had been involved by CIN III. We confirmed those observations and found crypts affected with CIN III in 79% of cones [19–21]. These fluctuations are probably the consequence of histological analysis. The more slices per cone, the greater chance of detecting affected crypts. We had in average 30 slices per cone with the high sensitivity of detecting CIN III within the crypts. We support previous investigations that there is no significant difference in ectocervical and crypts involvement by CIN III regarding parity and age [19, 20]. According to previous reports the maximal depth of the crypts involved by CIN III was 3.6–4.8 mm. We found only one case with the depth of crypts involvement of more than 4 mm, so we recommend the excision of 4 mm of the endocervical stroma for removing the 99.9% of CIN III from the endocervical crypts. Observed relationship between area of circumference and extension of CIN III into crypts has considerable clinical importance. We propose that if the circumference was affected with CIN III at $<1/2$ the maximal CIN III extension to the crypts would be 2 mm at nulliparous, and if the area was affected at $>1/2$ we could

Table 3 The relationship between cone circumference and endocervical crypts affected with CIN III

Cone circumference affected with CIN	N (%)	Endocervical crypts affected with CIN (mm)
<1/4	44 (20.2)	0.44 ± 0.83
1/4–2/4	103 (47.2)	1.13 ± 0.76
2/4–3/4	42 (19.3)	1.72 ± 0.96
>3/4	29 (13.3)	1.49 ± 0.61

Table 4 Residual CIN III at selected cone depth in correlation with affected circumference of endocervical crypts (mm) at nuliparous and multiparous women (N)

Cone depth (mm)*	Nulliparous (N=64)			Multiparous (N=154)		
	Affected cone circumference (N) **			Affected cone circumference (N) *		
	<1/2	>1/2	Total (N)	<1/2	>1/2	Total (N)
>2 mm	1	11	12(18.8%)	10	22	32(20.85%)
>3 mm	0	1	1(1.6%)	3	4	7(4.5%)
>4 mm	0	0	0(0%)	0	1	1(0.1%)

*depth of the crypts involvement

**number of patients with <1/2 or >1/2 of circumference area affected with CIN III

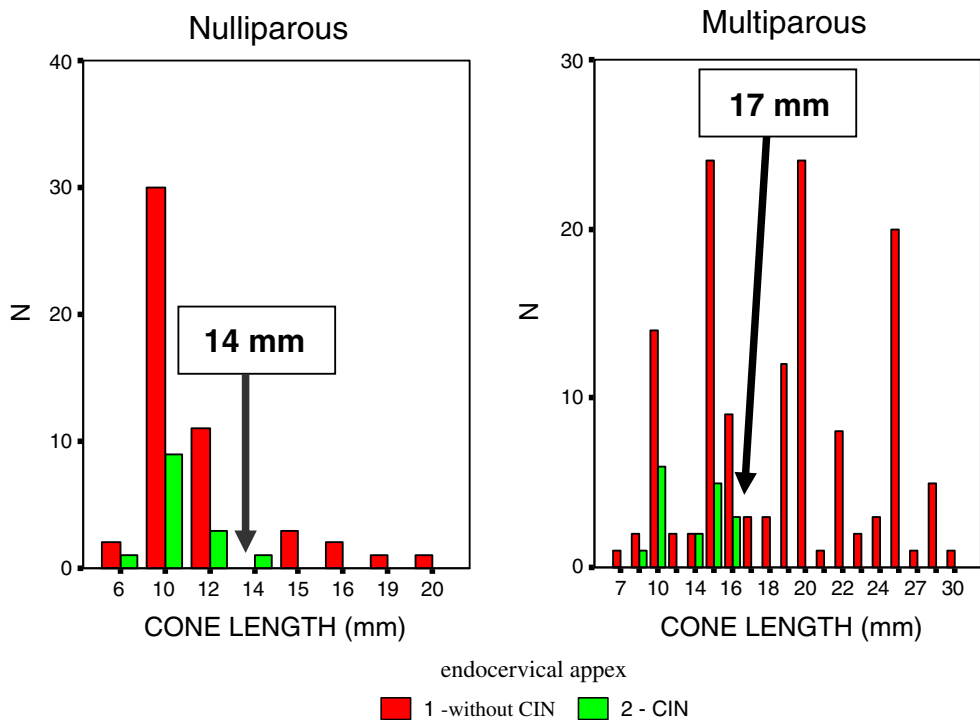
expect deeper extension of CIN III, up to 4 mm, especially in multiparous. Only one nullipara with >1/2 circumference affected with CIN III had crypt involvement of more than 2 mm. This observation suggests that colposcopy may indirectly predict the crypt involvement by CIN III [21, 22]. Moreover, we conclude that macroscopic changes of ectocervical circumference have great sensitivity in detecting the endocervical lesions, but unfortunately very low specificity [22].

The apex of the endocervical cone was affected with CIN III in 14% of patients of which 67% were nulliparous. Such results were expected since the nulliparous patients underwent less invasive conization with the shorter cone. The production of mucus required for preserving the fertility is related to the length of the cervical canal. Therefore the treatment of CIN III should be accomplished by single surgical procedure without further treatments.

Regarding the cone length our results are in accordance with previous publications [22, 23]. Eighteen mm is the minimal cone length needed to prevent residual CIN III on the apex in multiparous and 15 mm in nulliparous patients. We have to emphasize that shorter cone (10–12 mm) at nulliparous may result in residual CIN III at the cone apex and obligatory reconization which may seriously disrupt the fertile function [24–27]. Since the cone apex was free from CIN in 116/124 (95%) of patients, we propose the cone length of 15 mm for women who are planning pregnancy. If LETZ is chosen for treating the CIN III it is important to comprise 0.3–0.5 mm of thermal damage and therefore increase the necessary depth of incision for 1 mm [22].

The combined approach of histology screening and conical excision we performed contribute to further cervical cone length treatment for cervical intraepithelial neoplasia grade III in order to fertility preservation.

Fig. 1 CIN at endocervical margins according to cone length and parity



In conclusion, as the cone length is the most important determining factor for fertility preservation, the exact measurement of cervical cone could be essential for future pregnancies. Both optimal treatment and preserving the cervical function are needed in this group of patients.

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