Visual inspection with acetic acid for cervical cancer screening outside of low-resource settings

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ABSTRACT

Objectives. *To assess visual inspection with acetic acid (VIA) as a screening tool for use in a well-equipped health center in Peru, to evaluate VIA as an alternative or adjunct to the Papanicolaou (Pap) smear, and to determine if VIA can play a role in settings other than low-resource ones.*

Methods. *This was a prospective study of 1 921 asymptomatic women living in Lima, Peru, carried out in 1999 and 2000. The study was performed at a cancer center equipped with the latest-generation technology and highly trained oncologists. The women underwent a complete clinical evaluation, including a Pap smear and VIA. Participants with any positive test were referred for colposcopy and biopsy.*

Results. *More women tested positive by VIA than on the Pap smear (6.9% vs. 4.2%;* P = *0.0001). There were 35 women with histologic cervical intraepithelial neoplasia grade 1 (CIN 1); of these, 15 were detected by Pap and 20 by VIA (*P = *0.4). A diagnosis of CIN 2 or 3 (CIN 2–3) was confirmed in a total of 13 cases; Pap detected 5 of the cases and VIA 11 of the cases (*P = *0.06). The positive predictive value for detection of CIN 2+ was 8.3% for VIA and 6.3% for Pap (*P = *0.5). Most importantly, while only 2.3% of patients with a positive VIA were lost to follow-up before colposcopy, that was true for 26.3% of the women with a positive Pap smear (*P < *0.0001).*

Conclusions. *VIA is useful for detection of precursor lesions of cervical cancer not only in low-resource settings but also in well-equipped health centers and cancer centers. In these non-low-resource settings, VIA has a positive predictive value comparable to the conventional Pap smear, but it is more likely to achieve earlier diagnosis, follow-up, and treatment than cytology-based screening.*

Key words Cervix neoplasms, acetic acid, diagnostic techniques and procedures, mass screening, predictive value of tests, health resources.

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Cervical cancer is one of the most prevalent malignant neoplasms among women in developing countries (1), affecting them mainly in the fifth to sixth decade of life. Invasive cervical cancer is preceded by a long premalignant phase known as cervical intraepithelial neoplasia (CIN) (2). The goal of cervical cancer screening is the detection and treatment of precancer before cancer develops (3–5).

To detect cervical intraepithelial neoplasia grades 2 or 3 (CIN 2–3), which are considered to be true precancerous lesions, we need a well-implemented secondary prevention system that provides screening for all women at risk as well as treatment of detected abnormalities according to local policy. The Papanicolaou (Pap) smear has been shown to be highly effective in developed countries that have widespread screening programs (6–8). However, in Peru, as in most other Latin American countries, only a small proportion of women at risk are screened (9, 10).

In developing countries, because of the lack of trained cytotechnologists and cytology laboratories, there is often a long interval (1–3 months) between the Pap screening and when the test result is available. Additionally, only a small percentage of women with positive Pap smears have diagnostic evaluation and treatment (11), because of the lack of health centers that are able to treat preinvasive lesions. These problems with Pap smears have stimulated research on alternative tests, including visual inspection with acetic acid (VIA). VIA has demonstrated high sensitivity for detecting CIN and cervical cancer, but it is limited by low specificity (12–14). VIA is based on acetowhitening, with the CIN turning white when exposed to 5% acetic acid (vinegar). VIA has the advantage of requiring only low-technology equipment, and the result is available within a couple of minutes. These characteristics make VIA a realistic alternative for low-resource settings.

In Peru, cervical cancer screening based on the Pap smear is available in private and public health centers in rural and urban areas. However, there are several barriers to broad patient access to this screening. The test is not free. Even in public facilities, patients have to pay a fee, which in some cases is equivalent to a family's income for a day. In addition, there is no nationwide quality control system to assure accurate screening. VIA has been only available in one low-resource area, in the rain forest of Peru, in an experimental project that was launched by the Pan American Health Organization and the Peruvian Ministry of Health.

The protocol described in this article was developed to evaluate whether VIA has a role as a screening test not only in first-level health centers in low-resource areas, but also in a cancer center in Peru where Pap testing has been the norm. Located in the city of Lima, Peru, the Neoplastic Diseases Institute (*Instituto de Enfermedades Neoplásicas*) is part of the Ministry of Health, and it is the only institute in Peru that is dedicated exclusively to the prevention, diagnosis, and treatment of cancer. The Institute is highly prestigious in the country, and every year thousands of healthy individuals seek cancer screening there. The Institute differs from low-resource settings in that it has the latest-generation equipment, the physicians are highly trained cancer specialists, and there is a well-established cytology laboratory that provides evaluation and diagnosis of cervical cytology in less than one week.

MATERIAL AND METHODS

This study targeted sexually active women between 25 and 50 years old who had no history of CIN or cervical cancer. The women voluntarily visited the department of detection and early diagnosis of the Neoplastic Diseases Institute between July 1999 and July 2000 for a general checkup and cervical cytology.

We excluded from the study women who do not live in Lima. We also excluded women who were currently pregnant or who had a history of abnormal cytology, previous treatment for CIN or cancer, or obvious invasive cancer at the time of the clinical evaluation. Women with severe cervicitis were excluded until they had completed treatment. Women were included in the study after they were given information about the study, agreed to participate, and provided consent.

Study subjects had a complete physical examination and pelvic evaluation done by one of six oncologists highly trained in the evaluation of healthy people and the early detection of cancer. The Pap smear sampling and VIA were performed by the same evaluator. A speculum examination started with a direct visual evaluation of the cervix to identify cervicitis, leukorrhea, polyps, ulcers, etc. A Pap smear sample was then taken using a conventional wooden Ayres spatula. The smear was fixed with ethanol for 30 minutes. VIA involved gentle application of 5% acetic acid using a small piece of cotton to avoid bleeding. After 1–2 minutes a naked-eye evaluation was performed under 100-watt illumination.

The evaluator filled out a form with general information on each woman, clinical findings at pelvic evaluation, results of the VIA, and results of colposcopy when indicated. The results of the Pap smear were reported according to the Bethesda System (15).

We considered as positive any cytology diagnosis that included atypical squamous cells of undetermined significance (ASCUS), low-grade intraepithelial lesion (LSIL), high-grade intraepithelial lesion (HSIL), or invasive cancer. VIA was considered positive when an acetowhite lesion was observed within the transformation zone. We did not exclude acetowhite lesions thought to be CIN grade 1 (CIN 1), since institutional policy requested detection for follow-up. If an acetowhite lesion was detected, the participant was immediately informed, and a colposcopy appointment was scheduled for the following week. Women with a negative VIA were given an appointment within a week to receive their Pap results and to have colposcopy if the Pap was positive.

The time interval between the first evaluation, where the Pap smear and

VIA were performed, and colposcopy was one week in women with a positive Pap smear and in women with positive VIA. Colposcopy was performed by one of the six oncologists of our team, but it was never done by the oncologist who had evaluated the patient during her first visit. A directed biopsy was taken and fixed in 20% buffered formalin only if an acetowhite lesion was detected; women without acetowhite lesions during the colposcopic evaluation were considered as normal and did not have a biopsy. Pap smears were screened at the cytology laboratory by one of a team of three cytotechnologists. When screening was suggestive of an abnormality, the sample was reviewed by a pathologist. Biopsies were evaluated by pathologists blinded to the VIA results but who, following institutional guidelines, were aware of the cytological results.

For the statistical analysis, we considered as cases women with a final histology of CIN 2 or greater. Women with abnormal cytology or VIA but without colposcopy and biopsy were considered as lost to follow-up. They were excluded from the statistical analysis because they did not have a biopsy, and therefore, their final status is unknown.

RESULTS

We evaluated 1 921 women who fulfilled the eligibility criteria and provided informed consent. Their mean age was 38.6 years. In terms of parity, 14% of the women were nulliparous, 45% had had one or two live births, 29% had had three or four, and 12% had had five or more. The mean age of onset of sexual life had been 20 years (median, 19 years; range, 6–42 years). The mean number of sexual partners had been 1.7. The majority of the women (60%) had had one sexual partner, 27% had had two, 11% had had three or four, and 1% reported five or more.

With regard to cytology history, 13% of the women had never had a Pap smear, 35% had had one within the preceding year, 38% within one to three years, 6% within four to five years, and 8% more than five years before the study.

During the clinical evaluation (before the application of 5% acetic acid) 986 women (51.3%) were observed as having a normal cervix, 701 (36.5%) had cervicitis, 231 (12.0%) had ectopy, and 3 women had leukoplakia.

Of the 1 921 women, 132 of them (6.9%) had a positive VIA, and 80 (4.2%) had a positive Pap smear (P = 0.0001) (Table 1). VIA positivity varied over the course of the study. It was 13.5% during the first quarter of the study, and then 4.8%, 3.7%, and 4.8% during the following three quarters. In contrast, Pap positivity did not vary over the study period. It is important to mention that 12 women (0.6%) had a positive result on both tests; that is, 120 women (6.2%) were only VIA-positive, and 68 women (3.5%) were only Pap-positive.

Of the 132 women who had a positive VIA, 3 of them (2.3%) did not return for colposcopy and biopsy. In contrast, of the 80 women with a positive Pap smear, 21 of them (26.3%) did not return for colposcopy and biopsy (P < 0.0001). These patients were lost despite efforts to contact them with phone calls to them and/or their relatives.

Eighty-seven women underwent a biopsy during the study. Of these 87, 5 had a result of normal, 26 had cervicitis, 8 had metaplasia, 35 had CIN 1, and 13 had CIN 2–3. Among these 13 patients with a biopsy result of CIN 2-3, VIA was positive in 11 of them (84.6%), and cytology was positive in 5 of them (38.5%). The positive predictive value (PPV) for detection of CIN 2 or worse was 6.3% for the Pap smear and 8.3% for the VIA (P = 0.5).

TABLE 1. Screening for cervical cancer done with visual inspection with acetic acid (VIA) and with conventional Pap smears, Lima, Peru, 1999–2000[a]

	VIA positive		Pap smear positive			VIA and Pap positive	
	No.	%	No.	%	P[b]	No.	%
Total (n = 1 921)	132	6.9	80	4.2	0.0001	12	0.6
CIN 1 (n = 35)	20	57.1	15	42.9	0.4	1	2.9
CIN 2-3 (n = 13)	11	84.6	5	38.5	0.06	3	23.1
CIN 1 (n = 48)	31	64.6	20	41.7	0.09	4	8.3

[a] Using a threshold for cytology of equivocal/atypical squamous cells of unknown significance (ASCUS) or worse for detection of cervical intraepithelial neoplasia grade 2 or 3 (CIN 2-3). Women were referred to colposcopy if positive for either test.
[b] P value is for McNemar's chi-squared test.

DISCUSSION

Close to 80% of invasive cancer cases occur in developing countries, where either there are no screening programs or the programs are poorly developed and inefficient. Most of these programs are based on Pap smears and try to mimic the good results obtained in developed countries. Unfortunately, their results have been suboptimal due to lower coverage of women at risk, no standardized quality control systems, and a lack of follow-up and treatment of positive cases. For these reasons, in recent decades other alternatives have been explored, such as human papillomavirus (HPV) DNA testing and VIA.

HPV DNA testing has shown very high sensitivity and is being recommended in high-resource countries (16, 17). However, its current price and technology requirements make this option unrealistic for poor areas (18) until a low-cost, same-day HPV test and realistic strategies are developed (19).

VIA has arisen as a promising alternative for developing countries because it is inexpensive and fast and requires a low level of training and no special equipment. Some previous reports have observed that VIA can reach similar or better results than the Pap smear (12–14) in the detection of CIN, but none of those studies was per-

formed in Latin America. Further, it is important to mention that there had been no prior experience with using VIA in a high-resource setting in a developing country. In general, the sensitivity of VIA has been shown to be equal to or better than the Pap smear's, while its specificity has been lower.

We planned this study to determine the potential of VIA to supplement or replace the Pap smear in screening in a cancer center. One of our first findings was that VIA positivity changed over time, from 13.5% in the first months of the study, to close to 4% during the following months. We hypothesize that this change was related to a learning curve and that the more experience the evaluator has, the lower the positivity is. It is important to highlight that our positivity rate for VIA was less than that reported by other authors, but we should emphasize that in our study the evaluators were highly trained physicians with experience in colposcopy, while in other studies the evaluators were health workers with less training (13, 14). This finding highlights the importance of training and experience for the performance of visual evaluations. These issues should be considered during the development of protocols in remote areas, where we must ensure adequate training and volume of evaluations to maintain the expertise of the health worker.

Another important finding concerned the percentages of women with positive tests who were lost to follow-up before colposcopy and treatment. The percentage was significantly lower in VIA-positive women (2.3%) than in women with a positive Pap smear (26.3%) ($P < 0.0001$). We believe that this happened because the VIA-positive women knew their abnormal result immediately during the first visit, and they immediately received special counseling about that finding and the importance of returning in a week for colposcopy and biopsy. In contrast, to learn about their Pap smear result (either positive or negative), women had to return one week later for a second visit, which many of them did not do and so never received special counseling about the significance of any positive result. Although we actively searched for the women with an abnormal Pap smear, we were not able to find 26.3% of them. This percentage of participants with abnormal cytology lost before colposcopy might be considered a source of bias at the time of statistical analysis and comparison with VIA. However, this result does reflect the real problems faced with screening based on the Pap test in developing countries. For example, in a remote area of Peru where cervical cancer screening was based on conventional cytology, only 25% of the patients with a positive Pap smear received adequate diagnosis and treatment (11).

The positive predictive value we report for VIA is lower than that found by Sankaranarayanan et al. (13). This can most likely be explained by our institutional policies, which required us to diagnose and follow up women with any lesion (cytological or visual) suggesting CIN 1. However, the PPV was calculated considering as cases only women with CIN 2-3 histology. Sankaranarayanan et al. found a PPV for VIA of 17%, but they considered as positive at VIA only those cases with a distinctive and clear acetowhite area, which is more likely to be related to CIN 2–3.

Our results outline the potential benefits of using VIA at all levels of health care systems in developing countries. VIA increases detection of premalignant lesions of the cervix and diminishes the probability of losing women before they are appropriately followed up and treated. We believe that VIA can be used as a screening tool in poor countries not only in rural areas and small health centers, but also in hospitals, cancer institutes, and other health facilities with better resources.

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RESUMEN

La inspección visual con ácido acético para el tamizaje del cáncer cervicouterino donde no hay escasez de recursos

Objetivos. Determinar si la inspección visual con ácido acético (IVAA) es útil como prueba de tamizaje en un centro de salud peruano con buena dotación de equipo; si se presta para uso en lugar del Papanicolaou o en combinación con él, y si tiene alguna utilidad en lugares donde no hay escasez de recursos.

Métodos. En 1999 y 2000 se realizó un estudio prospectivo con 1 921 mujeres asintomáticas que habitaban en Lima, Perú. El estudio se llevó a cabo en un centro de cancerología dotado de las tecnologías más modernas y de oncólogos con una sólida formación. A las mujeres se les sometió a un examen clínico completo, con todo y prueba de Papanicolaou e IVAA. A las que tuvieron resultados positivos en cualquiera de estas pruebas se les remitió para estudio con colposcopia y biopsia.

Resultados. Hubo un mayor número de mujeres con resultados positivos a la IVAA que al Papanicolaou (6,9% frente a 4,2%; $P = 0{,}00001$). Treinta y cinco mujeres tuvieron una neoplasia cervical intraepitelial grado I (NCI I) en el examen histológico; a 15 de ellas se les detectó la lesión mediante el Papanicolaou y a 20, mediante la IVAA ($P = 0{,}4$). Se confirmó el diagnóstico de NCI 2 ó 3 (NCI 2–3) en 13 casos, de los cuales 5 se detectaron mediante el Papanicolaou y 11, mediante la IVAA ($P = 0{,}06$). El valor pronóstico de un resultado positivo en el diagnóstico de NCI 2+ fue de 8,3% en el caso de la IVAA y de 6,3% en el del Papanicolaou ($P = 0{,}5$). El resultado de mayor importancia es que 26,3% de las mujeres con un resultado de Papanicolaou positivo abandonaron el seguimiento antes de la colposcopia, mientras que eso solamente sucedió en 2,3% de las pacientes con un resultado positivo en la IVAA ($P < 0{,}0001$).

Conclusiones. La IVAA sirve para detectar lesiones precursoras del cáncer cervicouterino no solo en lugares con pocos recursos, sino también en centros de salud y de cancerología bien dotados de instrumental moderno. En lugares donde los recursos escasean, un resultado positivo en la IVAA tiene un valor pronóstico semejante al del Papanicolaou convencional, pero es más probable que culmine en el diagnóstico temprano, seguimiento y tratamiento de la paciente que el tamizaje de tipo citológico.

Palabras clave Neoplasmas del cuello uterino, ácido acético, técnicas y procedimientos diagnósticos, tamizaje masivo, valor predictivo de los tests, recursos en salud.