

Cytological Follow-Up of Cervical Intraepithelial Neoplasia 1 after Initial Management During 2-Year Period: Bhumibol Adulyadej Hospital Experience

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Objective: To evaluate the frequency of cervical cytological results in patients diagnosed as low-grade squamous intraepithelial lesion (LSIL) in cytology report between women younger than 30 and woman 30 or older after initial management and the completed 2-year follow-up to suggest the proper management for Thai women.

Materials and Methods: The present study was retrospectively conducted at Bhumibol Adulyadej Hospital, Bangkok, Thailand between January 2011 and December 2016. The medical records of 279 patients whose cervical cytology reported LSIL were reviewed. The prevalence of silent high grade cervical intraepithelial neoplasia (CIN 2/3) in LSIL cytology result was determined. The results of the cervical cytology after the patients completed the 2-year follow-up were evaluated.

Results: During the present study period, 279 cases of LSIL in cytology result were enrolled. In women with LSIL in the cytology report, two-third were in pre-menopausal status. The prevalence of CIN 2/3 in LSIL cytology in women younger than 30 and 30 or older were 11.9% and 11.2%, respectively. At 2-year follow-up, around 97% of the patients who completed the follow-up had a spontaneous regression of the disease in both aged groups. Three percent of cases (3/85) had persistent disease in women 30 or older only. There was no progressive disease in the present study.

Conclusion: Silent CIN 2/3 in LSIL cytology in the present study were high. Colposcopy should be recommended for diagnosis and follow-up in this setting. Abnormal Pap at 2-year follow-up was around three percent, therefore, abnormal cytology was still a problem. Continuous close cytology follow-up is still recommended.

Keywords: Low-grade squamous intraepithelial lesion, LSIL, Cervical intraepithelial neoplasia, CIN, Cytology

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Cervical cancer screening is a simple tool that can be used to detect precancerous and cancerous

cervical lesions. Early finding of the above conditions can reduce the incidence of invasive cervical cancer. Nowadays, there are three methods of cervical cancer screening, namely conventional Papanicolaou test (CPP), liquid based cervical cytology (LBP), and co-testing (LBP combine human papillomavirus [HPV] test). Most cervical cancer screening in Thailand utilizes the CPP method because it is the most economical. The limitation of LBP and co-testing usage are their high cost.

From many recent studies in Thailand, the prevalence of low-grade squamous intraepithelial lesion (LSIL) cervical cytology result has been between 0.42 to 3.13 percent⁽¹⁻⁴⁾. HPV infection is associated with abnormal cervical cytology. A pooled estimate of HPV positivity was reported at 77% in Europe⁽⁵⁾.

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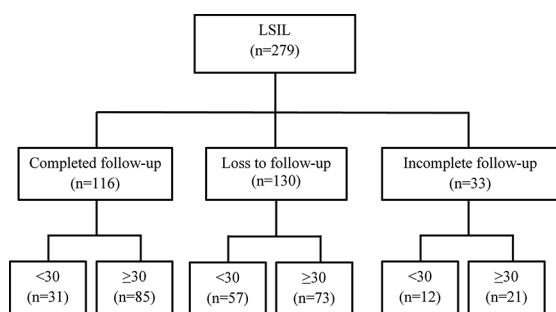


Figure 1. Medical record reviewed in this study.

LSIL=low-grade squamous intraepithelial lesion

In 2012, the American Society for Colposcopy and Cervical Pathology (ASCCP) had revised the consensus guideline for the management of abnormal cervical cancer screening tests and cancerous precursors⁽⁶⁾. The acceptable management in women with LSIL on cytology depended on their HPV test results. For women with LSIL cytology and no HPV test or a positive HPV test, colposcopy was recommended. If co-testing showed HPV-negative LSIL, repeat co-testing at 1-year was preferred, but colposcopy was acceptable.

HPV is the causative cause of CIN. Most of HPV infections were transient and some persisted, leading to development of neoplastic or even cervical cancer lesion⁽⁷⁾. The ASCCP⁽⁶⁾ recommended that women 30 and older get Pap cervical cytology and HPV (co-testing) test for cervical cancer prevention.

The objective of the present study was to evaluate the prevalence of the silent high grade cervical intraepithelial neoplasia (CIN 2/3 and cancer) in LSIL cytology result in women younger and older than 30 years old. The results of spontaneous regression, persistent disease, and progressive disease in both groups of patients after a 2-year follow-up would be studied.

Materials and Methods

The present study was a retrospective study, approved by the Institutional Review Board, Bhumibol Adulyadej Hospital (BAH), Bangkok, Thailand (IRB: 104/61). Data were reviewed from the medical records stored in the computerized program of all the patients with cervical cancer screening in a six-year period between January 2011 and December 2016. The specimens were prepared and interpreted by the certificated pathologists in a single institute. All normal specimens that reported negative were sampled and interpreted by a second pathologists

for internal quality control. Inclusion criteria were women who had cervical cytology result with LSIL cytology. Exclusion criteria were women with pregnancy, post hysterectomy, and known history of pre-invasive or invasive cervical lesion or other gynecologic cancers. The patients were then divided into age younger than 30 group and equal or more than 30 (30+) group. Data collected from medical records included age, type of cervical cancer test, cytology results, colposcopic examination, and histopathological reports. Demographic characteristic consisted of age, menstrual status, body mass index (BMI), parity, Pap proposal, contraceptive method, history of sexual transmitted disease (STD) including human immunodeficiency virus (HIV), history of multiple partners, smoking, alcohol consumption, education, and occupation. Management of LSIL cytology followed the ASCCP guideline by whether the patient had no HPV test or had a positive HPV test. Colposcopic directed cervical biopsy was performed and repeated cervical cytology tests for two consecutive years. Outcomes were classified as completed, loss to, and incomplete follow-up after the initial of LSIL management at two years appointment. Completed follow-up was defined as a completion of cervical cytology follow-up within two years. Loss to follow-up was defined as the cases where patients did not follow-up with cervical cytology within two years. Incomplete follow-up was defined as cases where the patient's cervical cytology had not been completed within two years.

Descriptive statistics were used to analyze patient demographic data. Continuous data were expressed as mean and standard deviation (SD). Categorized data were expressed as number and percentage. Pearson chi-square and Fisher's exact test were used in data analyses when appropriated. The p-value of 0.05 or less was considered to be statistically significant. Analysis was performed using the PASW Statistics software, version 18 (SPSS Inc., Chicago, IL, USA).

Results

The present study was conducted in the main hospital of the Royal Thai Air Force. Around twenty percent of the women in the present study were air force officers and their families. The remaining patients were people who lived and worked in the nearby area around this air force base. Patients also came from a retail and wholesale market, Ying Charoen Market and Talad Si Mum Muang, located in a nearby area.

Two hundred seventy-nine LSIL cytology were

Table 1. Demographic characteristics of enrolled women in this study

Characteristics	Age (years); n (%)		p-value
	<30 (n=100)	≥30 (n=179)	
Age (years); mean±SD	24.0±3.2	45.1±11.3	<0.001*
BMI (kg/m ²); mean±SD	21.6±4.3	23.4±4.7	0.003*
Parity			<0.001*
0 to 1	89 (89.0)	123 (68.7)	
≥2	11 (11.0)	56 (31.3)	
Pap proposal			0.027*
Check up	70 (70.0)	161 (89.9)	
Postpartum	25 (25.0)	9 (5.1)	
Leukorrhea	1 (1.0)	2 (1.1)	
Pelvic pain	2 (2.0)	3 (1.7)	
Follow-up	2 (2.0)	4 (2.2)	
Monogamy	94 (94.0)	175 (97.8)	0.105
Contraception			0.100
None	69 (69.0)	138 (77.1)	
Barrier	14 (14.0)	9 (5.1)	
COC	7 (7.0)	15 (8.3)	
Others	10 (10.0)	17 (9.5)	
HIV positive	3 (3.0)	7 (3.9)	0.695
Non smoking	97 (97.0)	178 (99.4)	0.133
Alcohol consumption	6 (6.0)	1 (0.6)	0.009*
Cytology technique			0.452
CPP	77 (77.0)	127 (70.9)	
LBP	23 (23.0)	52 (29.1)	
Adequacy of smear	57 (57.0)	92 (51.4)	0.368
Education			0.036*
Below high school	0 (0.0)	12 (6.7)	
High school	61 (61.0)	58 (32.4)	
Bachelor or above	39 (39.0)	109 (60.9)	
Occupation			0.671
Government officer	4 (4.0)	27 (15.1)	
Employee	46 (46.0)	85 (47.5)	
Housewife	17 (17.0)	13 (7.2)	
Student	22 (22.0)	0 (0.0)	
Others	11 (11.0)	54.2 (30.2)	

SD=standard deviation; BMI=body mass index; COC=combined oral contraceptive pills; HIV=human immunodeficiency virus; CPP=conventional Pap smear; LBP=liquid based cytology

* The result is significant at p<0.05

recruited. Only 116 cases of LSIL cases successfully completed their 2-year follow-up. Lost follow-up and incomplete follow-up groups were of 130 and 33 cases, respectively (Figure 1).

Table 2. Results of women who had cytology of LSIL

Results	Age (years); n (%)		p-value
	<30	≥30	
Colposcopic findings	(n=46)	(n=131)	0.012*
Satisfactory	38 (82.6)	82 (62.6)	
Unsatisfactory	8 (17.4)	49 (37.4)	
Cervical involvement from colposcopy	(n=46)	(n=131)	0.515
Less than half	33 (71.7)	111 (84.7)	
More than half	13 (28.3)	20 (15.3)	
Histopathologic results	(n=42)	(n=125)	0.900
≤CIN 1	37 (88.1)	111 (88.8)	
CIN 2/3	5 (11.9)	14 (11.2)	
CPC			
≤CIN 1 involvement	(n=35)	(n=113)	0.019*
• Less than half	24 (68.6)	97 (85.8)	
• More than half	11 (31.4)	16 (14.2)	
CIN 2/3 involvement	(n=5)	(n=14)	1.000
• Less than half	3 (60.0)	10 (71.4)	
• More than half	2 (40.0)	4 (28.6)	
Treatment	(n=46)	(n=136)	0.068
Cryotherapy	0 (0.0)	10 (7.4)	
Expectant	46 (100)	126 (92.6)	

≤CIN 1=cervical intraepithelial neoplasia grade 1 or less; CIN 2/3=cervical intraepithelial neoplasia grade 2 and 3; CPC=correlation between pathology results and cervical involvement from colposcopic findings; LSIL=low-grade squamous intraepithelial lesion

* The result is significant at p<0.05

The mean age of women in younger than 30 versus equal or 30+ group were 24.0 and 45.1 years, respectively. The participants in younger than 30 years had lower mean age of first time of sexual intercourse (coitarche) than women of equal or 30+ group with statistical significance (17.8 versus 20.5, p<0.001). Thirty percent of cases in women equal or 30+ group were in menopausal status.

Table 1 showed demographic characteristics of enrolled women in the present study. The cervical cytology reports of all women were LSIL. There were 100 and 179 cases in younger than 30 and equal or 30+ group, respectively.

Unsatisfactory colposcopic study (type 3) of women equal or 30+ was 37 percent. It was more than those in the younger than 30 group with statistical difference as presented in Table 2. Most of the cervical involvement from colposcopic findings in most patients of both groups were less than half as presented in Table 2.

Table 3. Pap smear results during follow-up

Cytologic report	Age (years); n (%)						p-value
	<30			≥30			
	NILM	LSIL	HSIL ⁺	NILM	LSIL	HSIL ⁺	
At 6 months	13 (81.3)	3 (18.7)	0 (0.0)	66 (85.7)	10 (13.0)	1 (1.3)	0.701
At 12 months	22 (100)	0 (0.0)	0 (0.0)	69 (81.2)	16 (18.8)	0 (0.0)	0.038*
At 18 months	22 (95.7)	0 (0.0)	1 (4.3)	75 (89.3)	7 (8.3)	2 (2.4)	0.721
At 24 months	31 (100)	0 (0.0)	0 (0.0)	82 (96.5)	3 (3.5)	0 (0.0)	0.566

NILM=negative for intraepithelial lesion or malignancy; LSIL=low-grade squamous intraepithelial lesion; HSIL⁺=high-grade squamous intraepithelial lesion or worse

* The result is significant at p<0.05

Table 4. Histopathologic results after colposcopic directed biopsy

Colposcopic pathology	Age (years); n (%)					
	<30			≥30		
	Negative	CIN 1	CIN 2/3	Negative	CIN 1	CIN 2/3
At 6 months	0 (0.0)	3 (100)	0 (0.0)	1 (9.1)	8 (72.7)	2 (18.2)
At 12 months	-	-	-	4 (25.0)	12 (75.0)	0 (0.0)
At 18 months	0 (0.0)	0 (0.0)	1 (100)	2 (22.2)	7 (77.8)	0 (0.0)
At 24 months	-	-	-	0 (0.0)	3 (100)	0 (0.0)

CIN 1=cervical intraepithelial neoplasia grade 1; CIN 2/3=cervical intraepithelial neoplasia grade 2 and 3

The histopathological reports of LSIL cytology and correlation between pathology results and cervical involvement from colposcopy were presented in Table 2. Histopathologic results revealed the prevalence of less than or equal to CIN 1 and CIN 2/3 in LSIL cytology at 88.1/88.8 and 11.9/11.2 percent in younger than 30 and equal or 30+ groups, respectively. No cancer was found in neither group.

During the follow-up periods after CIN 1 diagnosis, there were differences in the frequencies of abnormal cervical cytology between both groups at one year, especially when LSIL in cytology was examined. One-hundred sixteen patients (41.6%) had completed a 2-year follow-up. Of these patients, 113 (97.4%) had spontaneous regression of the disease, three patients (2.6%) aged equal or 30+ group had persistent disease. No progressive disease was reported in either groups as presented in Table 3.

Histopathological results from colposcopic directed biopsy in patients who had abnormal cytologic reports during the follow-up period were presented in Table 4. Cervical pathology demonstrated CIN-free, low grade (CIN 1), and high grade (CIN 2/3) lesions. At 12 months, four patients (25.0%) were in CIN-free and 12 patients (75.0%) were in CIN 1,

and at 24 months, only three patients (100.0%) were in CIN 1.

Discussion

LSIL has an extremely low cancer risk of cytological abnormality in cervical cytology⁽⁸⁾. It also has a high rate of spontaneous regression⁽⁹⁾. The management of women with LSIL cytological result is not an aggressive treatment. From the ASCCP guideline⁽⁶⁾, there are two types of management in women who had LSIL cytological reports, namely the repeat cervical cytology and the colposcopic directed biopsy. The choice depended on the results of HPV testing. The women who had LSIL reports with positive HPV testing or without HPV test would be required to undergo colposcopy. In women who had LSIL with negative HPV testing, a repeat co-testing at one year is an acceptable recommendation.

Demographic characteristics among women who had LSIL cytology in the present study showed that LSIL cytology result was found in one quarter of the women in the younger than 30 group during their postpartum check-up visit. As a result, it was suggested that the physician should recommend the patient to undergo cervical cytology to keep the

benefit of the examination. Ninety percent of the women who were recruited in the present study had only one sexual partner. No one know whether the information is true, as to report multiple partners is not an acceptable norm for Thai women. For contraception, it was interesting to find out that twice as many women in the younger than 30 group used barrier contraceptive method compared to the equal or 30+ group. The barrier method is well known to have a high Pearl index and could prevent sexually transmitted diseases⁽¹⁰⁾. About education and occupation, 20% of the women in the younger than 30 group were still in school. Two third of this group had high school education level. Sixty percent of the women in the equal or 30+ group were government officials and employees. Two third of the women in this group had bachelor's degree or higher.

In the present study, the unsatisfactory rate of colposcopy from the women in the equal or 30+ years group was higher than the other group with statistical difference (37.4% and 17.4%, respectively). One third of the former group were in menopause.

In the present study, the prevalence of CIN 2/3 in LSIL cytology were 11.9% and 11.2% from women younger than 30 and equal or 30+ group, respectively. Both were high prevalence of high grade cervical intraepithelial lesion. Thus, it was recommended that all women with LSIL cytology reports should undergo colposcopic directed biopsy. Colposcopic directed biopsy was, at the time, a gold standard method for diagnosis of pre- or invasive cervical cancer. It was an appropriate method in all women. Colposcopic directed biopsy was not a deep or extensive excisional procedure. It was not shown to induce any obstetric problems, such as incontinent cervix or preterm birth, in later date^(11,12).

In the present study, 10 patients in the equal or 30+ group had undergone cryotherapy. One case had CIN 2 pathologic result and the other nine cases had CIN 1. The colposcopic findings in five out of the nine patients showed cervical involvement. Four of the nine patients, aged 40 to 50 years old, were recommended cryotherapy as a treatment. At two years follow-up, the cytology reports showed negative results for intraepithelial lesion or malignancy (NILM) in eight cases (80%), and LSIL in cytology in two cases. The effectiveness of cryotherapy from the present study were comparable to a previous study by Wesley et al⁽¹³⁾. Wesley et al's work⁽¹³⁾, showed 93% and 86.7% cure for CIN 1 and CIN 2 lesion during any follow-up visit at least one year after cryotherapy, respectively.

In the present study, 116 out of 279 patients had completed the 2-year follow-up. Ninety-seven percent (113/116) of these patients had a spontaneous regression of the disease and 2.6% (3/116) had a persistent disease. The result of the present study supported the previous study that reported women with LSIL cytologic reports had a spontaneous regression around 80% to 90% during the first year follow up period⁽¹⁴⁾.

In the present study, loss follow-up rate at 2-years was high at 47%. The length of time between colposcopy and recommended cytology follow-up period may have an impact on the patient's compliance.

HPV testing had higher accuracy than repeat cytology method. It led to faster and more complete diagnosis of pre- and invasive cervical diseases. LSIL Pap abnormalities had a high incidence of HPV infection with HPV testing positive nearly 80 percent⁽⁵⁾. The U.S. national guideline recommended co-testing (liquid-based cytology combined HPV testing) for women aged between 30 and 64 years old. Katki's work showed that the 5-year risks of CIN 2+ and CIN 3+ in women between aged 30 to 64 years old with HPV-positive or LSIL results were larger than those of women with HPV-negative or LSIL result with statistical significance. The 5-year risk of CIN 3+ in HPV-negative or LSIL women was similar to that of women with atypical squamous cells of undetermined significance (ASC-US) Pap test result with unknown HPV test results⁽¹⁵⁾. Nowadays in Thailand, many patients cannot afford the cost of the standard co-testing per ASCCP guideline at 1 and 2-years. The usage of co-testing was limited because the patients covered by social welfare and universal coverage had limited access to the test. Most of the former group refused to pay the excess money above their health coverage price. In the present study, 5% (13/279) of the patients with LSIL in cytology underwent HPV testing. Eighty percent of HPV testing in LSIL cases had positive result. All cases of LSIL with positive or negative HPV testing had no CIN 2 or worse. Currently, conventional Pap test is a primary cervical cancer screening in Thailand. It is known that this test has a lower sensitivity than the co-testing⁽¹⁶⁾. To offset the disadvantages of the low sensitivity of conventional Pap smear, it is recommended to test every six months up to 2-years in LSIL group. In the present study, persistent LSIL was found in the women of the equal or 30+ group. Patients in this group should receive followed-up for two to three years.

Since the present finding showed a high

prevalence of high grade cervical intraepithelial lesions (CIN 2/3) (11.2% to 11.9%), it is suggested that all patients with LSIL cytology from both groups should undergo a colposcopic directed cervical biopsy. This suggestion followed the latest ASCCP guideline.

Conclusion

In conclusion, the silent high grade CIN in LSIL cases in all age groups women was high. The present study result was similar to the data of the ASCCP guideline. Colposcopic directed cervical biopsy was recommended in the women who had cervical cytology report of LSIL without HPV testing result. The continuous close cytology follow-up was an important tool in the women who had LSIL cytologic report because of persistent abnormal Pap results problems.

What is already known on this topic?

Cervical cancer screening is a simple tool that can be used to detect pre-cancerous and cancerous cervical lesions. Low grade pre-cancerous lesion (CIN 1) mostly spontaneous regressed within one year. High grade pre-cancerous lesion (CIN 2/3) was mostly silent and diagnosed during initial diagnosis of CIN 1.

What this study adds?

Silent CIN 2/3 in LSIL cytology in the present study were high. Persistent abnormal Pap at 2-year follow-up was around three percent, so persistent abnormal cytology was still a problem. Continuous close cytology follow-up is still recommended.

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Conflicts of interest

The authors declare no conflict of interest.

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