Original Article

Loop electrosurgical excision procedure versus expectant management to treat high-grade squamous intraepithelial lesion in women up to 25 years

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ABSTRACT

Introduction: The recommended treatment of high-grade intraepithelial lesion (HSIL) in women of up to 25 years varies considerably.

Aim: To determine outcome of regression in a cohort of women younger than 25 years old with cervical intraepithelial neoplasia grade 2 and 3 (CIN2/3) undergoing treatment with Loop Electrosurgical Excision Procedure (LEEP) or observational management.

Methods: Prospective cohort study was carried out between April 2015 and January 2017 with all newly diagnosed biopsy-proven CIN2/3 outpatients. Analysis was performed that compared women who had immediate surgical treatment with women who chose expectant management. The primary outcome was development of high-grade changes (defined as cytological evidence of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), HSIL, adenocarcinoma in situ, atypical glandular cells (AGC), or worse) from at least one Pap Smear (PS) collected every 6 months in the minimum follow-up of 1 year. Comparisons were made using Cox proportional hazards regression analysis.

Results: Sixty-four women were diagnosed through cervical biopsy with CIN 2/3 and could choose between conservative or surgical treatment. In the group up to 19 years of age, 6 (37.5%) with CIN2 chose the expectant management and 10 (62.5%) LEEP. While among 20-25-year-old women, 38 (79.2%) chose surgery and 10 (20.8%), being just 4 with CIN3, chose only follow-up for 1 year. The risk of cytological high-grade abnormality over the follow-up period was 62.5% for expectant management and 4.2% for LEEP group (p=0.001).

Conclusion: Women aged up to 25 years with CIN2/3 undergoing treatment with LEEP had a significantly lower risk of cytological high-grade abnormality at 12 months follow-up compared with those who remained only under clinical observation.

Key Words: Cervical intraepithelial neoplasia, conization, conservative management, prospective studies, young women

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INTRODUCTION

Routine cervical screening of women up to 25 years old is controversial and varies internationally. In Brazil, the National Cancer Institute (NCI) recommends starting the screening for cervical cancer (CC) only at 25 years of age, following the same recommendation from the United Kingdom. The US Preventive Services Task Force recommends commencing screening at age 21, while, in New Zealand, all women are offered screening from 20 years onward and in Australia and Canada cytology is recommended as early as 18.[1-3]

In addition, in the different countries cited, the recommended treatment of high-grade intraepithelial lesion (HSIL) in women of up to 25 years also varies considerably. Cervical intraepithelial neoplasia (CIN) grades 2 and 3 are collectively classified as HSIL. These lesions are generally managed similarly, using curative treatment through Loop Electrosurgical Excision Procedure (LEEP). However, the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines suggest that the initial observation of CIN2 lesions in adolescents may be considered.[1, 4] Although conservative management is often recommended for adolescents with CIN2, there is limited literature that has examined this issue in women aged 20-25 years.

There have been several recent retrospective and prospective observational studies indicating high CIN2 regression rates with observation of up to 24 months

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using both colposcopy and cytology every 6 months[4-7], but none that include young women diagnosed with CIN3. Although these studies support the hypothesis that the initial observational management of CIN2 is both safe and feasible, they provide incomplete information to inform medical practitioners and their patients about the outcome of expectant management.

AIM OF STUDY

The aim of this study was to compare the outcome of expectant management or LEEP for treatment of CIN2 or CIN3 diagnosed by colposcopy-directed biopsy in women up to 25 years old followed by Pap Smear (PS) and colposcopy every six months for 12 months.

PATIENTS AND METHODS

A prospective cohort study was carried out between April 2015 and January 2017 at the Cervical Pathology Center located in a Brazilian university. The Institutional Review Board of the Faculty of Medical Sciences approved this study.

In the study period, all patients not infected with HIV, not immunized with HPV vaccine and not pregnant up to 25 years of age with cervical biopsy revealing CIN2 or CIN3 were invited to participate. For the women who signed the consent form, the risks and benefits of the expectant management or LEEP were explained, allowing them to choose one of the two, with the consent of the responsible guardian in the cases of patients under 18 years. After opting for therapy, both women in the conservative and the surgical groups were instructed to maintain an ambulatory follow-up of at least twelve months, repeating PS and colposcopy every six months. For the patients with altered cervical biopsy, the guidelines recommended by Brazilian NCI were adopted[3]. The selection of women followed strict criteria to ensure that none of them suffered adverse effects due to delay of CIN 2/3 treatment.

A selection of cohort members with a diagnosis of CIN2/3 were managed conservatively and others through LEEP with 6 months cytological and colposcopic surveillance for 12 months; however, this decision was dependent on the individual patient. Treatment by LEEP was indicated if there was colposcopic or cytological suspicion of invasive or glandular disease; the colposcopy was unsatisfactory, and the patient requested treatment or was unable to attend further follow-up. LEEP conization was performed using loop diathermy with a blend setting and a power output of 40 W by three experienced gynecologists (RNC, FGB, and AFS). A 5-mm cautery ball with a power setting of 50 W was used to achieve hemostasis. Monsel solution was applied as needed. All specimens were marked for orientation with a delayed absorbable suture at the 12 o'clock position for pathology examination. Patients with persistent HSIL after 1 year underwent treatment by LEEP. Regression is defined as 2 consecutive cytology tests during 1-year follow-up showing Negative for Intraepithelial Lesion or Malignancy (NILM) or CIN1. Pap smears after the chosen treatment was always analyzed by the same pathologist using the 2014 Bethesda criteria[8], with the aim of avoiding variation in the cytological diagnoses in the first year of follow-up.

Baseline characteristics of the cohort across the 2 groups were compared using X^2 tests for categorical variables, and 1-way analysis of variance for continuous variables. Outcomes were determined from follow-up cytological results. The primary outcome was development of high-grade changes (defined as cytological evidence of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), HSIL, adenocarcinoma in situ, atypical glandular cells (AGC), or worse) from at least one PS 1 year after the initial diagnosis. A Cox proportional hazards model was used to calculate hazard ratios and confidence intervals and to adjust for potential confounders, assuming a significance level of 5%. Analyses were performed using SPSS 20.0 for windows (SPSS Inc, Chicago, IL).

RESULTS

One hundred and one women were attended to during the study period and underwent PS, colposcopy and cervical biopsy when there was suspected colposcopic lesion, 30 (29.7%) were up to 19 years of age and 71 (70.3%), aged between 20 and 25 years.

Table 1 shows baseline data of the cohort. There was no significant difference between groups in rates of smoking, use of hormonal contraceptives, and number of sexual partners. Only sexually transmitted disease (STD) was significantly different between groups.

Table 1: Descriptive data for the cohort

Variable	Age at diagnosis ≤ 19 y n (%)	20-25 y n (%)	p Value*
Hormonal Contraceptives			>0.05
No	13(43.3%)	24(33.8%)	
Yes	17(56.7%)	47(66.2%)	
Smoking Habit			>0.05
No	28(93.3%)	65(91.6%)	
Yes	02(6.7%)	06(8.4%)	
Sexual Partners			>0.05
< 3	11(36.6%)	24(33.8%)	
≥ 3	19(63.4%)	47(66.2%)	
STD Condyloma, Herpes, Syphilis or Trichomonas			0.04
No	17(56.6%)	56(78.8%)	
Yes	13(43.4%)	15(21.2%)	
Total	30	71	

Abbreviations: y= years; STD= sexually transmitted disease
* Determined from the X^2 distribution for categorical variables, and using one-way analysis of variance for continuous variables.

Among the 101 women, sixteen (53.3%) aged up to 19 years had a histopathological diagnosis of HSIL (14 CIN2/ 2 CIN3) and agreed to participate in the study. While four (13.3%) were diagnosed with low-grade intraepithelial lesion (LSIL) and 10 (33.3%) presented normal colposcopy, being released from follow-up.

In the group aged 20 to 25 years, 48 (67.6%) women had HSIL on cervical biopsy (22- CIN2/ 26- CIN3), and were included in the study. Two (2.8%) were diagnosed with invasive squamous cervical carcinoma and were treated immediately. Finally, 13 (18.3%) had CIN1 on biopsy and colposcopy was normal in eight (11.2%), and were released from follow-up.

Sixty-four (63.4%) from both groups were diagnosed through cervical biopsy with CIN 2/3 and could choose between conservative or surgical treatment. In the group of patients up to 19 years of age, 6 (37.5%) with CIN2 chose the expectant management and 10 (62.5%) LEEP. While among 20-25-year-old women, 38 (79.2%) chose surgery and 10 (20.8%), being just 4 with CIN3, chose follow-up for 1 year. The rates of regression and persistence of CIN2/3 at each follow-up visit are shown in Table 2. Hazard ratios for development of cytological high-grade abnormalities are presented in Table 3

Table 2: Cumulative frequency of the cytological high-grade abnormality outcome for every six-month follow-up.

Treatment	PS	6 Months	Age		12 Months	Age	
			≤19y	20-25y		≤19y	20-25y
		n (%)	n (%)		n (%)	n (%)	
CONSERVATIVE	HSIL	10 (62.5)	3 (30)	7 (70)	10 (62.5)	3 (30)	7 (70)
	NILM	6 (37.5)	3 (50)	3 (50)	6 (37.5)	3 (50)	3 (50)
LEEP	HSIL	2 (4.2)		2 (100)	2 (4.2)		2 (100)
	NILM	46 (95.8)	10 (21.7)	36 (78.3)	46 (95.8)	10 (21.7)	36 (78.3)
TOTAL		64	16	48		16	48

Abbreviations: PS= Pap Smear; LEEP= Loop Electrosurgical Excision Procedure; NILM= Negative for Intraepithelial Lesion or Malignancy; HSIL= high-grade intraepithelial lesion; y=year

Table 3: Hazard ratios for development of high-grade abnormalities after 1 year

Comparison	HR(CI95%)	p value	HR a(CI95%)	p value
LEEP compared with conservative management	0.39 (0.21-0.74)	.001	0.37 (0.19-0.71)	.001

Abbreviations: HR= Hazard Ratio; CI= Confidence Interval; HR a= Adjusted Hazard Ratio; LEEP= Loop Electrosurgical Excision Procedure.
* Adjusted for smoking status, age, STD at diagnosis, hormonal contraceptive use and number of sexual partners.

Adjustments were made for age at diagnosis, smoking status at diagnosis, STD at diagnosis, hormonal contraceptive use and number of sexual partners. After adjustment, no significant difference was found between the group that choose expectant management and the group that submitted to conization (p=0.93). However, the LEEP group was found to have a significantly lower risk of high-grade abnormality in PS performed semiannually for 1 year (p=0.001).

The risk of cytological high-grade abnormality over the follow-up period for each of the study groups was 62.5% for expectant management (10 out of 16) and 4.2% for LEEP (2 out of 48). High-grade abnormalities detected included HSIL, AGC, ASC-H or worse in both follow-up PS. The low number of cohort members developing such abnormalities precludes further analysis regarding the risk of developing a specific abnormality.

DISCUSSION

The main finding of this study is that, in the first year after treatment, women with histopathological diagnosis of CIN2/3 treated with LEEP have a significantly lower risk of presenting cytological high-grade abnormality in the PS collected half-yearly compared to those who chose expectant management.

The management of women up to 25 years old with CIN2/3 remains controversial. If there is no clear evidence that cervical cancer screening in this age group prevents cervical carcinoma, it is logical to conclude that the immediate treatment of screen-detected

HSIL abnormalities may not be necessary[9]. Although observational management is increasingly offered to young women with CIN2, there is little prospective data involving women with CIN3 that can advise clinicians and their patients of the likely outcome of this. There is a small but undetermined risk of adverse outcome and little information regarding the optimal observational regimen. There is also an increased potential of loss to follow-up with observational management compared with immediate surgical treatment.[4,10]

In our study, women were selected based on the biopsy revealing CIN2/3. Half of the women up to 19 years old with CIN2 who chose conservative therapy had regression of the lesion represented by two negative PS in the first year of follow-up, while 100% of those aged between 20 and 25 years old or with CIN3 had persistent HSIL in cytology. Whereas with monitored women with CIN2 diagnosed through colposcopy-directed biopsy, our findings are similar to those of some studies[4,11,12] , who observed rates of 42% to 65% of spontaneous regression in 8 to 18 months follow-up.

Although studies involving young women exclusively with CIN2[1,5-7,13] claim that the high regression rates found support only after clinical observation in these cases, prospective studies such as these that provide safety for clinicians and patients are scarce. In addition, it is important to consider that any patient with histopathological diagnosis of CIN2/3 is afraid to observe the lesion only every six months and many will not be able to guarantee the rigorous follow-up until spontaneous regression, or even the need for surgical therapy due to persistence or progression of the high-grade lesion.

The strengths of this study are the inclusion of women with CIN 3 in the group of conservative treatment and the fact that it is prospective. The weaknesses include the interobserver variation of histopathological diagnosis of CIN2/3, the number of patients and the lack of randomization.

The interobserver error in the diagnosis of CIN2/3 is well documented and not easily overcome[14]. Similarly, cervical biopsies may not accurately reflect the worst abnormality on the cervix[15]. The fact that the apparent regression and progression identified in patients in this study may to some extent reflect limitations in our diagnostic tools rather than biological changes is understood. The study reflects routine clinical practice where patients are managed based on cytology and biopsy results. An additional potential criticism is that follow-up was only for 1 year and the natural history of the disease points to a higher rate of spontaneous regression of high-grade lesions in young women 24 months after diagnosis[10].

CONCLUSION

Within these limitations, we conclude that women aged up to 25 years with CIN2/3 determined through cervical biopsy undergoing treatment with LEEP had a significantly lower risk of presenting cytological high-grade abnormality at 12 months follow-up compared with those who remained under clinical observation at that time. Randomized studies are required to confirm the safety of observational management in young women with high-grade intraepithelial lesion.

CONFLICT OF INTEREST

There are no conflict of interests.

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