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Factors Associated with Non-Regression of Cervical Intraepithelial Neoplasia Grade I After One Year of Expectant Management

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ABSTRACT

Background: Cervical intraepithelial neoplasia grade I (CIN1) is known to have a high rate of spontaneous regression, and expectant management is a viable option for women of reproductive age. However, there is limited understanding of factors that predict non-regression in South Asian populations. This study aimed to assess the histopathological results of expectant management of CIN1 after one year and to identify the factors associated with non-regression. **Methods & Materials:** This prospective observational study was conducted at the Gynecological Oncology OPD of the National Institute of Cancer Research and Hospital from January 2023 to December 2023, involving 71 women who had a histologically confirmed CIN1. Participants were managed expectantly, and a repeated cervical biopsy was performed after 1 year. Demographic, reproductive, contraceptive, lifestyle, gynecological, and human papillomavirus (HPV) data were compared between regression and non-regression groups. Data were entered and analyzed on SPSS version 26. **Results:** Regression was seen in 69.1% of women, persistence in 26.7%, and progression to CIN2 in 4.2%. Non-regression was significantly associated with older age (36.84 vs 31.06 years, p<0.001), age at marriage below 16 years (p=0.019), oral contraceptive use for five years or more (p=0.011), tampon use (p=0.035), and high-risk HPV positivity (p=0.040). There was no significant association with parity, age at first delivery, condom use, smoking, malodorous discharge, or genital warts. **Conclusion:** Most women with CIN1 will spontaneously regress within 1 year, making expectant management the first-line approach. Older women, married early, using oral contraceptives for a long time, using tampons, and having a long history of high-risk HPV infection are at higher risk of non-regression and may require more frequent monitoring.

Keywords: *Cervical intraepithelial neoplasia; Expectant management; Human papillomavirus*

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INTRODUCTION

Cervical cancer is one of the most preventable, yet most burdensome gynecological cancers in low- and middle-income countries. In Bangladesh, over 50 million women are estimated to be at risk of cervical cancer due to low screening coverage and delayed detection of precancerous lesions [1]. Nationwide visual inspection with acetic acid programs and emerging human papillomavirus self-sampling programs have been piloted to improve early detection in under-screened populations, including Bangladesh, India, and Uganda, but uptake and follow-up are inconsistent [2]. Recent global burden estimates also suggest that, if vaccination and screening efforts are not scaled up quickly enough, the burden of cervical cancer will continue to be disproportionately high in low- and middle-income countries in the next decade [3]. Persistent infection with high-risk human papillomavirus (HPV) genotypes is the main factor in the pathogenesis of cervical carcinogenesis, and the process follows a well-defined sequence of events from low-grade cervical intraepithelial neoplasia grade I (CIN1) to high-grade lesions and finally to invasive cancer. CIN1 is, however, different from higher grade lesions in that most cases will resolve without treatment. A large systematic review and meta-analysis of eighty-nine studies found that conservatively managed CIN1 resolves in about 60% of cases, remains unchanged in 25%, and advances to CIN2 or higher in 11%, and to invasive cancer in less than 1% [4]. Regression is always more common in younger women and women who test negative for high-risk HPV, which is the biological basis for expectant, watchful-waiting management rather than immediate excisional treatment, especially in women of reproductive age who want to maintain their fertility [5, 6]. Although this is a generally good natural history, a significant proportion of women do not regress within the first year of follow-up, and it is clinically important to identify which women are at risk of non-regression or progression, particularly in resource-limited countries where colposcopy and HPV testing facilities are limited. Persistent high-risk human papillomavirus genotype, particularly HPV types 16 and 18, younger age at marriage and early onset of sexual activity, prolonged use of hormonal contraceptives, active cigarette smoking, and unhygienic menstrual practices that may lead to chronic cervical inflammation have been reported as factors associated with non-regression in the wider literature [6-10]. The evidence supporting these associations is largely from high-income countries with established, long-term screening programs, and similar data from South Asian populations, where early marriage, illiteracy, and limited access to modern menstrual hygiene products are still common, are limited. Based on this evidence gap, the present study was conducted to describe the histopathological findings of CIN1 after one year of expectant management and to find the demographic, reproductive, contraceptive, lifestyle and virological factors associated with non-regression in women who attended a tertiary care gynecology and colposcopy clinic in Bangladesh.

METHODS & MATERIALS

The study was a prospective observational cohort study carried out at the Gynecological Oncology OPD of the National Institute of Cancer Research and Hospital from January 2023 to December 2023. Women who were diagnosed with cervical intraepithelial neoplasia grade I (CIN1) on cervical punch biopsy (N=71) were consecutively recruited. Inclusion criteria were: histopathologically

confirmed CIN1, consent to expectant (watchful-waiting) management with scheduled follow-up, and informed written consent. Women were excluded if they had a history of previous cervical treatment (excision, ablation, or conization), coexisting CIN2/3 or invasive malignancy on initial biopsy, pregnancy, known immunosuppression (including HIV infection), or if they were lost to follow-up before the end of the one-year observation period. Demographic variables (age, level of education, monthly household income, and residence), reproductive variables (parity, age at marriage, and age at first delivery), contraceptive and lifestyle variables (oral contraceptive pill use and duration, condom use, type of sanitary product used, and smoking status), and high-risk human papillomavirus status (determined by DNA testing where available) were recorded at enrollment by structured interviews and clinical examination. After 1 year of expectant management, all participants had repeat cervical biopsy and histopathological evaluation, with results categorized as regression (normal histology), persistent CIN1, or progression to CIN2 or higher. The data were entered and analyzed using SPSS (version 26). Categorical variables were summarized as frequencies and percentages and compared between the regression and non-regression groups by the chi-square test or Fisher's exact test, as appropriate. The independent-samples t-test was used to compare the continuous variable, mean age, and results were presented as mean ± standard deviation. Throughout, a p-value of < 0.05 (two-tailed) was regarded as statistically significant.

RESULTS

Table I represents the demographic characteristics of the 71 enrolled women. The majority (49.3%) were aged 31-35 years, and most had primary or secondary education (84.6%), indicating a predominantly low-level-educated study population. The majority of the participants (57.7%) lived in urban areas, and just over half (52.1%) had a monthly household income of 10,000 to 25,000 taka, suggesting that the majority were urban, lower- to middle-income women of reproductive age.

Table I
Distribution of participants according to demographic characteristics (*n* = 71).

Demographic variable	Category	n	Percentage (%)
Age (years)	25-30	19	26.8
	31-35	35	49.3
	>35	17	23.9
Level of education	Primary	26	36.7
	Primary to secondary	34	47.9
	Above secondary	11	15.4
Monthly income	<10,000	22	31.0
	10,000–25,000	37	52.1
	>25,000	12	16.9
Residence	Rural	30	42.3
	Urban	41	57.7

Table II shows the histopathological results after 1 year of expectant management. The majority of women (69.1%) had spontaneous regression to normal histology, 26.7% had persistent CIN1, and 4.2% had progression to CIN2. The results of this study support the use of expectant management for most women with CIN1, and the risk of progression to more severe disease is low during the first year of follow-up.

Table II
Histopathological outcomes of participants after one year of observation (*n* = 71).

Histopathological outcome	n	Percentage (%)
Regression	49	69.1
Persistent lesion	19	26.7
Progression to CIN II	3	4.2
Total	71	100.0

Table III shows the mean age of the regression and non-regression groups. The difference in age between women who regressed and those who did not regress was statistically highly significant (p<0.001), with the regressed women being younger (mean 31.06 ± 3.69 years) than the non-regressed women (mean 36.84 ± 2.84 years). This study has found that age has a clinically relevant association with poor histopathological outcomes in women treated expectantly for CIN1.

Table III
Comparison of mean age between the regression and non-regression groups (*n* = 71).

Final HPR	n	Mean age (years)	SD	p-value
Regression	49	31.06	3.687	<0.001
Non-regression	22	36.84	2.840	

Table IV shows the reproductive factors and outcome. The age at marriage was significantly associated with non-regression (p=0.019), with almost two-thirds of the women who married early not regressing. Neither parity nor age at first delivery was statistically significantly associated with outcome (p=0.080 and p=0.206, respectively), indicating that age at first delivery, not parity, is the more clinically relevant reproductive determinant of persistence of CIN1 in this cohort.

Table IV
Association of reproductive factors with regression and non-regression groups (*n* = 71).

Reproductive factor	Category	Regression, n	Non-regression, n	p-value
Parity	<3	29	10	0.080
	≥3	19	13	
Age at marriage (years)	<16	10	15	0.019
	≥16	38	8	
Age at first delivery (years)	<17	11	7	0.206
	≥17	37	16	

Table V shows contraceptive and lifestyle factors. Oral contraceptive pill use for 5 years or more (p=0.011) and use of tampons as the primary sanitary product (p=0.035) were both significantly associated with non-regression. Hormonal contraceptive duration and menstrual hygiene practice were the most significant modifiable lifestyle factors identified in this analysis, with no significant association with outcome found for condom use and smoking status (p=0.346 and p=0.506, respectively).

Table V
Association of contraceptive and lifestyle factors with regression and non-regression groups (*n* = 71).

Factor	Category	Regression, n	Non-regression, n	p-value
OCP use	No	11	4	0.011
	<5 years	25	3	
	≥5 years	12	16	
Condom use	Yes	15	9	0.346
	No	33	14	
Sanitary product used	Tampon	16	17	0.035
	Napkin	32	6	
Smoking	Yes	3	4	0.506
	No	45	19	

Table VI shows gynecological disorders by outcome group. The presence of genital warts (p=0.178) or malodorous per-vaginal discharge (p=0.133) was not statistically significant when compared to regression status, but was numerically more common in the non-regressors. These non-significant trends indicate that there may be a relationship between concurrent lower genital tract disease and impaired lesion clearance, which should be investigated in larger numbers.

Table VI
Association of gynecological disorders with regression and non-regression groups (*n* = 71).

Gynecological disorder	Category	Regression, n	Non-regression, n	p-value
Genital warts	Present	5	5	0.178
	Absent	43	18	
Malodorous per-vaginal discharge	Present	23	15	0.133
	Absent	25	8	

Table VII shows the relationship between high-risk HPV status and outcome. The rate of HPV positivity was significantly higher among women with lesions that did not regress than among those that regressed (57.1% vs 42.9%, p=0.040). This result confirms that persistent high-risk HPV infection is the main virological factor associated with poor CIN1 outcome, as it has been shown to play a central role in the process of cervical carcinogenesis.

Table VII
Association between HPV status and regression and non-regression groups.

HPV status	Regression, %	Non-regression, %	p-value
HPV positive	42.9	57.1	0.040
HPV negative	81.3	18.7	

DISCUSSION

Of the 71 women with histologically confirmed CIN1, 69.1% experienced spontaneous regression, 26.7% had persistent disease, and 4.2% developed into CIN2 during the 1-year follow-up period of expectant management. This distribution is similar to pooled active-surveillance data for low-grade cervical disease reported elsewhere, and is somewhat more favorable, and is consistent with the generally indolent natural history of CIN1, supporting expectant management as a reasonable first-line approach for women of reproductive age who do not wish to undergo excisional treatment [11, 12]. Age was associated with outcome, with women who did not regress being, on average, nearly six years older than those who regressed (36.8 vs 31.1 years, p<0.001). This is in line with Tainio et al., who showed that the evidence of regression capacity decreases with increasing reproductive age, which may be due to both increased exposure to HPV in humans and a diminished local immune clearance response in older women [13]. The two

outcome groups also differed in terms of reproductive and marital history. Women who were married before 16 years old were significantly more likely to not be regressed than women who were married at 16 years or older (p=0.019). Early marriage is a well-documented proxy indicator of early sexual debut and cumulative exposure to HPV, and adolescent marriage and childbearing are prevalent in South Asia despite legal prohibitions and are consistently associated with poorer reproductive health outcomes in this population [14]. Our results highlight the possible benefit of targeting cervical screening to women who have had early marriage in similar contexts. Long-term use of oral contraceptive pills (five years or more) was associated with non-regression (p=0.011), which is likely to represent hormonally mediated effects on the cervical transformation zone that could promote sustained viral persistence and not a direct carcinogenic effect [15]. In this cohort, condom use was not statistically significant, but barrier contraception has been reported as a weak protective factor of lesion clearance in other cohorts [16]. There was a significant difference in the type of menstrual sanitary product used between groups (p=0.035), with the non-regressors overrepresented in the tampon group. Although there is no specific evidence that the type of sanitary product is associated with regression of CIN, there is a consistent association between the use of absorbent products and inflammation and infection of the reproductive tract in South Asian populations, a setting that may be conducive to local inflammatory conditions that are not conducive to viral clearance [17, 18]. As in our results, which demonstrated persistent regional variation in human papillomavirus persistence and clearance, high-risk human papillomavirus positivity was significantly more prevalent among non-regressors than regressors (57.1% vs 42.9%, p=0.040), indicating that persistent viral infection, rather than histological grade alone, is the major biological determinant of lesion trajectory [19]. Notably, parity, age at first delivery, genital warts, and malodorous discharge were not significantly associated with outcome in this cohort, unlike a previous study by Tekalegn et al., who reported an increased risk of cervical neoplasia with multiparity [20]. This difference could be due to the relatively small parity distribution and limited sample size of the current study and should be verified in larger, well-powered populations. The findings also have implications for colposcopy services in low-resource areas where repeat biopsy and HPV genotyping may not be readily available. In addition to genotype-based risk stratification in better-resourced active-surveillance programs, simple, low-cost variables that can be captured at first presentation, such as age, marital status, contraceptive history, and menstrual hygiene practices, may help to triage women for closer surveillance or earlier referral for colposcopic re-evaluation. Taken together, these findings indicate that age, early marriage, long-term use of oral contraceptives, menstrual hygiene practices, and HPV status are all factors that can be used to define a higher-risk phenotype for non-regression of CIN1, which could be valuable for risk-stratified follow-up protocols in resource-limited cervical screening programs like those in Bangladesh.

LIMITATIONS

The small sample size, the single-center design, and the short follow-up period of one year might restrict the statistical power and the applicability of the results to longer follow-up periods and other populations.

CONCLUSION

This study demonstrates that expectant management is a safe and clinically appropriate first-line treatment for women of reproductive age with CIN grade I, and that most of these women will experience spontaneous regression within one year. However, there was a significant association between non-regression and age at marriage before 16 years, use of tampons, and persistent high-risk HPV positivity. The results of this study support the use of simple, low-cost demographic and behavioral markers, in addition to HPV status if available, to identify women who need more frequent colposcopy than routine follow-up. The use of such risk stratification in national cervical screening programs may enhance early detection of persistent or progressive disease, especially in resource-limited countries like Bangladesh.

RECOMMENDATIONS

These associations should be confirmed in larger, multi-center, longer duration cohort studies with HPV genotyping, and a risk-stratified follow-up protocol for the management of CIN1 in resource-limited settings should be developed.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee

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