

Effect of Cervicitis on Visual Inspection With Acetic Acid

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■ ABSTRACT

Objective. The objective of this study was to determine whether the presence of cervicitis influenced the accuracy of visual inspection with acetic acid (VIA).

Materials and Methods. In a pilot study, 502 women from rural El Salvador were screened for cervical cancer using methods including colposcopy and VIA. The presence of cervicitis was assessed by grading the amount of inflammation on each woman's cervical biopsy. Data from 495 women found to be free of cervical neoplasia were analyzed for the present study.

Results. In this study population, 74% of women were classified as having cervicitis. Both the result of visual inspection and the result of colposcopy were highly associated with the presence of cervicitis ($p = .007$ and $p = .006$, respectively). Women with cervicitis were twice as likely to have a positive VIA result as women without cervicitis (odds ratio = 2.0, 95% CI: 1.0–3.7).

Conclusions. The presence of cervicitis may influence the accuracy of results obtained from colposcopy and VIA. This observation may be of particular importance in low-resource settings such as El Salvador where visual inspection methods are more commonly used in screening for cervical cancer. ■

Key Words: cervical cancer screening, cervicitis, colposcopy, visual inspection with acetic acid

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This study was conducted in El Salvador.

Cervical cancer is the leading cause of cancer death in Latin American women [1]. In El Salvador, mortality is particularly high, 18.4/100,000. In developed countries, cytology-based screening programs have reversed trends of increasing rates [2, 3], significantly decreasing both incidence and mortality. In low-resource settings, cytology programs are limited by lack of infrastructure. Many developing countries are therefore seeking alternative screening methods.

Visual inspection with acetic acid (VIA) is gaining popularity for cervical cancer screening in developing countries. It involves application of 3% to 5% acetic acid to the cervix and examination with the naked eye. If acetowhite lesions are observed, the result of the examination is positive. Positive lesions are often treated immediately with cryotherapy. The decision to provide immediate treatment depends on the lesion size, suspicion of invasion, and the examiner's expertise [4–7]. Sensitivity of VIA is 66% to 96%, and specificity is 64% to 98% [4]. Advantages of VIA are as follows: low cost, use of readily available materials, and immediate results. A disadvantage is potential overtreatment because the positive predictive value of VIA is 18.6% [4].

Cervicitis complicates VIA because redness and inflammation may increase false-positive results. Some experts consider clinically apparent cervicitis a contraindication to cryotherapy. Others recommend initial antibiotic treatment of cervicitis and cryotherapy 2 weeks later [7]. Cervicitis is relatively common, with prevalence in high-risk populations reported as 33% [8, 9].

The goal of this study was to determine whether biopsy-confirmed cervicitis led to an increase in false-positive VIA and whether cervicitis influenced colposcopy results.

MATERIALS AND METHODS

This project was part of a larger health improvement program by the nongovernmental organization BasicHealth: El Salvador (BHES). It provides weeklong medical clinics in poor, rural communities in El Salvador. All BHES physicians are from US-based universities. This research was approved by the Institutional Review Board of the University of Southern California and by government and health officials in El Salvador.

Women who presented to the BHES clinic for cervical cancer screening during January 2003 were invited to participate in the study. Written informed consent was obtained from all participants before data collection. Demographic information and reproductive history were collected through questionnaire. Women were included if they were aged 18 to 75 years; had an intact uterus and no history of uterine, cervical, vaginal, or vulvar cancer; and were able to give voluntary written consent. Women were excluded if they had surgical removal of the cervix, history of cervical cancer, and history of endometrial or ovarian cancer; reported a Pap smear in the past 6 months; or were pregnant.

After a conventional Pap smear was taken, 5% acetic acid solution was applied to the cervix, and a visual inspection was performed with the naked eye by 1 examiner (VIA). Any acetowhite lesion conforming to the criteria established by JHPIEGO (Johns Hopkins Program in International Education in Gynecology and Obstetrics) for cervical cancer prevention for low-resource settings [7] was considered a positive result. A second examiner then performed an examination of the cervix using a Nikon Cool Pix 5400 digital camera (digital assessment of the reproductive tract [DART]). After obtaining a full view of the cervix, a digital photograph was taken. The digital image was then magnified on a television that was connected to the camera. Using criteria similar to those for VIA, the image was recorded as positive or negative.

Colposcopic examination and endocervical curettage were performed by a third examiner who recorded colposcopic impression as positive or negative and scored quality of colposcopic examination as satisfactory if the entire squamocolumnar junction could be visualized or unsatisfactory otherwise. This examiner took biopsies

of any suspicious lesion or a biopsy at 12 o'clock if no lesion was observed. Each of the 3 examiners was blinded to the results of the other examiners. Specimens were shipped to Pathnet Laboratories (Van Nuys, CA), processed for routine light microscopy, and read by a gynecologic pathologist who was blinded to all previous results. Analyses comparing results of VIA, DART, and Pap smear to biopsy have been published elsewhere [10].

Pathologic specimens were evaluated for the presence of cervicitis and erosion. Each biopsy specimen was examined by routine light microscopy and evaluated for the presence of inflammation. Biopsy specimens were judged to have significant inflammation if the cervical stroma contained an area of dense inflammation of greater than 5 mm composed of lymphocytes, plasma cells, and reactive stromal and epithelial changes. The presence of erosion was defined as cervical tissue where the epithelium was absent and the stroma immediately beneath the area of erosion contained inflammation and the presence of granulation tissue.

Differences in the demographic characteristics of women with and without biopsy-confirmed cervicitis were assessed using χ^2 tests. Unconditional logistic regression was used to investigate associations between cervicitis and results of screening tests (VIA and colposcopy) and associations between cervicitis, erosion, and quality of colposcopy by calculating odds ratios (OR) and 95% CIs. These associations were reanalyzed with adjustment for age. All statistical tests were 2-sided, and a *p* value less than or greater than .05 was considered statistically significant. Analyses were conducted using SAS statistical software (SAS version 9.0; SAS Institute, Inc, Cary, NC).

RESULTS

A total of 502 patients underwent these screening examinations, and data from the 495 patients whose biopsies showed no indication of cervical neoplasia were included in the present analysis. The prevalence of biopsy-confirmed cervicitis was 74%. Demographic characteristics of women with and without cervicitis are presented in Table 1. Age was the only measured characteristic that significantly differed between the 2 groups; younger women were significantly more likely to have cervicitis than older women (*p* = .03).

The presence of cervicitis was associated with the results of both VIA and colposcopy. Among women found not to have a lesion based on VIA, the prevalence

of cervicitis was 71% (285/401), whereas the prevalence among women in whom a lesion was detected on VIA was 85% (80/94) (Table 2). After adjustment for age, women with cervicitis were twice as likely to have a positive result based on VIA as women without cervicitis (OR = 2.0, 95% CI: 1.0–3.7; Table 2). Associations between cervicitis and results of the colposcopic examination were similar. After adjustment for age, women with cervicitis were 2 times as likely to have a positive colposcopic impression (low- or high-grade dysplasia) as women without cervicitis (OR = 2.1, 95% CI: 1.1–4.0; Table 2).

The quality of colposcopy was negatively associated with cervicitis, such that women with cervicitis were more likely to have a satisfactory colposcopy result than women without cervicitis (OR = 0.47, 95% CI: 0.30–0.73; Table 3A). Erosion was assessed to evaluate the possibility that this unexpected association arose, at

Table 2. Associations Between Cervicitis and the Screening Test Results Among Biopsy-Negative Patients (n = 495)

	Cervicitis (n = 365)	No Cervicitis (n = 130)	Crude OR (95% CI) ^a	Adjusted OR (95% CI) ^b
Result of visual inspection				
Negative	285	116	1.0 (ref)	1.0 (ref)
Suspect dysplasia	80	14	2.3 (1.3–4.3) <i>p</i> = .007	2.0 (1.0–3.7) <i>p</i> = .03
Result of colposcopy				
Normal	292	118	1.0 (ref)	1.0 (ref)
Low-grade dysplasia	64	10	2.6 (1.3–5.2)	2.2 (1.1–4.4)
High-grade dysplasia	9	2	1.8 (0.39–8.5)	1.6 (0.35–7.8)
Low or High Grade	73	12	2.5 (1.3–4.7) <i>p</i> = .006	2.1 (1.1–4.0) <i>p</i> = .03

p values calculated from χ^2 test.
^aCrude OR and 95% CI.
^bOR and 95% CI adjusted for age.
 OR, odds ratio.

Table 1. Demographic Characteristics for 365 Patients With Cervicitis and 130 Patients Without Cervicitis

	Cervicitis		No Cervicitis		<i>p</i>
	N	%	N	%	
Age, y					
≤35	124	34	30	23	.03
36–50	123	34	44	34	
>50	118	32	56	43	
Median (range)	42 (18–75)		47 (20–75)		
Gravida					
0	11	3	3	2	.63
1–3	143	39	47	36	
4–6	104	29	34	26	
>6	107	29	46	35	
Median (range)	4 (0–16)		4.5 (0–14)		
Smoking status					
Yes	14	4	8	6.2	.52
No	347	95	121	93	
Missing	4	1	1	0.8	
Previous Pap smear					
Yes	331	90.7	114	88	.48
No	33	9	16	12	
Missing	1	0.3			
Age at first intercourse, y					
<18	128	35	40	31	.62
18–20	114	31.5	44	34	
21–25	88	24	37	28	
>25	33	9	9	7	
Missing	2	0.5			
Median (range)	19 (11–39)		19 (9–35)		
Number of lifetime partners					
0	2	0.5	0	0	.27
1	211	58	67	52	
2	71	19.5	35	27	
>3	81	22	28	21	
Median (range)	1 (0–11)		1 (1–7)		

p values calculated from χ^2 test.

least in part, from a tendency for the perimeter of areas of erosion to resemble the squamocolumnar junction on colposcopic examination. Erosion was present in 23% (101/436) of women in whom it could be assessed and was associated with cervicitis (OR = 4.9, 95% CI: 2.3–10.4; Table 3B). However, the association between

Table 3. Associations Between Cervicitis and Both the Quality of Colposcopy and Presence of Erosion Among Biopsy-Negative Patients

	Cervicitis (n = 365)	No Cervicitis (n = 130)	OR (95% CI) ^a
A. Cervicitis and quality of colposcopy			
All women (n = 495)			
Satisfactory colposcopy	287	83	1.0 (ref)
Unsatisfactory colposcopy	75	46	0.47 (0.30–0.73)
Quality of colposcopy not determined	3	1	<i>p</i> < .0001
Erosion present (n = 101)			
Satisfactory colposcopy	79	5	1.0 (ref)
Unsatisfactory colposcopy	13	2	0.41 (0.07–2.3)
Quality of colposcopy not determined	1	1	<i>p</i> = .32
Erosion absent (n = 335)			
Satisfactory colposcopy	179	64	1.0 (ref)
Unsatisfactory colposcopy	56	35	0.57 (0.34–0.95)
Quality of colposcopy not determined	1	0	<i>p</i> = .03
Erosion results missing or could not be determined (n = 59)			
B. Cervicitis and presence of erosion			
All women (n = 495)			
No erosion	236	99	1.0 (ref)
Erosion present	93	8	4.9 (2.3–10.4)
Erosion status could not be determined	33	23	<i>p</i> < .0001
Quality of colposcopy not determined	3	0	

p values calculated from χ^2 test.
^aCrude OR and 95% CI.
 OR, odds ratio.

quality of colposcopy and cervicitis persisted even among the 335 women in whom erosion was not noted (OR = 0.57, 95% CI: 0.34–0.95; Table 3A). Adjustment for age did not significantly change these results (data not shown).

DISCUSSION

The data from this study strongly suggest that women with cervicitis are more likely to have false-positive VIA results than women without cervicitis. Most VIA programs currently use a “see and treat approach” for positive VIA results. This model is extremely useful in areas where it is difficult for women to return for a follow-up visit. Clinically, this means that most women who have a positive VIA will undergo cryotherapy, whereas a small percentage will be referred to a specialist for suspicion of invasion or for treatment of extremely large lesions. Cryotherapy is a treatment with a relatively low morbidity, and the benefits of treating all women with preinvasive disease are presumed to outweigh the amount of discomfort and inconvenience associated with cryotherapy. A systematic literature review conducted by the Alliance for Cervical Cancer Prevention concluded, “Cryotherapy is a safe method of treatment with no significant morbidity or mortality risks” [11].

In the current study population, 20% of the 502 screened patients (5 of 7 diagnosed with cervical intraepithelial neoplasia [CIN] plus 94 of 495 biopsy negative noncases) would have received cryotherapy using a see and treat model based on results of VIA, although only 1.4% (7 of 502) of them were diagnosed with CIN. This high false-positive rate [sensitivity = 71%, specificity = 82%, positive predictive value = 5% (10)] caused us to evaluate other factors that may have adversely influenced the accuracy of the test. Inflammation was detected among patients both clinically, during their examination, as well as pathologically, during the evaluation of the biopsy. In the clinical setting, inflammation may cause a false-positive VIA if the appearance of leukocytes in the submucosa mimics white epithelium. These data strongly support this possibility because associations between inflammation and positive examinations by both VIA and colposcopy are highly significant.

The presence of erosion was also frequently observed pathologically. Marked erosion can cause areas of the cervix to lack squamous epithelium. If this occurs near the external os of the cervix, the possibility of falsely

assuming that the squamocolumnar junction can be evaluated can occur. Our analysis found a strong association between erosion and cervicitis. However, we did not find that a substantial portion of the association between cervicitis and satisfactory colposcopy could be explained by the presence of erosion.

Our findings strongly suggest that the presence of cervicitis adversely impacts the accuracy of both VIA and colposcopy. Although the setting in which VIA is commonly performed is not readily amenable to multiple visits, clinicians performing VIA should be aware that cervicitis may impair their examination and may increase the proportion of falsely positive cases. Patients referred to colposcopy are however much more amenable to treatment before colposcopy. Our findings suggest that lowering the rate of severe cervicitis may optimize the colposcopic evaluation by lowering the false-positive rate of lesions. In El Salvador, it is relatively easy for women to return for follow-up. In this setting, it may be more cost-effective and cause less discomfort to patients if women with clinically apparent cervicitis were first evaluated to determine the etiology of cervicitis, given the appropriate treatment, and were asked to return for follow-up in 2 weeks.

The population studied had a low incidence of CIN. This fact may have led to a higher false-positive rate because the clinicians may have been anticipating higher rates of disease. In addition, there was no systematic assessment of clinically apparent cervicitis by the examiners conducting VIA, DART, and colposcopy, so we were not able to provide these data for comparison with the histologic assessment of cervicitis. This study is based in a population of Latina women in El Salvador rather than a more heterogeneous population worldwide. However, we believe that results on the associations between cervicitis and VIA and colposcopy may be similar across populations. Despite the limitations, this project has important implications. Because visual inspection programs are gaining in popularity, it will be important to investigate the clinical utility of immediate treatment with cryotherapy, as opposed to treatment with antibiotics followed by repeat of VIA after 2 weeks.

In light of these findings, we recommend further study of the role of cervicitis in determining the accuracy of VIA. It may be worthwhile to develop prospective studies, which include clinical and histologic assessments of cervicitis and cultures for chlamydia and gonorrhea to determine the correlations between these

measures and how they may be used in low-resource settings in which VIA is the primary screening method.

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