Accuracy of Visual Inspection with Acetic Acid (VIA) for Cervical Cancer Screening: A Systematic Review

Paskorn Sritipsukho MD*,
Yuthadej Thaweekul MD**

** Postgraduate Studies Program, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*
*** Gynecologic Oncology Unit, Department of Obstetrics & Gynecology, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*

Objective: *To systematically review the performance characteristics of VIA in cervical cancer screening*
Material and Method: *The Ovid (Medline) electronic database from January, 1996 to Febuary, 2007 was searched, using the following key search words of 1. MESH term "Uterine Cervical Neoplasms" with subheading "diagnosis", 2. Keywords "sensitivity" or "specificity" and 3. Keyword "visual inspection with acetic acid" Total of 11 studies were relevant and eligible for the review. Histology or combination of Colposcopy and histology were used as gold standard. Abnormal colposcopy must have histological confirmation by material obtained by colposcopic directed biopsy, loop excision, or endocervical curettage. Histologic threshold for positive outcome from screening tests was CIN2 (Cervical Intraepithelial Neoplasia 2) or higher (or equivalent categories by other classifications). A meta-analysis, yielding a quantitative summary measure was implemented with the random effect model.*
Results: *Using random effect method, the pooled estimates of sensitivity, specificity, positive predictive value and negative predictive value of VIA-VIAM were 71.8%, 79.4%, 16.7% and 99.0% respectively. When comparing with conventional cytology, VIA have favorably characteristics especially sensitivity and negative predictive value.*
Conclusion: *VIA may be incorporated in cervical cancer screening programme in low resource setting country because of high negative predictive value of the test is sufficiently high to assure screening for negative and CIN I women .*

Keywords : *Systematic review, Meta-analysis, Cervical cancer screening, Visual inspection after acetic acid, VIA, VIAM*

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Precise estimates of screening test accuracy including sensitivity and specificity are important to determine policy decision of screening program. Recommendation for optimal frequency screening, management of abnormalities, and use of newer technology depend on the screening test property[1]. Cervical cancer is highly preventable through cytology screening program with Papanicolaou (Pap) smears that facilitate the detection and treatment of precancerous lesions**.** Alternative methods, such as DNA testing for human papillomavirus (HPV) and simple visual screening with acetic acid (VIA) could be used as an adjunct to cytology to identify women at risk of cervical cancer. In developing countries often lack of the necessary resources to use the Pap smears as a screening tool for cervical abnormality. Nowadays cervical cancer prevention programmed that bases on cytology has not been successful for many different reasons[2]. Screening programmed based on Pap smears require technical capacities and system for transportation, communication, follow-up and training the cytoscreener that are beyond the capacity of health care infrastructure in most developing countries[3-5]. So that high loss of follow-up between screening, treatment and low screening coverage. HPV DNA testing is a newer screening technique but remain unaffordable in the low resource setting country. VIA is the method involves swabbing the cervix with a 3-5% acetic acid solution prior to naked eye visual examination. Visual inspection with acetic acid using low-level magnification (VIAM) is Visual inspection with acetic acid (VIA) using low level (2-4x) magnification. These methods showed difference in

Correspondence to:
Thaweekul Y, Gynecologic oncology unit, Department of Obstetrics & Gynecology, Faculty of Medicine, Thammasat University, Klongloung, Pathumthani 12120, Thailand.
Phone: 0-2926-9343, Fax: 0-2926-9485
E-mail: yuthadej06@yahoo.com

precancerous cell structure and opacity make abnormal cell temporarily appear white when exposed to acetic acid solution. Because of this method have met the basic criteria of good screening test (*e.g.* safe, practical, affordable, available) and has potential advantage over traditional screening techniques in poorly resourced location, there is immediate feedback of test results to the patients and importantly, treatment can be provided immediately after the test[6-8].

Objective

The aim of this study was to systematically review the performance characteristics of VIA-VIAM in cervical cancer screening.

Material and Method

Study sources

The Ovid (Medline) electronic database from January, 1996 to February, 2007 was searched, using the following key search words.

1. MESH term "Uterine Cervical Neoplasm" with subheading "diagnosis"

2. Keywords "sensitivity" or "specificity"

3. Keyword "visual inspection with acetic acid"

The search strategy was: #1 and #2 and #3, limited to English language. Only journal article type was included. Twenty articles were retrieved. The title and abstract of each citation were screened first, and full report was screened second if necessary to select the relevant articles according to selection criteria. Fulltexts of those selected studies were retrieved, reviewed and extracted for relevant data by two independent reviewers.

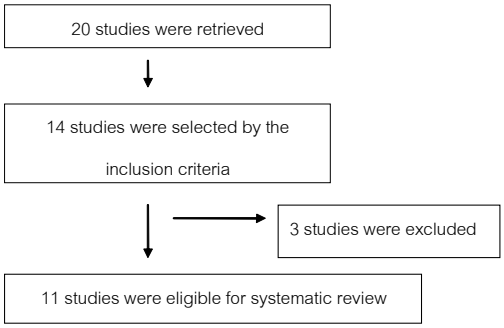
Inclusion criteria

The study must compare the VIA to the reference standard on the same patients or slides as histological confirmation and or Colposcopy. Of 20 studies, there were 11 studies fulfilled this criteria. Studies were excluded if the following criteria were met.

1. Some participants in the study were not evaluated for reference standard (histologic confirmation and or colposcpy)

2. No available data for all of true positive, false positive, true negative and false negative, according to criterion validity of the test (four cells of a 2 X 2 tables).

Nine studies were excluded[9-17]. There were eleven studies relevant for reviewing the operating characteristics of VIA-VIAM[18-28].



Threshold of screening tests

Abnormal VIA and VIAM were defined as 1) opaque, dull, well define, confluent acetowhite lesion touching the squamocolumnar junction or close to the external os. 2) Large opaque, dense, well defined, acetowhite lesion surrounding the cervical os. 3) Wart and leukoplakia close to the squamocolumnar junction. 4) Dense, opaque acetowhitening of clinically visible ulceroproliferative growth of the cervix.

Outcome and outcome threshold

Histology or combination of Colposcopy and histology were used as gold standard in this review. Normal colposcopy was defined as normal. Abnormal Colposcopy must have histological confirmation by material obtained by colposcopic directed biopsy, loop excision, or endocervical curettage. Histologic threshold for positive outcome from screening tests was CIN2 or higher (or equivalent categories by other classifications). This study used CIN 2 or higher in our study because higher rate to progression to cervical cancer. The lesion less than CIN2 usually spontaneous regression about 80%.

Covariate information

Characteristics of study population (place, inclusion and exclusion criteria, age distribution), screening setting (primary screening or screening among women with previous cytological abnormality), bias assessment of screening and gold standard (blinding of testing or not) were included. The following study characteristics were systematically summarized in Table 1.

Definition of accuracy measures and Statistical analysis

Descriptive statistics of each study was presented. True positive (TP), true negative (TN), false positive (FP), and false negative (FN) of the screening test against the gold standard from each study were

Table 1. Characteristics of the studies (11 studies)

Author-Year	Country	Population		Age (years)	Blinding
		Characteristics	Exclusion criteria		
University of Zimbabwe, 1999	Zimbabwe	Primary care setting	pregnant, previous history of cervical cancer or hysterectomy	25-55	yes
Singh, 2001	India	Women with gynecological symptoms	not mentioned	mean = 37.1	not mentioned
Basu, 2003 Eastern	India	Primary care setting	poor general health, pregnant women, prior hysterectomy or treatment for cervical precancers or cancer	30-64	yes
Winkler, 2003	USA	Women with prior abnormal pap smear	not mentioned	18–50	yes
Bhatla, 2004	India	Women with gynecological symptoms	prior hysterectomy, unmarried, pregnancy, and obvious growth on cervix	30-74	yes
Sankaranarayanan, 2004	India	Primary care setting	pregnant, history of cervical cancer or hysterectomy	25-65	yes
Sankaranarayanan, 2004	India and Africa	Primary care setting	pregnant and had previous history of cervical cancer or hysterectomy	25-65	yes
De Vuyst, 2005	Kenya	Primary care setting	pregnancy	25-55	yes
Goel, 2005	India	Screening setting	nulliparous, pregnant, active vaginal bleeding, frank growth on the cervix	30-34	yes
Shastri, 2005	India	Primary care setting	past history of cervical neoplasia	30–65	yes
Sangwa-Lugoma, 2006	Congo	Primary care setting	not pregnant, no intact uterus	30 up	yes

extracted to construct 2X2 tables for calculation of sensitivity and specificity, positive predictive value and negative predictive value. A meta-analysis, yielding a quantitative summary measure of each screening test, was implemented. Subgroup analysis was reported according to important covariate. Random-effects models were used for pooling all parameters in this review because of statistically significant inter study heterogeneity (when $p < 0.1$ for Cochran's Q test) in most cases[29]. Meta-analyses were performed by using the Stata statistical package version 9.0 with the command "pmeta"[30].

Results

There were 11 studies eligible for systematic review of the screening test of VIA or VIAM testing. True positive, true negative cases, false positive, and false negatives cases including sensitivity, specificity, positive predictive value, and negative predictive value with their standard errors were shown in Table 2. Using random effect method, the pooled estimates of sensitivity, specificity, positive predictive value, negative predictive value were 71.8% (95% CI: 66.4%-77.1%), 79.4% (95% CI: 77.2-81.7%) 16.7% (95% CI: 13.5%-19.8%) and 99.0% (95% CI: 98.8%-99.2%) respectively. Subgroup analysis between VIA and VIAM were performed and presented in Table 3.

Discussion

In more-developed countries, cervical cytology have formed as cervical cancer screening programmed and marked decline in the incidence and mortality from cervical cancer[7,8,31]. But yet in many less-developed countries to make an effectiveness of cervical cytology programmed[3,32,33]. Visual inspection with acetic acid (VIA) is the alternative method for cervical cancer screening that widely investigated. Visual inspection with acetic acid using low level (2-4x) magnification (VIAM) has been proposed to further improve the test characteristic of VIA. Many study showed that VIAM did not improve the test characteristic of naked eye visualization of VIA or marginally in sensitivity[20,24].

In this study provide the accuracy including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of VIA-VIAM for cervical cancer screening. An attempt was made to synthesize available information and using meta-analysis techniques, to demonstrate that there was sufficient clinical evidence to support the use of VIA-VIAM as alternative cervical cancer screening test, especially in low resource setting. In Thailand used VIA in the setting of rural area that low cytoscreener , appeared to have an effect in revealing an increased cervical cancer incidence rate by achieving higher coverage, resulting in increased case finding[34].

Application of VIA-VIAM

VIA and VIAM have been used for cervical cancer screening in many less developed countries. Because of this method have met the basic criteria of good screening, can be immediate feedback of the test result and importantly, treatment can be provided immediately in the same visit. From this review, many studies describe the performance of VIA-VIAM provided by a variety of health professionals ranging from nonmedical to highly trained medical care professionals practicing in both primary care and referral setting.

The appearance of high grade squamous intraepithelial lesion (HSIL) was used to dictate clinical treatment decision. The reference investigation (gold standard) for evaluating the accuracy of screening test in detecting true positive lesion in all 11 studies was histopathology from biopsy under colposcopy. We found that the pool estimate the sensitivity and specificity of VIA-VIAM are 71.8% (95% CI: 66.4%-77.1%) and 79.4% (95% CI: 77.2-81.7%) respectively. In comparison to the study of Nanda K et al[1] show that the mean sensitivity and specificity of Pap smear were 47% (range 30-87%) and 95% (range 86-100%) respectively. However, the pool estimate in PPV and NPV of VIA-VIAM are 16.7% (95% CI: 13.5%-19.8%), and 99.0% (95% CI: 98.8%-99.2%) respectively. The high NPV of the test is sufficiently high to assure screening negative and CIN I women.

In the major concern about the low specificity (less than 80%) and high false positive, this is inevitably leads to high rate of referal for colposcopy and high rate of treatment. Because of acetowhite lesion due to immature squamous metaplasia and inflammatory lesions seem to be responsible for high false positive rate.Its may be improved by intensive training and develope uniform definition of VIA-VIAM test.

VIA-VIAM are less expensive test and do not require a complicated labolatory infrastructure for testing and reporting, immediate available of test results and treatment to be carried out in the same visit (single visit approach). VIA-VIAM may be incorporated in cervical cancer screening programme in low resource setting since the higher sensitivity than Pap smear to

Table 2. Operating characteristics of VIA-VIAM (11 studies)

Study	Author-Year	Gold Standard	Screening test	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)
1	University of Zimbabwe, 1999	Colposcopy, with biopsy as indicated	VIA	HSIL+	158	1233	691	48	2130	76.7	64.1	18.6	96.3	9.7
2	Singh, 2001	Colposcopy, with biopsy as indicated	VIA	Moderate dysplasia+	118	218	49	17	402	87.4	81.6	70.7	92.8	33.6
3	Basu, 2003	Colposcopy, with biopsy as indicated	VIA	CIN 2+	68	4697	1024	54	5843	55.7	82.1	6.2	98.9	2.1
4	Basu, 2003	Colposcopy, with biopsy as indicated	VIAM	CIN 2+	74	4761	959	48	5842	60.7	83.2	7.2	99.0	2.1
5	Winkler, 2003	Colposcopy, with biopsy as indicated	VIAM	CIN 2+	24	60	27	16	127	60.0	69.0	47.1	78.9	31.5
6	Bhatla, 2004	Colposcopy, with biopsy as indicated	VIA	HSIL+	7	58	34	1	100	87.5	63.0	17.1	98.3	8.0
7	Sankaranarayanan, 2004	Colposcopy, with biopsy as indicated	VIA	HSIL+	194	14416	2187	103	16900	65.3	86.8	8.1	99.3	1.8
8	Sankaranarayanan, 2004	Colposcopy, with biopsy as indicated	VIAM	HSIL+	202	14406	2197	95	16900	68.0	86.8	8.4	99.3	1.8
9	Sankaranarayanan, 2004	Colposcopy, with biopsy as indicated	VIA	HSIL+	1056	45857	7792	276	54981	79.3	85.5	11.9	99.4	2.4
10	De Vuyst, 2005	Colposcopy, with biopsy as indicated	VIA	CIN II+	44	460	133	16	653	73.3	77.6	24.9	96.6	9.2
11	Goel, 2005	Biopsy	VIA	moderate dysplasia+	12	349	38	1	400	92.3	90.2	24.0	99.7	3.3
12	Shastri, 2005	Colposcopy, with biopsy as indicated	VIA	HSIL+	54	3470	454	31	4009	63.5	88.4	10.6	99.1	2.1
13	Shastri, 2005	Colposcopy, with biopsy as indicated	VIAM	HSIL+	57	3387	463	28	3935	67.1	88.0	11.0	99.2	2.2
14	Sangwa-Lugoma, 2006	Colposcopy, with biopsy as indicated	VIA	CIN 2+	22	221	306	7	556	75.9	41.9	6.7	96.9	5.2

VIA= Visual inspection with Acetic acid, VIAM= Visual inspection with Acetic acid and Magnifier
TP= true positve, TN= true negative, FP= false positive, FN= false negative
PPV=positive predictive value, NPV=negative predictive value

Table 3. Subgroup analysis, pooled effect of operating characteristics of VIA-VIAM method

Subgroup	Number of study	Sensitivity (%)	95% CI	Specificity (%)	95% CI	PPV (%)	95% CI	NPV (%)	95% CI
VIA	10	74.8	(68.5-81.0	77.2	(73.9-80.6)	18.5	(14.1-22.9)	98.8	(98.5-99.2)
VIAM	4	65.8	(61.8-69.7)	85.0	(82.4-87.6)	11.3	(7.4-15.2)	99.1	(98.7-99.6)

Random effect model were used for the estimations.

detect high grade cervical precancerous lesion and high NPV.

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ความแม่นยำของวิธีการตรวจปากมดลูกหลังจากชโลมด้วยน้ำส้มสายชูในการตรวจคัดกรองมะเร็งปากมดลูก: การทบทวนวรรณกรรมอย่างเป็นระบบ

ภาสกร ศรีทิพย์สุโข, ยุทธเดช ทวีกุล

วัตถุประสงค์*: ทบทวนวรรณกรรมอย่างเป็นระบบเกี่ยวกับคุณลักษณะวิธีการตรวจปากมดลูกหลังจากชโลมด้วยน้ำส้มสายชูในการตรวจคัดกรองมะเร็งปากมดลูก*

วัสดุและวิธีการ*: สืบค้นข้อมูลจากแหล่งข้อมูลทางอิเล็กทรอนิคส์ (Ovid Medline) ที่ตีพิมพ์ตั้งแต่เดือนมกราคม พ.ศ. 2539-เดือนกุมภาพันธ์ พ.ศ. 2550 โดยใช้คำสำคัญในการสืบค้นคือ เนื้องอกปากมดลูก (uterine cervical neoplasm) ความไว (sensitivity) ความจำเพาะ (specificity) และ วิธีการตรวจปากมดลูกหลังจากชโลมด้วยน้ำส้มสายชู (Visual Inspection with Acetic Acid) โดยได้ทั้งหมด 11 การศึกษา ซึ่งเกณฑ์การพิจารณาในการทบทวนงานวิจัยนี้มุ่งเน้นประเภทของงานวิจัยที่ใช้ผลตรวจทางพยาธิจากการตัดชิ้นเนื้อเป็นมาตรฐาน ในการศึกษาเปรียบเทียบกับสิ่งตรวจพบจากการตรวจปากมดลูกจากชโลมด้วยน้ำส้มสายชูโดยใช้คอลโปสโคปหรือไม่ก็ได้ ถ้าในรายที่ตรวจผ่านคอลโปสโคป ก็จำเป็นต้องมีผลตรวจชิ้นเนื้อยืนยันเช่นกัน โดยที่สิ่งตรวจพบขั้นต่ำที่นำมาศึกษาคือ ความผิดปกติของเซลล์ปากมดลูก ตั้งแต่ระดับที่ 2 ขึ้นไป (Cervical Intra-epithelial Neoplasia II)*

ผลการศึกษา*: พบว่าค่าความไว ความจำเพาะ ของการตรวจปากมดลูกหลังจากชโลมด้วยน้ำส้มสายชูในการตรวจหาความผิดปกติของเซลล์ปากมดลูกตั้งแต่ระดับที่ 2 ขึ้นไป เท่ากับ 71.8% และ 79.4% ตามลำดับส่วนความสามารถในการทำนายผลบวก และทำนายผลลบเท่ากับ 16.7% และ 99.0% ตามลำดับซึ่งเมื่อเปรียบเทียบกับการตรวจทางเซลล์วิทยาที่ใช้อยู่พบว่าการตรวจปากมดลูกหลังจากชโลมด้วยน้ำส้มสายชู มีคุณลักษณะที่น่าพอใจโดยเฉพาะความไว และความสามารถในการทำนายผลลบของการตรวจชนิดนี้*

สรุป*: การตรวจปากมดลูกหลังจากชโลมด้วยน้ำส้มสายชูอาจจะนำมาใช้ในการตรวจคัดกรองมะเร็งปากมดลูกได้ในสถานที่ที่มีทรัพยากรจำกัดแทนการตรวจทางเซลล์วิทยาโดยเฉพาะความสามารถในการทำนายผลลบที่สูงมาก สามารถนำมาตรวจคัดกรองสตรีที่ปกติหรือมีรอยโรคที่เซลล์ปากมดลูกขั้นต่ำ ออกไปได้*