Women in a Region with High Incidence of Cervical Cancer Warrant Immediate Colposcopy for Atypical Squamous Cells of Undetermined Significance on Cervical Cytology

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Objective: *To evaluate the histopathology of women who had "atypical squamous cells of undetermined significance" (ASC-US) on cervical cytology in a region with high incidence of cervical cancer.*

Material and Method: *Retrospective case-record review of 254 women with ASC-US cytology undergoing colposcopic examination at Nakornping Hospital between October 2003 and September 2007.*

Results: *Of the 254 patients who had ASC-US smears underwent colposcopic and histopathologic evaluation. The mean age was 45.3 years (range,18-72 years). The histologic diagnoses, obtained from colposcopically directed biopsy or endocervical curettage or loop electrosurgical excision procedure or cold knife conization after initial colposcopy, showed that 47 (18.5%) women had histologically confirmed high-grade lesions and 20 (7.9%) women had invasive cancers. There was no statistically significant difference in the incidence of high-grade or invasive lesions between who were 50 years old or more and those who were younger (50.0% and 50.5%, respectively, p = 0.39).*

Conclusion: *Reporting ASC-US cytology in our population is obviously associated with significant cervical pathology, particularly invasive cancer that is possible at a rate higher than previously reported. Women who have ASC-US smears should therefore be referred for immediate colposcopy regardless of age.*

Keywords: *Atypical squamous cells of undetermined significance (ASC-US), Cervical cytology, Colposcopy*

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Cervical cancer is the second most common cancers among women worldwide, with an estimated 471,000 new cases and 233,000 deaths in the year 2000. About 80% of cases occur in developing countries, and over in Asia, where it has become the leading cause of cancer-related death among women[1]. Among cancer in Thai women, cervical cancer is the most common with the age standardized incidence rate (ASR) of 19.5 per 100,000 person-year. The incidence is highest in Chiang Mai, a northern province with an ASR of 25.3, followed by Lampang (ASR = 23.6), Bangkok (ASR = 20.7) and Khon Kaen (ASR = 15.0)[2].

The Pap smear is the most successful cancers screening method to reduced the incidence of invasive cervical cancers in developed countries in a direct consequence of well established screening programs[3]. Based on the Bethesda 2001 subcategorization of atypical squamous cells, different guidelines for the management of atypical squamous cells undetermined significance(ASC-US) and cannot exclude high-grade squamous intraepithelial lesion(ASC-H) have been proposed[4]. If the initial Pap smears show ASC-H, colposcopy and histology results are the recommended management. In contrast, if ASC-US are detected, a program of repeat cervical cytology or DNA testing for high-risk type of human papilloma virus (HPV) or colposcopy are acceptable methods[4]. Each of these methods has advantages and disadvantages and widely used for a public health policy depends on the budget, new technologies and resource settings. There is a variable percentage of ASC-US cytology subsequently found to have high-grade lesions about 2-17% of women with biopsy confirmed high-grade squamous intraepithelial lesion (HSIL) or cervical intraepithelial lesion (CIN) 2 and CIN 3[5-14].

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The aim of cervical cancer screening is to early detect and treat precancerous lesion and the incidence of cervical cancer in Chiang Mai is high, it is therefore, our policy to perform colposcopy in all women with ASC-US cytology. The present study was conducted to evaluate the prevalence of high-grade lesions in women with ASC-US Pap smear.

Material and Method

Between October 2003 and September 2007, 254 women with a Pap smear featuring ASC-US were examined at colposcopy clinic of Nakornping Hospital. All women underwent colposcopy at the first time of their ASC-US cytology. Written informed consent was obtained from all participants after they were counseled about colposcopy and surgical procedures.

Colposcopic examination was performed following application of 5% acetic acid solution on the upper vagina and cervix. The severity of colposcopic findings was based on the density of acetowhite areas, sharpness of lesion margins and abnormal vascular patterns. Biopsies were obtained from the most abnormal appearing area of each separate lesion and endocervical sampling using curette was not routinely performed in cases of satisfactory colposcopy but was carried out in patients with unsatisfactory findings. Diagnostic loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) were performed if the initial work up results revealed high-grade lesions or suspicion of occult invasive cervical lesion. However, diagnostic LEEP or CKC following colposcopy without intervening histological diagnosis may be performed in women with colposcopic findings were suggestive of high-grade lesion or early invasive lesion.

Women with apparently normal colposcopy, those with unsatisfactory colposcopy and negative endocervical sampling, and those with satisfactory colposcopic findings and histologic diagnosis of low-grade squamous intraepithelial lesion (LSIL) were followed with Pap smear every 6 months for 2 years and then with annual examination if four consecutive Pap smear appeared normal. Women with Pap smear of ASC-US or higher during the follow-up period underwent further colposcopic evaluation. In addition, women who had ASC-US cytology of the vaginal cuff after hysterectomy for any indications were excluded. Tissue specimens were interpreted by the Department of Pathology, Falculty of Medicine, Chiang Mai University.

The data were retrospectively analyzed using SPSS computer software. Descriptive statistics were used for demographic baseline data. The Chi-square test was used whenever appropriate to compare between groups. A p-value of less than 0.05 was considered statistically significant.

Results

Mean age of the 254 women with ASC-US on their Pap smear undergoing colposcopic examination was 45.3 $\pm$ 9.2 years with a range of 18-72 years. The most of patients (56.5%) had 1 or 2 children with a range of 0-10 children. The most common contraceptive used were tubal resection (30.3%), non-contraception (28.3%), oral contraceptive pills (21.3%) and depot medroxyprogesterone acetate (11.0%).

Fig. 1 shows the results of colposcopy and subsequent diagnostic procedure in these patients. Normal and satisfactory colposcopic finding were noted in 107 patients (42.1%). Unsatisfactory colposcopy and no lesion were found in 29 patients, 14 patients had no histological diagnosis and endocervical curettage was performed in 15 patients. Women in these group that the results were normal histology or LSIL, were followed with semiannual Pap smear. The persistence and regression rates of ASC-US cytology in these women had no available data for analysis because most patients had cytologic surveillance at

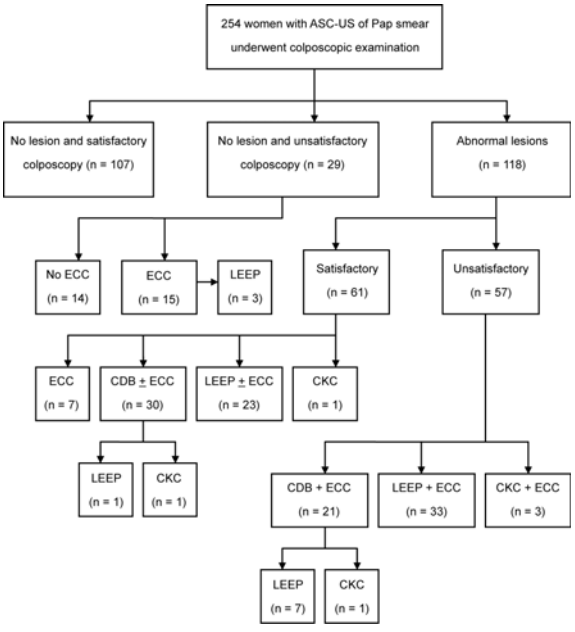

Fig. 1 Management and surgical procedures after colposcopic examination in 254 patients with ASC-US of Pap smear

other hospitals or private clinics and some patients were lost to follow-up.

One hundred and eighteen patients had abnormal lesions of colposcopic examinations, there were 61 patients with satisfactory colposcopy and 57 patients with unsatisfactory colposcopy. The colposcopically directed biopsy (CDB), endocervical curettage (ECC), LEEP and CKC were performed in these patients that shown in Fig. 1.

Table 1 contains the histological diagnosis of 254 patients who had ASC-US cytology. Fourty-two patients (16.5%) had no intraepithelial lesion, 24 (9.4%) patients had LSIL, 47 (18.5%) patients had HSIL and 20 (7.9%) patients had invasive squamous cell carcinoma on histological diagnosis (thirteen stage IA1, and seven IB1).

Table 2 shows the histopathology of women with ASC-US cytology, who were stratified by age groups. There was no significant difference in the incidence of HSIL and invasive cancer between women aged 50 years or older and those younger than 50 years (50.0% and 50.5% respectively, p = 0.39).

Table 1. The final histological diagnosis of 254 patients with ASC-US cytology.

Histologic diagnosis	Number (%)
No histology	121 (47.6)
Normal	17 (6.7)
Cervicitis	25 (9.8)
LSIL	24 (9.4)
HSIL	47 (18.5)
Microinvasive (CA cervix IA1)	13 (5.1)
Invasive cancer	7 (2.8)
Total	254 (100.0)

ASC-US = atypical squamous cells of undetermined significance, LSIL = low-grade squamous intraepithelial lesion, HSIL = high-grade squamous intraepithelial lesion, CA = carcinoma

Discussion

The present study showed that histologically confirmed high-grade lesions were identified in 26.4% of women with ASC-US cytology in our hospital, which is higher than those reported in the previous studies (2-19%)[5-14]. Furthermore, an extraordinary high prevalence of microinvasive and frankly invasive carcinomas (7.9%) was found in our study as compared to 0-2.4% in the previous reports[5-14]. This may reflect a high incidence of invasive cervical cancer in our country. The possible reason may be that 24% of women with ASC-US cytology in this study underwent LEEP suggested HSIL on colposcopic impression. The other reason may be the quality of cytology from several cytopathological laboratories and smear taking process that could not be controlled in the present study.

Lee et al reported a significantly higher detection rate of biopsy-proven CIN1 or high-grade lesions following a cytologic interpretation of ASC-US smears in women younger than 50 years of age[15]. In the present study, the proportion of women who had clinically significant lesions, when stratified by age (younger than 50 years or older), was not significantly different. Based on our findings, women with ASC-US should undergo immediate colposcopic and histologic evaluation in order to early detect and treat high-grade and invasive cervical lesions regardless of their age.

Appropriate management of women with ASC-US cytology remains inconclusive and many methods for managing[4]. The patients may be followed with repeat Pap smear periodically until they had negative for SIL or malignancy without initial

Table 2. The histopathology of 133 patients with ASC-US cytology stratified by age group

Variables	Histopathologic results, number (%)				p-value*
	No lesion	LSIL	HSIL	Cancer	
Age (years)					
< 50 (n = 93)	27 (29.0)	19 (20.4)	35 (37.6)	12 (12.9)	0.39
≥ 50 (n = 40)	15 (37.5)	5 (12.5)	12 (30.0)	8 (20.0)	

* Comparing the incidence of HSIL and cancer between groups

ASC-US = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion

Table 3. Underlying cervical lesions in ASC-US cytology from various studies

Authors	Year	Country	No. patients	LSIL (%)	HSIL (%)	Cancer (%)
Sheils et al[5]	1997	USA	366	8.5	5.0	0
Williams et al[6]	1997	USA	284	13.4	9.2	0
Ergeneli et al[7]	2001	Turkey	64	14.0	11.0	0
Chichareon et al[8]	2002	Thailand	83	19.2	16.9	2.1
ATLS Group[9]	2003	USA	849	35.3	12.5	0
Lonky et al[10]	2003	USA	278	17.6	11.9	0
Yarandi et al[11]	2004	Iran	266	10.5	6.0	0.8
Cheung et al[12]	2004	China	5,579	9.8	1.7	0.02
Feng et al[13]	2007	USA	846	20.6	5.7	0
Kantathavorn et al[14]	2008	Thailand	208	12.5	10.1	2.4
The present study	2008	Thailand	254	9.4	18.5	7.9

ASC-US = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion

colposcopic evaluation. The disadvantages of this approach are the problem for any follow-up that requires multiple visits and delayed the diagnosis of HSIL or cervical cancer. In contrast, referred of women with ASC-US cytology for immediate colposcopy allows women with significant lesion to be readily identified and could reduce the risk of follow-up. The disadvantages of colposcopy are that many women consider the procedure to be uncomfortable, more expensive and it has the potential for overdiagnosis and overtreatment[16]. While DNA testing for high risk types of human papillomavirus (HPV) infection could be another method for evaluating women with ASC-US, the sensitivity of HPV testing for the detection of CIN 2,3 in women with ASC-US is higher than the sensitivity of a single repeat cervical cytological test in the studies[17-19]. In addition, HPV testing proved useful, with sensitivity equivalent to immediate colposcopy and more effective and less costly than a strategy of repeated conventional cytology or immediate colposcopy[19]. Thus,it has been suggested all that the three follow-up diagnostic methods are acceptable for managing women with ASC-US. In our country, colposcopic examination should be recommended in all women with ASC-US cytology because the reason of high incidence of cervical cancer, poor compliance and psychological distress of these women. Furthermore, the cost of HPV testing is so higher than the cost of colposcopy and a repeat cervical cytological test in our country.

The limitations of the present study were the retrospective by nature, a lack of central slide review of cervical smears and the relatively small sample size. Women with ASC-US smears who had normal colposcopic finding defaulted from adequate follow-up and most women had cytologic surveillance at other hospitals. Consequently, the course of ASC-US in these women could not be exactly documented. However, the present study shows that significant lesions especially invasive cancer were identified in approximately 8% of women with ASC-US cytology. These lesions will go unrecognized without colposcopic workup.

In conclusion, women with atypical squamous cells of undetermined significance are associated with underlying high-grade squamous intraepithelial lesion and highly associated with underlying invasive cancers. Immediate colposcopy is recommended particularly in regions with high incidence of cervical cancer.

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การตรวจด้วยกล้องขยายทางช่องคลอดในสตรีที่มีผลตรวจเซลล์วิทยาของปากมดลูกชนิด atypical squamous cells of undetermined significance(ASC-US) และอยู่ในภูมิภาคที่มีอุบัติการณ์เกิดมะเร็งปากมดลูกสูง

วัชรินทร์ สุนทรลิ้มศิริ

***วัตถุประสงค์**: เพื่อศึกษาผลการตรวจทางพยาธิวิทยาของชิ้นเนื้อปากมดลูก ในสตรีที่มีผลการตรวจทางเซลล์วิทยาของปากมดลูกชนิด atypical squamous cells of undetermined significance (ASC-US)*

***วัสดุและวิธีการ**: ได้ทำการรวบรวมข้อมูลจากบันทึกทางการแพทย์ ของผู้ป่วยที่มีผลการตรวจทางเซลล์วิทยาของปากมดลูกชนิด ASC-US โดยรับการตรวจด้วยกล้องขยายทางช่องคลอด ณ โรงพยาบาลนครพิงค์ ระหว่างวันที่ 1 ตุลาคม พ.ศ. 2546 ถึงวันที่ 30 กันยายน พ.ศ. 2550*

***ผลการศึกษา**: จากผู้ป่วย 254 ราย ที่เข้าร่วมการศึกษามีอายุเฉลี่ย 45.3 ปี (พิสัย 18-72 ปี) วิธีการตรวจทางพยาธิวิทยาได้แก่ การตัดชิ้นเนื้อจากปากมดลูกโดยผ่านกล้องส่องขยาย (CDB) การขูดภายในปากมดลูก (ECC) การตัดปากมดลูกด้วยห่วงไฟฟ้า (LEEP) และการตัดปากมดลูกออกเป็นกรวยด้วยมีด (CKC) ผลการศึกษาพบว่าร้อยละ 18.5 มีผลการตรวจทางพยาธิวิทยาเป็น high-grade squamous intraepithelial lesion(HSIL) และร้อยละ 7.9 มีผลการตรวจทางพยาธิวิทยาเป็นมะเร็งปากมดลูกระยะลุกลาม ความชุกการเกิดรอยโรคของปากมดลูกชนิด HSIL หรือ มะเร็งระยะลุกลามในกลุ่มสตรีที่อายุน้อยกว่า 50 ปี และตั้งแต่ 50 ปี ขึ้นไปไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ*

***สรุป**: สตรีที่มีผลตรวจทางเซลล์วิทยาของปากมดลูกชนิด ASC-US มีความสัมพันธ์อย่างชัดเจนกับผลตรวจทางพยาธิวิทยาเป็น HSIL และมะเร็งระยะลุกลาม โดยเฉพาะพบมะเร็งปากมดลูกระยะลุกลามมีความชุกสูงกว่าการศึกษาที่ผ่านมาสำหรับสตรีที่มีผลตรวจทางเซลล์วิทยาชนิด ASC-US ควรได้รับการตรวจด้วยกล้องส่องขยายทางช่องคลอด*