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## International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo



## CLINICAL ARTICLE

## Adequacy of visual inspection with acetic acid in women of advancing age

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## ARTICLE INFO

## Article history:

Received 4 August 2010

Received in revised form 21 October 2010

Accepted 17 December 2010

## Keywords:

Cervical cancer

Examination adequacy

Menopause

Visual inspection with acetic acid

## ABSTRACT

**Objective:** The present study assessed the adequacy and predictive performance of visual inspection with acetic acid (VIA) in women over the age of 50 years and compared the specificity and sensitivity of VIA with that of the conventional cytology. **Methods:** In total, 588 Salvadoran women ages 50–79 underwent VIA, Pap smear, and cervical biopsy. VIA was considered adequate if the squamocolumnar junction was completely visible. A positive biopsy was defined as cervical intraepithelial neoplasia (CIN) 2 or worse. **Results:** Age was negatively correlated with VIA adequacy ( $P=0.04$ ). Nevertheless, the majority of women—even in the older age groups—had adequate examinations. The adequacy of VIA was positively correlated with gravida ( $P=0.01$ ) and was higher in women who had been treated by cryotherapy ( $P=0.02$ ). The rate of positive biopsies was unexpectedly low ( $n=6$  [1%]) making it difficult to assess the predictive performance of VIA. In this small sample, the sensitivities of VIA (17%) and Pap (33%) were low; the high number of false negatives could not be fully explained by inadequacy of the examinations. **Conclusions:** Adequacy of VIA declined with age. However, the squamocolumnar junction was visible to the naked eye in the majority of women, indicating that they are good candidates for VIA.

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## 1. Introduction

Approximately 500 000 women are diagnosed with cervical cancer each year, with 80% of cases occurring in low-income countries [1]. In El Salvador, as in most of Latin America, cervical cancer is the most common female malignancy, with an age-adjusted incidence of 33 per 100 000—a figure that is more than 3 times higher than that in the USA [2]. This disparity is attributed to the fact that cytology screening programs require multiple follow-up visits and good infrastructure, and to the lack of funding and the infrastructure required for timely and appropriate treatment of precancerous lesions [3].

Direct visual inspection of the cervix with acetic acid (VIA) is an economical and easily implemented method for cervical cancer screening. This method has been shown to decrease the mortality from cervical cancer on a population level and can be readily adapted to a same-day “see and treat” protocol that minimizes loss to follow-up [4]. Most screening efforts have focused on women of reproductive age, because cervical cancer precursors most often occur in younger

women. However, precursors can take as long as 30 years to progress to invasive cancer, which often appears after the age of 50 years [5,6].

The ability to see the squamocolumnar junction (SCJ) is a requirement for VIA. Hence, it is thought that it is not possible to perform VIA in women aged 50 years and older, given that the SCJ recedes into the endocervical canal with age [7]. Although many VIA studies [8–13] have included women of advancing age, these studies were heavily weighted toward younger, premenopausal women, and none has specifically addressed a postmenopausal population. One study included subgroup analyses by age and showed that the sensitivity and specificity values in older women were similar to those in younger women [10]. Another showed that the specificity of VIA is actually higher in postmenopausal women [14].

The primary objective of the present study was to evaluate the visibility of the SCJ when VIA is performed (examination adequacy) in women over the age of 50 years. A secondary objective was to compare the detection of lesions by VIA with that by the Pap smear in this population, using biopsy readings as the gold standard.

## 2. Materials and methods

The study was reviewed and approved by the Institutional Review Board of New York University School of Medicine (New York, NY, USA) and El Comité Nacional de Ética del Consejo Superior de Salud

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Pública (San Salvador, El Salvador), the National Review Board of El Salvador. The project also received assistance from the Ministry of Health of El Salvador. The study was conducted by Basic Health International, a nongovernmental organization that focuses on cervical cancer prevention.

The study participants were recruited from 4 communities in the paracentral region of El Salvador from January 1, 2007, to December 31, 2009. Women over the age of 50 years were invited by health promoters from the Ministry of Health to attend an upcoming screening at their regional public hospital. On the day of the screening, trained nurses explained the purpose and procedures of the study to prospective participants and obtained informed consent before any procedures were done. Those who did not or could not give informed consent received routine screening. Postexamination exclusion criteria included history of hysterectomy, history of uterine or ovarian cancer, and inability to visualize the cervix.

The participants verbally completed a questionnaire on demographics and medical, reproductive, and sexual history. Gynecologic examinations were performed by obstetrics and gynecology specialists, nurse practitioners with colposcopy training, and 4th-year obstetrics and gynecology residents from New York University. All examiners received training before performing the study procedures. A Pap smear was taken, followed by VIA with 5% acetic acid and a subsequent colposcopy. Finally, all participants had biopsies taken. If the VIA examination was negative, biopsies were taken at 10 and 2 o'clock [15]. If both VIA and colposcopy were positive, biopsies were taken only in the abnormal area. Endocervical curettage was performed on all participants. Pap smears and biopsy specimens were processed and reviewed locally, and were later re-read by an expert pathologist in the USA for quality control. For the analysis, the US biopsy reading was considered as reflecting the true disease status, and was compared with the VIA result in the field and the Salvadoran Pap result. A positive biopsy was defined by the finding of cervical intraepithelial neoplasia (CIN) 2 or worse. A positive Pap result was defined by the finding of atypical squamous cells of undetermined significance (ASCUS) or worse and VIA was deemed positive based on the presence of acetowhite lesions. An examination was considered adequate if the entire SCJ was visible, as seen by the naked eye (VIA) or with magnification (colposcopy).

Exact 95% confidence intervals (CI) are provided for all estimates of proportions, including sensitivity and specificity values. The sensitivity and specificity values of VIA and Pap for the detection of CIN 2 or worse were estimated relative to the gold-standard biopsy result from the USA. The McNemar test was used to compare the sensitivities and specificities of VIA and the Pap smear; only women who had a VIA result, a Salvadoran Pap result, and a US biopsy result were included in these comparisons. The 2-sample *t* test and the Fisher exact test were used to evaluate the adequacy of VIA by age and other demographic variables. Multivariate logistic regression analysis was used to assess the independent effects of various factors on VIA adequacy. Statistical analyses were completed using Stata version 10 (StataCorp, College Station, TX, USA).  $P < 0.05$  was considered statistically significant.

### 3. Results

Initially, 621 patients were enrolled in the study. Of these, 33 patients were excluded from the final analysis: 4 because of an inability to see the cervix secondary to severe atrophy; 6 because of a history of hysterectomy found on examination after enrollment; and 23 because of lost or missing pathology specimens. The final analysis included 588 women (Fig. 1).

The percentage of VIA examinations judged to be adequate is presented in Table 1. Age was negatively correlated with the adequacy of VIA ( $P = 0.040$ ). The examination was adequate in 150 (69.4%; 95% CI, 62.8–75.5) women aged 50–54 years; in 110 (71.4%; 95% CI, 63.6–

78.4) women aged 55–59 years; in 71 (61.7%; 95% CI, 52.2–70.7) women aged 60–64 years; in 19 (52.8%; 95% CI, 35.5–69.6) women aged 65–69 years; in 24 (53.3%; 95% CI, 37.9–68.3) women aged 70–74 years; and in 13 (81.3%; 95% CI, 54.4–96.0) women aged 75–79 years. Overall, the majority ( $n = 387$  [66.5%; 95% CI, 62.5–70.3]) had an adequate examination.

VIA adequacy was positively associated with the number of pregnancies (Table 1), increasing from 55.7% in gravida 1–4 women to 71.4% in women described as gravida 9 or higher ( $P = 0.01$ ). It was also significantly higher for women who reported prior treatment with cryotherapy ( $P = 0.02$ ). A history of a Pap smear in the past 2 years and current symptoms of infection had no effect on the adequacy of VIA. Multivariate logistic regression analysis indicated that age (odds ratio 0.93 for 1-year intervals,  $P = 0.004$ ) and number of pregnancies (odds ratio 1.03 for each additional pregnancy,  $P = 0.02$ ) are both independent predictors of VIA adequacy. Table 2 shows a comparison between the adequacy of VIA and that of colposcopy. The kappa value for agreement between VIA and colposcopy adequacy was 0.942 (95% CI, 0.912–0.970).

Twelve (2.1%) women had at least CIN 1 and 6 (1.0%) women had CIN 2 or worse: 3 (0.5%) women received a diagnosis of CIN 2; 2 (0.3%) women had CIN 3; and 1 (0.2%) woman had invasive cancer. The sensitivities of both Pap and VIA for detecting CIN 2 or worse were very poor. The Pap smear was positive in 2 of 6 (33.3%; 95% exact CI, 4.3–77.7) women with positive biopsies, and VIA was positive in 1 of 6 (16.7%; 95% exact CI, 0.4–64.1). The specificity was 551/579 (95.2%; 95% CI, 93.1–96.8) for the Pap smear and 533/566 (94.2%; 95% CI, 91.9–96.0) for VIA. The sensitivity and specificity values for the detection of CIN 2 or worse were not significantly different for the Pap smear and VIA ( $P = 0.999$  and  $P = 0.597$ , respectively).

### 4. Discussion

To our knowledge, this is the first study to examine age-related trends in the visibility of the SCJ during a VIA examination. In the present population of rural Salvadoran women aged 50–79 years, age was negatively correlated with the adequacy of the examination. However, in the majority of women—including those in the older age categories—the SCJ was visible to the naked eye, indicating that they are good candidates for VIA. From a public health perspective, it is easier and more cost-effective to conduct a VIA examination than to perform cytology screening [16].

The prevalence (1%) of CIN 2 or worse in the present sample of women aged 50–79 years was unexpectedly low, perhaps because this population had been screened more often than is typical in rural areas. Approximately 46% of the women reported having had a Pap smear in the past 2 years—a proportion that is high for such a rural area; 95% reported that they had had a Pap smear at some point in their lifetime. The mean number of reported lifetime partners was a low 1.9.

With only 6 women having had CIN 2 or worse, it was impossible to reliably evaluate the predictive performance of VIA, let alone stratify the analysis by adequacy to see if incomplete visualization of the SCJ might explain the false negatives. However, the preliminary impression provided by this small sample is not encouraging. Among the 6 women with CIN 2 or worse, VIA identified only the woman with invasive cancer (sensitivity 16.7%). The VIA examination was judged to be adequate in 3 of the 5 women (60.0%) with CIN 2 or CIN 3, so incomplete visibility of the SCJ does not fully explain the poor performance. Interestingly, the Pap smear was also a weak predictor of CIN 2 or worse and correctly identified only 2 of 6 cases, resulting in a sensitivity of 33.3%.

We considered the possibility that the poor performances of Pap smear and VIA were caused by a problem with data entry or the biopsy data. All data sheets were reviewed and all biopsy specimens were re-read in the USA, but no errors were found.

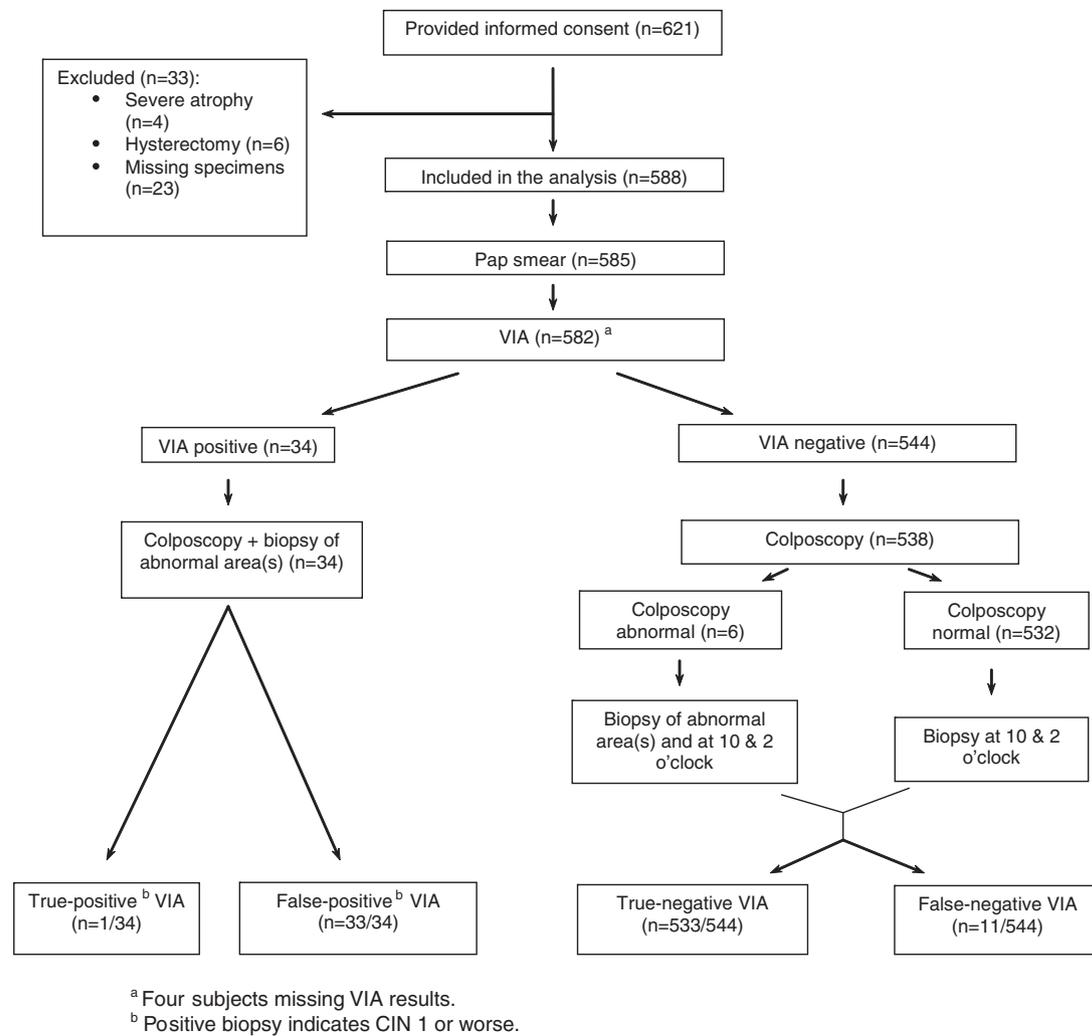


Fig. 1. Patient flow chart. Abbreviation: VIA, visual inspection with acetic acid.

Table 1  
VIA adequacy by demographic and other characteristics.<sup>a,b</sup>

Characteristic	Adequate VIA	Inadequate VIA	Total
Age, y			
50–54	150 (69.4)	66 (30.6)	216 (100.0)
55–59	110 (71.4)	44 (28.6)	154 (100.0)
60–64	71 (61.7)	44 (38.3)	115 (100.0)
65–69	19 (52.8)	17 (47.2)	36 (100.0)
70–74	24 (53.3)	21 (46.7)	45 (100.0)
75–79	13 (81.3)	3 (18.8)	16 (100.0)
Total gravity			
Nulliparous	5 (83.3)	1 (16.7)	6 (100.0)
1–4	68 (55.7)	54 (44.3)	122 (100.0)
5–8	135 (65.9)	70 (34.1)	205 (100.0)
9+	167 (71.4)	67 (28.6)	234 (100.0)
Treated with cryotherapy			
Yes	13 (100.0)	0 (0.0)	13 (100.0)
No	373 (65.8)	194 (34.2)	567 (100.0)
Current symptoms of infection			
Yes	94 (67.1)	46 (32.9)	140 (100.0)
No	237 (66.6)	119 (33.4)	356 (100.0)
Don't know	16 (59.3)	11 (40.7)	27 (100.0)
Pap smear in the past 2 years			
Yes	161 (65.4)	85 (34.6)	246 (100.0)
No	191 (65.9)	99 (34.1)	290 (100.0)

Abbreviation: VIA, visual inspection with acetic acid.

<sup>a</sup> n = 582; some totals are lower than 582 because of missing data.

<sup>b</sup> Values are given as number (percentage).

Hence, the sensitivity estimates for both the Pap smear and VIA in the present small sample are lower than is commonly reported. A meta-analysis by Fahey et al. [17] estimated the sensitivity of the Pap smear to be 50%, but Fahey et al. did not focus on women of advancing age. Similarly, a review [18] of several large trials on VIA found that the sensitivity ranged from 65% to 96%, but again, these findings were primarily based on younger women. It is possible that the low sensitivities for both Pap and VIA in the present study might be related to a difficulty in sampling the SCJ even if visible, secondary to moderate atrophy and vaginal dryness.

Although this was the first trial to assess the adequacy of VIA in an elderly population, several studies have looked at the SCJ visibility on colposcopy in women of advancing age [7,19–21]. These studies showed that the SCJ visibility on colposcopy is worse among

Table 2  
Comparison of the adequacies of VIA and colposcopy.<sup>a</sup>

	Colposcopy adequate	Colposcopy inadequate	Total
VIA adequate	380	4	384
VIA inadequate	11	184	195
Total	391	188	579

Abbreviation: VIA, visual inspection with acetic acid.

<sup>a</sup> An examination was considered adequate if the entire squamocolumnar junction was visible, as seen by the naked eye (VIA) or with magnification (colposcopy).

postmenopausal women. It is certainly possible that this is also true for VIA.

If it can be established in a larger sample that the adequacy of VIA is acceptably high and that VIA is as good as the Pap smear in detecting cervical cancer precursors in women above the age of 50 years, it might be necessary to create new guidelines for VIA screening that replace age with adequacy as a criterion for the suitability of VIA. If the SCJ is visible, then VIA could be performed; if not, a Pap smear should be taken.

Although the present study was confined to women aged 50–79 years, an age-related decline in VIA adequacy might occur in younger women as well. We examined trends of VIA adequacy using data from a Basic Health International patient care database that included 380 women aged 20–49 years who had attended a screening clinic in the rural community of Jucuaran, El Salvador, in 2005 (unpublished data). Age was negatively correlated with VIA adequacy. The examination was adequate in 116 (98.3%; 95% CI, 94.0–99.8) women aged 20–29 years; in 129 (92.1%; 95% CI, 86.4–96.0) women aged 30–39 years; and in 103 (84.4%; 95% CI, 76.8–90.4) women aged 40–49 years. These findings are comparable to the present data on women of advancing age, as evident if the patients are classified into 10-year age groups. The VIA examination was adequate in 260 (70.3%; 95% CI, 65.3–74.9) women aged 50–59 years; in 90 (59.6%; 95% CI, 51.3–67.5) women aged 60–69 years; and in 37 (60.7%; 95% CI, 47.3–72.9) women aged 70–79 years. In the group of women over 80, VIA adequacy was high ( $n = 13$  [81.3%; 95% CI, 54.4–96.0]). The sample size of this age group was small ( $n = 16$ ), but the findings strengthen the hypothesis that the SCJ is sometimes visible in women of advancing age. Although the data on younger women were collected for clinical rather than research purposes, the results are strong and compelling and indicate that VIA adequacy in younger women might also be stratified by age.

We recognize that the recommendation in some very low resource settings is to screen women between the ages of 30 and 50 years, because this has been shown to be the most cost-effective model [22]. In some countries, however, enough resources exist to screen the entire population. Using the VIA modality would decrease the burden on the cytology system and most likely decrease costs.

The main strength of the present study is that it is the first report on SCJ visibility with VIA in women of advancing age. All clinicians performing VIA were experienced colposcopists or, in the case of residents, were supervised by an experienced colposcopist, and were therefore likely to identify the SCJ accurately. Another strength was the use of universal biopsies as a predictor of actual disease.

The present study also had significant limitations, most notably the low incidence of positive biopsies and the inability to evaluate test sensitivity. In addition, age trends were extended to younger women by comparing the present sample of women aged 50–79 years with a sample of women aged 20–49 years. The latter group of women had participated in a separate screening program, albeit in a similarly rural part of the country and with similarly experienced colposcopists. However, there could have been some detection bias, because the clinicians in the study involving the sample of younger women were evaluating adequacy for clinical rather than research purposes and might have had less rigorous standards.

The study's limitations do not invalidate the main conclusion that the majority of women aged 50–79 years have a completely exposed SCJ. Because the VIA examination was adequate in most women, this modality may be a reasonable screening tool in women over the age of 50 years whose SCJ is visible. Larger studies investigating the

predictive performance of VIA need to be conducted before this method can be used on a widespread basis.

## Acknowledgments

The present study was funded by a grant from the Einhorn Family Trust.

## Conflict of interest

The authors have no conflicts of interest.

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