ORIGINAL PAPER

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Conservative management of cervical intraepithelial neoplasia 2 and prediction of its progression – a retrospective study

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Abstract

Aim: Cervical intraepithelial neoplasia 2 (CIN2) evolution is controversial, and some of them regress spontaneously in a two-year follow-up. The purpose of this work was to evaluate the percentage of CIN2 progression or persistence during a 24-month follow-up, using clinical predictors such as human papillomavirus (HPV) genotype and cytology results. *Patients, Materials and Methods*: This is a retrospective case-control study and included patients of reproductive age who had a new diagnosis of CIN2 who were monitored for lesion regression (Group 1, *n*=72 patients), and progression or persistence (Group 2, *n*=36 patients). A multinominal logistic regression was preferred to evaluate the impact that various categorical risk elements can lead to outcomes of persistence or progression of CIN2. We also performed a linear regression to assess the risk of CIN2 progression or persistence using the interaction between clinical predictors. *Results*: A previous cervical cytology indicative of high-grade squamous intraepithelial lesion (HSIL) [relative risk ratio (RRR): 3.85, 95% confidence interval (CI): 1.66–8.90] or atypical squamous cells, cannot exclude HSIL (ASC-H) can highly raise the probability of a CIN2 progression or persistence. The presence of HPV16 increased the risk of CIN2+ with 3.77 (95% CI: 0.78–5.00), the presence of HPV18 increased the probability of CIN2+ with 4.39 (95% CI: 1.35–14.33), and other high-risk HPV (HR-HPV) strains increased the probability of CIN2+ with 3.62. The highest risk issue was produced by the interaction between HSIL* HPV16, ASC-H* HPV16, and ASC-H* HPV18. *Conclusions*: When discussing follow-up for CIN2 lesions, it is important to offer careful consideration and monitoring of patients with a previous HSIL or ASC-H cytology, with or without HPV 16, 18 or other HR-HPV strains, as their presence significantly increased the risk of CIN2 progression and persistence.

Keywords: cervix, colposcopy, HPV, Pap smear, biopsy.

Introduction

The human papillomavirus (HPV) tends to be one of the leading pathogens to cause cervical dysplasia, covering up to 99% of the main factors in epithelial dysplasia [1]. Intraepithelial lesions are described in three categories based on the epithelial layer damage. Cervical intraepithelial neoplasia 1 (CIN1) is considered to be a low-grade squamous intraepithelial lesion (LSIL) concerning 1/3 of the basal epithelium, with high chances of recovery, also meaning a LSIL in Pap smear results [2]. Regression often occurs in the first two years following the infection and no surgical treatment is required if cervical biopsy shows limited lesions [3, 4].

CIN2 and CIN3 are considered to be high-grade squamous intraepithelial lesions (HSILs). The associated Pap smear results correspond to HSIL, atypical glandular cells (AGCs) or *in situ* neoplastic lesions [5]. CIN2 is considered moderate dysplasia that affects 2/3 of the basal epithelium, while for CIN3, the results correspond to severe dysplasia with high chances of neoplastic cells, because the affected areas are considered to fully occupy the epithelial layers with intact basal membrane [6]. In this case, some of the lesions are called *in situ* carcinoma.

Considering medical treatment, the first step in counseling is primary prevention. Primary prevention consists in HPV vaccination, since early ages, before the onset of sexual life. Nowadays, three vaccines are offered for primary

vaccination: Gardasil, a quadrivalent vaccine protecting against HPV 6 and 11 low oncogenic types and HPV 16 and 18 that cause more than 70% of cervical cancer forms [7]. Three doses are necessary to achieve full immunization.

As for a second vaccine, we have Cervarix, a bivalent vaccine offering protection for HPV 16 and 18, divided in three doses [7]. The most complex vaccine is considered to be Gardasil 9, a nonvalent form that offers protection against nine subtypes of HPV (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) divided in three doses [7, 8]. Romania had a poor preventive result in the early 90's in early ages, but nowadays the government is promoting low prices, in order to be accessible for a wide population with ages between 9–45 years old [9–12].

Although vaccination offers a good protection, considering that countries where vaccination was successful, have very low rates of cervical neoplasia, we cannot ignore recommendations for further Pap smear and HPV testing. When HPV testing alone is negative, the recommendation is to test the patients after three years. If the HPV test is positive, annual testing is required, associated with cytology result and colposcopy recommendation [1, 13].

Patients diagnosed with CIN1/LSIL are often managed conservatively, as around 80% of these lesions exhibit spontaneous regression [14]. Conversely, excisional therapy is the optimal choice for CIN3 because of its elevated risk of progressing to cervical cancer. CIN2, categorized as HSIL on cytology report, has a debatable management because of spontaneous progression or regression rates of approximately 11–18% and 50–61%, respectively, after 24 months of follow-up [15].

Aim

Due to the absence of well-defined risk indicators for predicting disease progression complicates the therapy of CIN2. This study aimed to assess the risk of CIN2 progression or persistence during a 24-month follow-up using clinical predictors such as HPV genotype and cytology results.

Patients, Materials and Methods

This retrospective observational case-control analysis included patients of reproductive age with a new diagnosis of CIN2 who attended Noelle Clinic in Iași, Romania, between July 2021 and July 2024.

The inclusion criteria comprised the following: age between 25 and 45 years old; patients who opted for watch and wait management; patients who had a CIN2 histological diagnosis; providing informed consent for data collection. The exclusion criteria comprised the following: inadequate colposcopy evaluation of the cervical lesions; primary diagnosis of CIN2+; loss of follow-up.

All our patients were treated in accordance with the prevailing guidelines and received cytology and colposcopy evaluations biannually for a duration of two years. Cervical biopsy was conducted according to the national regulations.

When the biopsy indicated CIN3, patients were subjected to prompt intervention through the loop electrosurgical excision procedure. A complete regression was considered, when two successive cervical cytology, colposcopy, and biopsy findings indicated no lesion, a partial regression if the final biopsy revealed CIN1, the persistence of the lesion was considered when a biopsy at 24 months of follow-up indicated CIN2, and the lesion progression was considered if a CIN3 lesion was identified at a biopsy performed anytime during the follow-up.

The main outcomes were considered the following: regression (partial/complete) and persistence of progression (CIN2+) and corresponded to the main study groups: Group 1 (n=72) and Group 2 (n=36).

Cervical cells were collected in ThinPrep vials for liquid-based cytology and further HPV genotyping. The cervical cytology was classified according to the Bethesda system, and HPV genotyping was done using real-time polymerase chain reaction (PCR) and nucleic acid hybridization.

The histopathological specimens from cervical biopsies and conizations were described according to the *World Health Organization* (WHO) criteria.

Descriptive statistics using Pearson's χ^2 (*chi*-squared) test were employed for assessing the difference regarding the categorical variables rates. A multinomial logistic regression was used to assess the impact of various categorical risk factors on the outcome of persistence or progression of CIN2. The analysis was adjusted for potential confounders, and the results were reported as relative risk ratios (RRRs) and 95% confidence intervals (CIs). We also performed a linear regression to assess the risk of CIN2 progression or persistence using the interaction between clinical predictors and reports the results as standardized coefficients (StdCs). Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS; version 25.0, IBM Corp., Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant.

Results

Data from a total of 108 patients that completed the 24 months follow-up was used for analysis in this study. Fifty-one (47.22%) patients had a CIN2 complete regression, 21 (19.44%) patients had a partial regression, 22 (20.37%) patients had CIN2 persistence, and 14 (12.96%) patients had CIN2 progression. The main groups further analyzed were represented by Group 1 (partial/complete regression, 72 patients) and Group 2 (CIN2 progression and persistence, 36 patients). Their clinical characteristics are presented in Table 1 and were as follows: age (in years), parity, if they were using, or not, contraception, smokers or not, vaccinated or not, if they had previous cytological evaluation and HPV genotyping. The data were correlated with the first group, totaling a number of 72 patients and with Group 2, consisting of 36 patients.

Our results indicated that the study groups were relatively homogenous considering their clinical characteristics such as age (p=0.86), parity (p=0.82), use of contraceptive methods (p=0.77), smokers (p=0.19), and vaccination status (p=0.68). However, the second group of patients had significantly higher rates of HPV16 (47.22% *versus* 31.94%) and HPV18 infections (25% *versus* 6.94%) compared to the first group (p=0.003). Also, patients who later had a progression or persistence of HPV infection, had higher rates of HSIL on cytological examinations (63.88% *versus* 33.33%, p=0.004).

We used a multinomial logistic regression to evaluate the risk of CIN2 progression or persistence using clinical predictors, and the results are showed in Table 2. Our results indicated that a previous cervical cytology indicative of HSIL (RRR: 3.85, 95% CI: 1.66–8.90, p=0.02) or atypical squamous cells, cannot exclude HSIL (ASC-H) (RRR: 1.54, 95% CI: 1.25–1.89, p=0.03) significantly increased the risk

of CIN2 progression or persistence. Moreover, the presence of HPV16 increased the risk of CIN2+ with 3.77 (95% CI: 0.78–5.00, $p<0.001$), the presence of HPV18 increased the risk of CIN2+ with 4.39 (95% CI: 1.35–14.33, $p=0.014$), and other high-risk HPV (HR-HPV) strains increased the risk of CIN2+ with 3.62 (95% CI: 1.55–8.49, $p=0.003$).

Table 1 – *Clinical characteristics of the study groups*

Clinical characteristics	Group 1 (partial/complete regression, *n*=72)	Group 2 (CIN2 progression and persistence, *n*=36)	*p*-value
Age, years (mean ± SD)	31.72±4.31	32.40±4.79	0.86
Parity, *n* (%)	Nulliparous: 31 (43.66%)	Nulliparous: 16 (44.44%)	0.82
	Multiparous: 40 (56.33%)	Multiparous: 20 (55.55%)	
Contraception, *n* (%)	Yes: 23 (31.94%)	Yes: 10 (27.77%)	0.77
Smokers, *n* (%)	Yes: 29 (40.27%)	Yes: 19 (52.77%)	0.19
Vaccination, *n* (%)	Yes: 13 (18.05%)	Yes: 8 (22.22%)	0.68
Previous cytology, *n* (%)	ASCUS: 16 (22.22%)	ASCUS: 4 (11.11%)	0.004
	LSIL: 17 (23.61%)	LSIL: 8 (22.22%)	
	HSIL: 24 (33.33%)	HSIL: 23 (63.88%)	
	ASC-H: 15 (20.83%)	ASC-H: 1 (2.77%)	
HPV genotyping, *n* (%)	HPV16: 23 (31.94%)	HPV16: 17 (47.22%)	0.003
	HPV18: 5 (6.94%)	HPV18: 9 (25%)	
	Other HR-HPV: 43 (61.11%)	Other HR-HPV: 11 (30.55%)	

ASC-H: Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL); ASCUS: Atypical squamous cells of undetermined significance; CIN2: Cervical intraepithelial neoplasia 2; HPV: Human papillomavirus; HR: High risk; LSIL: Low-grade squamous intraepithelial lesion; *n*: No. of patients; SD: Standard deviation.

Table 2 – *Multinomial logistic regression to assess the risk of CIN2 progression or persistence using clinical predictors*

Predictor	RRR	95% CI	*p*-value
ASCUS	2.40	0.73–7.79	0.140
LSIL	1.14	0.43–2.96	0.780
HSIL	3.85	1.66–8.90	0.020
ASC-H	1.54	1.25–1.89	0.030
HPV16	3.77	0.78–5.00	<0.001
HPV18	4.39	1.35–14.33	0.014
Other HR-HPV	3.62	1.55–8.49	0.003

ASC-H: Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL); ASCUS: Atypical squamous cells of undetermined significance; CI: Confidence interval; CIN2: Cervical intraepithelial neoplasia 2; HPV: Human papillomavirus; HR: High risk; LSIL: Low-grade squamous intraepithelial lesion; RRR: Relative risk ratio.

We used a linear regression to evaluate the risk of CIN2 progression or persistence using the interaction between the cytology results and interaction effects, and the results are presented in Table 3.

Table 3 – *Linear regression to assess the risk of CIN2 progression or persistence using interaction between clinical predictors*

Interaction effect	StdC	SE	*p*-value
ASCUS* HPV16	0.70	0.08	0.46
ASCUS* HPV18	0.72	0.09	0.32
ASCUS* HR-HPV	1.42	0.10	<0.001
LSIL* HPV16	0.98	0.10	0.89
LSIL* HPV18	3.12	0.81	<0.001
LSIL* HR-HPV	1.09	0.27	0.70
HSIL* HPV16	1.78	0.18	<0.001
HSIL* HPV18	1.43	0.11	0.002
HSIL* HR-HPV	1.55	0.25	0.008
ASC-H* HPV16	1.88	0.12	<0.001
ASC-H* HPV18	1.92	0.09	<0.001
ASC-H* HR-HPV	1.67	0.10	<0.001

ASC-H: Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL); ASCUS: Atypical squamous cells of undetermined significance; CIN2: Cervical intraepithelial neoplasia 2; HPV: Human papillomavirus; HR: High risk; LSIL: Low-grade squamous intraepithelial lesion; SE: Standard error; StdC: Standardized coefficient.

Our results indicated that the highest risk increment was determined by the interaction between HSIL* HPV16 [StdC: 1.78, standard error (SE): 0.18, $p<0.001$], ASC-H* HPV16 (StdC: 1.88, SE: 0.12, $p<0.001$), and ASC-H* HPV18 (StdC: 1.92, SE: 0.09, $p<0.001$).

Discussions

HR-HPV subtypes 16 and 18 are the main cause for more than half of untreated cervical cancers. They are mostly associated with HSILs, but endocervix adenocarcinoma occurs especially in HPV18-positive patients [16].

In a review assessing cervical dysplasia, the authors evaluated the gynecological management associated with the risk of progression to cervical pathology. They found that patients who were managed with both Pap smear and HPV testing had better follow-up strategies and lower risk of CIN2+ progression, compared to women who were managed with only one of the previous methods [17]. In our study, we investigated the risk of CIN2 progression or persistence during a 24-month follow-up using clinical predictors such as HPV genotype and cytology results. Our results showed that a previous cervical cytology indicative of HSIL or ASC-H significantly increased the risk of CIN2 progression or persistence. Moreover, the presence of HPV16 increased the risk of CIN2+ with 3.77, the presence of HPV18 increased the risk of CIN2+ with 4.39, and other HR-HPV strains increased the risk of CIN2+ with 3.62. When we studied the cumulative effect of various combinations of cervical cytology reports and HPV genotypes, we found out that highest risk increment was determined by the interaction between HSIL* HPV16, ASC-H* HPV16, and ASC-H* HPV18.

Our results are close with previously published evaluations. For example, research conducted by Salvadó *et al.* that followed-up 291 patients demonstrated that HPV16 infection [odds ratio (OR): 1.97, 95% CI: 1.13–3.43] and previous HSIL cytology (OR: 3.46, 95% CI: 1.99–6.02) significantly increased the risk of persistence or progression of CIN2 lesions [18]. Moreover, Khan *et al.*, conducted a cohort study in a 10-years' timeframe that examined the risk

stratification of cervical lesions based on HPV genotype [19]. The authors included a total of 20 810 women in the study and demonstrated a global incidence of 17.2% of CIN3+ among HPV16+ women and 13.6% among HPV18+ women.

In our study, 47.22% of patients had a CIN2 complete regression, 19.44% patients had a partial regression, 20.37% patients had CIN2 persistence, and 12.96% patients had CIN2 progression. A comprehensive meta-analysis encompassing 36 studies described the outcomes of nonpregnant patients diagnosed with CIN2, who underwent conservative management at various follow-up intervals [20]. At the 24-month mark, 819 out of 1470 (55.71%) untreated women with CIN2 experienced regression to CIN1 or less (CIN1–). In contrast, 334 of 1257 (26.57%) women maintained their CIN2 status, while 282 of 1445 (19.52%) women advanced to CIN3 or more severe conditions (CIN3+) [20].

While it is true that untreated CIN2 could present a greater long-term risk of cervical cancer compared to immediate intervention, the blanket treatment for all CIN2+ cases results in over-treatment and unwarranted complications [21]. One potential consequence following treatment is the heightened likelihood of subfertility. Another is the risk of premature birth during pregnancies. Maintaining fertility is crucial as the age for childbearing is postponed and the trend of having multiple children gains traction. Furthermore, current research indicated that women diagnosed with CIN2 expressed a readiness to pursue conservative treatment [22]. Therefore, if the progression without any treatment of the CIN2 lesion could be known before, will help women with CIN2 in choosing the best solutions for this disease.

In our study, both groups had similar HPV vaccination rates (18.05% *versus* 22.22%), and these rates were significantly lower than those previously reported in the literature, which confirms the need for improvement of the national vaccination campaigns in Romania and for awareness increase among premenopausal patients for vaccinal options, especially if they are included in high-risk categories for cervical cancer.

Our study has several limitations: small sample size, limited number of clinical predictors and generalizability, retrospective and unicentric design, as well as a low reported vaccinal rate among patients. Multicentric studies should better assess the opportunity for conservative management of CIN2 lesions, especially for young women of reproductive age who did not complete their family planning.

Conclusions

Cervical dysplasia affects an important number of women worldwide regardless of each country's guidelines and follow-up. When considering young women, it is important to know if surgical management will affect future follow up or even further affect their ability to conceive and carry a pregnancy to term. When discussing follow-up for CIN2 lesions, it is important to offer careful consideration and monitoring of patients with a previous HSIL or ASC-H cytology, with or without HPV 16, 18 or other HR-HPV strains, as their presence significantly increased the risk of CIN2 progression and persistence in a two-years' timeframe.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: August 22, 2024

Accepted: October 25, 2024