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Original Article

Adherence to follow-up in women with cervical intraepithelial neoplasia grade 1

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ABSTRACT

Objectives: Adherence to follow-up is crucial for cervical intraepithelial neoplasia grade 1 (CIN1) because these women have a chance of progression to high-grade premalignant cervical lesions and cervical cancer. This study aimed to evaluate the rate of adherence to follow-up in women who were initially diagnosed with CIN 1 over a period of 24 months and to evaluate the regression and progression rate of CIN 1.

Material and methods: Of 1050 women who visited a colposcopy clinic from October 2013 through March 2017, 138 with histologically proven as CIN 1 were recruited. Adherence to follow-up, the regression and progression rate of CIN 1 were retrospectively assessed.

Results: Of the 138 women, 86 (62.3%) followed regularly until the study endpoint at 24 months. During the study period, 10 women received ablative treatment. The regression rate in women who had surveillance with cervical cytology was 69.7%, persistent disease of 18.4%, and progression to CIN 2–3 of 11.8%. In contrast, 80% of women who received ablative treatment had regression, 20% of them had persistent disease but none had progression.

Conclusions: Nearly 40% of women with CIN 1 were lost to follow-up at 24 months. Adherence to the follow-up should be emphasized to all women. Intensive interventions to improve adherence and clinical outcome might be an option, particularly among women with poor compliance.

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Introduction

Adherence to follow-up schedule and adequate treatment of persistent disease in cervical intraepithelial neoplasia (CIN) is crucial for cervical cancer prevention. Although cervical screening coverage in Thailand has recently improved to nearly 60% [1], cervical cancer is still the leading gynecologic cancer. Failure to return after diagnosis of CIN can be detrimental [2]. Increased screening coverage, early detection of preinvasive cervical lesions, and optimal follow-up of precancerous disease play an important role in eliminating cervical cancer.

Histological diagnosis of CIN 1 is recognised as a disease of benign viral replication. With the aid of the host's immune system, CIN 1 might recover to normal cervix without any treatment; however, persistent infection may develop into CIN 1–2 within two to three years [3]. Previous literature review has shown that CIN 1 had a spontaneous regression rate of 57%, disease persistence of 32%, progression to CIN 2–3 of 11%, and progression to invasive cancer of 1% over a follow-up range of 1–18 years [4]. According to the American Society for Colposcopy and Cervical Pathology (ASCCP) 2012 guidelines, CIN 1 should be managed conservatively until persistence of disease for two years [5], consistent with the 2019 ASCCP risk-based management guidelines which recommend follow-up unless the cytology result was high-grade intraepithelial lesion (HSIL) [6]. Therefore, compliance and adherence with follow-up appointments are necessary.

Research studies focused on adherence have shown follow-up rates after abnormal cervical cytology results were less than 50% [2,7]. Return rates for cytology surveillance in women with CIN 1 were decreasing; 83.2%, 59.2%, 45.6% and only 12% of them received first, second, third and more than three cervical cytology follow-up visits, respectively [8]. Predictors of low adherence rates are low-income, less educated and minority women [9]. High rates of being lost to follow-up tends to affect an incorrect estimations of the

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remission rate of disease [10]. Thailand has a unique socio-economy and culture, the rate of follow-up in Thai women might differ from those of other countries. Accordingly, loss to follow-up rate in Thais would better inform how far management guidelines from the first world countries can be generalised in ours.

This retrospective study aims to review the adherence to follow up in CIN 1 women and evaluates the regression and progression rate of CIN 1 at two years after initial diagnosis.

Materials and methods

This study was conducted at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand. This protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB No. 650/61). All medical records of 1050 women who visited the colposcopy clinic between October 2013 and March 2017 were retrospectively reviewed. Of these women, 138 who were histologically proven as CIN 1 were recruited to the study. Inclusion criteria were as follows: adequate colposcopic examination, negative endocervical curettage, and follow-up data available. Exclusion criteria were patients with prior hysterectomy, having a history of cervical or endometrial cancer and referred to follow-up at the other hospitals according to their welfare schemes.

Management of CIN 1 is based on ASCCP guidelines. All patients in our study had undergone colposcopic examination with cervical biopsy. The treatment options for CIN 1 was follow up but treatment either ablation or cone excision if indicated. Surveillance every 6–12 months with cytology alone or co-testing every 12 months is recommended. Duration of follow-up, cervical screening results, adherence to appointment, management and treatment outcome were recorded. Patients who had appointments and adhered to follow-up until 24 months were defined as having successfully completed follow-up. Cervical cytology and/or histologic diagnosis from colposcopic directed biopsy or cone excision were used for confirmation of regression, persistence, or progression of disease.

Descriptive statistics were used to describe patients' characteristics. A percentage was used to examine adherence rate, and rate of regression, persistence, and progression during follow-up.

Results

Of 1050 women who visited a colposcopy clinic during October 2013 and March 2017, 138 were histologically confirmed and diagnosed for CIN 1. Demographic data are shown in Table 1. The median age was 37 years old. Almost all women were in the reproductive age group. 13.8% of them had coexisting HIV infection. Initial cervical cytology was ASC-US of 34.8%, LSIL of 47.8%, ASC-H of 7.2%, and HSIL of 9.4%. Nearly half of them (48.6%) were tested for HPV DNA. HPV type 16, type 18, and other high-risk types accounted for 13.7%, 2.1% and 23.2%, respectively.

During the 24 months follow-up period, 24 women (17.4%) received treatment. Cryotherapy was the most common ablative treatment in 13 women (9.4%), followed by laser ablation in 2 women (1.4%), and electrocauterization in 1 woman (0.7%). LEEP was performed in 8 women (5.8%) due to initial high-grade cervical cytology caused cytopathodiscrepancy and disease progression during the follow-up period.

The 111 of 138 women (80.4%) returned for follow-up at six months. This number decreased to 99 women (71.7%) at 12 months, and only 86 women (62.3%) had successfully completed followed up at 24 months. Loss to follow-up was 19.6%, 28.3% and 37.7% at six, 12, and 24 months, respectively (Table 2). Of the 86 women who completed follow-up at 24 months, 16 women required the treatments. Ten women were treated with cervical ablation and six women performed loop electrosurgical excision procedure (LEEP) due to persistence or progression of disease. Ten women (11.6%) were treated with cervical ablation during the follow-up period due to persistence of disease. The decision for treatments depended on the physician's preference. Therefore, only 70 women without any treatments completed follow-up at 24 months. Table 3 summarizes the data on the clinical courses of CIN 1 over 12 and 24 months follow-up periods. At 12 months, the rate of regression was 73.7%, persistence was 20.2%, and progression to CIN 2–3 was 6.1%. At 24 months, the rate of regression was 70.9%, persistence was 18.6%, and progression to CIN 2–3 was 10.5%. Within 24 months of the

Table 1
Baseline characteristics.

Demographics	N
Median age (years)	37
<20	3 (2.2%)
20–30	17 (12.3%)
31–40	70 (50.7)
41–50	31 (22.5%)
51–60	12 (8.7%)
61–70	3 (2.2%)
>70	2 (1.4%)
Menopausal status	
Pre-menopause	123 (89.1%)
Menopause	15 (10.9%)
HIV status	
Positive	19 (13.8%)
Negative	37 (26.8%)
Unknown	82 (59.4%)
Initial cervical cytology	
NILM	1 (0.7%)
ASC-US	48 (34.8%)
LSIL	66 (47.8%)
ASC-H	10 (7.2%)
HSIL	13 (9.4%)
HPV DNA testing	
Type 16	19 (13.7%)
Type 18	3 (2.1%)
Other high-risk types	32 (23.2%)
Negative	13 (9.4%)
Not tested	71 (51.4%)
Length of follow up (months)	
0–6	34 (24.6%)
7–12	7 (5.1%)
13–18	7 (5.1%)
19–24	18 (13%)
>24	72 (52.2%)
Treatment during follow up	
None	114 (82.6%)
Cryotherapy	13 (9.4%)
Laser ablation	2 (1.4%)
Electrocauterization	1 (0.7%)
LEEP	8 (5.8%)

Table 2
Adherence rate at 6, 12, 24 months.

	Complete follow-up	Lost follow-up
6 months	111 (80.4%)	27 (19.6%)
12 months	99 (71.7%)	39 (28.3%)
24 months	86 (62.3%)	52 (37.7%)

Table 3
Clinical courses of CIN 1 over 12- and 24-month follow-up period.

	Regression	Persistence (CIN 1/HPV)	Progression (CIN 2/CIN 3)	Progression (Invasive cancer)	Total
12 months	73 (73.7%)	20 (20.2%)	6 (6.1%)	0 (0%)	99
24 months	61 (70.9%)	16 (18.6%)	9 (10.5%)	0 (0%)	86

Table 4
Clinical courses of CIN 1 at 24-month follow-up period.

	Expectant management (N = 76)	Ablative treatment (N = 10)	Total
Regression	53 (69.7%)	8 (80%)	61 (70.9%)
Persistence	14 (18.4%)	2 (20%)	16 (18.6%)
Progression to CIN2-3	9 (11.8%)	0 (0%)	9 (10.5%)
Total	76 (100%)	10 (100%)	86 (100%)

study, none of the women had progressed to invasive cervical cancer.

Among the 76 women who had no treatments completed the 24 months follow-up, spontaneous regression was occurred in 53 women (69.7. Nine women (11.8%) had progression to CIN 2–3 and 14 women (18.4%) had persistence of disease). Among the 10 women who received cervical ablation, eight (80%) had regression and two (20%) had persistence of disease. None of the women in the ablative treatment group had progression to CIN 2–3 (Table 4).

Discussion

CIN 1 is the most common premalignant cervical intraepithelial lesion. Our previous study reported 60% of women with abnormal cervical cytology had CIN 1 [11]. Long-term follow-up is necessary in women with CIN 1 for early detection and treatment of high-grade precancerous lesions aiming to prevent cervical cancer. Previous studies have shown a wide range of low adherence, 11.5%–42% of women with abnormal PAP smear return to follow-up at more than six months [12,13]. A range of 16.1%–65.6% of women with CIN 1 adhere to follow-up at 12–24 months [8]. In the present study, 80.4% of CIN 1 patients adhered to follow-up at six months. Adherent rate was dropped to 71.7% at 12 months and only 62.3% of women had complete follow-up at 24 months.

Adherence to follow-up for CIN 1 women had an inverse correlation with follow-up time. Nearly 40% of them were lost to follow up at 24 months. This rate might be much increased after a longer follow-up time. Compliance with follow-up is crucial and would enhance the ability to detect high-grade premalignant cervical lesions and invasive cervical cancers. To improve return rates in poor adherent women, home visits and behaviour change interventions would be helpful [14]. Besides, there have been few studies that described more intensive interventions being positively correlated with adherence [8,15]. Hartz et al. reported that about 40% of women with CIN 1 chose immediate ablative treatment with cryotherapy instead of cytology surveillance [8]. These women were more likely to return for at least one visit after treatment compared with cytology surveillance patients. A previous study in Thailand reported that 44% of women with CIN 1 chose early treatment with cryotherapy. At 12 months, the adherence rate was 68.4% compared with a rate of 63.3% in women with cervical cytology surveillance [16].

According to the natural history of CIN 1, the likelihood of regression is 57%, 32% persistence, 11% progression to CIN 2–3 and 1% progression to invasive cancers [4]. The current study was also reported similar findings. The rate of regression at 24 months in women who had cervical cytology surveillance was 70%, 18% persistence, and 12% progression to CIN 2–3. However, a better regression rate of 80% and persistence of 20% were reported in women who received ablative treatment during the follow-up period, but none had progression. However, the exact spontaneous regression rates in this study might be inaccurate because nearly 40% of them were lost to follow-up. Furthermore, the criteria for the diagnosis of regression are inconclusive. It was based on either cervical cytology, HPV testing or histological confirmation by colposcopic directed biopsy. Almost all the women who had regression of CIN 1 in this study were diagnosed by negative cervical cytology at 24 months, very few of them were confirmed by colposcopic directed biopsy. Although, the sensitivity of cervical cytology for screening of CIN 2+ among the Thai population was only 53.8%, it had a high specificity of 96.7% and a negative predictive value of 99.2% [17]. Thus, negative cervical cytology is acceptable for the diagnosis of regression.

Recently, the ASCCP guidelines recommended following CIN 1 until the cervical cytology result shows HSIL [6]. This recommendation may not be suitable in Thailand where there is a high incidence of cervical cancer. Two previous studies in Thailand reported that women with low-grade cytology had high-grade lesions up to 10%, which is much higher than 2.6% in the USA [11,18]. Although, the spontaneous regression rate of CIN 1 in this study was 70%, the progression rate was also as high as 12%. Expectant management with cervical cytology surveillance required strict adherence. Adherence to follow-up is especially problematic in low resource settings. Nearly 40% of women with CIN 1 in this study had loss to follow-up at 24 months. Therefore, this practice guideline should be adjusted in areas with a high incidence of cervical cancers and poor adherence to follow-up. Early treatment with ablative treatment may be considered, especially for women with the chance to loss follow-up. The regression rate of ablative treatment in this study was as high as 80%, with a persistence rate of 20% but none had progression. The risks and benefits of all treatment options should be discussed with all women. The limitation of this study was the retrospective design, baseline characteristics about the education level and socioeconomic status which might affect patients' adherence were not evaluated. Also, attitudes and knowledge towards disease were not assessed. The clinical outcomes were assessed at the 24-month period; therefore, a longer follow-up with a larger prospective trial would provide more accurate outcomes. The small number of women who received ablative treatment in this study might be inadequate to provide an exact rate of regression or progression. Furthermore, difference of the adherence rates among women with and without treatment interventions should be evaluated.

In conclusion, adherence to follow up at 24 months in women with CIN 1 was 62.3%. Surveillance with cervical cytology alone had a spontaneous regression of 70% compared to 80% in women with ablative treatment. However, 12% of the women who followed with cervical cytology had progression to CIN 2–3. Adherence to the follow-up should be emphasized to all women during the follow-up visits. Intensive interventions being positively correlated with adherence or improved clinical outcomes may be an option, particularly in women with poor compliance.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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