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MANAGEMENT OF HSIL (CIN II) IN NULLIPAROUS PATIENTS

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***MANAGEMENT OF HSIL (CIN II) IN NULLIPAROUS PATIENTS (Abstract)**:* Cervical carcinogenesis evolves in several stages over a relatively long period of time (7-20 years) and it can be diagnosed by multiple non-invasive screening methods (PAP smear, HPV genotyping, colposcopy) and consecutively treated. It is known that 50% of CIN II cases regress spontaneous and 30% progress to CIN III or cervical cancer. Management of HSIL (CIN II) has a major importance for clinicians because many patients are young and it is important to preserve the obstetrical outcome. Therefore, in this study, 3 types of management for CIN II were proposed in nulliparous patients: 1. conservative management; 2. LOOP / LLETZ; 3. conization. The main goal of the study was to evaluate if, in very carefully selected cases, conservative and minimally invasive management may be a viable therapeutical option, in order to preserve obstetrical outcome of the patients, knowing that conization determine a moderate to severe shortening of the cervix and increases the risk of second trimester abortion or preterm delivery, especially by premature rupture of membranes; conization can determine infertility by cervical stenosis. In our limited study a less aggressive management of cervical lesions provided better obstetrical outcomes both in terms of getting pregnant and in duration of pregnancy. Although current management of CIN II is considered to be similar to CIN III, in carefully selected nulliparous patients (high social status, high education, compliant patients), with satisfactory colposcopy (squamous-cylinder junction visible in colposcopy, lesions at a distance from the cervical os and endocervical cytology without pathological changes) and the CL less than 30-32 mm, we can opt for conservative management (by follow-up) or loop diathermy (single or multiple) or LLETZ, with a rigorous follow-up, thus preserving the obstetrical outcome.

KEY WORDS: CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN); LOW GRADE SQUAMOS INTRAEPITHELIAL LESION (LSIL); HIGH GRADE SQUAMOS INTRAEPITHELIAL LESION (HSIL); LARGE LOOP EXCISION OF THE TRANSFORMATION ZONE (LLETZ/LEEP); COLD KNIFE CONIZATION

SHORT TITLE: Management of HSIL (CIN II)

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INTRODUCTION

Cervical intraepithelial neoplasia II (CIN) lesions have major importance in practice because they have partial characters of low grade squamos intraepithelial neoplasia (LSIL) (the possibility of spontaneous involution in 54% of cases or stagnation in 16% of cases), and partial character of high grade squamos intraepithelial neoplasia (HSIL) (rapid evolution to CIN III or invasive cancer in 30% of cases) [1-3].

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Because many patients diagnosed with cervical lesions are young and the obstetrical outcome is very important to be preserved, it is important to modulate the management, due to the fact that conization increases the risk of second trimester abortion or preterm delivery, especially by premature rupture of membranes, and also can determine infertility by cervical stenosis. [1, 4-7]

Management of CIN II is now considered to be mainly surgical, but in some very carefully selected cases a "less aggressive" management is preferred, in order to preserve the obstetrical outcome in young patients. [1-3, 7-11].

The main goal of the study was to evaluate if, in selected cases, conservative and minimally invasive management can be a viable therapeutic option, knowing that conization can determine a moderate to severe shortening of the cervix.

MATERIAL AND METHOD

A total of 19 nulliparous patients, aged between 28 and 32, diagnosed with CIN II, were enrolled in this study, from January 2008 to October 2011. Diagnostic algorithm consisted in Papanicolaou test smear (PAP), Human Papilloma Virus (HPV) genotyping, colposcopic examination, colposcopic guided biopsy with histopathological exam and transvaginal ultrasound measurement of the cervical length (CL) before and after management.

Management of the cases was based on: lesion localization, endocervical cytology, age, family planning, the presence or absence of ectropion, CL. Based on these criteria there were formulated several therapeutic strategies:

1) Conservative management by follow-up at 6 months (PAP smear, HPV genotyping, colposcopy). This therapeutic strategy was applied to a group of 3 nulliparous patients, Human Papilloma Virus - high risk (HPV-HR) positive, with squamous-cylinder junction visible in colposcopy, lesions at a distance from the cervical os, with negative endocervical cytology and CL less than 27 mm in ultrasound.

2) Minimally invasive surgical management by single or multiple loop diathermy or excision of the transformation zone (LLETZ – large loop excision of the transformation zone). This therapeutic strategy was applied to a group of 9 nulliparous patients, HPV-HR positive, with CL between 27 and 32 mm, with squamous - cylinder junction visible in colposcopy, lesions at a distance from the cervical os and benign endocervical cytology.

3) Conization was applied to a group of 7 nulliparous patients, HPV-HR positive, with confirmed progression of the lesion inside the cervical canal (positive endocervical cytology, not visible squamous-cylinder junction and/or development the lesion(s) in the cervical canal, not fully visible at the colposcopic exam), to a patient with persistent CIN II at 6 months's follow-up from the group with conservative management and to a group of 2 patients with recurrence of CIN at 6 months after loop diathermy. Cold-knife conization patients were selected primarily from patients with ectropion and cervical hypertrophy (over 4 centimeters in two opposed diameters).

Postconization follow-up consisted in PAP smear every 6 months, HPV genotyping at 9 to 12 months, colposcopy and CL at 6 months.

RESULTS

In two cases with conservative management, spontaneous regression of the lesion was diagnosed and in one case it was noted persistence of the lesion. In patients with spontaneous regression of the CIN II, colposcopy revealed that lesion's area regressed to half compared to the initial one and showing CIN I characters; PAP smear was LSIL and HPV genotyping was negative. In the 3rd case the PAP smear was HSIL, colposcopy revealed a persistent CIN II lesion and HPV genotyping revealed persistent HPV-HR infection.

Follow-up of the patients with LLETZ revealed recurrence of the cervical lesion in 3 cases: in 2 cases CIN II (one case with persistent HPV-HR infection and one case infection with another HPV-HR genotype) and in one case CIN I (colposcopy - LSIL, PAP smear - LSIL, HPV positive different from the initial genotypes). Conization was practiced in the first 2 cases, and follow-up by colposcopy, PAP smear and HPV genotyping was practiced in the 3rd case.

In the conization group there was no case with recurrence or positive margins. PAP smears at 6 and 12 months ranged from benign to LSIL. HPV genotyping was negative in 5 cases at 12 months, one patient was infected with other HPV genotype than the initial one and one patient presented persistent HPV infection (with another LSIL lesion diagnosed colposcopically, distanced from the conization scar).

The maximal decrease of the CL in ultrasound measurement 6 months after conization was 13 mm, in one case; in 3 cases the decrease of the CL was 7 to 8 mm, in 3 cases was 5 to 6 mm and in 2 cases the CL decreased less than 5 mm. In 2 cases no changes in the CL were observed.

Cases with benign PAP smear, HPV negative and without colposcopical findings after LLETZ or conization were considered cured but they were included in a high-risk group for recurrence and a rigorous follow-up was proposed: PAP smear every 6 months, colposcopy and HPV genotyping every at 12 months.

We present 3 cases, one case with conservative management, one case with minimally invasive surgical management and one with conization:

- *1st case:* 32 years old nulliparous patient. Initial PAP smear was LSIL, HPV positive for genotypes 16 and 59. Colposcopy revealed LSIL on congenital ectropion (Fig. 1) CL was 24 mm (Fig. 2). Histopathological result of the biopsy was CIN II. Conservative management was decided. Follow-up at 6 months revealed HSIL in PAP smear, HSIL (CIN II) in colposcopy (Fig. 3), HPV persistent positive for 16 and 59 genotypes, histopathological result of the biopsy was persistent CIN II. The patient was proposed for loop diathermy. Histopathological result was CIN II. Postoperative follow-up revealed LSIL in PAP smear at 6 and 12 months, HPV positive for genotypes 16 and 59 at 12 months, LSIL in colposcopy distanced from the conization scar. CL at 6 months was 21 mm. Histopathological result of the biopsy was CIN I.

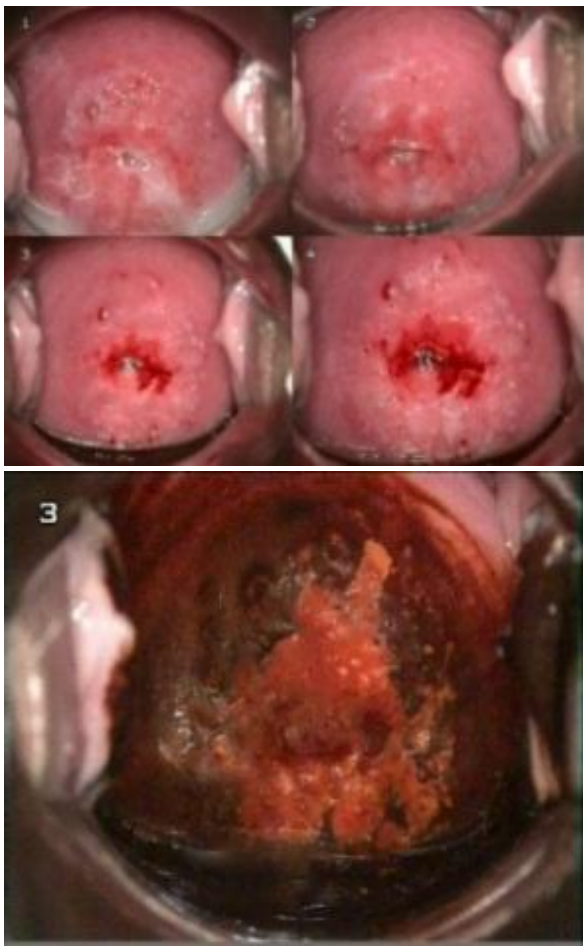

Fig 1 1st case colposcopy
LSIL on congenital ectropion, after acetic acid A (up) and Lugol (bottom)

- *2nd case*: 25 years old nulliparous patient. Initial PAP smear was ASC-US (Atypical squamous cells of undetermined significance**)**, HPV positive for genotypes 6 and 39. Colposcopy revealed condylomatosis

(Fig. 4). Initial CL was 31.7 mm. Histopathological result of the LLETZ was CIN II. Follow-up: LSIL in PAP smear at 6 months and benign at 12 months, LSIL in colposcopy at 6 months and smaller LSIL in remission At 12 months, HPV persistent positive for genotypes 6 and 39 at 9 months and negative at 18 months.

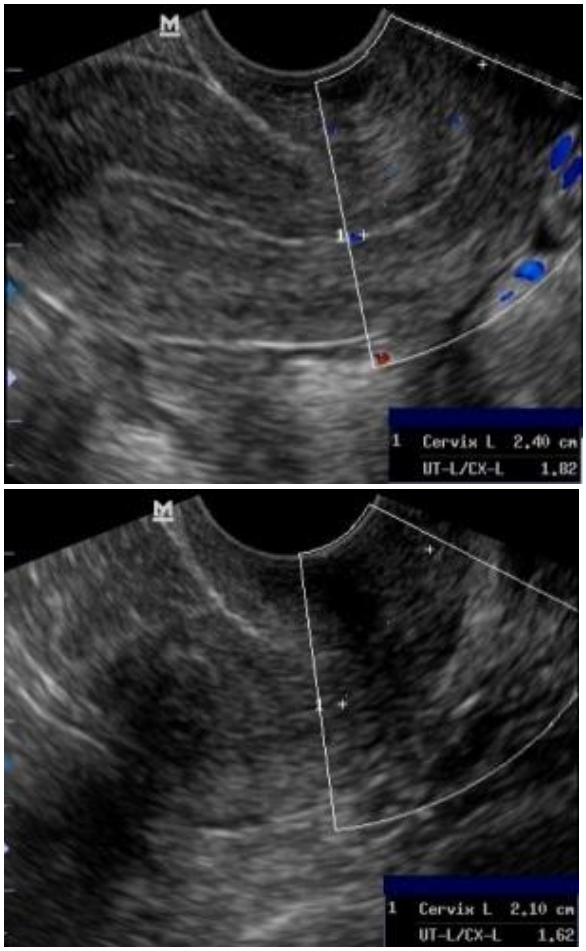

Fig. 2 1st case**,** transvaginal ultrasound measurement of the cervical length: initial (up) and 6 months after loop diathermy (bottom)

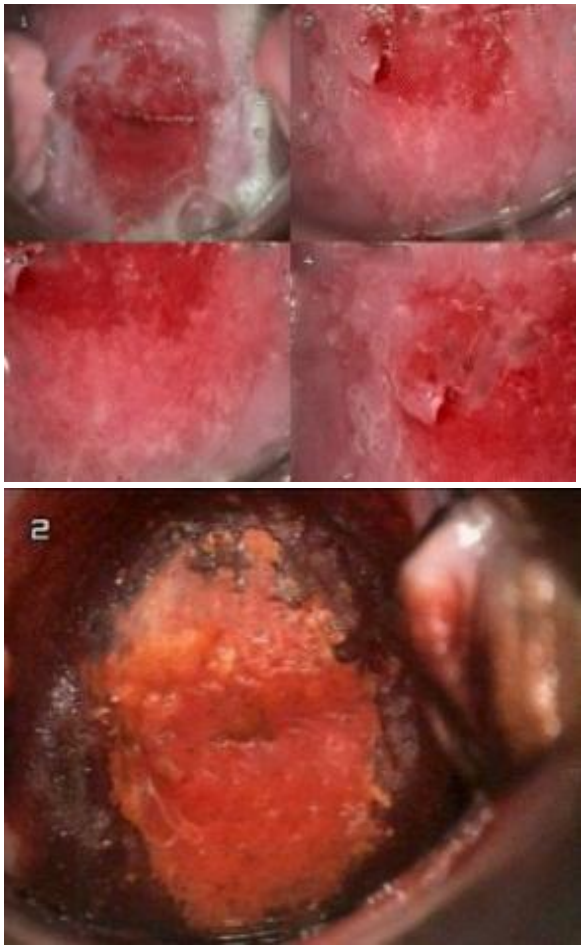

Fig. 3 1st case, colposcopy six months after procedure: after acetic acid (up) and Lugol (bottom)

- *3rd case*: 31 years old nulliparous patient. Initial PAP smear was HSIL, HPV positive for genotypes 18, 54 and 56, HSIL in colposcopy (Fig. 5). CL was 38 mm. Histopathological result of the biopsy was CIN II. The histopathological result of the cone specimen was CIN II, without positive margins. Follow-up: LSIL in PAP smear at 6 months and benign at 12 months, HPV positive for genotype 39 at 9 months and negative at 18 months. Colposcopy revealed plan condiloma disseminated on the cervix and vagina. CL at 6 months after conization was 29.3 mm.

Post therapeutic fertility was evaluated in 13 patients who desired to get pregnant. Among them, 9 patients obtained pregnancy during the first year after follow-up: two patients from the conservative management group, 4 patients from the minimally invasive surgical management group and 3 patients from the conization group (2 patients that underwent diathermy conization and one patient that underwent CKC (cold knife conization)). Only 2 premature births were noted among the 9 patients, one from the minimally invasive management group (late prematurity, 36 weeks), and one from the CKC group (early prematurity, 33 weeks).

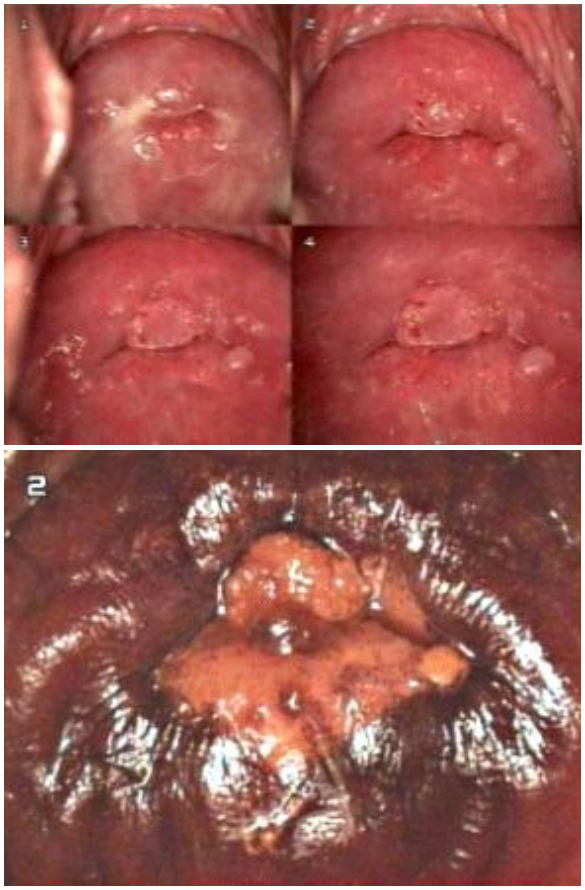

Fig. 4 2nd case, colposcopy; cervical condylomatosis: native and after acetic acid (up) and after Lugol (bottom)

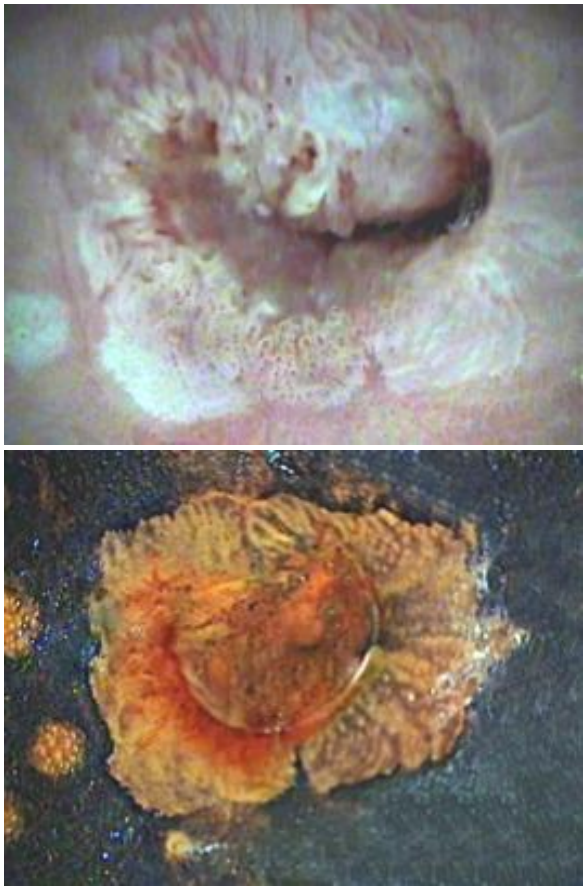

Fig. 5 3rd case, colposcopy; HSIL**:** after acetic acid (up) and after Lugol (bottom)

DISCUSSIONS

The annual incidence for CIN I and CIN II/III was evaluated at 1.6 and 1.2 per 1,000 women, respectively, with the highest incidence among women aged 21 to 30 years (3.3 and 3.6 per 1,000) and women aged 31 to 40 years (2.9 and 2.7 per 1,000) [4,11].

In Romania is very difficult to evaluate the real incidence of HPV infection, CIN I, II or III in population because there is no cervical neoplasia screening program.

Cervical carcinogenesis evolves in several stages over a relatively long period of time (7-20 years) that can be diagnosed by multiple non-invasive screening methods (PAP smear, HPV genotyping, colposcopy) and consecutively treated. [1,13-19]

Many studies demonstrated that cervical length measured by transvaginal ultrasound in the first or second trimester of pregnancy provides a sensitive prediction of preterm birth. Preterm birth is a major cause of perinatal morbidity and is a leading cause of infant and neonatal mortality. Therefore it is necessary to personalize the management of HSIL cases, especially in patients with open family planning, in order to limit the shortening of the cervix [1,4,6,7,20].

In our study we tried to evaluate if personalized therapeutic strategy may reduce the obstetric complications.

From the 3 cases with conservative management applied, in 2 cases spontaneous regression of the cervical lesion was observed. Also, from the 9 cases to who minimally invasive surgical management was applied, in 6 cases complete healing was achieved. So, the percentage of healing both in conservative management group and in minimally invasive surgical management group was 66%. In one third of cases we noted persistence or recurrence of the lesions, which required a radical management by conization.

The major advantage of conservative management and minimally invasive surgical management by single or multiple loop diathermy or LLETZ is that the CL is not affected or hardly affected. As a consequence, of the 12 patients, 6 obtained a pregnancy in the first year and we noted only one preterm birth, at 36 weeks of gestation.

Even if conization is the preferred management strategy in HSIL (CIN II) lesions, this therapeutic option has the disadvantage of shortening the cervix and cervical stenosis. Of the 10 patients with conization as therapeutic strategy, 8 patients presented shortening of the cervix in transvaginal ultrasound measurement that ranged from 4 to 13 mm. In this group 3 patients obtained a pregnancy in the first year after surgery; one early premature birth was noted (33 weeks), one birth at 37 weeks of gestation and one at 39 weeks.

CONCLUSION

Although current management of CIN II is considered to be similar to CIN III, in carefully selected nulliparous patients (high social status, high education, compliant patients), with satisfactory colposcopy (squamous-cylinder junction visible in colposcopy, lesions at a distance from the cervical os and endocervical cytology without pathological changes) and the CL less than 30-32 mm, we can opt for conservative management (by follow-up) or loop diathermy (single or multiple) or LLETZ, with a rigorous follow-up, thus preserving the obstetrical outcome.

In our limited study a less aggressive management of cervical lesions provided a better obstetrical outcome, both in terms of getting pregnant and in duration of pregnancy, but larger population studies are required to draw a conclusion.

CONFLICT OF INTERESTS

None to declare

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