Thieme

Does CIN2 Have the Same Aggressive Potential As CIN3? A Secondary Analysis of High-Grade Cytology Recurrence in Women Treated with Cold-Coagulation Cervical Treatment

Haben CIN-II dasselbe aggressive Potenzial wie CIN-III? Eine Sekundäranalyse von zytologisch nachgewiesenen hochgradigen Rezidiven nach Kaltkoagulation der Zervix

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ABSTRACT

Introduction To determine whether women with CIN2 versus CIN3 on pretreatment cervical punch biopsy have less high-grade cytology recurrence following cold-coagulation cervical treatment.

Materials and Methods This was a retrospective study of women having had cold coagulation between 2001–2011 in our colposcopy unit. Women with previous cervical treatment were excluded.

Results We identified 402 women with 260 (64.7%) cases of CIN2 and 142 (35.3%) cases of CIN3 on pretreatment cervical punch biopsy. In the total sample, the mean age of women was 27.5 years (SD = 4.9), 75.1% were nulliparous and 36.6% were smokers. Referral cytology and pretreatment colposcopic appearance were high-grade in 62.7% and 57.1%. The mean follow-up period was 2.8 years (SD = 2.1). Women with CIN2 on pretreatment cervical biopsy when compared to those with CIN3 had less frequently high-grade referral cytology and high-grade pretreatment colposcopic appearances, and had less pretreatment cervical biopsies taken. During the follow-up period, women with CIN2 on pretreatment cervical biopsy had less high-grade cytology recurrence when compared to those women with CIN3 (1.9 vs. 5.6%, p = 0.046). Multiple stepwise Cox regression analysis showed that women with CIN3 on pretreatment cervical biopsy had 3.21 times greater hazard for high-grade cytology recurrence (HR = 3.21, 95% CI: 1.05–9.89; p = 0.041) in comparison with CIN2 cases.

Conclusion We found that women with CIN2 on pretreatment cervical punch biopsy had less high-grade cytology recurrence following cold-coagulation treatment in comparison to those with CIN3. This finding lends support to the theory that CIN2 even though a high-grade abnormality might not have the same aggressive potential as CIN3.

ZUSAMMENFASSUNG

Einleitung Ziel der Studie war es, die Häufigkeit von hochgradigen Rezidiven bei Frauen mit CIN-II-Läsionen zu ermitteln, verglichen mit Frauen mit CIN III. Der CIN-II- bzw. CIN-III-Befund basierte auf Stanzbiopsien. Nach der Befundung bestand die Behandlung bei allen Frauen aus einer Kaltkoagulation.

Material und Methoden Es handelt sich um eine retrospektive Untersuchung von Frauen, die zwischen 2001 und 2011 in unserer Kolposkopie-Abteilung behandelt wurden. Frauen, die sich bereits zuvor einer anderen Zervixbehandlung unterzogen hatten, wurden von der Studie ausgeschlossen.

Ergebnisse Insgesamt wurden 402 Frauen untersucht; davon hatten laut Stanzbiopsie 260 Frauen (64,7%) CIN-II- und 142 Frauen (35,3%) CIN-III-Läsionen. Das Durchschnittsalter aller in der Studie eingeschlossenen Frauen war 27,5 Jahre (SD = 4,9); davon waren 75,1% Nullipara und 36,6% waren Raucherinnen. Basierend auf dem zytologischem Befund und dem kolposkopischen Erscheinungsbild vor der Behandlung hatten 62,7 bzw. 57,1% der untersuchten Frauen hochgradige Läsionen. Die mittlere Nachbeobachtungszeit betrug 2,8 Jahre (SD = 2,1). Frauen, bei denen vor der Behandlung eine CIN II durch Stanzbiopsie ermittelt wurde, hatten seltener einen hochgradigen zytologischen Befund bzw. ein hochgradiges Erscheinungsbild verglichen mit Frauen mit CIN III, und die Anzahl der vor der Behandlung entnommenen Zervixbiopsien war geringer. Im Nachbeobachtungszeitraum gab es weniger hochgradige Rezidive bei Frauen mit CIN II verglichen mit Frauen, bei denen zuvor eine CIN III zytologisch nachgewiesen wurde (1,9 vs. 5,6%, p = 0,046). Nach der schrittweisen multiplen Regression nach Cox war das Risiko bei Frauen, bei denen vor der Behandlung eine CIN III mit Stanzbiopsie nachgewiesen wurde, nach der Behandlung ein hochgradiges Rezidiv zu entwickeln, 3,21-mal höher (HR = 3,21, 95%-KI: 1,05–9,89; p = 0,041) als bei Frauen mit CIN II.

Schlussfolgerung Unsere Ergebnisse zeigen, dass Frauen, bei denen vor der Behandlung eine CIN II durch Stanzbiopsie ermittelt wurde, weniger zytologisch nachweisbare hochgradige Rezidive nach der Behandlung mit Kaltkoagulation entwickelten als Frauen mit CIN III. Dieses Ergebnis stützt die Hypothese, dass, auch wenn die CIN II als hochgradige Anomalie eingestuft wird, CIN II nicht dasselbe aggressive Potenzial wie CIN III hat.

Introduction

High-grade cervical intraepithelial neoplasia (CIN) is considered a precursor lesion to the development of invasive cervical cancer [1]. According to the 2012 Lower Anogenital Squamous Terminology (LAST) for high-risk human papilloma virus (HPV)-related lesions of the lower genital tract, CIN2 and CIN3 lesions are grouped together as "high-grade" and are managed in the same way [2]. There is evidence that the risk for progression of a CIN2–3 lesion to microinvasive cancer is less than 10% with estimated time intervals ranging from 10 to 25 years [3]. However, there are recent reports that the invasive potential of CIN2 and CIN3 lesions is not the same and even though both are considered as "high-grade" they demonstrate different rates of progression to cervical cancer and possess varying rates of spontaneous regression. In studies with biopsy proven but untreated CIN3, the risk of progression to cervical cancer has been reported about 40% (1% annually) in England and Wales [4] and 15–23% in Sweden [5]. In a study from New Zealand, the estimated risk of cervical cancer for biopsy proven but untreated CIN3 was 31% at 30 years as compared to a 0.7% cancer risk at 30 years in women receiving cervical treatment for biopsy proven CIN3 [6].

In contrast, there is a growing body of evidence that CIN2 lesions have a high rate of spontaneous regression such that they should not always warrant an immediate intervention as in the case of CIN3 but could be managed conservatively. For women under 25 years of age with biopsy proven CIN2, the spontaneous regression rates described in the literature range between 59 to 68% [7–10], with annual regression rates being reported of 15–23% [3]. Moreover, for women over 25 years of age with biopsy proven CIN2, the spontaneous regression rates described vary between 40 to 74% [11, 12].

The primary objective of our study was to investigate whether women with CIN2 vs. CIN3 on pretreatment cervical punch biopsy had a different high-grade cytology recurrence rate following ablative cervical treatment thus lending support to the literature evidence that CIN2 has a different aggressive potential and might be regarded as a different entity to CIN3 even though they are both considered as "high-grade".

Materials and Methods

Study design

This was a secondary analysis of data from an observational cohort study of women treated with a single cold coagulation cervical treatment at the Shrewsbury and Telford Hospitals (SaTH) NHS Trust, between January 2001 and December 2011 [13]. Those women with a previous excisional or ablative treatment or with no cytology follow-up data were excluded from further analysis.

We selected to identify the high-grade cytology recurrence of women in our cohort which was defined as moderate or severe dyskaryosis following cold coagulation treatment. The high-grade cytology recurrence was determined at the time intervals of 6 months, 12 months, and then annually thereafter. We chose the high-grade cytology recurrence as our primary endpoint instead of the overall cytology recurrence because this rendered a repeat excisional treatment in almost all cases of women initially treated with cold coagulation.

The cytology history of the patients before and after treatment was taken from the SaTH colposcopy and cytology databases. Follow-up of women was done mainly in primary care settings in accordance to the National Health Service-Cervical Screening Programme (NHS-CSP) guidelines with the exception of the first post-treatment cytology test that was done in the colposcopy unit. Information on cytology follow-up was obtained until December 2012.

Other data collected from the SaTH colposcopy and histopathology databases involved the patients' demographics (age, parity, smoking), referral cytology (normal, low-grade cytology: borderline nuclear changes in squamous cells/mild dyskaryosis, high grade cytology: moderate/severe dyskaryosis), pretreatment cervical punch biopsy features (number, maximum depth, endocervical crypt involvement [ECI], histology: CIN2 or CIN3) and pretreatment colposcopic appearance (normal, HPV/inflammation/benign, low-grade, high-grade).

Criteria for colposcopically directed punch biopsies

British Society of Colposcopy and Cervical Pathology (BSCCP) accredited colposcopists performed all colposcopy procedures. The decision to perform cervical punch biopsies in women attending for colposcopy was based on the combination of cytological and colposcopical findings [14]. A colposcopically directed biopsy was carried out when most of the ectocervix was replaced with a high-grade abnormality, when a low-grade colposcopic appearance was associated with high-grade dyskaryosis on cytology testing, and when a lesion extended into the endocervical canal [15].

Cold-coagulation cervical treatment procedure

Cold coagulation treatment was offered to women with no suspicion of invasive disease on examination and all women had pretreatment cervical punch biopsy in accordance to national guidelines [15]. The Semm cold coagulator (WISAP company, model no. 60001; Brunnthal, Munich, Germany) was applied to the cervix with a minimum temperature of 110 °C and maximum of 120 °C. Treatment application lasted for a minimum of 20 seconds with a minimum of one application and a maximum of four applications. Prior to treatment the cervix was infiltrated with local anaesthetic using 1–3 vials (Citanest 3% with Octapressin, 2.2 ml vials).

▶ **Table 1** Total sample characteristics (n = 402).

	n (%)
Age at time of treatment (years) (mean ± SD)	27.5 (4.9)
Smoking	
▪ No	234 (63.4)
▪ Yes	135 (36.6)
Parity	
▪ 0	302 (75.1)
▪ 1	61 (15.2)
▪ ≥ 2	39 (9.7)
Referal cytology	
▪ Negative	5 (1.2)
▪ Low-grade	145 (36.1)
▪ High-grade	252 (62.7)
Histology of pretreatment cervical punch biopsy	
▪ CIN2	260 (64.7)
▪ CIN3	142 (35.3)
Endocervical crypt involvement by high-grade CIN in biopsy	
▪ No	348 (86.6)
▪ Yes	54 (13.4)
Number of pretreatment cervical punch biopsies (mean ± SD)	2 (1)
Maximum depth of pretreatment cervical punch biopsies (mm) (mean ± SD)	3.9 (1.5)
Colposcopy image	
▪ Normal/HPV/inflammation/benign	37 (9.6)
▪ Low-grade	128 (33.2)
▪ High-grade	220 (57.1)

▶ **Table 2** Characteristics for CIN2 and CIN3 cases.

	CIN2 n (%)	CIN3 n (%)	p
Age at time of treatment (years), (mean ± SD)	27.5 (4.8)	27.5 (5.2)	0.853*
Smoking			
▪ No	148 (63)	86 (64.2)	0.818**
▪ Yes	87 (37)	48 (35.8)	
Parity			
▪ 0	195 (75)	107 (75.4)	0.523**
▪ 1	37 (14.2)	24 (16.9)	
▪ ≥ 2	28 (10.8)	11 (7.7)	
Referal cytology			
▪ Negative	3 (1.2)	2 (1.4)	< 0.001***
▪ Low-grade	118 (45.4)	27 (19)	
▪ High-grade	139 (53.5)	113 (79.6)	
Endocervical crypt involvement by high-grade CIN in biopsy			
▪ No	241 (92.7)	107 (75.4)	< 0.001**
▪ Yes	19 (7.3)	35 (24.6)	
Number of pretreatment cervical punch biopsies (mean ± SD)	1.9 (1)	2.1 (0.9)	0.044*
Maximum depth of pretreatment cervical punch biopsies (mm), (mean ± SD)	3.8 (1.5)	4.1 (1.5)	0.095*
Colposcopy image			
▪ Normal/HPV/inflammation/benign	29 (11.7)	8 (5.8)	0.016**
▪ Low-grade	90 (36.3)	38 (27.7)	
▪ High-grade	129 (52)	91 (66.4)	

* Student's t-test; ** χ^2 test; *** Fisher's exact test.

Statistical analysis

Quantitative variables are presented with mean and standard deviation (SD) or with median (interquartile range) values. Qualitative variables are presented with absolute and relative frequencies. For the comparison of proportions, χ^2 and Fisher's exact tests were used. Student's t-tests were computed for the comparison of mean values. Kaplan–Meier survival estimates for high-grade cytology recurrence and survival were graphed over the follow-up period. A multiple Cox proportional-hazard model was performed in order to evaluate if the histology of pretreatment cervical punch biopsy was independently associated with high-grade cytology recurrence. Hazard ratios (HR) with 95% confidence intervals (95% CI) were computed from the results of the Cox regression analyses. The assumption of proportional hazards was evaluated by testing for interaction with a continuous time variable. All reported p values were two-tailed. Statistical significance was set at $p < 0.05$ and analyses were conducted using SPSS statistical software (version 19.0).

Ethical approval

Ethical approval for collection and management of data in our study was obtained from the Research and Development Department of the Shrewsbury and Telford Hospitals NHS Trust.

Results

From January 2001 to December 2011, a total of 402 consecutive women were identified having had cold coagulation treatment, with 260 (64.7%) having CIN2 and 142 (35.3%) having CIN3 on pretreatment cervical punch biopsy. The mean follow-up period in the cohort was 2.8 years (SD = 2.1) with a median equal to 2.1 years (IQR = 1.1–3.9).

Demographics and clinical features of the total sample

▶ **Table 1** presents the demographics and clinical characteristics of the sample. The mean age of women was 27.5 years (SD = 4.9)

▶ **Table 3** Data of patients (n = 13) with high-grade cytology recurrence at follow-up.

Years of follow-up	No.	Age at ablative treatment	Punch biopsy	FU	FU cytology	Subsequent treatment (excised cervical tissue histology)
< 2 years	1	21	CIN2	6 M	Severe	LLETZ (CIN3)
	2	38	CIN2	3 M	Severe	LLETZ (CIN2)
	3	29	CIN3	6 M	Severe	LLETZ (CIN3)
	4	38	CIN3	5 M	Severe	LLETZ (CIN3)
	5	25	CIN3	6 M	Severe	LLETZ (CIN2)
	6	25	CIN3	5 M	Severe	LLETZ (Cervical cancer stage IB1)
	7	25	CIN2	6 M	Moderate	LLETZ (CIN2)
	8	35	CIN2	14 M	Moderate	LLETZ (Negative histology)
	9	25	CIN3	11 M	Moderate	LLETZ (CIN3)
	10	24	CIN3	12 M	Severe	LLETZ (Cervical cancer stage IB1)
	11	33	CIN3	14 M	Moderate	LLETZ (CIN1)
	12	29	CIN2	20 M	Moderate	Declined any form of treatment; 1st follow-up smear was inadequate; then was subsequently lost to follow-up
> 2 years	13	26	CIN3	35 M	Severe	LLETZ (CIN2)

with 75.1% being nulliparous and 36.6% smokers. Referral cytology and pretreatment colposcopy were high-grade in 62.7 and 57.1% of women. Endocervical crypt involvement on pretreatment cervical punch biopsies was found in 13.4% of cases. The mean number of pretreatment cervical punch biopsies taken was 2 (SD = 1.0) and the mean maximum depth was 3.9 mm (SD = 1.5). The percentage of women in our cohort having had a follow-up cytology test at 6 months and 12 months was 100 and 97.5%. The overall cytology (mild-moderate-severe dyskaryosis) recurrence rates at 6 and 12 months follow-up were 6.9 and 3.1%. The high-grade cytology (moderate-severe dyskaryosis) recurrence rates at 6 and 12 months follow-up were 2.2 and 0.7%. During the entire follow-up period overall cytology recurrence occurred in 43 (10.7%) women while high-grade cytology recurrence occurred in 13 (3.2%) women.

Sub-group analysis in women with CIN2 versus CIN3 on pretreatment cervical punch biopsy

▶ **Table 2** shows the clinical characteristics of the two subgroups of women according to the histology of pretreatment cervical punch biopsy. Women with CIN2 on pretreatment cervical biopsy when compared to those with CIN3 had less frequently high-grade referral cytology and high-grade pretreatment colposcopic appearances, and had less pretreatment cervical biopsies taken.

Clinical features of women with high-grade cytology recurrence at follow-up

▶ **Table 3** shows the clinical features of the n = 13 women who had high-grade cytology recurrence in the follow-up period. The majority of women (92.3%) had high-grade cytology recurrence within the first two years of treatment. Twelve women had subsequent excisional treatment of which n = 4 had CIN3, n = 4 had CIN2, n = 1 had CIN1, n = 1 had negative histology and n = 2 had stage Ib1 cervical carcinoma. Those with invasive cancer in the excisional tissue specimen were both from women with CIN3 on pretreatment cervical biopsy.

Multiple regression analysis for high-grade cytology recurrence in women with CIN2 versus CIN3 on pretreatment cervical punch biopsy

During the follow-up period, women with CIN2 on pretreatment cervical biopsy had less high-grade cytology recurrence when compared to those women with CIN3 (5/260 or 1.9% vs. 8/142 or 5.6%, p = 0.046). Inversely, cold-coagulation treatment for CIN2 was over 98% successful versus only 94.4% for CIN3 on pretreatment punch biopsy. Multiple stepwise Cox regression analysis showed that women with CIN3 on pretreatment cervical biopsy had 3.21 times greater hazard for high-grade cytology recurrence (HR = 3.21, 95% CI: 1.05–9.89; p = 0.041) in comparison with CIN2 cases. Kaplan–Meier estimates for high-grade cytology recurrence according to CIN2 versus CIN3 on pretreatment cervical punch biopsy are shown in ▶ **Fig. 1** (log rank test, p = 0.049).

Discussion

We have shown that women with CIN2 on pretreatment cervical biopsy when compared to those women with CIN3 had less frequently high-grade referral cytology, less high-grade pretreatment colposcopic appearances, less pretreatment cervical punch biopsies taken, and smaller rates of endocervical crypt involvement in pretreatment cervical biopsies. In addition, during the follow-up period women with CIN2 when compared to those with CIN3 had less high-grade cytology recurrence rates. If CIN2 and CIN3 had presumably the same aggressive potential since they are both grouped together as 'high-grade', then we would expect

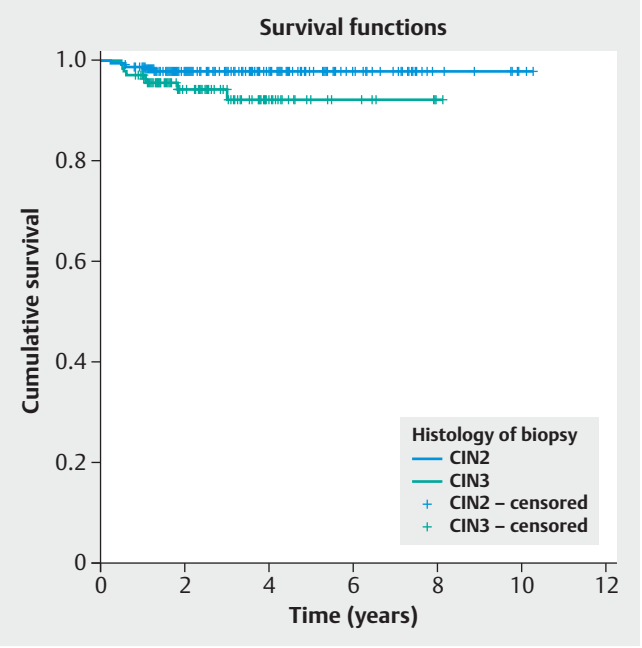
the high-grade cytology recurrence potential following treatment to be similar. Nevertheless, the high-grade cytology recurrence was significantly different between the two subgroups of women with CIN2 versus CIN3 on pretreatment cervical biopsy, even though patient demographic features such as age, parity and smoking status were similar.

There are some explanations reported in the literature why CIN2 lesions seem to have a less aggressive potential when compared to CIN3. First, even though a cervical tissue specimen may be reported as CIN2 there is always an important consideration of misclassification of diagnosis and over-reporting of CIN2 when the abnormality is in fact low-grade [9, 16, 17]. There are reports that CIN2 is the least reproducible of all cervical diagnoses, and it is possible that the less aggressive nature and the regression of CIN2 is dependent on the individual pathologist reporting the lesion [17–19].

Second, even if there is no misclassification of diagnosis, there are several reports in the literature that support that there is a true regression potential in women with biopsy proven CIN2 [3, 7–12]. For women under 25 years of age with biopsy proven CIN2, spontaneous regression rates have been reported as high as 68 % [8–10]. For this reason the American Society for Colposcopy and Cervical Pathology (ASCCP) in their 2012 updated consensus guidelines have quoted that in young women with a histologic diagnosis of CIN2, treatment is acceptable but observation is preferred [20]. Furthermore, a population-based study has shown that screening women with cytology tests under the age of 25 did not reduce the incidence of cancer in young women which supports the hypothesis that in this age group there might be high spontaneous regression rates of high-grade lesions [21]. For women over 25 years of age with biopsy proven CIN2, there are reports that spontaneous regression rates of CIN2 are higher if the referral cytology test is low-grade [11] and the tissue sample is HPV-16 genotype negative [12]. Moreover, it has been suggested that a biopsy of a small lesion can possibly remove it entirely or it may initiate an inflammatory response that may be curative [22–23].

Since cervical treatment has been associated with obstetric morbidity in subsequent pregnancies [24], there are several reports on how to stratify the risk of women with biopsy proven CIN2 and guide clinical management to either conservative management or cervical treatment. Functional biomarkers such as Ki67, pRB, p53, cytokeratin 13/14 and cytokeratin 2 have proven to be helpful in predicting regression of CIN2 or not [25, 26]. Other studies have shown that HPV-genotyping in CIN2 diagnosed young women with low-grade cytology tests is a useful stratifier of risk, with those that are HPV16-negative being potentially able to be managed less aggressively through increased surveillance rather than immediate treatment [12].

There are certain limitations to be considered about our study. First, we measured the cytology-only recurrence at follow-up in our cohort. HPV test of cure had not been introduced at our Trust until after our data collection had been completed in December 2012. Second, recruitment of patients went as far back as 2001 meaning that some may have had Pap testing instead of liquid-based cytology which may have influenced the cytology recurrence rates recorded [27]. Third, smoking status was available for women at the time-point of their cervical treatment and not during follow-up. For this reason, we were not able to adjust for smoking as a confounding factor at follow-up when assessing cytology recurrence after cervical treatment. Fourth, if more pretreatment cervical punch biopsies had been taken in women attending for colposcopy then perhaps more patients with CIN2 or CIN3 may have been detected and therefore treated, thus possibly altering the final results. Finally, the lesion size could not be accurately identified and measured. Even though data were available for the number of quadrants of the cervix that were involved by the lesion, this could not be considered as an accurate representation of lesion size. For this reason, we were not able to adjust for the lesion size as a confounding factor during our analyses.



▶ **Fig. 1** Kaplan–Meier estimates for high-grade cytology recurrence according to CIN2 versus CIN3 in pretreatment cervical punch biopsy (log rank test, p = 0.049).

The main strength of our study is that most patients have been followed up in the primary care settings of the wider area covered by SaTH hospital with few women relocating to other areas. For this reason, we had a relatively small number of missing values from the cytology follow-up as recorded in our colposcopy databases. Another strength includes our sample size and the ten-year length of follow-up.

Conclusion

Our study has shown that women with CIN2 on pretreatment cervical punch biopsy in comparison to those with CIN3 had less high-grade cytology recurrence following cold-coagulation treatment. Our findings lend support to the literature reports that CIN2 even though a high-grade abnormality might be considered a different entity with a lower aggressive potential in comparison

with CIN3. At present, it is recommended that women with the histologic diagnosis of CIN2 have some type of cervical treatment either in the form of excision or ablation [15, 20]. Further studies are needed to clarify when it is safe to adopt an expectant management for CIN2.

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None.

Conflict of Interest

The author(s) declare that they have no competing interests.

References

[1] Katki HA, Schiffman M, Castle PE et al. Five-year risks of CIN 3+ and cervical cancer among women with HPV-positive and HPV-negative high-grade Pap results. J Low Genit Tract Dis 2013; 17: S50–S55

[2] Darragh TM, Colgan TJ, Cox JT et al.; Members of LAST Project Work Groups. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. J Low Genit Tract Dis 2012; 16: 205–242

[3] Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. BMC Infect Dis 2009; 9: 119

[4] Peto J, Gilham C, Fletcher O et al. The cervical cancer epidemic that screening has prevented in the UK. Lancet 2004; 364: 249–256

[5] Gustafsson L, Adami HO. Natural history of cervical neoplasia: consistent results obtained by an identification technique. Br J Cancer 1989; 60: 132–141

[6] McCredie MR, Sharples KJ, Paul C et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol 2008; 9: 425–434

[7] Moore K, Cofer A, Elliot L et al. Adolescent cervical dysplasia: histologic evaluation, treatment, and outcomes. Am J Obstet Gynecol 2007; 197: 141.e1–141.e6

[8] McAllum B, Sykes PH, Sadler L et al. Is the treatment of CIN 2 always necessary in women under 25 years old? Am J Obstet Gynecol 2011; 205: 478.e1–478.e7

[9] Munro A, Powell RG, A Cohen P et al. Spontaneous regression of CIN2 in women aged 18–24 years: a retrospective study of a state-wide population in Western Australia. Acta Obstet Gynecol Scand 2016; 95: 291–298

[10] Moscicki AB, Ma Y, Wibbelsman C et al. Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women. Obstet Gynecol 2010; 116: 1373–1380

[11] Discacciati MG, de Souza CA, d'Otavianno MG et al. Outcome of expectant management of cervical intraepithelial neoplasia grade 2 in women followed for 12 months. Eur J Obstet Gynecol Reprod Biol 2011; 155: 204–208

[12] Castle PE, Schiffman M, Wheeler CM et al. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. Obstet Gynecol 2009; 113: 18–25

[13] Parry-Smith W, Underwood M, De Bellis-Ayres S et al. Success rate of cold coagulation for the treatment of cervical intraepithelial neoplasia: a retrospective analysis of a series of cases. J Low Genit Tract Dis 2015; 19: 17–21

[14] Milenković V, Sparić R, Dotlić J et al. Reliability and relationship of colposcopical, cytological and histopathological findings in the diagnostic process. Vojnosanit Pregl 2012; 69: 869–873

[15] NHSCSP. Colposcopy and Programme Management. Guidelines for the NHS cervical Screening Programme. 3rd ed. Sheffield, England: NHSCSP Publication No. 20; March 2016

[16] Castle PE, Stoler MH, Solomon D et al. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. Am J Clin Pathol 2007; 127: 805–815

[17] Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA 2001; 285: 1500–1505

[18] Dalla Palma P, Giorgi Rossi P, Collina G et al. The reproducibility of CIN diagnoses among different pathologists: data from histology reviews from a multicenter randomized study. Am J Clin Pathol 2009; 132: 125–132

[19] Carreon JD, Sherman ME, Guillén D et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population-based cervical samples. Int J Gynecol Pathol 2007; 26: 441–446

[20] Massad LS, Einstein MH, Huh WK et al. 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol 2013; 121: 829–846

[21] Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. BMJ 2009; 339: b2968

[22] Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993; 12: 186–192

[23] Chenoy R, Billingham L, Irani S et al. The effect of directed biopsy on the atypical cervical transformation zone: assessed by digital imaging colposcopy. Br J Obstet Gynaecol 1996; 103: 457–462

[24] Kyrgiou M, Mitra A, Arbyn M et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database Syst Rev 2015; (9): CD008478

[25] Uleberg KE, Munk AC, Brede C et al. Discrimination of grade 2 and 3 cervical intraepithelial neoplasia by means of analysis of water soluble proteins recovered from cervical biopsies. Proteome Sci 2011; 9: 36

[26] Baak JPA, Kruse AJ, Robboy SJ et al. Dynamic behavioural interpretation of cervical intraepithelial neoplasia with molecular biomarkers. J Clin Pathol 2006; 59: 1017–1028

[27] Abulafia O, Pezzullo JC, Sherer DM. Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. Gynecol Oncol 2003; 90: 137–144