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Justifying conservative management of CIN2 in women younger than 25 years - A population-based study

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HIGHLIGHTS

- New guideline for management of CIN2 in young women well implemented in Nova Scotia
- High regression rates of CIN2 in young women in this population-based study
- Women experienced more regression and less progression in the post-guideline change period.
- Conservative management seems a safe and justified approach for young women with CIN2.

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ABSTRACT

Objective. In 2012, the joint clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada (SOGC) changed from immediate treatment to a more conservative management of Cervical Intraepithelial Neoplasia (CIN) grade 2 in young women. In this study, the outcomes before and after this management change were reviewed in Nova Scotia, Canada.

Methods. A retrospective population-based cohort study was performed among women younger than 25 years with biopsy-proven CIN2, who were diagnosed in one of the colposcopy clinics in Nova Scotia between 2010 and 2014. Regression and progression rates were compared pre- and post-guideline changes.

Results. Of the 636 women included in the study, 286 women were diagnosed with CIN2 before and 350 women after the management in Nova Scotia was changed. After implementation of the 2012 guidelines patients were more likely to receive conservative management (78.6% versus 44.1%; $p < 0.001$); which differs from the patients who underwent treatment during follow-up prior to the change in guidelines (73.4% versus 38.9%; $p < 0.001$). Regression occurred in 73.1% of all women, but women seen in the post-guideline change period had a higher regression rate and lower progression rate ($p < 0.05$). Histologic results from treatment specimen did not show a significant difference in low-grade or high-grade lesions before or after the guideline had been changed ($p = 0.59$).

Conclusion. Conservative management seems a safe and justified approach for women younger than 25 years with CIN2.

1. Introduction

While cervical cancer screening has successfully decreased the incidence and mortality of cervical cancer, there remains controversy surrounding the age of screening initiation. Women under the age of 25 years comprise only 1.4% of all women with cervical cancer and screening these women does not reduce the incidence of cervical cancer [1–6]. Human papillomavirus (HPV) infection and low-grade

Abbreviations: AGC-NOS, Atypical Glandular Cells – Not Otherwise Specified; AIS, Adenocarcinoma In Situ; ASC-H, Atypical Squamous Cells – suspicious for High-grade squamous intraepithelial lesions; ASC-US, Atypical Squamous Cells - of Undetermined Significance; CIN, Cervical Intraepithelial Neoplasia; HPV, Human PapillomaVirus; HSIL, High-grade Squamous Intraepithelial Lesions; LSIL, Low-grade Squamous Intraepithelial Lesions; SOGC, Society of Obstetricians and Gynaecologists of Canada.

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precancerous lesions of the cervix are very common in young women, but are also transient for the majority of these women, with 70–90% clearing infection and showing regression to normal within 2–3 years [7–11]. The treatments of choice for high-grade lesions are excisional procedures, however these are also associated with pregnancy related morbidity [12–14]. Therefore, overtreatment of lesions which are likely to regress spontaneously should be avoided. CIN2 is a heterogeneous group including a mixture of HPV infections and precancerous lesions [15,16] while regression occurs in 60–70% of these cases in young women [17–24].

In 2012 the joint clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada (SOGC) changed from immediate treatment to a more conservative management of CIN2 in young women, including follow-up with repeat colposcopy and cytology at 6-months intervals for up to 24 months before treatment is considered for persistent disease (see Supplementary Table 1 for detailed information) [25,26].

The purpose of this population-based study is to evaluate outcomes of this management change by reviewing the regression and progression rates pre- and post-guideline changes in Nova Scotia, Canada.

2. Methods

This retrospective population-based cohort study included women younger than 25 years at the time of diagnosis with biopsy proven CIN2, who were diagnosed in one of the colposcopy clinics in Nova Scotia between the 1st of January 2010 to the 31st of December 2014, with follow-up registered until October 2015 or until treatment.

Management was based on local practice, which included immediate treatment pre-guideline changes and conservative management, with repeat colposcopy and cytology at 6-months intervals for up to 24 months before treatment is considered for persistent disease, post-guideline changes (see Supplementary Table 1 for the local practice guidelines overview). However, treatment decisions were the responsibility of the individual colposcopist. Although the new guidelines were not published until the end of 2012, local implementation of this new management strategy had begun at the beginning of 2012 in Nova Scotia (see Fig. 1). Therefore we have chosen to compare the outcomes in the period between 1st January 2010 to 31st December 2011 (pre-guideline) with those between 1st January 2012 to 31st December 2014 (post-guideline).

We excluded women who were pregnant at time of diagnosis, women with a histologic diagnosis of CIN3 or worse, those who received treatment prior to the CIN2 diagnosis, and those with no follow-up.

Age at time of diagnosis and the highest referral cytology result were obtained from the Nova Scotia Cervical Cancer Prevention Program database and the Provincial Cervical Screening Database. Results of the first visit and all subsequent follow-up visits were obtained, including the most severe colposcopic impression, cytologic and histologic findings. The specimens were classified according to the 2001 Bethesda cytology terminology and the CIN histologic grading system [27]. The cytologic and histologic findings were reviewed by the local pathology departments in Nova Scotia.

Immediate treatment was defined as treatment within 6 months after CIN2 diagnosis. For women with a conservative approach for 6 months or longer, the regression, persistence and progression rates were calculated. Regression was defined as a low-grade lesion or less on histology. In absence of histologic results cytology was used; including the results of negative for malignancy, low-grade squamous intraepithelial lesions (LSIL) or atypical squamous cells of undetermined significance (ASC-US). Persistent disease was defined as a lesion which remained CIN2 during follow-up. A Pap test showing high-grade squamous intraepithelial lesions (HSIL) or atypical squamous cells suspicious for high-grade squamous intraepithelial lesions (ASC-H) was defined as persistence if there was a lack of histologic results. Women showing progression included a diagnosis of CIN3, adenocarcinoma in situ (AIS) or (micro)invasive cancer. If a woman had evidence of regression, but at a later visit persistence or progression was documented the latter diagnosis was used. Histologic results from the last biopsy done during follow-up and from treatment specimens were reviewed pre- and post-guideline changes.

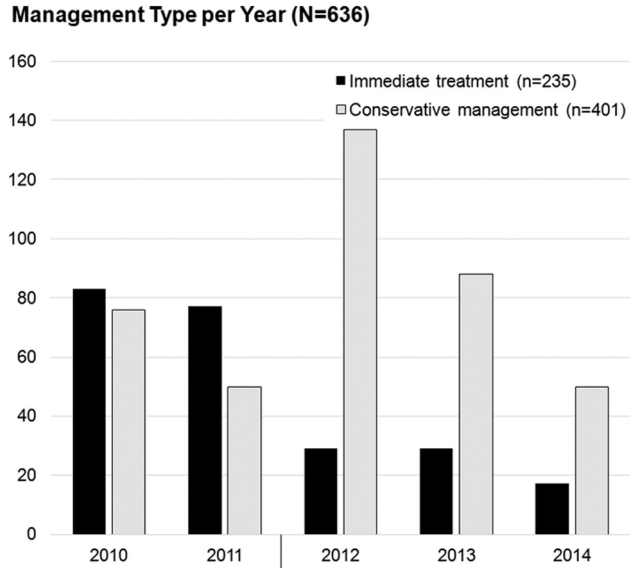

Fig. 1. Management type per year of CIN2 diagnosis in young women in Nova Scotia. In 2012, the SOGC joint clinical practice guideline changed from immediate treatment to a more conservative management for young women with CIN2, including follow-up with repeat colposcopy and cytology at 6-months intervals for up to 24 months before treatment is considered for persistent disease.

The Research Ethics Board of the Nova Scotia Health Authority and the Nova Scotia Department of Health and Wellness Data Access Committee granted approval to the study.

Data were analyzed using descriptive statistics. Differences were compared by Student's *t*-test for continuous variables and Pearson Chi-Square or Fisher Exact Test for categorical variables. All analyses were carried out using the statistical software package SPSS 22.0 (IBM SPSS Statistics; New York, United States).

3. Results

In total 730 young women were identified with biopsy-proven CIN2. Ninety-four women were excluded from the study; 2 women were pregnant, 25 women had a history of CIN3 or treatment, and 67 women had no follow-up. From the remaining 636 women, 286 women were seen pre-guideline changes and 350 women post-guideline changes.

Table 1 shows no differences in baseline characteristics between the pre-guideline and post-guideline change period; including age, referral Pap test, and Pap test and colposcopic impression at initial visit. However, women in the post-guideline change period received significantly more often a conservative approach (78.6% versus 44.1%; $p < 0.001$). In total 73.4% of the women in the pre-guideline change period underwent treatment compared to 38.9% in the post-guideline change group ($p < 0.001$).

The median follow-up for the pre-guideline change group was 4 months (95% CI 3–5) compared to 11 months (95% CI 9–12) for the post-guideline change group ($p < 0.001$). The women with no treatment in the pre-guideline change period (26.6%) had a median follow-up of 33 months (95% CI 30–36), while these women in the post-guideline change period (61.1%) had a median follow-up of 16 months (95% CI 13–17; $p < 0.001$). Women pre-guideline and post-guideline changes received treatment with a median of 3 (95% CI 2–3) and 4 months (95% CI 3–6; $p = 0.01$).

Table 1
Characteristics of young women with CIN2 in Nova Scotia by pre- and post-guideline change group.

	Pre-guideline changes[a] ($n = 286$)	Post-guideline changes[b] ($n = 350$)	Total ($n = 636$)	p-Value
Management type, no. (%)				<0.001
Conservative management[c]	126 (44.1)	275 (78.6)	401 (63.1)	
Immediate treatment[d]	160 (55.9)	75 (21.4)	235 (36.9)	
Age, no. (%)				0.79
<21 years	77 (26.9)	90 (25.7)	167 (26.3)	
21–24 years	209 (73.1)	260 (74.3)	469 (73.7)	
Mean ± standard deviation	21.93 ± 1.9	21.86 ± 1.7	21.89 ± 1.8	0.64
Referral Pap test, no. (%)[e]				0.96
Negative	16 (5.6)	18 (5.1)	34 (5.3)	
Low grade[f]	160 (55.9)	200 (57.1)	360 (56.6)	
High grade[g]	102 (35.7)	127 (36.3)	229 (36.0)	
Unknown/not done	8 (2.8)	5 (1.4)	13 (2.0)	
Pap test result at initial visit, no. (%)				0.08
Negative	53 (18.5)	40 (11.4)	93 (14.6)	
Low-grade[f]	96 (33.6)	124 (35.4)	220 (34.6)	
High-grade[g]	61 (21.3)	59 (16.9)	120 (18.9)	
Unknown/not done	76 (26.6)	127 (36.3)	203 (31.9)	
Colposcopic impression at initial visit, no. (%)				0.43[h]
CIN1 or less	151 (52.8)	182 (52.0)	333 (52.4)	
- Negative	42 (14.7)	59 (16.9)	101 (15.9)	
- CIN1	109 (38.1)	123 (35.1)	232 (36.5)	
CIN2	95 (33.2)	130 (37.1)	228 (35.8)	
CIN3	27 (9.4)	25 (7.1)	52 (8.2)	
Unknown/not done	13 (4.5)	13 (3.7)	26 (4.1)	
Treatment type				<0.001
No treatment, no. (%)	76 (26.6)	214 (61.1)	290 (45.6)	
Treatment, no. (%)	210 (73.4)	136 (38.9)	346 (54.4)	
- LEEP	200 (95.2)	128 (94.1)	328 (94.8)	0.53
- Laser evaporation	0 (0)	1 (0.7)	1 (0.3)	
- Cautery	0 (0)	1 (0.7)	1 (0.3)	
- Cryotherapy	8 (3.8)	5 (3.7)	13 (3.8)	
- Surgical cone	2 (1.0)	1 (0.7)	3 (0.9)	

[a] Pre-guideline changes: <2012.
[b] Post-guideline changes: ≥2012.
[c] No treatment or treatment after 6 months.
[d] Treatment within 6 months.
[e] Most severe result of the last two Pap tests before CIN2 diagnosis.
[f] Low-grade: ASC-US or LSIL.
[g] High-grade: AGC-NOS, ASC-H or HSIL.
[h] Statistical analysis of CIN1 or less versus CIN2 versus CIN3.

For the conservatively managed women, regression, persistence and progression rates are shown in Table 2. Regression occurred in 73.1% of all women, but women seen in the post-guideline change period had a higher regression rate and lower progression rate ($p < 0.05$). Regression occurred with a median time of 6 months (95% CI 6–7), while progression occurred with a median time of 10 months (95% CI 8–11).

Final histologic result from treatment or the last biopsy done during follow-up is shown in Table 3. Women diagnosed with CIN2 prior to the guideline changes had more often a high-grade lesion as final histologic result (56.6% versus 36.6%; $p < 0.001$). Histologic results from treatment specimen only however, did not show a significant difference in low or high-grade lesions before or after the guideline had been changed ($p = 0.59$) (Table 4). From the 138 women with CIN3 or worse during follow-up, 131 women had severe dysplasia and 7 women had AIS. There was no progression to invasive cancer in this study population.

4. Discussion

This population-based study on conservative management of CIN2 in young women found similar regression rates as previous studies [17–24] and a recent meta-analysis with a sub-analysis of women younger than 30 years [28]. Women diagnosed with CIN2 after the local implementation of the new guideline had higher regression rates and lower progression rates, which supports the safety of conservative management and seems a justified approach of CIN2 in young women (Table 2).

Table 2
Regression, persistence or progression of CIN2 in young women in Nova Scotia with conservative management divided by pre- and post-guideline change group.

	Pre-guideline changes[a] ($n = 126$)	Post-guideline changes[b] ($n = 275$)	Total ($n = 401$)	p-Value
Outcome of conservatively managed CIN2				<0.05
Regression, no. (%)	83 (65.9)	210 (76.4)	293 (73.1)	
Persistence, no. (%)	23 (18.3)	28 (10.2)	51 (12.7)	
Progression, no. (%)	20 (15.9)	37 (13.5)	57 (14.2)	
Time to regression Median, months (95% CI)	6 (6–7)	6 (6–7)	6 (6–7)	0.27
Time to progression Median, months (95% CI)	9 (7–12)	10 (7.5–12)	10 (8–11)	0.64

[a] Pre-guideline changes: <2012.
[b] Post-guideline changes: ≥2012.

Table 3
Final histologic result by pre- and post-guideline change group in young women with CIN2 in Nova Scotia[d].

	Pre-guideline changes[a] ($n = 286$)	Post-guideline changes[b] ($n = 350$)	Total ($n = 636$)	p-Value
CIN1 or less, no. (%)	93 (32.5)	154 (44.0)	247 (38.8)	<0.001[e]
- Negative	41 (14.3)	60 (17.1)	101 (15.9)	
- CIN1	52 (18.2)	94 (26.9)	146 (23.0)	
CIN2 or worse, no. (%)	162 (56.6)	128 (36.6)	290 (45.6)	
- CIN2	88 (30.8)	64 (18.3)	152 (23.9)	
- CIN3	74 (25.9)	64 (18.3)	138 (21.7)	
Unknown/not done, no. (%)[c]	31 (10.8)	68 (19.4)	99 (15.6)	

[a] Pre-guideline changes: <2012.
[b] Post-guideline changes: ≥2012.
[c] In some cases there was no histologic result available because Pap test and/or colposcopy impression were used to determine outcome or the treatment was laser evaporation, cautery or cryotherapy.
[d] Most severe histologic result from treatment or last biopsy done during follow-up.
[e] Statistical analysis of CIN1 or less versus CIN2 or worse.

A limitation of this study is that long-term follow-up was not available. However, with a median time to regression of six months and a median time to progression of ten months, a median follow-up time of 33 and 16 months in women receiving no treatment in the pre- and post-guideline change group seems adequate to review the outcomes.

The final histologic result during follow-up (biopsy or treatment specimen) showed a statistical significant difference in low or high-grade outcomes in women seen before and after the implementation of the new guideline ($p < 0.001$) (Table 3). This shows that expectant management, which is more prominent in the post-guideline change group, results in more histologically proven regression as well. Overtreatment occurs in approximately 20% of women receiving treatment (69/346); Table 4). These women had a low-grade lesion or less in their treatment specimen, which means that selection of the right group of women for treatment remains a challenge. Histologic results are generally used as the gold standard, but it is well known that biopsy interpretation has limited reproducibility and accuracy [29–32]. One of the reasons is the continuum of morphologic features of low to high-grade precancerous lesions, causing a subjective interpretation. This makes the meaning of a CIN2 diagnosis on biopsy less clear, and might explain part of the overtreatment. A retrospective cohort study stated that women younger than 25 years have an even higher likelihood of overtreatment after biopsy-proven CIN2/3 compared to women older than 25 years [33]. Unfortunately the cytologic and histologic findings were not reviewed by a central pathology department, which could have improved the accuracy of the results. Also biomarkers, such as p16 (INK4a) immunostaining, could help distinguish between low and high-grade lesions [34,35]. However, with a conservative approach the absolute number of women receiving treatment will decline, which indicates overtreatment could be prevented. On the other hand, of interest is the high rate of CIN3 present in the treatment specimens with a median time to treatment of 3 months (Table 4). It could be argued whether these women truly progressed, or whether sampling error or variation in pathologic interpretation has occurred. Although this is not a prospective randomized study, these findings may suggest a higher than expected rate of regression of occult CIN3.

Uptake of a new guideline by clinicians takes time. Noticeable is the declining adherence to the new guideline in the subsequent two years after an initial high rate of adherence (Fig. 1). Seventy-five women (21.4%) were treated immediately in the post-guideline change period. However, clinician judgement based on, for example, patient history, colposcopic impression or inadequate sampling, and patients' preferences could be an acceptable reason to deviate from a guideline. The impact on psychological well-being from the patient's perspective in management of a CIN2 lesion requires attention, as conservative management implies increased and on-going colposcopic or cytologic follow-up of an untreated lesion. Taghavi et al. examined this particular group of women and found no difference in health-related quality of life, anxiety or sexual functioning by management strategy [36].

Progression to cervical cancer is a potential risk of conservative management, although the progression rate was significant lower in the post-guideline group, no women progressed to invasive cancer in this study and the prevalence of cervical cancer in this age group is low [1]. Clinics need to develop and implement strategies to ensure that loss to follow-up is minimised if a conservative approach to management is implemented. In a meta-analysis with 16 prospective cohort studies the adherence to follow-up was around 90% for up to two years [28].

A persistent HPV infection is necessary for development of cervical cancer. A limitation of this study is the lack of information about the HPV-status of these women. However, based on the high prevalence of HPV in young women and high regression rates, HPV testing in routine cervical cancer screening in women younger than 30 years or as initial triage of management of women younger than 25 years with any cytologic abnormality is not recommended [37].

Unfortunately there is little evidence from large prospective clinical trials on the safety and practicality of conservative management of young women with CIN2. A large multicentre prospective observational cohort study is underway to assess the safety of conservative management of CIN2 in women younger than 25 years and to evaluate predictors of regression and progression [38].

Table 4
Histologic result from treatment specimen by pre- and post-guideline change group in young women with CIN2 in Nova Scotia.

	Pre-guideline changes[a] ($n = 210$)	Post-guideline changes[b] ($n = 136$)	Total ($n = 346$)	p-Value
CIN1 or less, no. (%)	44 (21.0)	25 (18.4)	69 (19.9)	0.59[d]
- Negative	11 (5.2)	6 (4.4)	17 (4.9)	
- CIN1	33 (15.7)	19 (14.0)	52 (15.0)	
CIN2 or worse, no. (%)	158 (75.2)	103 (75.7)	261 (75.4)	
- CIN2	85 (40.5)	43 (31.6)	128 (37.0)	
- CIN3	73 (34.8)	60 (44.1)	133 (38.4)	
Unknown, no. (%)[c]	8 (3.8)	8 (5.9)	16 (4.6)	

[a] Pre-guideline changes: <2012.
[b] Post-guideline changes: ≥2012.
[c] In some cases there was no histologic result available because the treatment was laser evaporation, cautery or cryotherapy.
[d] Statistical analysis of CIN1 or less versus CIN2 or worse.

5. Conclusion

In total 73.1% of women younger than 25 years with biopsy proven CIN2 with expectant management showed regression. Women diagnosed with CIN2 after the local implementation of the new guideline experienced more regression and less progression, while the high-grade results from treatment specimen did not differ comparing the pre- and post-guideline change group. Reviewing the outcomes before and after the 2012 guideline changes from immediate treatment to a more conservative management, conservative management seems a safe and justified approach for young women with CIN2 considering the potential harms of treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.10.038.

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Conflict of interests

None.

Author contribution

Diede Loopik, Ruud Bekkers, Leon Massuger and James Bentley have made substantial contributions to the conception and design of the work. Diede Loopik and James Bentley contributed in the acquisition of the data. Diede Loopik performed the analysis and all authors contributed in the interpretation of the data. Diede Loopik wrote the manuscript with support and participation in drafting the final manuscript from all authors. All authors gave approval of the final version to be published.

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Submission of declaration and verification

This manuscript has not been published previously, is not under consideration for publication elsewhere, and this publication is approved by all authors and the responsible authorities where the work has been carried out. This manuscript will not be published elsewhere in the same form.

IRB-status

The Research Ethics Board of the Nova Scotia Health Authority granted approval before the study began. The Nova Scotia Department of Health and Wellness Data Access Committee approved the study before the Nova Scotia Cervical Cancer Prevention Program database has been accessed.

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