

## Conservative Approach to Preneoplastic Cervical Lesions in Postmenopause

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**Abstract.** *Aim: To evaluate the recurrence rate of high-grade squamous intraepithelial lesions in postmenopausal women previously submitted to laser CO<sub>2</sub> conization and the role of persistent oncogenic HPV types. Patients and Methods: Fifty-five patients with a cytological diagnosis of high-grade squamous intraepithelial lesions were triaged with a standard colposcopy. Hormonal replacement therapy was considered as significative in influencing cervical trophism. Vaginal smears for microbiological examination were obtained. H-R HPV test was performed by PCR. The follow-up checks including cytology, colposcopy and HVP test were performed for a minimum of 5 years. Results: Histological analysis revealed 19 CIN2 (cervical intraepithelial lesions) and 36 CIN3 lesions. The cumulative failure rate at first treatment was 14%. HPV test was positive for HPV 16 type in all patients. Forty-two patients during the follow up checks resulted negative to cytology, colposcopy and HR HPV test. At the one-year follow-up check, 7 patients revealed normal cytological and abnormal colposcopic findings and persistent positive HR HPV test. At the five-year follow-up check, 14 patients with a normal cytological smear had a recurrence of CIN2/3 and positive HR HPV test. Conclusion: In postmenopause, the correct management of H-R squamous intraepithelial lesions is still debated. However, a satisfactory follow-up is the main requirement for the conservative management. HPV typing in the follow-up is important to detect persistent types to identify women at risk of developing cervical abnormalities. The incidence of cervical neoplasia does not decrease with increasing age. Since HPV positivity predicted subsequent infection, testing postmenopausal patients for the virus may be a cost-effective method of disease prevention.*

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**Key Words:** Postmenopause, preneoplastic cervical lesions, laser conization.

Cytological screening programmes for cervical cancer include women between 25 and 65 years of age and their beneficial efficacy effects have been recognized.

A high proportion of screened women are of postmenopausal age and a diagnosis of high-grade squamous intraepithelial lesions (HG-SIL) in these patients is not infrequent (1).

The casual role of HPV in all cancers of uterine cervix has been firmly established biologically and epidemiologically (2).

The duration of infectivity is an important component of the rate of spread of an STI in a population, with infections of longer duration having a potentially greater impact (3).

High-risk HPV (HR HPV) infections seem to persist longer than low-risk ones (4).

Among high-risk types, there is some evidence that HPV-16 may persist longer than other types.

This suggests that the rate of spread of HR HPV in populations, including HPV-16, would be greater than for low-risk HPV (LR HPV), assuming equivalent sexual contact patterns and transmissibility (5).

HPV age-specific prevalence is an important remaining task that is tied to our need for a better understanding of viral persistence, clearance, and possible latency. HPV prevalence and incidence appears to peak in women under 20 years of age, with a decline noted in women 30 or older which is secondary to the clearance of HPV (6). Infections in cross-sectional screening of older women might persist longer than in younger women because they are more likely to represent infections that are already persistent (7, 8).

Clinical strategies requiring repeated abnormalities or repeated specific HPV detection lasting more than a year take advantage of this fact of natural history to sort out the transient infections and associated lesions from the persistent ones which pose the greatest risk to the patient (7, 9).

HPV 16 appears to be remarkably carcinogenic with an absolute risk of CIN3 approaching 40% at 5 years of persistence (6).

Primary risk factors for HPV acquisition and persistence are young age and sexual behaviour. Other mediating factors include smoking, alcohol, high parity, early age at first full-

Table I. Colposcopic and histological findings before treatment.

Characteristic	Postmenopausal patients (n=55)
Previous treatment for CIN	11 (20%)
Esocervical SCJ	41 (75%)
Endocervical SCJ	14 (25%)
CIN2	19 (35%)
CIN3	36 (65%)

SCJ: squamous cellular junction; CIN: cervical intraepithelial neoplasia.

term pregnancy, oral contraceptives, other sexually transmitted infections and immunosuppressive conditions (4).

In postmenopause the correct management of high-grade squamous intraepithelial lesions is still debated.

However a satisfactory follow-up is the main requirement for the conservative management (10).

The objective of this study was to evaluate the recurrence rate of high-grade squamous intraepithelial cervical lesions in postmenopausal women previously submitted to laser CO<sub>2</sub> conization and the role of persitent oncogenic HPV types as markers of disease progression.

## Patients and Methods

Fifty-five patients of postmenopausal age with a cytological diagnosis of high-grade SIL formulated in agreement with the Bethesda System (11), from January 1991 to December 2002, attended the Department of Gynaecology, Perinatology and Child Health, University "Sapienza".

A questionnaire regarding personal history (age, parity, sexual habits, tobacco use, menopausal status and years of menopause, hormonal replacement therapy [HRT] use, previous cervical treatments and past genital infections) was available for every patient. All participants gave their full informed consent.

Patients with a minimal time of 12 months spontaneous amenorrhea were considered in postmenopausal age and HRT was considered as significative in influencing cervical trophism and healing process when systemically administered and carried on from at least one year previous laser surgery till 1 year after (10).

The patients were triaged with standard colposcopy (Carl Zeiss, OM50, Oberkochen, Germany) using a 5% acetic acid solution followed by Lugol test.

The colposcopic findings were interpreted according to the International Nomenclature (12).

The histological diagnosis was assessed by colposcopic direct biopsies in the areas revealing the greatest degree of abnormalities.

Vaginal smears for microbiological examination were obtained through microbiological culture of the material collected by sterile plugs from the vagina for mycetes and common microbes, while *Trichomonas vaginalis* was detected by fresh bacterioscopic examination.

Cytological samples of HR HPV test was performed by polymerase chain reaction (PCR) (13).

A preoperative colposcopic evaluation has been performed to identify the external limit of the lesion.

Table II. Failure rate in relation to margin status and lesions site.

Size of the lesion	Margin status		Failure %
	Complete	Incomplete	
1 Section	16	1	2
2 Sections	21	2	4
≥ 3 Sections	11	4	8
Total	48	7	14

Patients were treated by CO<sub>2</sub> laser conization by means a Laser CO<sub>2</sub> Coherent 400 – Model 451 instrument under colposcopic guidance in outpatient setting and local anesthesia. The maximum power output was of 40 W, used in continuous mode. To assure the complete clearance of the lesion, the crater base and the walls were vaporized.

Patients were discharged from the day-care unit after 2-3 hours. The patients returned to normal activities within 4/5 weeks of treatment.

The follow-up checks, including cytology and colposcopy, were performed every 3 months for the first year, every 6 months during the second year and once every year minimum for 5 years. The mean follow-up was of 80 months (range 72-192).

HPV test was performed at pre-treatment check, 12 months after conization and then annually. Recurrences were confirmed by colposcopic direct biopsy.

## Results

The mean age of patients was 54 years (range: 43-68), the mean parity 1.05 (0-4), the mean age for the first sexual intercourse 17 years (14-28), the mean number of sexual partners 3 (1-8), 47% reported tobacco use, 20% previous cervical treatment for HPV lesions or cervical intraepithelial neoplasia (CIN) and 86% a past genital infection.

Of the 55 patients with abnormal cervical cytology referring high-grade squamous intraepithelial lesions, histological analysis of colposcopy-directed biopsies revealed in 19 out of 55 (35%) patients CIN2 and in 36 out 55 (65%) patients CIN3 lesions.

The preoperative colposcopy visualized an entirely detectable squamous columnar junction (SCJ) in 41/55 (75%) and an endocervical unseen SCJ in 14/55 (25%) (Table I).

The pre-treatment lesion size was determined by mean colposcopy and the number of sections involved by abnormal epithelium was recorded dividing the cervix into three sections (one section or 25% of the cervix, two sections or 25-50% of the cervix, three sections or more than 50% of the cervix).

Patients with one section involved had a failure rate of 2% (1 case) those with two sections involved 4% (2 cases) and those with more than two sections involves 8% (4 cases) (Table II).

The cumulative failure rate at first treatment was 14% (7 cases). Patients had a uniformly low rate of complications.

The patients underwent a second session of treatment at 6 months.

All cases submitted to a second laser conization procedure, subsequently underwent follow-up checks.

The microbiological examination of the vaginal secretion was positive in 4 (8%) for mycetes, in 7 (13%) for *Gardnerella vaginalis*, in 5 (10%) for *Trichomonas vaginalis*, in 8 (15%) for *Chlamydia trachomatis*, in 5 (9%) for *Trichomonas* and *Gardnerella*, in 3 (5%) for *Streptococcus agalactiae*, in 2 (4%) for enterococci, in 4 (8%) for cocci, and negative in 14 (26%).

The patients were submitted to proper local and systemic therapy.

HPV test was positive for HPV 16 type in 19 (35%) CIN2 and 36 (65%) CIN 3.

An unsatisfactory colposcopy, due to the endocervical localization of the squamous columnar junction (SCJ), was observed in 19 patients (35%) before laser conization. A postoperative unsatisfactory colposcopy was revealed after the treatment in 12 patients (22%). In 4 cases (7%) cervical stenosis was observed.

Three months after treatment the complete re-epithelization of the cervical surface in every case was shown.

Forty-two patients during the follow-up checks had negative cytology, colposcopy and HR HPV test.

At the one-year follow-up check 7, patients revealed normal cytological and abnormal colposcopic findings and persistent positive HR HPV test (type 16).

Histological analysis of punch biopsy specimens detected two cases of CIN2 and one of CIN3, and four cases of cervical HPV lesions.

At the five-year follow-up check, 14 patients with a normal cytological smear had a recurrence of CIN2 (5 cases) and CIN3 (9 cases) histologically confirmed by mean colposcopy direct biopsy and positive HR HPV test.

In 12 patients the final histological analysis of the excised specimens confirmed the degree of the lesions that had been characterized at the previous biopsy. In one case, the final histological analysis revealed a microinvasive carcinoma (stage IA1, invasion <1 mm). The patient underwent a total vaginal hysterectomy.

## Discussion

Laser CO<sub>2</sub> conization represents a low-morbidity procedure because there are no intra- or postoperative complications at postmenopausal age (7-9).

A total vaginal hysterectomy could represent an excessive procedure for CIN at postmenopausal age and its benefits are slightly better than conservative treatment. The advantage of hysterectomy is that it is easier to check the vaginal cuff by colposcopy, cytology or when HRT is used, if conization is not in sano (eradication is always complete in the case of a

hysterectomy) but there are also disadvantages and pitfalls (e.g. it is an excessive procedure for dysplasia, mortality increases with age) (1).

The patients in postmenopause must be examined by an experienced and skilled colposcopist because the most important factor determining the quality of clearance results is the accuracy of the diagnosis. The skilled colposcopist must also have an intimate knowledge of cytology and histopathology so that an accurate selection of patients can be made (14).

Cytologic follow-up alone leads to 20% of false-negative results; when this is associated with colposcopy, the false-negative rate falls to 3-8% (15-16). A combined cyto-colposcopic long-term follow-up is therefore indicated after conservative treatment of CIN in postmenopausal age (10).

Persistence of HPV is associated with an increase risk of developing SIL and cancer. In younger women, it has been shown that persistent viral detection represents a more accurate measure of risk for development of cervical neoplasia than do tests taken at a single point in time. Like younger aged women, the cumulative prevalence of HPV among postmenopausal women was much higher than at individual time points. In postmenopause, the cumulative persistence rate of oncogenic type is similar to younger ages and incidence of cervical neoplasia does not decrease with increasing age. Premenopausal women who test positive for HPV persistently over time have been shown to be at the highest risk of developing preneoplastic genital disease (17).

Several prospective studies have shown that women who are HPV-DNA-positive at baseline have a higher risk of developing CIN3 or invasive cervical cancer during the follow-up than HPV-DNA-negative women. Furthermore, results from these studies are sometimes difficult to interpret and compare because the HPV-type detected in the cervical smears may not be the same HPV-type detected in the subsequent CIN2-3 lesions or cervical cancer (2).

In some of these studies, CIN2-3 developed within 2 years of HPV-DNA detection, thus indicating that, contrary to the theory that prolonged HPV infection is necessary for progression to CIN2-3, these precancerous lesions can be an early manifestation of HPV infection (18, 19).

When a specific HPV type is found consecutively, it is very likely to represent the same variant as well, thus suggesting true persistence and not sequential infections. A number of other cofactors are therefore likely to be involved in the disease process: environmental or exogenous cofactors, including hormonal contraceptives, tobacco smoking, parity and co-infection with other sexually transmitted agents, viral cofactors. Regarding the other sexually transmitted agents, the role of *Chlamydia trachomatis* has been studied intensively, and the majority of studies restricted to HPV-positive women have demonstrated an association with high-grade cervical lesions and invasive cancer (20).

*Chlamydia trachomatis* has also been reported to be associated with increased HR HPV persistence in two recent prospective studies (21, 22).

In contrast, the findings related to other sexually transmitted infections such as herpes simplex virus and *Trichomonas vaginalis* have been much less consistent (20).

Other factors such as different nutrients (e.g. vitamin E, lutein, lycopene, beta-carotene, and vitamin C), intake of fruit and vegetables, as well as alcohol intake have also been suggested as modulating the natural history of HPV cervical neoplasia, but the results do not yet permit any firm conclusions (6).

HPV typing in the follow-up of patients of postmenopausal age treated for CIN 2/3 is important to detect persistent types to identify women at risk of developing cervical abnormalities, either by repeated DNA genotyping or potentially by RNA based techniques may be more predictive of persistent infection (23).

That incidence of cervical neoplasia does not decrease with increasing age also supports the argument that, because HPV is a necessary cause of this cancer and because HPV positivity predicted subsequent infection, testing postmenopausal patients for the virus may be a cost-effective method of disease prevention (17).

In postmenopause, the correct management of H-R squamous intraepithelial lesions is still debated. However, a satisfactory follow-up is the main requirement for conservative management.

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Received March 26, 2008

Revised August 29, 2008

Accepted September 8, 2008