

## RESEARCH ARTICLE

# Accuracy of Cervical Visual Inspection with Acetic Acid Guide for 4-Quadrant Random Cervical Biopsies by General Practitioners in Women with Abnormal Pap Smears

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### Abstract

**Objective:** To study the performance of visual inspection with acetic acid plus 4-quadrant cervical biopsy (V4B) by general practitioners in detecting high grade cervical lesion, compared to highest histopathologic grade from the American Society for Colposcopy and Cervical Pathology American Society for Colposcopy and Cervical Pathology (ASCCP) 2013 work up guidelines. **Materials and methods:** Patients with abnormal cervical cytologic screening results suggesting low grade lesions underwent V4B by general practitioners followed by colposcopy on the same day bases on ASCCP 2013 guidelines. Those with Pap smears indicative of high grade lesions or cervical cancer were sent to V4B before confirmed diagnosis and and therapeutic excisional procedures. Predictive performance of V4B was evaluated against the reference diagnosis. **Results:** Compared with the reference diagnosis in 100 of patients, V4B by general practitioners had sensitivity, specificity, PPV, and NPV of 67.9%, 100%, 100%, and 88.9%, respectively. There were 11.1% false negatives with no false positives. No complications were observed following this technique. **Conclusion:** Overall, V4B by general practitioners demonstrates moderate accuracy when compared with definite diagnosis by colposcopy and/or LEEP. This novel strategy performed better in those with low grade lesions on cervical cytological screening.

**Keywords:** VIA- cervical biopsy- endocervical curettage- colposcopy- high grade lesion- low grade lesion

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### Introduction

Cervical cancer is one of the most common malignancy in Thai women. The incidence of 14.4% was reported by Thai National Cancer Institute (NCI) in 2011, with 7,000 new cases annually. Despite of highly effective diagnostic procedure and treatment, mortality rate from cervical cancer remain high.

It's been known for more than 60 years that Papanicolaou (PAP) smear plays an important role in screening for cervical cancer (Gaffikin et al., 2003). Colposcopy is recommended if an abnormal cervical cytological screening occurs. As colposcopy is not available in every health-care facility, simpler diagnostic procedures may be needed.

In 1982, Visual inspection with acetic acid (VIA) was introduced as an alternative technique by using 3-5% acetic acid for detecting abnormal cervical lesions is highly sensitivity as well as cost-effective, and it not need colposcopy to identify where the lesion is. (Jonathan, 2012; Kantathavorn et al., 2015).

*Accuracy to study by VIA with random cervical biopsy and endocervical*

Curettage (ECC) was equally effective for detection of high grade cervical lesion compared to colposcopy (Lee et al., 2012). Therefore VIA guide for 4quadrant biopsy might represent an alternative to use in a more diverse healthcare settings. This setting resident was trained about VIA before start the study that not represents the real situation of general practitioners who was not trained about VIA.

Now ASCCP 2013 guideline HPV DNA testing used compatibility with cytological cervical screening test that is call "Co-testing" In 2012, the prevalence of high risk Human Papillomavirus (HPV) infection is 24.15% and only 4.83% had positive PAP smear.(5) Similar study in Thailand, the prevalence of High-risk HPV infection in Thai women is 15.1 %,while the incidence of cervical cytologic abnormalities only 4.9 %.(6) Thus the patients who have positive HPV DNA more required colposcopy in the future.

In the future, prevalence of abnormal Co-test will be increase so as colposcopy required. This research was desired to find procedure that could detected high grade

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lesion in the low resource setting.

Because colposcopy need Experian hand, expensive and not available on every hospital, In the other hand we know that VIA could detect cervical lesion ,not need expensive instrument, not need Experian hand and available on every hospital near the patient.

The objective of this study was arrived to compare the accuracy of Visual inspection with acetic acid guide for 4 quadrants cervical biopsy (V4B) by general practitioners (who was not trained about VIA) to detected high grade cervical lesions, compare to highest histopathologic grade that come from the step of American Society for Colposcopy and Cervical Pathology American Society for Colposcopy and Cervical Pathology (ASCCP) 2013 work up guideline by gynecologic oncologist.

## Materials and Methods

The patients who visited the obstetric and gynecologic department of abnormal cervical cytological screening were asked to participate in the study, either those first or repeated abnormal cervical cytological screening. Exclusion criteria included the pregnant patients, untreated abnormal uterine bleeding patients, patients who had no cervix, cervical radiation, already diagnose cervical cancer, cervical gross lesion and patients who refused to participate. Those who previously Therapeutic cervical excisions were also excluded.

There were 100 patients between September to November 2014 were included. This study was approved by the ethical committee of Sappasithiprasong Hospital.

### *Abnormal cervical cytological screening*

Abnormal cervical cytological screening was abnormal finding from Pap smear and liquid base cytology. There were Atypical squamous cells of undetermined significant(ASC-US), Atypical squamous cells –cannot exclude HSIL(ASC-H), Low grade squamous intraepithelial lesion(LSIL), High grade squamous intraepithelial lesion(HSIL), Squamous cell carcinoma, Atypical endocervical cell(not otherwise specified(NOS)or specify in comments), Atypical grandular cell(NOS or specify in comments), Atypical endocervical cells, favor neoplastic Atypical grandular cells, favor neoplastic, Adenocarcinoma in situ(AIS), Adenocarcinoma.

Divided in two group as Low grade lesion: ASC-US, LSIL, Atypical endocervical cell (not otherwise specified(NOS)or specify in comments), Atypical grandular cell(NOS or specify in comments) and High grade lesion : ASC-H, HSIL, Squamous cell carcinoma, Atypical endocervical cells, favor neoplastic, Atypical grandular cells, favor neoplastic, Adenocarcinoma in situ(AIS), Adenocarcinoma.

### *V4B*

Visual inspection with acetic acid guide for 4 quadrants cervical biopsy means VIA with directed cervical biopsy (VDB) any quadrants if there were lesion and VIA with random cervical biopsy (VRB) in the rest of quadrants to become 4 pieces tissue

### *Colposcopy*

Colposcopiae is a diagnostic procedure to examine an illuminated, magnified view of the cervix. A colposcope, which provides an enlarged view of the areas, and apply 3-5% acetic acid to allowing the colposcopist to visually distinguish normal from abnormal appearing tissue and take directed biopsies for further pathological examination. If do not biopsy that means normal finding.

### *LEEP*

Loop Electrosurgical Excisional Procedure used a thin low voltage wire loop to remove abnormal tissue in a woman's cervix. It is used as part of the diagnosis and treatment. It may be performed after abnormal cells are found during a Pap test, colposcopy, or biopsy.

### *Reference diagnosis*

A definite diagnosis base on highest histopathologic grade from either diagnostic and therapeutic excisional procedure or endocervical curettage (ECC) or colposcopic directed biopsy (CDB) or V4B whereas the step of work up guide come from ASCCP 2013 guideline, and reviews pathology was done if result of biopsy superior than excisional procedure.

### *Methods*

The patients were classified into two group by using abnormal cervical cytologic screening; the patients with high-grade cervical cytologic screening and the patients with low-grade cervical cytologic screening lesion. High-grade lesion patients or cervical cancer were arranged for V4B by general practitioners and immediate followed by therapeutic excisional procedure by gynecologic oncologists. Low-grade lesion patients were underwent V4B by general practitioners and immediate followed by CDB plus ECC by gynecologic oncologists. Every patient was arranged to follow up for pathological results in 1-2 weeks after procedure. The patients with high-grade lesion were received diagnostic and therapeutic excisional procedure.

Complication of the procedure including bleeding and infection was evaluated at 30 days after the procedure was done when the patient came back for pathological result.

### *Statistical Analysis*

Data on demographic data; patients age, education, occupation and Obstetric and gynecologic data; term birth, preterm birth, abortion, number of child, Route of delivery, number of sexual partners, age of first sexual intercourse, history of sexual transmitted disease and number of screening pap smear were obtained using interviewer administered questionnaire.

Categorical and continuous data were presents as number (%) and mean(SD) respectively. Comparison across two groups (low grade lesion VS high grade lesion) was performed using chi square and T test respectively. P value of less than 0.05 was considered statistic significant.

SPSS version 19 was used to compare between the results of V4B by general practitioner and CDB or diagnostic excisional procedure as ASCCP guideline 2013

by gynecologic oncologists. Negative predictive value, positive predictive value Sensitivity and specificity were calculated.

### Sampe size

Based on the problem that the sensitivity of V4B by general practitioners in abnormal cervical cytologic screening women from the study by Pongson et al in 2011(4), P=? 95% confident of interval, this study want sample size 88 participants and for the error we increase the sample size 10%, overall 100

## Results

Of the 100 patients have average age was 43.52±7.942 yrs (35-52 of age). The most education is primary school and the most occupation is government officer. Comparison between two groups found no significant difference, as shown in table 1.

High grade lesion patients were significant increase in number of term birth (2.37±1.24 vs 1.64±0.89, p=0.002), number of alive child (2.36±1.22 vs 1.64±0.90, p=0.007) and number of patients who diagnosed PID (4.2% vs 17.9%, p=0.023). Age of first sexual intercourse appeared to be significantly lower in high-grade lesion patients (18.39±2.71 vs 20.41±3.43, p=0.003). Whereas number of preterm birth, number of abortion, route of delivery, number of sexual partners and other history of sexual transmitted disease were not significantly different, as shown in Table 2

Abnormal cervical cytologic screening test shown in table 3, most common abnormal cytology is ASC-US (40%) and LSIL (39%).

Table 1. Demographic Data in Woman with Abnormal Cervical Cytologic Screening

	Total <sup>a</sup>	Low grade lesion	High grade lesion	p-value <sup>b</sup>
Demographic data	100	73	27	
Age (years) (mean±SD)	43.5±7.9	43.2±7.4	44.5±9.4	0.499
Education, N(%)				0.159
- Primary	43(43.0%)	30(41.1%)	13(48.1%)	
- Secondary	17(17.0%)	10(13.7%)	7(25.9%)	
- diploma	7(7.0%)	4(5.5%)	3(11.1%)	
- Bachelor degree	23(23.0%)	20(27.4%)	3(11.1%)	
- Master degree	10(10.0%)	9(12.3%)	1(3.7%)	
Occupation, N(%)				0.226
- Housekeeper	7(7.0%)	3(4.1%)	4(14.8%)	
- Employee	11(11.0%)	6(8.2%)	5(18.5%)	
- Farmer	28(28.0%)	20(27.4%)	8(29.6%)	
- Government officer	34(34.0%)	29(39.7%)	5(18.5%)	
- Merchant	7(7.0%)	5(6.8%)	2(7.4%)	
- Business	12(12.0%)	9(12.3%)	3(11.1%)	
- Others	1(1.0%)	1(1.4%)	0(0.0%)	

<sup>a</sup>, Data are presented as mean ±SD and number(%) for categorical and continuous variable; <sup>b</sup>, comparison across two groups perform using chi square and T test for categorical and continuous variable respectively.

Table 2. Obstetric and Gynecologic Factors in Woman with Abnormal Cervical Cytologic Screening

Obstetric and gynecologic factors	Total <sup>a</sup>	Low grade lesion	High Grade lesion	p-value <sup>b</sup>
Term birth	1.84±1.04	1.64±0.89	2.37±1.24	0.002
Preterm birth	0.01±0.10	0.01±0.12	0	0.536
Abortion	0.33±0.62	0.36±0.66	0.25±0.52	0.377
child	1.84±1.04	1.64±0.90	2.36±1.22	0.007
Route of delivery N(%)				0.489
none	11(11.0%)	9(12.5%)	2(7.1%)	
normal delivery	82(82.0%)	57(79.2%)	25(89.3%)	
cesarean delivery	7(7.0%)	6(8.3%)	1(3.8%)	
Sexual partner N(%)	1.67±0.82	1.63±0.81	1.79±0.83	0.387
Age of first sexual intercourse (yrs.)	19.84±3.35	20.41±3.43	18.39±2.71	0.003
History of sexual transmitted disease N(%)				
1.fever with pelvic pain	7(7.0%)	3(4.2%)	4(13.3%)	0.075
2.pelvic pain with abnormal vaginal discharge	25(25.0%)	19(26.4%)	6(21.4%)	0.607
3.fever during menstrual	9(9.0%)	7(9.7%)	2(7.1%)	0.686
4.history of PID	8(8.0%)	3(4.2%)	5(17.9%)	0.023
Number of screening pap smear	5.30±3.99	5.44±4.05	4.93±3.88	0.558

<sup>a</sup>, Data are presented as mean ±SD and number(%) for categorical and continuous variable; <sup>b</sup>, comparison across two groups perform using chi square and T test for categorical and continuous variable respectively.

Pathology of reference diagnosis shown in Table 4, most frequent is normal (38%), followed by LSIL (31%) HSIL (25%) cervical carcinoma(3%) and cervicitis(3%)

Showing in Table 5, V4B plus ECC by general practitioner could detected 19 out of 28 high-grade lesion patients. It came to a sensitivity of 67.9%, specificity of 100%, positive predictive value of 100% and negative predictive value of 88.9%, with false-negative of 11.1% and no false-positive.

Showing in Table 6, In subgroup of low grade cervical cytologic screening patients ,V4B by general practitioner could detected 3 out of 13 high-grade lesion patients. It came to a sensitivity of 76.9%, specificity of 100%, positive predictive value of 100% and negative predictive value of 95.7%, with false-negative of 4.4% and no false-positive.

No complication following procedures performed by

Table 3. Result of Abnormal Cervical Cytology.

Abnormal cytology	N (%)
ASC-US	40 (40%)
ASC-H	5 (5%)
AGC	3 (3%)
LSIL	39 (39%)
HSIL	13 (13%)
Total	100 (100%)

Table 4. Pathology of Reference Diagnosis

Reference diagnosis	N (%)
Normal	38 (38%)
Cervicitis	3 (3%)
LSIL	31 (31%)
HSIL	25 (25%)
Cervical carcinoma	3 (3%)
Total	100 (100%)

Table 5. Compare between V4B Plus ECC by General Practitioner and Reference Diagnosis

		reference diagnosis		Total
		Low grade lesion	High grade lesion	Cases (%)
V4B by GP	Low grade Lesion	72	9	81 (100%)
	High grade lesion	0	19	19 (100%)
Total		72	28	100

general practitioner was observed after 30 days of study

## Discussion

The obstetrics and gynecologic data of the participants shown that multiparity, younger age of first sexual intercourse and history of pelvic inflammatory disease more associate with high grade lesion as known as risk of cervical cancer.

V4B in which performed by general practitioners showed sensitivity of 67.9% and negative predictive value of 88.9%, but specificity and positive predictive value of 100%. Focusing in low-grade cervical cytological screening test patients showed negative predictive value of 95.7% and sensitivity of 76.9%, and specificity and positive predictive value remained 100%. The accuracy of V4B by general practitioners to detected high grade lesion was higher in setting of low grade cervical cytologic screening patients.

Because the study population was very close to Puntachai Pongson study (Lee et al., 2012) but sensitivity of V4B by general practitioners to detected high grade lesion was lower 67.9% vs that cause by variation of operators, so we believe that training for VIA can improve sensitivity of V4B

The diagnostic accuracy of this technique improved in those with low grade cervical cytologic screening (sensitivity of 76% and false negative of 4.3%).

Anyway, the study has show that the procedure of V4B by general practitioners who had not train for VIA, in which possibly done in setting of primary and secondary care units, has less effective accuracy and outcome when comparing with diagnosis by ASCCP guideline 2013.

### Limitation

If pap smear and CDB and V4B and ECC show low grade lesion all step, due to ethical issue we not done LEEP. After LEEP, there was more risk of cervical

Table 6. In Subgroup of Low Grade Cervical Cytologic Screening Patients to be Compare between V4B Plus ECC by General Practitioner and Reference Diagnosis

		reference diagnosis		
		Low grade lesion	High grade lesion	
Tota Cases(%)				
V4B by general practitioners	Low grade lesion	66	3	69 (100%)
	High grade lesion	0	10	10 (100%)
Total		66	13	79 (100%)

infection, bleeding, cervical stenosis that can cause hematometra or infertility, cervical incompetent and higher risk of preterm birth. Therefore if cytological or histopathological results show low grade lesion, we not done LEEP by the reason of ethic.

By theoretical LEEP should be the best answer but in these situation ASCCP 2013 guideline not recommended.

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