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Outcomes of Conservative Management of High Grade Squamous Intraepithelial Lesions in Young Women

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Objective: The aim of the study was to determine regression rates of cervical intraepithelial neoplasia (CIN) 2 and 3 in women younger than 24 years, followed conservatively for up to 24 months.

Materials and Methods: This is a retrospective chart review of colposcopy patients in clinic database based on the following: (1) younger than 24 years at first visit; (2) first visit January 1, 2010, to May 31, 2013, and at least 1 follow-up visit after diagnosis; (3) histologic diagnosis of CIN2+; and (4) optimal conservative management (observation for up to 24 months or to 24 years, whichever occurred first). Patient information and clinical/pathologic data were extracted from charts to examine patient characteristics and treatment outcomes, CIN2+ regression rates, median times to regression for CIN2 versus CIN3 (Kaplan-Meier survival analysis), and predictors of regression (multivariate logistic regression analysis).

Results: A total of 154 women met criteria. The most severe histological diagnoses were CIN2 in 99 (64.3%), CIN3 in 51 (33.1%), and adenocarcinoma in situ in 4 (2.6%). Adenocarcinoma in situ was immediately treated. In follow-up, CIN2 regressed to CIN1 or negative in 74 women (74.7%)-median time to regression, 10.8 months. Cervical intraepithelial neoplasia 3 regressed in 11 women (21.6%)-median time to regression not reached (last follow-up censored at 52.7 months). Cervical intraepithelial neoplasia 2 on biopsy, low grade referral Pap, and younger age predicted regression. Overall, 49 women (31.8%) were treated.

Conclusions: Conservative management should continue to be recommended to young women with CIN2. Rigorous retention mechanisms are required to ensure that these women return for follow-up.

Key Words: cervical intraepithelial neoplasia, uterine cervical dysplasia, squamous intraepithelial lesions of the cervix, spontaneous neoplasm regression, unnecessary procedures

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The effectiveness of cervical cancer screening in women younger than 25 years is questionable.[1] Reasons for this include low incidence of cervical cancer,[1–5] high rate of false-positive screening tests,[6] and spontaneous resolution of precancerous lesions.[7–16] An increasing number of studies have demonstrated a high rate of regression of high grade squamous intraepithelial lesion (HSIL) (52.4%–71.1%)[7,8,10,11,13–16] in women younger than 25 years, suggesting that treatment is often unnecessary. One UK study estimated that at most, 1.5% of young women treated for HSIL would have developed cancer by the age of 25 years, if left untreated, whereas more than half of them would have regressed by the age of 25 years.[3]

Thus, not only is there a significant proportion of women younger than 25 years undergoing potentially unnecessary treatment, but they are also exposed to short- and long-term risks of treatment. The major long-term risks are increased premature rupture of membranes, preterm delivery, and low birth weight.[17–20] Young women also report psychological stresses associated with colposcopy referral and diagnosis and treatment of precancer.[21,22]

At the time of this study, provincial screening guidelines recommended cytology screening for women aged 21 to 69 years. Those with cytology greater than low grade squamous intraepithelial lesion (LSIL) or recurrent LSIL/atypical squamous cells of undetermined significance for 24 months (cytology every 6 months) were sent for colposcopy. In recognition of high regression rates and potential harms of treatment in young women, in 2010, provincial guidelines for colposcopists in the study setting recommended conservative management of HSIL (cervical intraepithelial neoplasia [CIN] 2 and 3) in women younger than 24 years. This guideline was more conservative than those suggested in 2012 by the American Society of Colposcopy and Cervical Pathology[23] and the Society of Obstetricians and Gynaecologists of Canada,[24] which recommended treatment of CIN3 while allowing conservative management of CIN2, and CIN2,3.[11,24] Although several studies have reported clinical outcomes or protocols of conservative management in young women with CIN2 and CIN2/3,[7,8,10,11,15,16,25] there are no published studies examining outcomes in young women with CIN3 (versus CIN2,3) managed conservatively.

The primary objective of this study is to determine the following: (1) rate of lesion regression and (2) median time to regression, in young women with CIN2 and/or CIN3 who undergo conservative management with observation rather than immediate treatment. Secondary objectives of this study are to (3) determine patient characteristics and clinical factors associated with an increased chance of regression and (4) determine patient adherence.

MATERIALS AND METHODS

Study Setting

This study took place within a regional centralized colposcopy program that is affiliated with a regional centralized Pap smear screening program. Colposcopists within the program complete a regional colposcopy training program and use regional guidelines, which are regularly updated and reviewed for consensus at the regional annual colposcopy education day. During the study period, new guidelines for managing young women were piloted in the study clinic and then implemented regionally (see

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The study was approved by the Clinical Research Ethics Board of the University of British Columbia (CREB# H14-00812) and Vancouver Coastal Health Research Institute.

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Appendix 1, http://links.lww.com/LGT/A94), whereby women younger than 24 years with CIN2 or CIN3 were recommended conservative management if considered reliable for follow-up (judgment call by the colposcopist and referring provider in discussion with the patient), and otherwise, they were recommended to have a loop electrosurgical excision (LEEP). Women with adenocarcinoma in situ (AIS) discovered during follow-up were recommended to have immediate LEEP. The observation protocol consisted of a colposcopic examination and at least 1 biopsy every 6 months for up to 2 years or until age of 24 years (whichever occurred first), at which point a LEEP was recommended if CIN2+ persisted. Patients were discharged after at least 1 biopsy result of CIN1 or negative.

The study clinic is located in a tertiary care hospital with more than 7,000 colposcopy appointments per year. Colposcopic biopsies are all reported by regionally certified gynecologic subspecialty pathologists who also report cytology for the regional cytology laboratory.

Study Design

A retrospective cohort study (chart review) was conducted to examine outcomes of conservative management of CIN2+ in women younger than 24 years.

Study Population

Potential subjects were identified through the colposcopy clinic's electronic encounter database. This clinic includes women of various ages and races, with the majority being white and Asian.

Eligibility Criteria

The criteria for inclusion are the following: younger than 24 years at first visit; histologic diagnosis of CIN2+; first visit between January 1, 2010, and May 31, 2013, with at least 1 follow-up visit; and optimal conservative management was carried out (not treated for CIN2 or CIN3 until age of 24 years or until 24 months of follow-up, whichever occurred first).

Data Collection

Demographic (age, smoking status, distance of home from clinic) and clinical characteristics (referral pap smear/cytology results, pathology results, attendance record) were obtained from clinical records. Cervical cytology and pathology results in the electronic record were checked against actual reports from the pathology laboratory to ensure accuracy.

Primary Outcome

The primary outcomes are lesion regression rate and median time to regression, stratified by most severe histological grade (CIN2 versus CIN3). Patients were only categorized as having regressed if they did not receive a LEEP (i.e., if LEEP pathology was CIN1/negative, they were categorized as *not* regressed). Time to regression was calculated from the date of first CIN2+ detection to the date of the first visit with CIN1 or negative pathology, when there was no CIN2+ at potential subsequent visits. Patients were censored at the last visit or at the date of LEEP treatment if regression did not occur. The most severe diagnosis was categorized as CIN3 for those with results (including LEEP) of CIN2 and CIN3, or CIN2,3.

Secondary Outcomes

The proportion of women who regressed and comparison of characteristics between women whose disease regressed versus those whose disease did not regress were examined. This included logistic regression analysis to determine predictors of regression. We also examined number of visits, rate of no show appointments, and loss to follow up. Patients were categorized as lost to follow up if there was no appointment booked as of the recommended interval for colposcopy or treatment plus 3 months.

Statistical Analysis

Analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp. 2011. Armonk, New York, NY). Comparisons were done using t tests for continuous variables and χ^2/Fisher exact test for categorical variables, as appropriate. Median time to regression was determined using Kaplan-Meier method. Univariate and multivariate logistic regression analysis was used to determine whether there were any significant associations between clinical and demographic factors and likelihood of regression. An α level of 0.05 was used for all statistical tests.

Missing values were excluded for smoking status; however, χ^2 analysis was performed with and without missing values included. The missing values did not impact the direction or magnitude of the association between smoking status and factors of interest (i.e., baseline CIN2+ characterization or regression).

Institutional Review Board

This study was approved by the University of British Columbia Research Ethics Board (CREB# H14-00812) and the Vancouver Coastal Health Research Institute.

Role of the Funding Source

This study was made possible through the University of British Columbia Work Learn Program and the University of British Columbia, Division of Gynecologic Oncology, who provided salary support for a research assistant. The funding sources had no role in any part of the study design, data collection/analysis/interpretation, report writing, or decision to publish.

RESULTS

A total of 224 women younger than 24 years were diagnosed with CIN2+ between January 1, 2010, and May 31, 2013, at the study clinic for colposcopy, and 188 of these women were advised conservative management. However, 34 women (18.1% of 188) had no further follow-up and were excluded from the rest of the analysis for a final cohort of 154 patients. Figure 1 outlines inclusions and exclusions, clinical outcomes and mean follow-up times, categorized according to their most severe diagnosis (CIN2, CIN3, or AIS). Eighty-five (55.2%) women demonstrated lesion regression; overall, 43 regressed to CIN1, and 42 regressed to negative biopsy. Of those with CIN2, 74.7% regressed, and of those with CIN3, 21.6% regressed. For a more conservative estimate, regression rates were also calculated using the initial group of 188 as the denominator (assuming lesions did *not* regress in any of the 34 women excluded because of lack of follow-up). In this case, lesion regression to CIN1 or negative occurred in 74 of the women who had CIN2 (n = 131, 56.5%) and 11 of the women who had CIN3 (n = 53, 20.8%). Almost half of the 34 patients who were excluded because of lack of follow-up had cytology performed subsequently elsewhere in the region/province (see Figure 1, legend).

Table 1 describes demographic and clinical characteristics (n = 154) stratified according to the most severe pathological diagnosis. The most severe diagnosis (including LEEP) was CIN2 in 99 women (64.3%), CIN3 in 51 women (33.1%), and AIS in 4 women (2.6%). Based on provincial database records, 11 women (7.1%) had a history of previous dysplasia (HSIL Pap or CIN2+): 3 (1.9%) CIN2, 1 (0.6%) CIN3 (and previous LEEP), and 7

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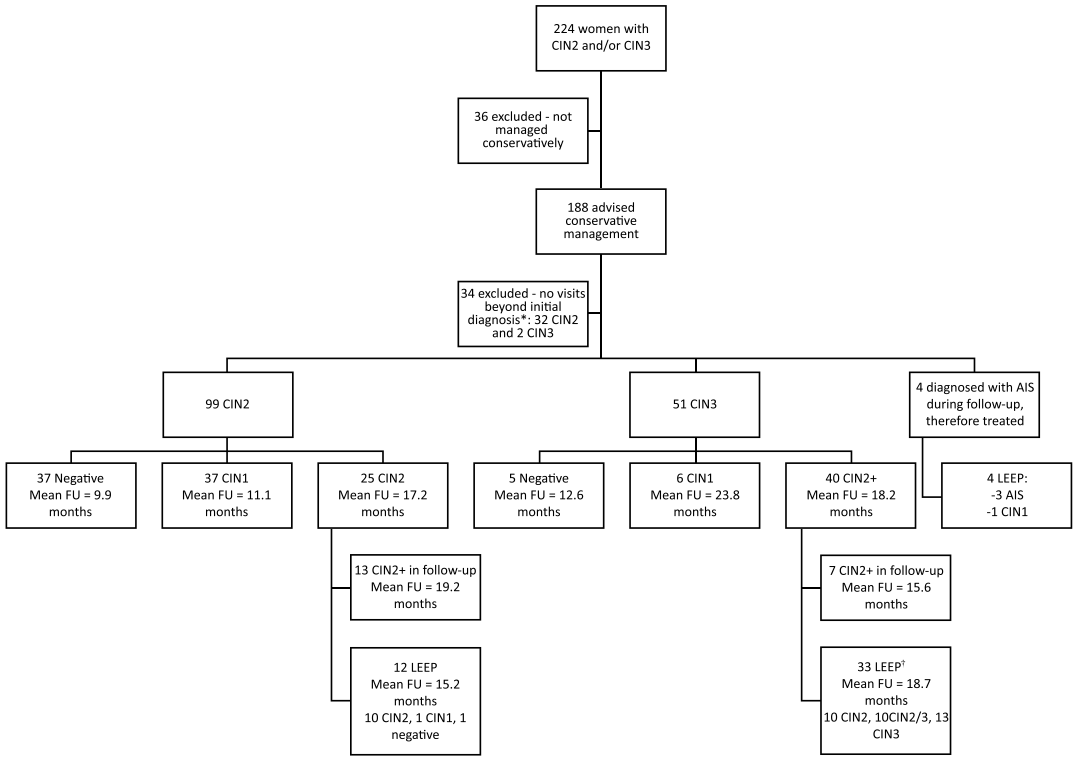

FIGURE 1. Histological outcomes of women <24 years diagnosed with CIN2+ and managed conservatively. *Provincial database records indicated that 15 of the 32 women with initial CIN2 had subsequent follow-up cytology outside of the study clinic: 13 negative, 1 moderate, 1 ASC-H; 1 of the 2 women with initial CIN3 had subsequent LSIL cytology. †One patient with CIN3 also had a second LEEP during the study period for recurrent disease (not counted in the figure).

(4.5%) HSIL Pap. Interestingly, 2 of 3 women with previous CIN2+ demonstrated lesion regression during the study, including one with a previous LEEP for CIN3 two years before the study.

Kaplan-Meier curves are shown in Figure 2 for time to lesion regression in women with CIN2 versus CIN3 (log rank test $p < .0001$). The median time to regression was 14.6 months

TABLE 1. Characteristics of Women <24 Years Diagnosed With CIN2+ Managed Conservatively

Patient characteristic	CIN2 (n = 99) n (%)	CIN3 (n = 51) n (%)	AIS (n = 4) n (%)	Overall (n = 154) n (%)
Age at diagnosis, mean ± SD	21.80 ± 1.28	22.12 ± 1.54	21.76 ± 1.23	21.91 ± 1.37
Reason for colposcopy[a]				
Low grade cytology	13 (13.4)	3 (5.9)	1 (25.0)	17 (11.2)
ASCUS	2 (2.1)	0	1 (2.5)	3 (2.0)
LSIL/mild	11 (11.3)	3 (5.9)	0	14 (9.2)
High grade cytology	84 (86.6)	48 (94.1)	3 (75.0)	135 (88.8)
Moderate	63 (64.9)	27 (52.9)	2 (50.0)	92 (60.5)
Severe	8 (8.2)	12 (23.5)	0	20 (13.2)
HSIL, NOS	1 (1.0)	2 (3.9)	0	3 (2.0)
AGC	1 (1.0)	0	0	1 (0.7)
ASC-H	11 (11.3)	7 (13.7)	1 (25.0)	19 (12.5)
Smoking status				
Never smoker	55 (55.6)	31 (60.8)	3 (75.0)	89 (57.8)
Ever smoker	34 (34.3)	16 (31.3)	1 (25.0)	51 (33.1)
Missing	10 (10.1)	4 (7.8)	0	14 (9.1)

[a]For calculation of proportions of high versus low grade cytology referral categories and subcategories, 2 patients with reasons for colposcopy categorized as "other" (both of whom had CIN2) were excluded. One patient was diagnosed during post-LEEP follow-up for a previously treated lesion, and 1 was referred for a suspicious lesion.

CIN indicates cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ; ASCUS, atypical squamous cells of undetermined significance; LSIL, low grade squamous intraepithelial lesions; HSIL NOS, high grade squamous intraepithelial lesion, not otherwise specified; AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot rule out high grade squamous intraepithelial neoplasia.

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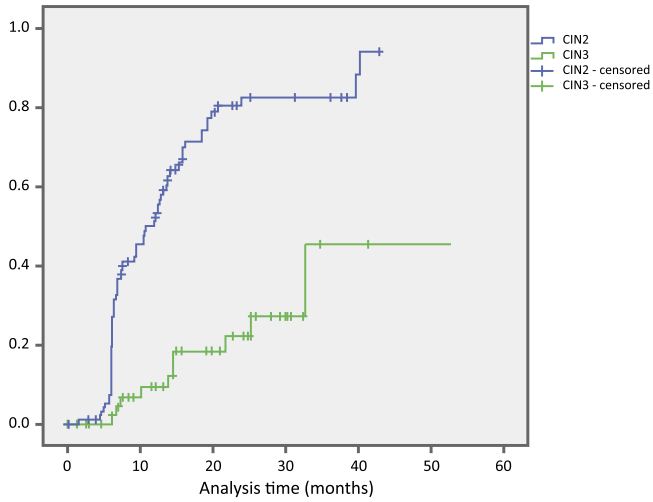

FIGURE 2. Kaplan-Meier analysis of CIN2 versus CIN3 lesion regression (1-survival) in women <24 years managed conservatively. Log rank test $p < .0001$.

overall, and 10.8 months for women with CIN2. The median was not reached for CIN3, and last observation censored at 52.7 months. There was a total of 2256 months of follow-up, median 12.1 months. Because some patients entered the study with less than 24 months until they reached the age of 24 years, there were 3 patients with CIN2 who had LEEP before median regression time (10.8 months) and 20 patient with CIN3 who had a LEEP who were greater than 22.0 years at first visit.

Table 2 compares select patient factors and outcomes between women with a most severe diagnosis of CIN2 versus CIN3. A greater proportion of women with CIN2 demonstrated lesion regression, and fewer received LEEP. The number of biopsies was greater for women with CIN3, which goes along with their longer follow-up time (increased number of visits). Mean age at referral, ever smoking, and referral Pap test (low versus high grade) were not significantly different between women with CIN2 versus CIN3.

Table 3 presents results of multivariate logistic regression examining predictors of lesion regression in women with CIN2 versus CIN3, adjusted for all variables in the table. Lower grade referral Pap smear, lesion grade (CIN2 versus CIN3), and younger mean age at diagnosis were independent predictors of lesion regression. Older age was associated with a 34% decrease, CIN3 (versus CIN2) was associated with a 91% decrease, and low grade referral Pap was associated with a 92% decrease in the odds of lesion regression.

The median number of visits attended by each patient was 3, with a median of 4 scheduled visits. Just more than half (53.2%) of patients did not miss or cancel any follow-up appointments. Of the cohort of 154 patients, 15.6% ($n = 24$) of patients were lost to follow-up (did not return and did not have evidence of pending visits in the electronic chart within 3 months of recommended time frame). Five of these patients were lost to follow-up before regression or LEEP, 9 were lost after LEEP, and 10 were lost to follow-up but had already demonstrated regression on the last biopsy.

DISCUSSION

This retrospective chart review examines regression rates and median times to regression in young women with CIN2 versus CIN3. To our knowledge, this is the first study to compare regression rates between women with CIN2 versus CIN3 managed conservatively, and it is one of the largest cohorts published regarding outcomes of conservative management of CIN2 in young women.

TABLE 2. Comparison of Characteristics and Outcomes of Women <24 Years With CIN2 Versus CIN3 Managed Conservatively

Variable	CIN2 ($n = 99$) n (%)	CIN3 ($n = 51$) n (%)	p^b
Lesion regressed (to CIN1 or negative)	73 (73.7)	11 (21.6)	**<.001**
Received LEEP treatment	12 (12.1)	33 (64.7)	**<.001**
Age at referral, mean ± SD	21.55 ± 1.28	21.93 ± 1.55	.12
Referral Pap test[a]			.26
Low grade	13 (13.4)	3 (5.9)	
High grade	84 (86.6)	48 (94.1)	
Ever smoker	34 (38.2)	16 (34.0)	.63
Total number of biopsies for all visits, mean ± SD	3.10 ± 1.61	3.88 ± 1.83	**.008**
Time from diagnosis to LEEP or censoring, mean ± SD	12.35 ± 8.98	21.93 ± 1.55	**.001**

[a]For calculation of proportions of high versus low grade cytology referral categories and subcategories, 2 patients with reasons for colposcopy categorized as "other" (both of whom had CIN2) were excluded; 1 patient was diagnosed during post-LEEP follow-up for a previously treated lesion, and 1 was referred for a suspicious lesion.

[b]t test, Fisher exact test, or χ^2 test.

CIN indicates cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure.

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TABLE 3. Predictors of CIN2 and CIN3 Regression in Women <24 Years Managed Conservatively - Multivariate Logistic Regression

Characteristic	Did not regress $n = 65$, n (%)	Regressed $n = 85$, n (%)	OR (95% CI)[c]
Most severe diagnosis			
CIN2	25 (38.5)	74 (87.1)	Reference
CIN3	40 (61.5)	11 (12.9)	**0.09 (0.03–0.24)**
Age at diagnosis, mean ± SD	22.34 ± 1.41	21.59 ± 1.27	**0.66 (0.47–0.93)**
Referral Pap test result[a]			
Low grade	2 (3.1)	14 (16.7)	Reference
High grade	62 (96.9)	70 (83.3)	**0.08 (0.01–0.94)**
No. biopsies, mean ± SD	3.77 ± 1.69	3.06 ± 1.69	0.78 (0.60–1.03)
Distance from clinic, mean ± SD, km[b]	11.03 ± 19.57	15.35 ± 47.53	0.10 (0.99–1.01)
Smoking status			
Never smoker	42 (65.6)	44 (61.1)	Reference
Ever smoker	22 (34.4)	28 (38.9)	1.26 (0.52–3.06)

[a]For calculation of proportions of high versus low grade cytology referral categories and subcategories, 2 patients with reasons for colposcopy categorized as "other" (both of whom had CIN2) were excluded; 1 patient was diagnosed during post-LEEP follow-up for a previously treated lesion, and 1 was referred for a suspicious lesion.

[b]Distance to clinic was calculated using distance between patient residence and clinic postal codes using http://www.cawebdir.com/ymlink/DistanceCalculator.aspx. If a postal code was not recognized in this site, then postal codes were input into https://www.google.ca/maps. Excludes outliers ≥500 km.

[c]Adjusted for all variables included in the tables. OR 95% CI that do not include 1 are in bold.

OR indicates odds of regression.

Importantly, in terms of the primary outcome, it confirms previously published high regression rates in this age group for those with CIN2[7,8,10,11,15,16] with a median time to regression of 10.8 months. In addition, we have documented a regression rate of 21.6% for women with CIN3, median not reached. It is encouraging that more than half of women in the study demonstrated lesion regression and avoided potential treatment related harms.

In terms of secondary outcomes, younger women and those with lower grade referral Pap smears and lesion histology (CIN2 versus CIN3) are significantly more likely to experience regression.[7,9,11,15,16,26–28] On average, women who experienced regression were nearly 9 months younger than those who did not, and women with CIN2 had more than 10 times the odds of regression than those with CIN3.

Reassuringly, there were no cases of progression to cancer, adding to the growing literature supporting the safety of a conservative management policy for women with CIN2. The number of women with CIN3 was relatively small, so results of this study do not prove the safety of conservative management in these women, but they suggest that it may be an option for motivated, reliable, and informed young women in a system with safeguards to prevent loss to follow-up.

The number of women who were excluded from this study because they did not return for follow-up at the study clinic is concerning and suggests that better systems are needed to retain and engage patients. Because of the results of this study, young women undergoing conservative management in the study clinic are now placed on a list such that patients who do not present for recommended follow-up or treatment are sent a letter to remind them to return. If they still do not present, then referring providers are also notified.

There are several strengths to this study. First of all, it has a relatively large number of women and it uniquely includes data and results for more than 50 women with CIN3 managed conservatively. In addition, because of the regional data registry, we were able to obtain cytology data for almost half of the women who were excluded because they did not present for follow-up visits, but who were subsequently seen by other clinics in the region for Pap smears. Although the study was retrospective, the existence of regional colposcopy guidelines specifically endorsing conservative management of CIN2+ in young women, and the fact that the study population was recruited from 1 large volume clinic with the exclusion of women not optimally conservatively managed, meant that the management of this group was fairly standardized. Another strength is in the almost universal practice of biopsies with every visit, whereas many other colposcopy studies often show data where management decisions are made with cytology and/or colposcopic findings without histology. Finally, because full-chart review was performed, more details were extracted about the patients and their course in colposcopy.

There are also some limitations to this study. As with any retrospective study, data were not collected for study purposes and were not always complete particularly in terms of demographic and lifestyle variables. There was no verification of CIN2 or CIN3 diagnosis by a second pathologist, although all pathologists who process histology specimens for the study clinic work at a cancer center and are provincially certified gynecologic subspecialty pathologists. In this context, p16/Ki67 staining is often, but not universally used. In addition, because protocols called for at least 1 biopsy, the appearance of regression to CIN1 or negative could actually represent persistent disease missed on colposcopy, because chances of disease detection increase with number of targeted biopsies.[29] This could overestimate regression rates.

There are also limitations that could lead to underestimation of regression rates. We do not know outcomes of the 34 women excluded because of lack of follow-up, limiting accuracy of regression rates—we do not know whether this group is inherently different from the final study cohort. When these patients are included in the denominator, assuming that they did not regress for the most conservative estimates, results still indicate high regression rates for CIN2 of 56.5% (versus 74.7% for the final cohort). The upper age limit of 24 years at the time of the study could also contribute to underestimation of regression rates because many patients would age out before a full 24 months to allow regression.

The follow-up time in this study is limited, and it would be useful to gain more long-term data on this population with respect to

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recurrence rates after lesion regression and discharge from colposcopy. There is only 1 published study examining this, which suggested recurrence rates of 17% with a median of 4.1 years of follow-up.[28]

Although many jurisdictions still screen women younger than 25 years, in June 2016, the regional cervical cancer screening guidelines in the study setting increased screening start the age from 21 to 25 years.[30] As more practitioners incorporate these new guidelines into their practices, the number of women younger than 25 presenting for colposcopy will decrease. In the meantime, and in other jurisdictions where these women are still screened, these results can be used to inform management of those with positive screening results and/or CIN2+ at colposcopy.

Further investigation is needed to determine specific and accurate predictors of regression.[8,10–13,15,16,28,31] If there was a mechanism to more accurately predict lesion regression versus persistence, then perhaps conservative management may be offered to women older than 25 years. Conversely, if we could tell which lesions were not going to regress, then we could save women and the system extra visits and treat them immediately rather than going through repeated assessments before eventual treatment. Human papillomavirus typing[9,15,26,32–34] and/or biomarkers such as p16 and Ki67[35–37] and DNA methylation[38–41] offer potential mechanisms of triage and predicting regression of CIN2+. Prospective studies correlating outcomes with these potential predictors are needed.

In summary, this study supports the practice of conservative management of young women who have CIN2. Indeed, given what we know about the incidence of cancer in women younger than 25 years and the high rate of regression of CIN2 in this age group, the results of this study add further support to the assertion that women in this age group need not actually be screened, and in many jurisdictions including the study setting, this is now being recommended. Although regression does occur in some women with CIN3, the safety and long-term results of conservative management of CIN3 in young women are not known, although the incidence of cancer in this age group alone offers some reassurance. If conservative management is offered for women with CIN3, it should be performed with a more in-depth discussion with the patient and rigorous mechanisms to prevent loss to follow-up.

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