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*Review article* ■

# Controversies in the Choice of the Optimal Therapeutic Approach to High Grade Intraepithelial Lesions (HSIL) of the Cervix

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## SUMMARY

The incidence of preinvasive changes in the cervix is constantly rising. It is particularly alarming that there is a larger number of younger patients in whom some stage of these changes has been diagnosed or who had already received some type of treatment before. Technological development and improvement of various forms of treatment have led to changes in the surgical approach to intraepithelial lesions of the cervix. The techniques that have been developed for this purpose, besides the cold-knife conization, include loop excision, radio wave conization, laser conization and, recently, the conization by Harmonic scalpel. The question that inevitably arises is: Has the technological development led to more conservative approaches and improvement in the results of surgical treatment? This paper will try to partly answer this question and initiate some new questions and dilemmas. A comparative review of all of the abovementioned surgical techniques and their detailed analysis is expected to provide at least some answers to the controversial opinions for and against the new surgical procedures. The results of surgical treatments and their complications were analyzed with particular emphasis on the influence that these methods have on fertility. The conclusion is that there is no ideal surgical procedure which could replace and neglect the experience of a colposcopist. New surgical techniques have brought more surgical comfort and faster recovery but have not demonstrated significant change in the final results of treatment and recurrence.

**Key words:** conization, HSIL, laser conization

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## INTRODUCTION

The degree of invasiveness of a surgical method represents a dynamic category which has been modified by the evolution in technological methods as well as the modern understanding of the pathogenesis of intraepithelial neoplasms of the cervix. There is a larger number of sparing surgical procedures both in gynecology and in gynecologic oncology, so that some procedures which were considered conservative are now regarded as radical. Knife conization was a sparing procedure in the treatment of SIL and is now 'radical' and is 'advised in cases where high grade of change is suspected, when even the smallest thermal artifact cannot be tolerated, such as suspicion of microinvasion (due to grading) as well as in adenocarcinoma in situ'.

In the future, the topic of discussion will be not only the effectiveness of a method but also how the method influences the quality of a woman's life. Some trials from 2009 analyzed both the post-effect of surgical methods of treatment and the effect of applied diagnostic procedures.

The TOMBOLA trial from 2009 analyzed the post-effect and discomfort symptomatology (up to 6 months) following colposcopy and cervix biopsy. After colposcopy, 14% of patients had some problems (pain, discomfort, secretion or slight bleeding). On the other hand, about 50% of patients with biopsy had some of the changes, 53 % experienced pain and discomfort, 46% had bleeding and secretion. Such studies show that in the future every diagnostic procedure will have to be explained in detail (1).

The development of diagnostic procedures, primarily HPV typization, will result in an increase in the number of young patients with 'a terrifying positive diagnosis of oncogenic viruses'. On the other hand, the fact that great percentage of HPV-associated lesions in younger patients, under the influence of biological and immunological processes, is spontaneously regressing, might point to the need for shifting the diagnostics and the treatment of these changes to a period after 25 years of age (2).

Increase in the incidence of HPV infection and HPV-associated intraepithelial lesions with reproduction achieved at a relatively later age increases the percentage of women whose anamnesis includes some of the diagnostic and therapeutic procedures performed on the cervix. The increase in the number of treatments of the cervix is also influenced by the popularization of the Loop excision as a method, See and treat approach, the popularization of colposcopy as a method with low specificity and the particular situation that exists in our country (with more colposcopists than cytologists) as well as patients' frustration caused by the theory that CIN I is a precursor of invasive carcinoma (although there is a monoclonal theory of a malignant HPV clone which can immediately create Ca in situ) (3). One of the reasons for the larger number of

treatments is probably the fact that new technologies in surgical gynecology are more available. The techniques that have been developed for this purpose, beside Cold-knife conization, include Loop excision, radio wave conization, laser conization and lately conization by Harmonic scalpel. The question that inevitably arises is: Has the development of technology caused any improvement in surgical results of the treatment and preservation of reproductive abilities?

The application of any type of excision therapeutic procedures of the cervix, regardless of the technique, influences the reproductive abilities. Any shortening of the endocervical canal leads to incompetence, the path for an ascendant infection and PROM is shorter, the production of protective cervical mucus is reduced because endocervical glands are removed. Normal cervical and vaginal secretion is important both during, after and before pregnancy because it prevents adherence and colonization by bacteria and their transfer to GGT and it contains carbohydrates (bind microorganisms) defensin, lactoferrin (binds Fe), lysosomes (lysosom-hydrolyzed 1, 4 bonds) and antibodies (IgA), cytotoxic T lymphocytes CD3, CD4, CD8, macrophages and immune-presenting cells. Considering the influence of a surgical method on later complications and cervical incompetence, it is important to have in mind that a surgical method can be compromised by factors that are not directly associated with the method itself: surgeon (his incompetence, aggressiveness, lack of knowledge in pathophysiology, negligence, inappropriate choice of method with regard to the pathology of change), surgical technique (Sturmdorf, Burghardt ... ), degree of change (both the size of the conus and the size of the cervix are important) and inappropriateness between the size and the type of conus and the type of change and its localization.

### Comparison of success and complications of Loop excision and cold knife conization

For the last 15 years, the Loop excision has been a popular method of treatment because it is fast, relatively simple to perform and can be done under local anesthesia. Some data also show that in cases of shallow conus, Loop excision without reintervention has no effect on premature delivery. However, even with this relatively conservative and comfortable procedure, the risk of preterm delivery is three times higher (4.6:12%) compared to the remaining population of women, whereas in cases of repeated treatment, the risk is up to five times higher (4.6:23.7%). The percentage of preterm delivery (12%) is classified into preterm occurring during weeks 32 to 36 (77.3%), very preterm from week 28 to 31 (14.7%) and extremely preterm occurring before week 28 (8%). The size of the conus and its association with preterm delivery was particularly analyzed. A 10x10 mm conus was classified as small, 15x12mm conus was

considered middle-sized whereas 20x12 mm was large. The risk of preterm delivery was 2.45% greater in larger conus or in reconization (4). Age, smoking habits, previous deliveries and the degree of neoplasm did not show any significance in the prediction of preterm deliveries (5).

The highest percentage of preterm deliveries (45.3%) starts with prelabor preterm rupture of membranes (PPROM). The reasons for the rupture of the amniotic sac are located in the shortening of the cervix, reduced production of the cervical mucus, defects in immune response because all these factors contribute to an ascending infection and to PROM.

Similar percentages of preterm deliveries after Loop excision (13.8%) are also stated in other studies which particularly emphasize the size of conus, so that the risk is as much as three times greater if the removed part of the conus exceeds 1-1.7 cm (6, 7).

In addition to the size, the volume of the removed part is also important. A 2010 study assesses the volume of the cervix removed by various surgical techniques. The volume is the smallest with Loop excision and amounts to 0.78 cm<sup>3</sup> (0.62 in LSIL and 0.82 in HSIL); it is somewhat greater with laser conization amounting to 1.84 cm<sup>3</sup> (1.55 in LSIL and 2.53 in HSIL) whereas with cold knife conization the volume of the removed conus is the greatest and amounts to 2.6 cm<sup>3</sup> (8).

However, probably the most important element in morphometrics is the assessment of the tissue that remains after the surgery. In this case, the experience of the colposcopist is essential and he/she is expected to establish a balance between the maximum eradication of the change and minimum impairment of the cervical anatomy.

The comparison of premature deliveries after cold knife conization and Loop excision, probably based on the above stated data on the greater volume of the conus removed by knife, shows that the risk percentage of preterm delivery is greater after knife conization (risk is 6 times greater) compared to LOOP (3.5 times greater risk), whereas it is the greatest with cervix amputation and amounts to 30.8% (9).

Some later researches have shown that the percentage of preterm deliveries in the group of patients undergoing cold knife conization exceeds 14% while the group undergoing LOOP excision is smaller than 11%. The percentage of PPRM and children with low weight (<2500 g) is greater with CKC and amounts to 12% while in the LOOP group it is 8% (10).

As for other complications with LOOP excision, literature states infection in 0.6% of patients, bleeding in 2.6% of patients, stenosis in 3.8%, unsatisfactory colposcopic findings in 1.3-9% while 9.4% of patients had retreatment in anamnesis (11).

A comparison of total complications with LOOP excision and cold knife conization, also analyzed by other authors, shows a somewhat higher percentage of

complications with cold knife conization (6:11%). The percentage of positive conus margins between these two types of conization is not significantly different statistically, 20:19%, as well as the percentage of residual disease and recurrence. Treatment success percentage is identical, 96:97%, with statistically significant short hospitalization time in the group with LOOP excision (12).

The literature states the recurrence percentage with LOOP which is 1.9-10.5%, with cold knife conization it is 7.1%, while with laser conization it is 1.4-2.3% (13).

Hysterectomies performed after cold knife conization and LOOP excision showed no statistically significant difference considering the percentage of the discovered residual disease; 37% of residual disease was discovered with the LOOP group and 27% with cold knife conization. However, the emphasized disadvantage of the LOOP excision is the thermal artifact which is present in 8.2-48% (14). The depth of the thermal artifact in LOOP excision is around 0.32-0.38 mm (15).

A mild thermal artifact was present in 51.5 % of cases, moderate form was present in 32.6% of cases while severe form was found in 12.3%. In 5% of cases the thermal artifact prevented the evaluation of the conus margin. It is in this group of the most severe thermal artifacts that the residual disease is most commonly found (80%) (16).

A particular problem in the evaluation of histopathological findings in LOOP excision is conus fragmentation which appears in 40-72% of the treated patients. Fragmentation is the cause of positive conus margins in 12-19 % of cases (17).

Thermal degeneration of cells may cause problems in evaluation because of the so-called 'signet ring cells' in the stroma (eccentric nucleus, single cytoplasmic vacuole) which present a differential-diagnostic problem with Signet Ring Carcinoma (18).

The use of high temperature in electrosurgical conization procedures sometimes presents a problem not only in postoperative diagnostics but also in further cytological monitoring of the patients. Hence, the first postoperative findings of cytobrush screening were false positive in 44% of patients due to cytomorphologic changes caused by increased temperature after LOOP (19).

A particular, relatively late problem after conization is stenosis of the cervical canal which includes its impermeability to 2.5 mm Hegar dilator. It appears 2-5 months after conization and in more than 50 % of patients it starts with the following symptoms: dysmenorrhea, dyspareunia, amenorrhea, infertility and in about 1% of cases there is also hematometra (20, 21). Average stenosis incidence is about 7.66% (22).

The highest percentage of stenosis, from 1.6 to 17%, appears after cold knife conization (23), somewhat smaller percentage, up to 10.2%, is found with laser conization (24), and the smallest after LOOP ex-

cision, 4.3% (25). Other authors deny the significance of the conization techniques in the development of stenosis but point out that the volume of conus is the only statistically significant factor with cut off value of 20-25 mm (26). Beside the conus volume, the patient's age is also important, so that after 45 years of age the risk of developing stenosis is 1.6 times greater, while bleeding after operation followed by sutures or reinterventions cause three times more risk for cervical canal stenosis (27).

In addition, recurrence is also more common in these older patients with stenosis (66.7%:8.6%). Such data direct to postoperative local hormone therapy (28).

### **Laser conization in the treatment of HSIL changes in the cervix**

Laser conization, as a surgical method, has been famous since 1980 but it is expensive and demands good training and practice. Its advantage is the possibility of combining it with vaporization whereby less tissue is lost. Average percentage of complications with laser conization is around 8%. Thermal artifact is smaller compared to Loop (38%:48%) (29) and the most common complication is bleeding during the first two weeks (74.2% compared to all complications, i.e. 6.1% of all performed conizations) (30).

New technologies in the surgery of changes in the cervix have led to the use of ultrasonic mechanic vibrations, harmonic scalpel (HS) which simultaneously cuts and coagulates the tissue of the cervix. Compared to LOOP, this method enables the removal of the changes in one piece, and compared to Laser there is no smoke which enables good visualization (31).

### **Harmonic scalpel in the treatment of HSIL changes in the cervix**

Compared to Laser conization, the harmonic scalpel rarely creates the thermal artifact in 1.96% of patients (vs. Laser 18.5%). The size of the thermal artifact is also smaller in HS conization than in Laser and LOOP and amounts to 0.20 (vs. 0.32-0.38 Loop). With regard to the volume of the conus, duration of the operation and loss of blood, there are no statistically significant differences (32). The question that surfaces concerning further, more conservative approach in the treatment of HSIL is: Can an ablative procedure, or a combination of excision and ablative procedure, help in the treatment of HSIL? It is important to follow the established criteria: there has to be a completely visible transitive zone, there cannot be discrepancies between cytology and histology, an invasive and glandular disease must be excluded cytologically, colposcopically, and histologically, no previous treatment should have been done on the cervix. It is also important to know that destruction by laser is up to 7 mm whereas by Cryo it is 4 mm. There is a possibility of combining them or performing a two-

act destruction. Ablative approach is more significant in younger patients with clearly turned transitive zone and a mild HSIL grade change (CIN II). Some of the new trials recommend that the diagnostics and treatment of CIN changes should be postponed after the age of 25-30 because CIN II + changes have a different clinical course in younger patients and they spontaneously regress in high percentage of cases (which is associated with biological and immune nature of HPV infection and persistence) (33).

## **CONCLUSION**

Instead of a conclusion, it can be stated that after all these diametrically opposed percentage data on the success and complications of various old and new surgical procedures used in the treatment of malignant changes in the cervix, there is no ideal surgical procedure which would replace and neglect the experience of a colposcopist. The new surgical techniques have led to more surgical comfort, faster recovery but they have not significantly changed the total treatment results and recurrence. When choosing a surgical technique, some individual factors should be considered: colposcopic and cytologic findings, histopathological findings of biopsy and canal curettage, patient's age and parity, hormone status, possibilities of a local surgical approach, availability of various types of anesthesia, availability of technological instruments and individual preferences and doctor's training in a specific surgical technique.

#### *Abbreviations in the text:*

HPV - human papillomavirus

SIL - squamous intraepithelial lesion

HSIL - high-grade squamous intraepithelial lesion

HS - harmonic scalpel

CIN - cervical intraepithelial neoplasia

PPROM - prelabor preterm rupture of membranes

LOOP - loop excision

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## KONTRAVERZE U IZBORU NAJOPTIMALNIJEG TERAPIJSKOG PRISTUPA INTRAEPITELNIM LEZIJAMA GRLIĆA MATERICE VISOKOG GRADUSA (HSIL)

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### Sažetak

Incidenca preinvazivnih promena grlića materice je u stalnom porastu. Ono što je posebno zabrinjavajuće je da sve veći procenat bolesnica mlađe starosne dobi ima dijagnozu nekog od stadijuma ovih promena ili je već imala neki od vidova lečenja. Sa razvojem tehnologije i usavršavanjem različitih vidova lečenja došlo je i do promena u operativnom pristupu intraepitelnih lezija grlića materice. Uporedo sa klasičnom konizacijom nožem, razvijala se i tehnika Loop excizija, konizacija radiotalasima, konizacija laserom i u novije vreme konizacija ultrazvučnim nožem. Ono što se nameće kao pitanje je da li je razvoj tehnologije doveo do konzervativnijeg pristupa i boljitka u hirurškim rezultatima lečenja? Ovaj rad će pokušati da delimično odgovori na ovo pitanje i da pokrene neka nova pitanja i dileme. Uporednim prikazom svih gore pomenutih hirurških tehnika i njihovom detaljnom analizom očekujemo da dobijemo bar neke odgovore na kontraverzne stavove - za i protiv novih hirurških procedura. Analizirali smo rezultate hirurškog lečenja i njihove komplikacije, sa posebnim akcentom na uticaj ovih metoda na fertilitet. Došlo se do zaključka da ne postoji idealna hirurška procedura koja će zameniti i zanemariti iskustvo lekara kolposkopičara. Nove hirurške tehnike su dovele do većeg operativnog komfora, bržeg oporavka bolesnica, ali nisu bitno promenile ukupne rezultate lečenja i pojavu recidiva.

**Ključne reči:** konizacija, HSIL, laser konizacija