A prospective cohort study of the conservative management of focal cervical intraepithelial neoplasia 2

Gabriela McMahon[1], Sinead Griffin[1], Jennifer Curley[1], Paul Hartel[2], Clive Kilgallen[2], Nirmala Kondaveeti[1]

[1] Department of Obstetrics and Gynaecology, Sligo University Hospital; [2] Department of Pathology, Sligo University Hospital

ABSTRACT

Background and Purpose: Traditionally, cervical intraepithelial neoplasia 2 (CIN 2) is managed by the removal of affected tissue in a procedure known as a large loop excision of the transformation zone (LLETZ). In our unit, pathology reports on LLETZ specimens done for a diagnosis of CIN 2 often are reported as CIN 1 or a normal result. So we wondered – are we over-managing CIN 2?

Methods: This study was designed to assess the acceptability and outcomes of the conservative management of focal CIN 2. We wanted to establish if monitoring of the disease is sufficient in selected women. In this prospective cohort, women were selected for inclusion in the study by having a histological diagnosis of focal CIN 2 from a cervical biopsy and after discussion at the colposcopy multi-disciplinary team meeting. After explanation of CIN 2 and its future implications, women were informed of the risks and benefits of conservative management versus LLETZ. Women who opted for conservative management were seen in the colposcopy clinic for colposcopy examination, cervical biopsy ± cervical smear and HPV testing at six monthly intervals for two years.

Results: Over the two-year follow-up period, 20/31 women (64.5%) had regression of disease, 7/31 women (22.6%) had persistence of CIN 2 and 4/31 women (12.9%) had progression of disease to CIN 3. There were no reported cases of cervical carcinoma in situ or invasive cervical carcinoma. During the follow-up period, patients were offered treatment if there was progression to CIN 3 or worse, persistence of CIN 2 or if they wished to undergo treatment at any stage.

Conclusions: Conservative management of CIN 2 may be considered in women who are under the age of 30 with focal CIN 2. However, larger studies should be carried out to define the safety or acceptability of changing this practice.

KEYWORDS

CIN 2, conservative management, LLETZ.

Introduction

Cervical Intraepithelial Neoplasia (CIN) is a premalignant disease of the cervix [1]. It is divided into three subtypes based on grade of disease – CIN 1, CIN 2, and CIN 3. CIN 1 is consistent with low grade disease, has a high rate of regression and accepted management is monitoring of the disease [2]. CIN 3 is considered to be a high-grade disease and has an estimated 12% risk of developing into malignancy.

It is therefore treated with removal of the affected tissue in a procedure known as a large loop excision of the transformation zone (LLETZ). Complications of LLETZ include infection, bleeding, cervical stenosis, preterm labour and late miscarriage.

The grey area lies in the management of the intermediate grade, CIN 2. Studies suggest that in two years, 40% of CIN 2 will regress, 40% will persist, 20% will progress to CIN 3 and 5% will develop into cervical cancer [2,3]. Traditionally, diagnosis of CIN 2 is managed with LLETZ.

However, recent studies suggest observation of the disease may be sufficient and people are now offering selected patients conservative management [4,5].

Article history
Received 16 Jan 2020 - Accepted 10 May 2020

Contact
Gabriela McMahon; gabrielamcmahon1@gmail.com
Registrar in Obstetrics and Gynaecology, Sligo University Hospital, Sligo, Ireland
Kiltullagh, Athenry, Co. Galway, Ireland

Conservative management of CIN 2 - evidence to date

There have been a few studies to date detailing outcomes in women who have been managed conservatively for CIN 2. However, most studies have been retrospective or observational in nature and of low quality evidence. The PRINCess trial is currently underway. This multicentre prospective trial plans to recruit 600 women who are under the age of 25 undergoing conservative management of CIN 2. Primary outcomes to be reported include clinical regression of CIN, progression to invasive disease and women lost to follow up. Retrospective reviews done to date report regression rates of 63-74%, persistence rates of 12.7-16.6% and progression to CIN 3 rates of 14.2-24%. Of the women who were conservatively managed, there were no reported cases of progression to cervical can-

cer [3,5-9]. A meta-analysis was published in 2018 and included 36 studies of 3160 women with CIN 2 who were managed conservatively. The pooled rate of regression was 46% at twelve months (13 studies, 300/628 women, 95% confidence interval 36% to 56%; I2=81%) and 50% at twenty-four months (11 studies, 819/1470 women, 43% to 57%; I2 =77%) [10].

Methods

Objectives

This study was designed to assess the rate of progression, regression and persistence of focal CIN 2 in women who were managed conservatively. We also measured the number of LLETZ treatments that were prevented in this cohort, thereby avoiding the associated complications. This is particularly relevant to our cohort of women under the age of 30 to prevent the future obstetric complications of LLETZ. Recruitment of patients to be part of the study commenced in April 2016 and was completed in September 2017.

Ethical Approval

Ethical approval was sought and approved from the Research Ethics Committee at Sligo University Hospital.

Inclusion Criteria

We included women who were seen in colposcopy clinic who met the following criteria:

- No more than 30 years of age at the time of recruitment.
- A confirmed histological diagnosis of focal CIN 2. This was defined as an area of CIN 2 occupying less than 50% of the cervical biopsy or measuring less than 1mm.
- Deemed suitable for conservative management after discussion and professional agreement at the colposcopy multi-disciplinary meeting.
- Agreeable to be included in the study and to be compliant with follow up visits every 6 months for 2 years.
- Entire lesion accessible and/or adequately viewed on colposcopy examination.

Exclusion Criteria

Women were excluded from the study if they met any of the following criteria.

- Pregnant at the time of diagnosis of focal CIN 2.
- Suspicion of invasive disease or a concurrent histological diagnosis of CIN 3 or worse on recruitment to the study.
- Women undergoing immediate treatment with LLETZ.

Primary Outcome

The rate of regression of CIN 2 to either CIN 1 or a normal cervical biopsy, persistence of CIN 2 and progression of CIN 2 to CIN 3 or invasive cervical carcinoma.

Secondary Outcomes

Baseline characteristics such as age, smoking status, current contraceptive use, medical history, immunosuppression and the number of women who were treated with a LLETZ.

Statistical Analysis

Data was collected and analysed using the statistical software package IBM SPSS V26.0. Data was analysed using descriptive statistics. Categorical data was compared using Chi-squared test. Results were considered significant if $p<0.05$.

Results

Study population

During our study period, 51 women were identified as having focal CIN 2 on a cervical biopsy and were therefore eligible to be considered for inclusion in the study. Five women chose to undergo immediate treatment with a LLETZ so were excluded from the study.

Three women had co-existing CIN 3 on the cervical biopsy so were also excluded. Twelve women were over the age of 30 years, thus were also excluded as they did not meet the inclusion criteria. The mean age of women involved in the study was 26.2 years (Range of 19-30 years).

Primary outcome

Over the two-year follow-up period:

- 20/31 women (64.5%) had regression of disease,
- 7/31 women (22.6%) had persistence of CIN 2,
- 4/31 women (12.9%) had progression of disease and
- 11/31 women (35.5%) had a LLETZ.

Effect of smoking

Of the 12 women who were non-smokers, 9/12 (75.0%) had regression of disease and 1/12 (8.3%) had progression of disease. Of the 15 women who were current smokers, 8/15 (53.3%) had regression of disease and 2/12 (13.3%) had progression of disease. There was no difference in outcomes in women who smoked compared to those who did not smoke (p=0.546).

Table 1 Baseline characteristics.

	NUMBER OF WOMEN (N=31)	PERCENTAGE OF WOMEN (%)
Parity		
- Nulliparous	23	74.2
- Multiparous	8	25.8
Medical or surgical history		
- Nil	24	77.4
- Anxiety/depression	4	12.9
- Asthma	2	6.5
- Epilepsy	1	3.2
Immunosuppression		
- Yes	0	0
- No	31	100
Smoking status		
- Never smoked	12	38.7
- Currently smoking	15	48.4
- Previously smoked	4	12.9
Contraception		
- Combined hormonal	18	58.1
- Progesterone only	5	16.1
- Non-hormonal	6	19.4
- No contraception	2	6.5

Table 2 Referral details.

	NUMBER OF WOMEN (N=31)	PERCENTAGE OF WOMEN (%)
Symptoms		
- Asymptomatic	25	80.6
- Post-coital bleed	2	6.5
- Intermenstrual bleed	1	3.2
- Post-coital bleed and intermenstrual bleed	2	6.5
- Suspicious cervix	1	3.2
Cervical smear		
- Normal	2	6.5
Low grade intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance		
- (ASC-US)	26	83.9
High grade intraepithelial lesion		
- (HSIL)	3	9.7
HPV status		
- Positive	27	87.1
- Negative	4	12.9

Table 3 Initial colposcopy visit.

	NUMBER OF WOMEN (N=31)	PERCENTAGE OF WOMEN (%)
Colposcopy impression		
- Normal	3	9.7
- Low grade	23	74.2
- High grade	5	16.1
Transformation zone		
- Type 1	25	80.6
- Type 2	6	19.4
- Type 3	0	0.0
Cervical biopsy		
- Focal CIN 2	7	22.6
- Focal CIN 2 with co-existing CIN 1	24	77.4
Inflammation on biopsy		
- Yes	3	9.7
- No	28	90.3

Table 4 LLETZ information.

	NUMBER OF WOMEN (N)	PERCENTAGE OF WOMEN (%)
LLETZ		
- Yes	11/31	35.5
- No	20/31	64.5
Indication		
- HSIL on smear	2/11	18.2
- CIN 3 on biopsy	2/11	18.2
- Increasing size of CIN 2	4/11	36.4
- Patient preference	3/11	27.2
Time to LLETZ		
- 6 months	4/11	36.4
- 12 months	6/11	54.5
- 18 months	1/11	9.1
- 24 months	0/11	0.0
Histology result of LLETZ		
- CIN 1	2/11	18.2
- CIN 1 and CIN 2	5/11	45.5
- CIN 1, CIN 2 and CIN 3	1/11	9.1
- CIN 2 and CIN 3	1/11	9.1
- CIN 3	2/11	18.2

Effect of inflammation

All three women with inflammation present on their cervical biopsy had regression of disease (100%). Of the 28 women who did not have inflammation on their biopsy, 17/31 (60.7%) had regression of disease, 7/31 (25.0%) had persistence of CIN 2 and 4/31 (14.3%) had progression of CIN 2 to CIN 3. This was not found to be statistically significant (p=0.401).

Effect of referral HPV status

Of the 4 women who did not have HPV detected on initial cervical smear, 3/4 (75.0%) had regression of disease and 1/4 (25.0%) had persistence of CIN 2.

Of the 27 who had HPV detected on initial cervical smear, 17/27 (63.0%) had regression of disease, 6/27 (22.2%) had persistence of disease and 4/27 had progression of disease. There was no significant difference between the two groups (p=0.711).

Discussion

Summary of Findings

Over the two-year follow-up period, 20/31 women (64.5%) had regression of disease, 7/31 women (22.6%) had persistence of CIN 2 and 4/31 women (12.9%) had progression of disease. In this cohort, only 11/31 (35.5%) of women had a LLETZ. These findings appear promising and support the hypothesis that conservative management might be sufficient in certain women with focal CIN 2. The biggest challenge within this is selecting the appropriate women to offer conservative management to.

Unfortunately, with a small sample size of only 31 women, it was difficult to ascertain statistical significant differences between various groups to see if the rate of regression, persistence or progression was influenced by factors such as age, smoking status, immunosuppression, medical conditions and the presence of current HPV infection.

It would be a prudent to undertake further, larger studies in the future to see what effect these factors have on the regression, persistence or progression of CIN 2.

Strengths

In comparison to most of the published literature to date which is comprised of retrospective cohort studies or retrospective chart reviews, our study was a prospective study. This enabled us to standardise the management plan to allow for comparison between women. This study also appears to be the one of the only studies which takes into consideration the size of CIN 2 on cervical biopsy.

Weaknesses

Our total follow up time for women was two years. During this period, there were no reported cases of invasive cervical cancer or carcinoma in situ. This may be explained by the length of the follow-up period and may require further studies to assess for any later progression. We are also limited in that we had a small sample size who met our inclusion criteria during the recruitment time frame.

Conclusions

This study suggests that conservative management of focal CIN 2 may be considered in selected groups of women. We included women under the age of 30, as the incidence of cervical cancer increases with age. Also, as these women are of childbearing age, they are likely to benefit the most from avoiding an unnecessary LLETZ and the resulting obstetric complications that these may cause. However, compliance with follow up is essential in order to detect and treat any cases of progression of disease and prevent invasive cancer in women who have not been treated for focal CIN 2.

We propose that larger scale studies be carried out in an attempt to recommend the most appropriate inclusion criteria, conservative management plan and adequate follow up time period for women who are conservatively managed to ensure they do not have a higher incidence of developing cervical cancer in the future. Further, stronger evidence is needed before practice and guidelines can be changed to reflect these promising findings.

References

1. Kyrgiou M, Athanasiou A, Kalliala I, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. Cochrane Database Syst Rev. 2017;11:CD012847.
2. Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993;12:186-92.
3. 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;116:1373-80.
4. Sykes P, Innes C, Harker D, et al. Observational Management of CIN 2 in Young Women: A Prospective Multicenter Trial. J Low Genit Tract Dis. 2016;20:343-7.
5. Loopik DL, Doucette S, Bekkers R, Bentley J. Regression and Progression Predictors of CIN2 in Women Younger Than 25 Years. J Low Genit Tract Dis. 2016;20:213-7.
6. Loopik DL, Bekkers RLM, Massuger LFAG, Melchers WJG, Siebers AG, Bentley J. Justifying conservative management of CIN2 in women younger than 25 years - A population-based study. Gynecol Oncol. 2019;152:82-6.
7. McAllum B, Sykes PHH, Sadler L, Macnab H, Simcock BJ, Mekhail AK. Is the treatment of CIN 2 always necessary in women under 25 years old? Am J Obstet Gynecol. 2011;205:478.e1-7.
8. 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;155:204-8.
9. Moore K, Cofer A, Elliot L, Lanneau G, Walker J, Gold MA. Adolescent cervical dysplasia: histologic evaluation, treatment, and outcomes. Am J Obstet Gynecol. 2007;197:141.e1-6.
10. Tainio K, Athanasiou A, Tikkinen KAO, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. BMJ. 2018;360:k499.

Conflict of Interest: *The authors declare that there are no conflicts of interest.*