Spontaneous regression of CIN2 in women aged 18-24 years: a retrospective study of a state-wide population in Western Australia

Short title: CIN2 regression in young women

A Munro BExSc, MExSc, PhD Candidate[1,3,5], R.G Powell BExSc (Hons), MBBS[2,5], P Cohen BM BCh, MA (Oxon) Dip Obs FRANZCOG MD[3,4,7], S Bowen B.Med, MM, FRACP, FACHSM[2], K Spilsbury BSc PhD GradDipPH MBiostats[5], P O'Leary BSc, PhD, MAACB, ARCPA, FFSc (RCPA)[6], JB Semmens BSc, MSc, GDip ED, PhD, GAICD[5], J Codde PhD, BSc, GDip Ed[7], V Williams PhD, MSc, BAppSci, FAIMS CF (IAC), FFSc (RCPA)[8], N Steel[1], Y. Leung MBBS FRANZCOG CGO[4.]

Affiliations:

1. WA Cervical Cancer Prevention Program, Perth WA
2. School of Medicine, University of Notre Dame Australia, Fremantle WA
3. St John of God Hospital Bendat Family Comprehensive Cancer Centre, Subiaco WA
4. School of Women's and Infants' Health Research, University of Western Australia, Crawley WA
5. Centre for Population Health Research, Curtin University, Bentley WA
6. Faculty of Health Science, Curtin University, Bentley WA
7. Institute of Health Research, University of Notre Dame Australia, Fremantle WA
8. School of Biomedical Sciences, Curtin University, Bentley WA

Corresponding author's details:
Ms Aime Munro
WA Cervical Cancer Prevention Program
Level 2, Eastpoint Plaza, 233 Adelaide Terrace
Perth WA Australia 6000
(W) 6189323 6781
(M) 61 8 404 990 169
(E) aime.munro@health.wa.gov.au

Conflicts of Interest notification

Two authors (A Munro and N Steel) are employed at the WA Cervical Cancer Prevention Program that is responsible for maintaining and operating the Cervical Screening Register of WA.

ABSTRACT

Introduction:

CIN2 has a high rate of spontaneous regression in young women and may be managed conservatively in appropriately selected patients. This study aimed to investigate health outcomes in women aged 18–24 years with biopsy-confirmed CIN2.

Methods:

A retrospective cohort study of Western Australian women aged 18 to 24 years diagnosed with CIN2 on cervical biopsy from 1st January 2001 to 31st December 2010. Women who had not received treatment at ≥4 months following CIN2 diagnosis were classified as managed 'conservatively'. Subsequent cervical cytology and/or biopsy test results were used to report lesion regression (absence of dysplasia or an epithelial lesion of lower grade than CIN2) and disease persistence (CIN2, CIN3 or ACIS).

Results:

Follow up data were available for 2,417 women of whom 924 (38.2%) were 'conservatively' managed. One hundred fifty two (16.4%) conservatively managed women had a lesion more severe than CIN2 detected within 24 months of initial diagnosis, of which 144 were CIN3 and 8 were ACIS. There was no statistically significant association between rates of regression and patient age, Socio-Economic Indexes for Areas or Accessibility/Remoteness Index of Australia indices. The two-year regression rate for CIN2 was estimated to be 59.5% (95% CI 0.5–0.6) in this cohort of women.

Conclusion:

In conservatively managed young women with CIN2 there was a high rate of spontaneous disease regression. Thus, excisional or ablative treatments may be avoided in selected patients who receive appropriate counselling and who are able to comply with more intensive and prolonged follow-up requirements.

Key words

Cervical abnormality, squamous, CIN, young women, cervical dysplasia, pre-invasive

Abbreviations

ACIS	Adenocarcinoma in situ
CIN	Cervical intraepithelial neoplasia (grade 2/3)
HSIL	High-grade squamous intraepithelial lesion
LSIL	Low-grade squamous intraepithelial lesion
LEEP	Loop electrosurgical excisional procedure
WA	Western Australia

Key messages

Conservatively managed young women with CIN2 had a 59.5% spontaneous regression rate. Conservative management is an option for selected patients who receive appropriate counselling and who are able to comply with follow-up**.**

Introduction

High-grade cervical intraepithelial neoplasia (CIN) is a precursor to cervical squamous cell carcinoma(1-3). The peak incidence of high-grade CIN is in women under age 25 years but cervical squamous cell carcinoma is rare in this age group(4-7). There are data to show that a significant proportion of cases of CIN2 in adolescent and young women (under age 21 years) will spontaneously regress(7-9) and because the risk of progression to malignancy appears to be low in this age group, excisional or ablative treatment may not be indicated. Young women diagnosed with CIN2 who are likely to comply with follow up may be offered conservative management including observation with colposcopy and cytological evaluation every 4 to 6 months to permit spontaneous regression of CIN2 and to avoid potentially unnecessary and costly treatment(7-12). Excisional treatments such as the loop excisional procedure (LEEP) are associated with physical, psychological(13-15) and obstetric morbidity(16-18) and may have a negative impact on sexual function(14,19,20).

Guidelines suggest that conservative management for adolescents with CIN2 may be considered in appropriately selected cases, but few studies have addressed this issue in women aged 20 to 25 years(7,10). Given the potential for treatment-related complications many practitioners have offered women in this age group who are diagnosed with CIN2 the option of conservative management. The aim of our study was to investigate the rate of spontaneous regression of CIN2 in Western Australian women aged 18 to 24 years to determine whether conservative management for appropriately selected patients in this age group might be a reasonable alternative to immediate treatment.

Material and methods

This study was a retrospective cohort study. Women aged 18 to 24 years, were followed-up from the time of their first CIN2 diagnosis (cervical biopsy test result) until their last cytology/histology record. Ethical approval for this study was granted from the Human Research Ethics Committees of Curtin University (ethics research project number: HR 86/2012 and the Western Australian Department of Health Human Research Ethics Committee (ethics research project number: 2012/49).

The Western Australian Data Linkage System provided a de-identified extraction of linked data for the period 1st January 2001 to 31st December 2010 from the Cervical Screening Register of WA and the Hospital Morbidity Data System (HMDS). The Western Australian Data Linkage System is an internationally renowned, population-based, validated

and ongoing data linkage system that creates links among a number of state health administrative data sets(21-23).

The National Cervical Screening Program encourages eligible women (women that have not had a hysterectomy and have commenced sexual activity) aged 18 to 69 years to have a cervical smear every two years. As part of the National Cervical Screening Program, the WA Cervical Cancer Prevention Program maintains and operates the Cervical Screening Registry of Western Australia (WA). The Cervical Screening Registry of WA is a voluntary "opt-off" confidential register which compiles all cervical test results (cervical smear, cervical biopsy and Human Papillomavirus (HPV) tests) that cytopathology laboratories are legislatively required to report. A de-identified dataset was extracted from the CSR of WA that contained cervical screening histories for all women aged less than 25 years and who resided within WA at the time of their CIN2 diagnosis. Cervical Screening Registry follow-up data was available until May 2013.

Women were allocated measures of socioeconomic status using the Socio-Economic for Indexes for Areas for Australia obtained through the Australian Bureau of Statistics(24). Additionally, women's postcodes were assigned to one of four Accessibility/Remoteness Index of Australia categories(25). Due to small numbers remote and very remote postcodes were collapsed into one category for the purposes of this study.

The Hospital Morbidity Data System records discharge summaries from all Western Australian hospitals (private and public and day surgery clinics). For women that did not have a biopsy treatment record, the International Classification of Disease code N87.1 for moderate cervical dysplasia and associated procedural codes were used to identify women that had ablative and excisional techniques performed. Procedural codes included excision (cone biopsy by cold knife or laser) and ablation (radical diathermy of cervix, large loop excision transformation zone, laser ablation of cervix and other ablative procedures of the cervix).

Cervical cytology test results were classified according to the Australian Modified Bethesda System 2004. This classification system is comparable internationally and reflects the increased understanding of HPV biology and the development of cervical cancer. In the present study we refer to findings from cervical cytology as HSIL or LSIL, whereas histological findings are referred to as CIN2 and CIN3.

Only women aged 18 to 24 years with a histological confirmation of CIN2 were included in this study. Women were excluded if they i) had a past history of a histologically

confirmed high-grade intraepithelial lesion that was more severe than a CIN2 or (ii) 12 months of follow-up data (cervical cytology or histology) was unavailable.

The Australian Guidelines recommend that women with a cervical smear test result of HSIL should be referred to a gynaecologist for colposcopic assessment and targeted biopsy[4]. Ideally women with cervical cytology showing HSIL, or possible HSIL should be assessed within two months of diagnosis. Assessment includes colposcopy +/- cervical biopsy. As such, women were allocated into a group dependent on when CIN2 treatment (excisional or ablative) was performed. To allow for women's attendance for gynaecological assessment and treatment, timeframes were slightly extended to the following:

1. If the woman was treated for CIN2 within 4 months they were allocated to the "immediate treatment" group(4).
2. If treatment for CIN2 was performed > 4 months women were allocated to the "conservative management" group(4,7).

Outcome measures were disease regression (i.e. negative or low-grade lesions including a low-grade squamous intraepithelial lesion (LSIL) on cytology and/or mild dysplasia (CIN1) or atypia on a subsequent biopsy), disease persistence including HSIL (CIN2, CIN3 or adenocarcinoma-in-situ) and disease progression (cervical cancer). Disease regression, persistence or progression was determined from histology test results where possible.

In the absence of histology, cytological findings were used and a hierarchical system was adopted to report the most severe diagnosis for the patient. In the event that a patient had evidence of regression but at a later follow-up visit cytology or histology confirmed persistence or disease progression, the latter diagnosis was reported.

Statistical analysis

Equality of demographic and clinical characteristics of women on different treatment pathways were tested using χ^2 tests. Time-to-event analyses were performed to investigate factors associated with the rate of regression for women that remained untreated (n=924) for CIN2 by 24 months. The follow-up interval was recorded as the time from the CIN2 diagnosis to disease regression (the event) defined as negative cytology and/or biopsy, LSIL or a low-grade glandular abnormality. Participant follow-up was censored at treatment of CIN2 disease, progression or at the time of the last available cervical cytology and/or biopsy result. If women underwent treatment but had a negative treatment specimen on histopathology they were recorded as having had disease regression. Covariates included in

the time-to-event analysis were age, socio-economic status and an index of accessibility to services.

Statistical significance was determined as a p-value < 0.05. Stata Version13.0 (Stata Corporation, College Station, USA) was used for data manipulation and statistical analysis.

Results

During the ten-year study period, 2,692 women were aged 18 to 24 years at the time of their initial CIN2 diagnosis. Two hundred seventy five women were excluded from the study because 12 months of follow-up data (cytology or histology test results) were unavailable (n=275). For the remaining 2,417 women, demographic information and comparative statistics are reported in Table 1. Conservative management was more likely the younger the age of the woman and in those living in urban areas. Management approach did not vary by socioeconomic status. Thirty eight percent of women had a HSIL (CIN2/3) detected on their referral cytology test result within 24 months prior to their CIN2 diagnosis.

There were 1,493 (61.8%) women who underwent treatment within 4 months of diagnosis (immediate treatment group). The mean time from initial diagnosis to treatment was 1.5 months in this group. Of the 1,493 women immediately treated, 58 (3.9%) women underwent laser ablation of the cervix and no histological specimen was available. Of these 58 women, 56 had negative follow-up cytology and/or histology findings and two women were confirmed to have disease persistence. The remaining 1,435 women were treated by either LEEP or cold knife cone biopsy. The majority of women immediately treated had CIN2 (62.5%) in their surgical specimen findings (Table 2) and a smaller proportion of women either had either negative histopathology or a low-grade cervical abnormality (17.3%).

There were 924 (38.2%) women managed ‘conservatively’. During the 24 month follow-up period 25 women subsequently underwent laser ablation and their follow-up cytology test results were negative (n=17), LSIL (n=5), possible HSIL (n=<5) and persistent HSIL (n=<5). Four hundred thirty seven women who were initially managed conservatively subsequently underwent treatment within the 24-month follow-up period by either LEEP (n= 402) or cervical cold knife cone biopsy (n=35). Their histopathology findings are reported in Table 2. Most were CIN2 (22.9%) although a proportion of women (15.6%) had CIN3 confirmed in their treatment specimen. One hundred fifty two (16.4%) women that had a

lesion more severe than CIN2 detected within 24 months of their initial CIN2 diagnosis, of which 144 were CIN3 and 8 were ACIS.

There were 462 women with a histological diagnosis of CIN2 (on cervical punch biopsy) who did not undergo treatment during the follow up period. The majority (n=404) of these women had repeat cervical cytology within 6 months of initial diagnosis. A small proportion (3.7%) subsequently had cervical cytology reported as CIN3 during the study follow-up period but are yet to have histological confirmation (outside the study period). In 445 women follow-up cervical cytology and histology indicated disease regression. The median follow-up time for women without a treatment record was 1.8 years.

Multivariate time to event analysis was performed for those women (n=924) conservatively managed to obtain the disease regression hazard rate ratio. Women were censored after treatment and/or when disease progression was confirmed. There was no statistically significant association identified between the rate of regression and patient age (potentially due to age intervals being very narrow, HR 1.2, 95% CI 1.0 – 1.5), Socio-Economic for Indexes for Areas for Australia (HR 1.1, 95% CI 1.0 - 1.2) or Accessibility/Remoteness Index of Australia indices (HR 1.0, 95% CI 0.8 - 1.1).

A Kaplan Meir graph (Figure 1) was constructed (censoring women at the time of treatment and/or if disease progression was identified) which highlights that the majority of women within the “conservative management” group regressed within 12 months following their initial CIN2 diagnosis. The two-year CIN2 regression rate was estimated to be 59.5% (95% CI 0.5 – 0.6) in this cohort of young women.

Discussion

The aim of our study was to investigate disease outcomes of conservatively managed women aged 18 to 24 years with biopsy confirmed CIN2. Outcome variables measured included rates of CIN2 regression, persistence or progression to higher grade dysplasia or invasive cervical cancer or other associated gynaecological disease. Linked administrative health data sets were used to ascertain these outcomes in a large cohort of Western Australian women with biopsy confirmed CIN2. From Kaplan Meir analysis it was estimated that 59.5% of conservatively managed women with CIN2 regressed by 24 months post diagnosis. There were no cases of invasive cervical cancer amongst the conservatively managed cohort. Furthermore, 331 (13.7%) patients who received immediate or conservative treatment were found to have either normal or low-grade histology in the excisional specimen.

The management of young women (<25 years) with screen-detected cervical abnormalities is contentious as there is no clear evidence to suggest that screening patients under this age prevents cervical cancer(26-28). Thus, previous management strategies are no longer universally accepted for young women with biopsy confirmed CIN2(7,9,11). As such, specialist obstetrician/gynaecologists are encouraged to consider offering conservative management to appropriately selected patients, in order to minimise potential treatment related physical, psychological and obstetric morbidity(7).

To date there is evidence demonstrating CIN2 regression in up to 65% of adolescents and young women (<21 years) over an 18-month period and hence conservative management in this population may be warranted(8,9,12). However, only a small number of studies have investigated the rate of CIN2 regression in women up to 25 years of age, most of which are limited due to their small sample size(7). To our knowledge this is the largest population-based study to have analysed outcomes by patient age and socio-economic status in women aged 18 to 24 years with biopsy confirmed CIN2. This study contributes to, and reinforces the health outcomes highlighted in previous research(7).

In any study of natural history outcomes in untreated CIN2 an important consideration is misclassification of histopathological diagnosis. The reporting of cervical specimens (cytology and biopsy specimens) possesses a degree of subjectivity and CIN2 may be over-diagnosed in some cases. In Australia, laboratories that report cervical abnormalities are required to comply with mandatory annual Performance Measures(29) and are subject to independent verification of data submitted by the laboratory to the Royal College of Pathologists Australasia Cytopathology Quality Assurance Program. These measures have enhanced external quality assurance procedures in Australia(29).

Limitations of our study include its retrospective design and the error inherent in all databases. For example, excisional procedures may have been performed on an outpatient basis and not captured in hospital records. However, the mandatory reporting of the histological findings of cervical specimens to the Registry ensures data completeness is obtained. The quality assurance processes employed ensure the level of error within the register is acceptable. A further limitation of our study is the lack of information regarding colposcopy findings and therefore no information on other factors, which may have influenced whether women were treated immediately or not. This could introduce bias in the results. The reason women had treatment performed was not clearly identified and consequently treatment intervals were varied. Additionally, disease regression could not always be confirmed histologically.

Furthermore, our inclusion criteria to this study required biopsy confirmation of a CIN2 lesion. As such, the lesion may not have 'truly' spontaneously cleared as the biopsy may have accelerated the clearance of the disease (i.e. specifically if it was a very small lesion). It is important to note that CIN2 is the least reproducible of all cervical diagnoses, and it is possible that the 'regression' of CIN2 is dependent on the individual pathologist reporting the lesion(30-33). The potential inclusion of 'equivocal' CIN2 lesions could also be expected to increase the overall regression rate and consequently, regression may have been over-reported(30,31). These limitations emphasize the need for further prospective studies that report treatment determinants and also report reproducible biomarkers (i.e. p16 staining of CIN2 specimens).

In recommending conservative management following the diagnosis of CIN2 patient safety is paramount. In our study amongst those patients who were treated conservatively, none progressed to invasive cervical cancer, although eight cases of adenocarcinoma in situ (ACIS) were identified (0.9%). Amongst those women who received immediate treatment, there were cases of ACIS (n = 11), squamous cell carcinoma (n = < 5), and adenocarcinoma (n = < 5) that had not been identified initially. These cases highlight the need for cautious implementation of a conservative management protocol in young women diagnosed with CIN2, and the need for careful selection of patients, regular follow-up evaluation, maintenance of clinical standards and appropriate follow-up systems.

Potential sequelae of conization and LEEP include not only the physical and psychological, but also adverse obstetric outcomes such as second trimester miscarriage and early pre-term delivery(34,35,36,37). Epidemiological data suggest that these risks correlate with depth of excision and are more frequent following conization(34,37). Based on the

59.5% regression rate reported in this study conservative treatment of CIN2 may be an appropriate option, in the form of regular surveillance, for patients less than 25 years of age. These women should remain under specialist care which routinely provides colposcopy, cytological testing and quality assurance throughout the patient's clinical management, for at least 24 months prior to invasive treatment.

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Table 1 Women's baseline demographic information by management category

	Immediate treatment group (N=1,493)	Percentage (%)	Conservative treatment group (N=924)	Percentage (%)	Chi-square P-value
Women's age (years)					
18 – 19	208	13.9	176	19.1	
20 – 21	464	31.1	281	30.4	0.003
22 – 24	821	55.0	467	50.5	
Women's referral cytology test result (within 24 months of biopsy confirmed CIN2 diagnosis)					
Negative	7	0.5	4	0.4	
Low-grade squamous intraepithelial lesion (CIN 1)*	19	1.2	61	6.6	
Possible high-grade squamous intraepithelial lesion (HSIL)	6	0.4	20	2.2	0.000
HSIL (CIN2/3)	567	38.0	439	47.5	
No referral cytology test result present	894	59.9	400	43.3	
Accessibility/Remoteness Index of Australia					
Major city	995	66.6	690	74.7	
Inner regional	235	15.7	109	11.8	
Outer regional	128	8.6	60	6.5	0.002
Remote/very remote	117	7.9	58	6.3	
Unknown	18	1.2	7	0.7	
(Post Office Box)					

Socio-Economic Indexes for Areas of Australia					
Least disadvantaged	467	31.3	323	35.0	
Less disadvantage	243	16.3	155	16.8	
Middle	334	22.4	181	19.6	0.315
More disadvantaged	266	17.8	165	17.8	
Most disadvantaged	165	11.0	93	10.1	
Unknown	18	1.2	7	0.7	
(Post Office Box)					

*CIN – cervical intraepithelial neoplasia

Table 2 Treatment performed and final histologic condition at time of treatment by management category (within 12 months of CIN2 diagnosis)

	Immediate treatment group (N=1,493)	**Percentage (%)**	**Conservative treatment group (N=924)**	**Percentage (%)**
Treatment performed				
Laser destruction	58	3.9	25	2.7
Cold knife cone biopsy	138	9.2	35	3.8
LEEP	1,297	86.9	402	43.5
No treatment record present (within 24 months of CIN2 diagnosis)*	0	0	462	50.0
Treatment outcome				
Negative	82	5.5	24	2.6
Low-grade intraepithelial abnormality	176	11.8	49	5.3
CIN2	933	62.5	212	22.9
CIN3	231	15.5	144	15.6
Adenocarcinoma-in-situ	11	0.7	8	0.9
Squamous cell carcinoma	<5**	-	0	0.0
Adenocarcinoma	<5**	_	0	0.0
No treatment outcome available	58	3.9	487	52.7

* No histologic condition was reported because cervical cytology test results were used to determine the outcome in the conservative treatment group, or the treatment was ablation and no histologic condition was available.

** Due to small case numbers, <5 has been reported to ensure women's confidentiality.

Figure 1 Kaplan Meir Curve showing the proportion of women who underwent conservative treatment (n=924) who remained with CIN2 within 24 months of initial diagnosis. Women were censored at time of treatment or when disease progression was identified as they could not contribute further time at risk of regression.