

Research Article

Conservative Management of CIN 2: A Retrospective Study in A Single Colposcopy Unit

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Abstract

Cervical cancer is the third most diagnosed malignancy in women and the fourth leading cause of cancer death worldwide (1). In 2014, WHO had combined CIN2 and CIN3 and labeled them as HSIL (high grade squamous intraepithelial dysplasia) (2). As a result, LLETZ (long loop of excision of transformation Zone) is done to treat CIN2. This treatment has ramifications for future fertility, particularly in the younger reproductive age group (3). However, numerous studies have estimated CIN 2 spontaneous regression rates in a range of reproductive age groups reaching up to 50–60%. An increasing body of evidence has emerged in recent years to support conservative management in this category as an alternative (5). This retrospective study examines conservative treatment which was carried out on 40 patients in Lister hospital as a new alternative with no negative consequences on future fertility.

Keywords: Conservative management, CIN 2, treatment.

Introduction

A precancerous condition of the cervix known as CIN2 is frequently identified by cervical screening. The aim of the NHS national cervical screening program is to reduce the incidence of cervical cancer by detecting the cervical cancer precursor high-grade cervical intraepithelial neoplasia, typically thought to be CIN 2 and CIN 3 (2). According to UK criteria, CIN 2 and 3 were both considered high-grade cancerous lesions, and cervical treatment was advised for management. However, there is uncertainty regarding the pathogenesis and natural history of CIN 2. Several studies have documented high spontaneous regression rates, particularly in young women (5). Evidence in young women points to CIN2 regression rate of 40-74% Within two years of diagnosis (6).

CIN 2 treatment is associated with obstetric morbidities such as increased prevalence of preterm labour, and second trimester miscarriage (3). Recently, a growing number of colposcopy centres in the UK are moving towards conservative management of CIN 2. A survey by the British society of colposcopy to assess the attitudes towards conservative management of CIN 2 found that around 68% of the participants do offer conservative management in their units (7). Conservative management of CIN 2 was

commenced at East and north Hertfordshire trust in November 2020.

Aim of the study

The aim of this study is to determine the safety of this relatively novel approach in terms of rates of regression, persistence or progression of CIN and also to evaluate the current management pathway and its compliance to the standard local guideline.

Material and Methods

Study design and setting: the current study is retrospective design. Data were collected from the colposcopy digital system “inflex” and clinic letters in Lister hospital. Data were collected from November 2020 till March 2023.

Study population and data collection tool: A total of 40 Women with histologically proven CIN 2 were included as they fit the inclusion criteria of conservative management as per the local policy which is (1) Adequate colposcopy examination (2) CIN 3 and an invasive lesion has been excluded (3) Multiple biopsies have been taken (4) CIN 2 diagnosed on histology (5) The CIN 2 lesion occupies no more than 2 quadrants of the cervix.

Participant women were all discussed in the colposcopy multidisciplinary team meeting where cytology and histology results were reviewed. All participant women were offered both treatment options and had informed consent, irrespective of the type of management agreed. They were provided with a written patient information leaflet and all can request LLETZ treatment at any point. Any women with evidence of progression to CIN3 either on colposcopic opinion or histological biopsy or worsening of cytology to severe dyskaryosis or persistence over 12 months were advised to have standard LLETZ treatment and excluded from conservative management.

Data collected included sociodemographic data as age, as well as, medical data about HPV vaccination status, initial cytology on referral to the unit, colposcopic impression, results of cytology, histology, duration of follow up and outcome of conservative management. The method of surveillance used was six monthly colposcopy and cervical smears. Successful conservative management was defined as no evidence of high-grade dysplasia on colposcopy with negative cytology on two consecutive visits. The final outcome is classified as:

- **Progression:** Biopsy showing CIN 3 at any point during follow up
- **Persistence:** persistence of CIN 2 or high grade dyskaryosis over 12 months follow up
- **Regression:** cervical smear, colposcopy and biopsies without neoplasia observed at any time during the follow-up and confirmed at the twelve-month follow-up.

All data collected were revised for completeness and logical consistency, and data were coded and entered anonymous on the computer using "Microsoft Office Excel Software" version 2013. The pre-coded data was then transferred and analysed with the Statistical Package for Social Science version 24 "SPSS v.24". For quantitative variables, mean and standard deviation, minimum and maximum, and frequency and percentage were used to summarize the qualitative data.

Results

Patient Characteristics and vaccination status:

A total of 40 patients were included but one was excluded from the analysis as she left the country during the follow up. Around half of the included participants were in 25-30 years age range. Only one woman was aged under 25 years. The mean age of the included participant was (+-). Only one fifth of the included women were vaccinated. The greatest

portion of them were not vaccinated (n=25,64%). For detailed information refer to table 1.

Table 1: patient age and vaccination status.

Participants	N=39 (100%)
Age group:	
20-25	1 (2.5%)
25-30	18 (46%)
30-35	10 (26%)
35-40	6 (15%)
40-45	2 (5%)
45-50	2 (5%)
Vaccination status	
not vaccinated	25 (64%)
vaccinated	7 (18%)
No information on HPV vaccination	7 (18%)

Initial Cytology On referral:

Most patients (n=19, 48%) were referred with high grade dyskaryosis moderate. Near one fourth (26%) patients were referred with High dyskaryosis severe and only (18% n= 7) patients with low grade dyskaryosis (table 2).

Table 2: initial cytology results of included women.

Cytology	N=39 % (100%)
Low Grade Dyskaryosis	7 (18%)
High Grade dyskaryosis moderate	19 (48.5%)
High Grade Dyskaryosis Severe	10 (26%)
Borderline Changes in Squamous cells	2 (5%)
Negative cytology	1 (2.5%)

Follow up duration and participants compliance to follow up:

The follow-up visit schedule for the purpose of performing a colonoscopy and smear was communicated to all cases. The majority of participants were compliant with follow up visits. Due to travel outside of the nation, just one patient missed her follow-up and dropped out within the first six months. Most patients had completed a follow up duration for 18 months and 24 months, respectively (33%, n = 13, and 31%, n = 12). Figure 1 provides details.

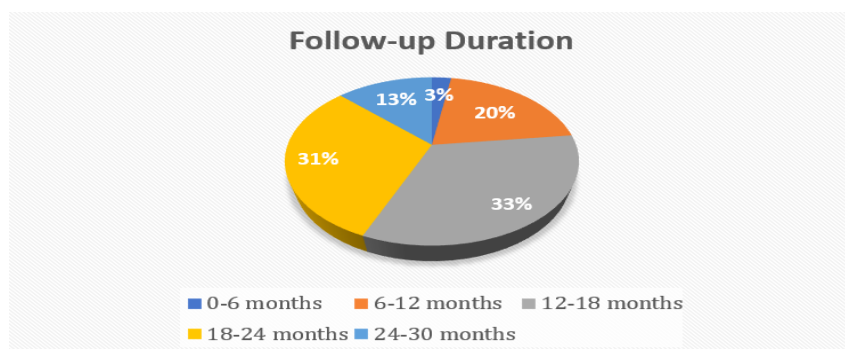


Figure 1: follow up duration of the participants.

Cytology Results on follow up:

All cases were reviewed in colposcopy MDT before beginning conservative management. MDT reviewed all smears and biopsies before deciding on conservative management versus LLETZ treatment. In all cases where treatment was proposed, an MDT discussion took place prior to treatment. With the MDT results, a documented

letter was sent. The Surveillance method currently utilised is 6 monthly colposcopy and smear. The cytology results on follow up found that half of the cases (54%, n=21) shown evidence of cytological regression during follow up from high grade dyskaryosis to Low grade and negative. One fifth of cases (n=8) showed persistent high grade dyskaryosis severe. All results illustrated in Figure 2.

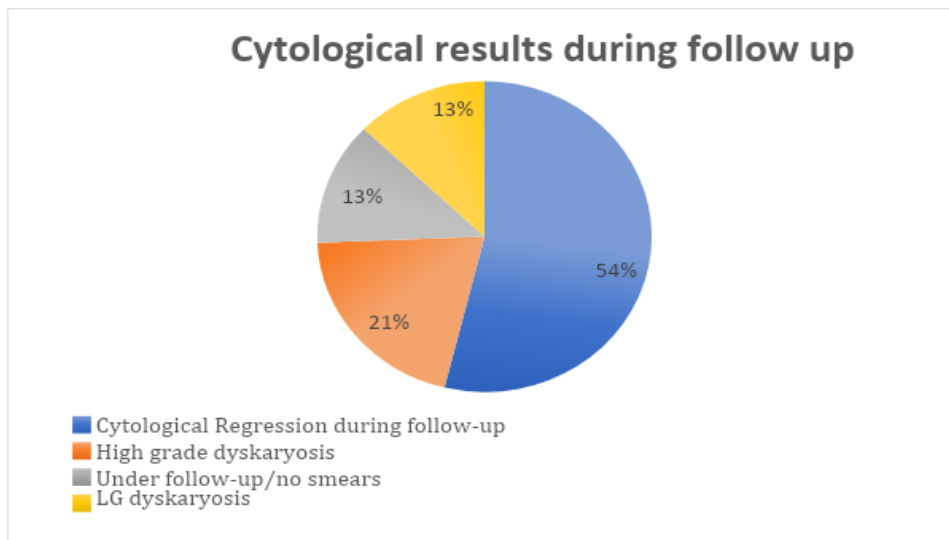


Figure 2: Participants cytological results during follow up visits.

Colonoscopy features during follow up:

In most of participants (n=16, 41%), there was a resolution of HG features by colposcopy. In 13% of cases (n=7) there was change of low-grade features to normal colposcopy. In less than 10% (n=3) there were persisted low grade features, however, in one fifth of cases (n=8, 21%) the High-Grade features persisted on colposcopy. In fifteen percent

cases (n=6), there was progression to HG during follow up. Only one case had no second follow up yet for comparison (figure 2). Colposcopy was noted to be satisfactory in all cases and all cases were examined by colposcopists accredited from the British Society of Colposcopy and Cervical pathology. (BSCP).

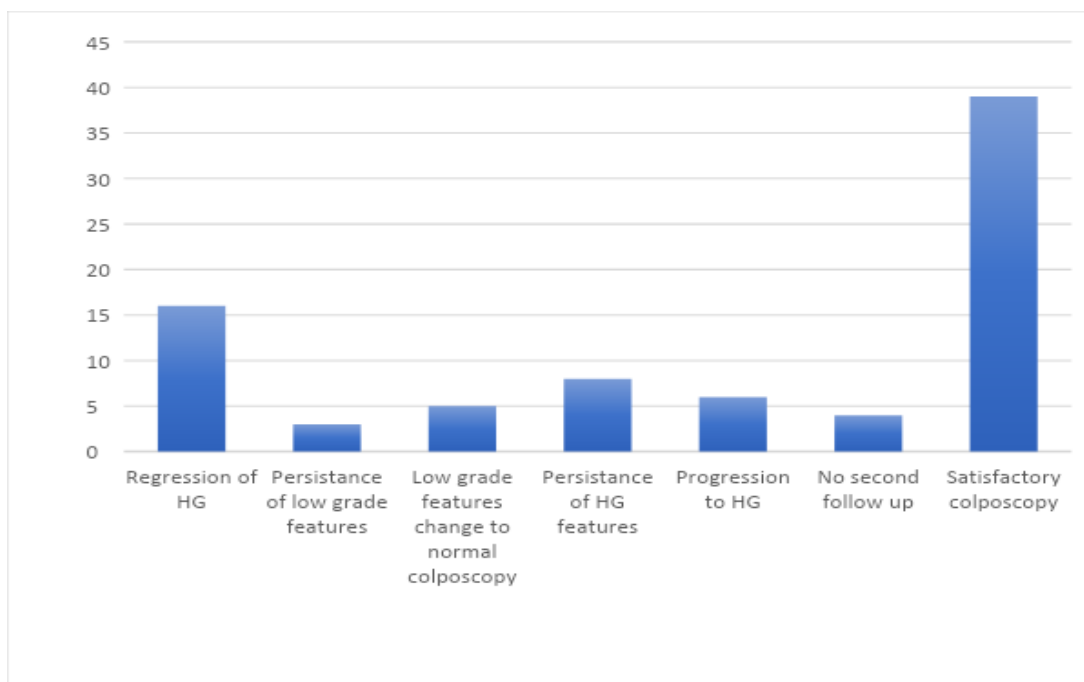


Figure 3: changes in colposcopy impression during follow up.

Histology Results during follow up:

In total, there were no repeat biopsies in 20 patients (51%) as it is not repeated routinely. For cases who had a repeat biopsy, there was evidence of histological regression in Nine

participants (23%), (6 out of them were from CIN 2 to CIN 1 and the others from to CIN 2 to no CIN. During follow-up, 7 patients (18%) had persistent CIN 2. There was no evidence of progression to CIN 3 except in three patients (8%).

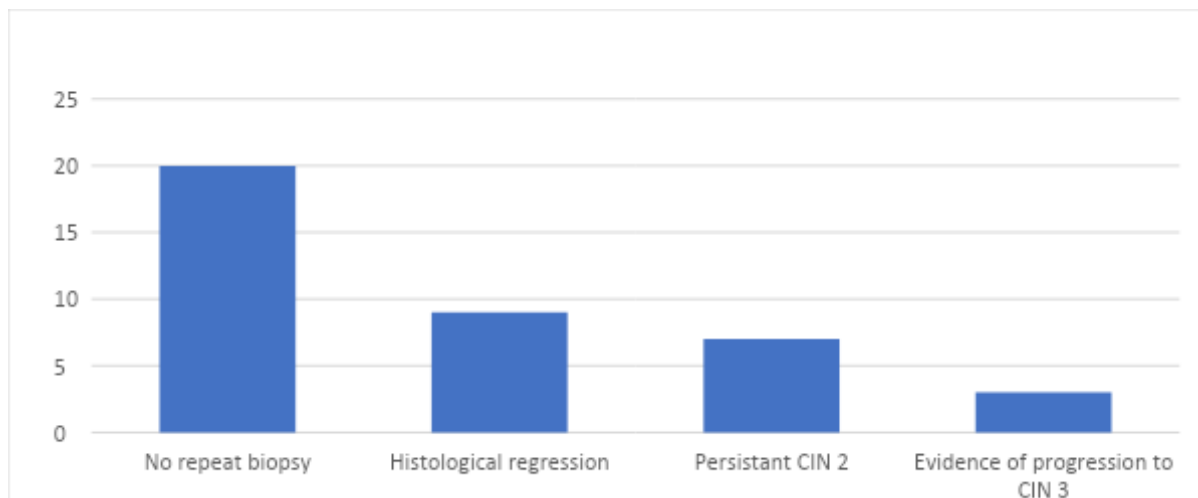


Figure 4: Histology changes during follow up.

Participants outcome and LLETZ treatment:

During the course of the research figure 5 illustrates the patients’ outcomes. Five out of 40 patients, or 13%, were advised to get LLETZ therapy. In view of a 12-month period of severe high-grade dyskaryosis as determined by cytology and high-grade characteristics as determined by colposcopy, two patients were recommended for LLETZ. In both cases, CIN 3 was confirmed by histology results later. Following her initial follow-up, a patient was offered LLETZ after confirming her family is complete. Because of the biopsy-verified progression to CIN 3, two patients were offered

LLETZ. After two years, a patient with persistent CIN 2 was offered LLETZ. She had a prior LLETZ and was worried about the possibility of preterm labour, so she declined therapy. After an additional year of follow-up, a second biopsy that solely detected HPV alterations was conducted, and yearly smears are now conducted. In summary, 13% (n= 5) of patients underwent LLETZ treatment, 28% (n=9) were discharged from colposcopy for yearly follow up following successful conservative management, and 38% (n=15) are still being watched.

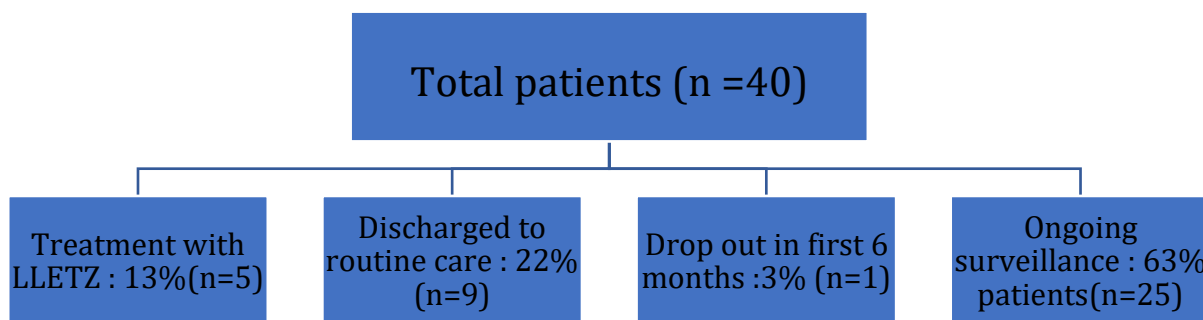


Figure 5: patient outcome during the research duration.

Discussion

Conservative management relies on observing the lesion until it regresses. It involves 6 monthly colposcopic and cytologic review with repeat biopsies where necessary at least for a period of 2 years initially. As a relatively new approach in lister hospital colposcopy department, most patients are under surveillance. Only 13 % of cases completed the full 24 months period of monitoring. The results so far have shown regression in terms of cytology and histology in the majority of cases. There were no reported cases of cervical cancer and only a small

percentage (8%) progressed to CIN 3. These results are consistent with a population-based study from Canada that showed that regression occurred in 73.1% of all women total women in the study 636, all under age 25 years with conservative approach of management concluding this a safe and justified approach (8). Another study in the UK demonstrated 57% regression with a default rate of 11% (9).

There were strong indications to offer LLETZ in cases of failed conservative management. There was good compliance to the standard local guideline. Patient selection was appropriate in 100% of cases. A multidisciplinary approach was employed before decision for conservative management and before decision for treatment. It should be noted that this is a retrospective study based on medical record data. As a result, we lack information on parameters linked to predicting the outcome of conservative care, such as the initial CIN2 lesion not being tested for p16 by IHC, thus we can't say whether that triage signal would have helped predict the outcome (10).

More than half of patients were compliant to six monthly follow up, but 48 % missed one or more appointment for various reasons. This represents an area for improvement. Although the current patient information leaflet emphasises on this aspect, more counselling of patients is vital to avoid delay in diagnosis and treatment. Previous case studies have wide variation in research methodology and outcome definitions such as "regression" and "persistence"(3,6,7&8). We observed less evidence of complete recovery to normalcy during our auditing, instead finding a substantial proportion of women with persistent but non-progressing low-grade lesions. In the absence of progression, the inability to "clear" or return to normal screening resulted in a long-term cycle of repeated follow-up visits, several of which included repeat colposcopies and/or biopsy procedures. This loop is costly to the patient in terms of time, money, and emotional anguish or anxiety (11).

These findings call for a rethinking of current guidelines that require a return to complete normalcy before discharge from the colposcopy clinic and returning to routine screening. More research is needed to determine whether it is possible to identify which women with an initial CIN2 who are under increased surveillance can be safely returned to routine screening after fewer follow-ups without increasing their cancer risk significantly. Perhaps HPV genotyping, and/or a lack of high-grade cytology could be used to distinguish which women are at higher cancer risk and require continued surveillance, and which are at lower cancer risk and can be safely released from such intensive surveillance and returned to routine screening. More research is needed to determine whether younger women with an untreated, transient CIN2 diagnosis but persistent low-grade abnormalities can safely return to routine screening (12).

Conclusion and Recommendations

Conservative management of CIN 2 is a safe option, as demonstrated by this study, when close monitoring and appropriate patient selection are used. Conservative management of CIN 2 is more patient-centered and may help reduce rates of preterm labour and second trimester miscarriage. As more units are adopting this approach, hopefully this will contribute to less poor obstetric outcomes and better patient satisfaction.

A prospective study focusing on future pregnancy outcomes would be helpful to assess the impact of this management. As more units are adopting this approach, we expect more

Robust evidence to support a national guidance for conservative management of CIN 2.

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Role played by each co-author declaration: Iman Makramallah: Data collection and analysis, writing - Vernika Sharma: Review of writing

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References

1. American Cancer Society. *Cancer Facts & Figures 2023*. Atlanta, Ga: American Cancer Society; 2023.
2. Darragh TM. (2015) The LAST Project and the diagnostic bottom line. *Cytopathology*. Dec;26(6):343-5. [PubMed]
3. Rezniczek GA, Severin S, Hilal Z, Dogan A, Krentel H, Buerkle B, Tempfer CB. (2017) Surgical performance of large loop excision of the transformation zone in a training model: A prospective cohort study. *Medicine (Baltimore)*. Jun;96(23):e7026. doi: 10.1097/MD.0000000000007026. PMID: 28591034; PMCID: PMC5466212. [PubMed]
4. McCredie MR, Sharples KJ, Paul C, et al. (2008) Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*; 9:425. [PubMed]
5. Tainio K, Athanasiou A, Tikkinen KAO, et al. (2018) Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ*; 360: k499.
6. Godfrey MAL, Nikolopoulos M, Garner JE, Adib TR, Mukhopadhyay D, Rains JS, Harper CA, Wuntakal R. (2018) Conservative management of cervical intraepithelial neoplasia grade 2 (CIN2) in women under 30 years of age: A cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2018 Sep; 228:267-273. doi: 10.1016/j.ejogrb.2018.07.018. Epub Jul 17. PMID: 30048921. [PubMed]
7. Madeleine Macdonald, John H. F. Smith, John A. Tidy & Julia E. Palmer (2018) Conservative management of CIN2: National Audit of British Society for Colposcopy and Cervical Pathology members' opinion, *Journal of Obstetrics and Gynaecology*, 38:3, 388-394, DOI: 10.1080/01443615.2017.1316973. [PubMed]
8. Sykes PH, Simcock BJ, Innes CR, Harker D, Williman JA, Whitehead M, van der Griend RA, Lawton BA, Hibma M, Fitzgerald P, Dudley NM, Petrich S, Eva L, Bergzoll C, Kathuria J, McPherson G, Tristram A, Faherty J, Hardie D, Robertson A, Robertson V, Pather S, Wrede CD, Gastrell F, Fentiman G, John M, White E, Parker C, Sadler L. (2021) Predicting regression of cervical intraepithelial neoplasia grade 2 in women under 25

- years. Am J Obstet Gynecol. 2022 Feb;226(2): 222.e1-222.e13. doi: 10.1016/j.ajog.2021.09.009. Epub 2021 Sep 14. PMID: 34534506. [PubMed]
9. Dwivedi, R., Kar, A., Melson, L. et al. (2021) Conservative Management of CIN2. Indian J Gynecol Oncolog 19, 42.
 10. Silver MI, Gage JC, Schiffman M, Fetterman B, Poitras NE, Lorey T, Cheung LC, Katki HA, Locke A, Kinney WK, Castle PE. (2018) Clinical Outcomes after Conservative Management of Cervical Intraepithelial Neoplasia Grade 2 (CIN2) in Women Ages 21-39 Years. Cancer Prev Res (Phila). 2018 Mar;11(3):165-170. doi: 10.1158/1940-6207.CAPR-17-0293. Epub 2018 Feb 5. PMID: 29437696. [PubMed]
 11. Dwivedi, R., Kar, A., Melson, L. et al. (2021) Conservative Management of CIN2. Indian J Gynecol Oncolog 19, 42.
 12. Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, Cheung LC, Raine-Bennett T, Gage JC, Kinney WK. (2013) Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. J Low Genit Tract Dis. Apr;17(5 Suppl 1): S78-84. doi: 10.1097/LGT.0b013e31828543c5. PMID: 23519309; PMCID: PMC3616418. [PubMed]