International Journal of Gynecology and Obstetrics (2005) **90**, 167—170

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

SPECIAL ARTICLE

Liquid-based cytologic specimen studies to screen for cervical dysplasia in rural El Salvador

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Received 13 December 2004; received in revised form 27 April 2005; accepted 27 April 2005

KEYWORDS
Cervical cancer screening;
Liquid based cytology;
El Salvador

Abstract

Objective: To evaluate an alternative tool (ThinPrep; Cytye Corporation, Boxborough, Mass, USA) for cervical cancer screening in rural El Salvador. *Methods:* Cervical samples were obtained from 471 women attending health fairs in rural El Salvador. The samples were read by American and Salvadoran pathologists after a 1-week training course in liquid-based cytologic studies in the United States. *Results:* The system evaluated detected a significantly higher number of high-grade and above lesions than conventional cytologic studies ($P=0.01$). There were 0.4% and 1.7% of high-grade lesions and above detected with conventionally prepared slides in the United States and El Salvador, respectively, and 3.2% and 3.8% of such lesions detected with liquid-based samples in the United States and El Salvador. Intraobserver agreement among the pathologists reading the samples was substantial for the ThinPrep system, with a κ value of 0.6. *Conclusion:* A short workshop is effective in training pathologists to use ThinPrep. In the studied population, liquid-based studies appear to offer significant advantages over conventional cytologic studies for detecting high-grade lesions.
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doi:10.1016/j.ijgo.2005.04.009

1. Introduction

Cervical cancer is the leading cause of death from cancer in Central American women [1]. In developed countries with organized screening programs, the morbidity and mortality caused by cervical cancer have significantly decreased. In developing countries such as El Salvador, however, there are so many obstacles to effective screening that a large number of women are at risk of dying from this disease.

There are many barriers to conventional screening programs, including a lack of education and resources. Another impediment to accurate screening is the susceptibility of the conventional Papanicolaou (Pap) smear test to preanalytical error. The problems that can arise anywhere in the chain of steps prior to microscopic analysis can impair the outcome of the conventional Pap smear test. Among these difficulties are air drying, poor sampling technique, microbial action, obscuring erythrocytes, and other forms of specimen degradation. According to a meta-analysis, the sensitivity of conventional Pap smears ranges between 30% and 87% (mean, 47%) [2]. Sensitivity improves with the introduction of significant quality assurance measures for specimen handling, as was noted in a study in which the sensitivity of conventional smear tests was determined to be 91% [3]. However, because most laboratories in the developing world cannot exercise significant control over the process, sensitivity suffers and false-negative results are numerous. In developed countries, it is possible to compensate for poor sensitivity by frequent screening intervals. In developing countries, frequent screening intervals are not feasible.

Choosing a screening method that eliminates many of the preanalytical problems should allow for increased screening intervals as well as improve the detection rate of precancerous lesions [4]. One of the newer technologies (well known in the United States) that facilitates Pap smear studies is liquid-based cytology. A liquid-based system, ThinPrep (Cytyc Corp., Boxboro, Mass, USA), assures rapid fixation, removes blood, and filters out most of the inflammatory cells, thereby improving sample quality. Several studies [3,6–8] have suggested that cytologic studies using ThinPrep are more sensitive than conventional ones.

The purposes of this study were threefold: to investigate the barriers to effective Pap smear screening in a rural developing country; to evaluate the use of the ThinPrep liquid-based technology; and to determine whether a 1-week workshop adequately trains experienced Salvadoran pathologists to process and interpret liquid-based cytology.

2. Materials and methods

Prior to a health fair, health care promoters in [5] Salvadoran communities were trained to obtain cervical smears. These health care promoters were critical in the recruitment and follow-up of women. Their training took place in small-group sessions with Spanish-speaking US physicians. Two health care promoters were paired up with 1 physician, and they were encouraged to ask questions. A plastic model was used to demonstrate a speculum examination and how to obtain a Pap smear. The promoters were then observed as they performed a speculum examination.

A total of 471 women consented to participate in the study. A conventional Pap smears was obtained from each woman and the residual cells were placed in a ThinPrep solution. All slides were first read by Salvadoran cytotechnologists and pathologists. Then, the samples were brought to the Wisconsin State Laboratory of Hygiene to be analyzed by specialists blinded to the results of the Salvadoran physicians. Two experienced Salvadoran pathologists underwent a 1-week training program at the Wisconsin State Laboratory of Hygiene on ThinPrep technology. Blinded to all previous results, these pathologists then reread the slides prepared with ThinPrep.

The age and the sexual/reproductive history of the study participants were analyzed using SAS (SAS, Cary, NC, USA) and summarized as descriptive statistics. The results of the parallel analysis comparing ThinPrep and conventional slides in the Unites States and El Salvador were compared using the McNemar test for matched pairs.

3. Results

Between April 1998 and May 1999, a total of 471 women participated in the study. Demographic information about the participants is shown in Table 1. The mean ± SD age of the participants was 38.7 ± 13.8 years, their mean age at first inter-

Table 1 Demographics

Measure	*N*	Range	Mean	Standard deviation
Age	466	18–80	38.7	±13.3
Coiarche	443	18–36	17.5	±3.6
Number of lifetime partners	444	1–20	1.89	±1.61
Number of pregnancies	445	0–20	5	±3.85
Number of children	455	0–16	5	±3.36
Number of abortions	455	0–5	0.52	±0.93

course was 17.5 ± 3.6 years, and 79.2% reported 1 or 2 lifetime partners. Of all the women in the study, 24.5% had never had a Pap smear taken.

The cytologic studies results are listed in Table 2. Bethesda criteria were used to evaluate the samples. Fewer lesions of high-grade and above dysplasia were detected using conventional cytologic studies (0.4% and 1.7%, respectively) than using liquid-based cytologic studies (3.2% and 3.8). When the trained Salvadoran pathologists analyzed smears prepared with ThinPrep, there was no significant difference in the detection of high-grade lesions and above ($P=0.41$).

The University of Wisconsin pathologists noted that there were many artifacts in the conventional smears due to irregular thickness, air drying, and sample degeneration, but that the ThinPrep samples had a better appearance and were much easier to interpret. It was obvious that the older smear technology was more difficult to use than the newer, liquid-based technology, at least with regards to the quality of the samples. Conventional slides, whether read in the United States or El Salvador, were significantly less likely to allow the detection of high-grade squamous intraepithelial lesions or above ($P=0.01$ and $P=0.001$, respectively).

To evaluate the efficacy of this brief ThinPrep training program, a concordance between the training program in El Salvador and the training program in the United States was calculated, using the κ statistic and the McNemar test (Table 3). These results showed significant inter-observer agreement between the US and Salvadoran pathologists regarding the ThinPrep but not the conventional slides.

Table 2 Cytology results

Result	Number of observations	Percent of total (%)
Thin Prep—US		
WNL	370	78.9
LGSIL	27	5.8
HGSIL	14	3.0
CIS	1	0.2
Inv CA	0	0.0
ASCUS	48	10.2
Unsatisfactory	9	1.9
Total	469	100.0
Thin Prep—El Salvador		
WNL	347	73.8
LGSIL	36	7.7
HGSIL	15	3.2
CIS	0	0.0
Inv CA	3	0.6
ASCUS	54	11.5
Unsatisfactory	15	3.2
Total	470	100.0
Conventional—US		
WNL	345	76.5
LGSIL	24	5.3
HGSIL	0	0.0
CIS	2	0.4
Inv CA	0	0.0
ASCUS	70	15.5
Unsatisfactory	10	2.2
Total	451	100.0
Conventional—El Salvador		
WNL	417	88.9
LGSIL	36	7.7
HGSIL	5	1.1
CIS	3	0.6
Inv CA	0	0.0
ASCUS	0	0.0
Unsatisfactory	8	1.7
Total	469	100.0

Table 3 Intra-observer variability

	K	95% CI (*K*)	McNemar test *p* value
Negative vs. ASCUS, positive			
Thin Prep	0.615	(0.526, 0.703)	0.027
Conventional slides	0.211	(0.106, 0.317)	0.001
Thin Prep	0.651	(0.536, 0.766)	0.028
Conventional slides	0.201	(0.059, 0.343)	0.017

Kappa	Agreement
0 to 0.2	Slight
0.2 to 0.4	Fair
0.4 to 0.6	Moderate
0.6 to 0.8	Substantial
0.8 to 1.0	Almost perfect

4. Discussion

In the United States, yearly screening has been used to compensate for the preanalytical problems encountered with the conventional Pap smear. Annual screening is unrealistic in the Salvadoran population, and the use of a better screening tool in this population with a high prevalence of disease and inadequate access to health care could allow for adequate screening intervals. Concern has been raised about the high cost of the new Pap smear systems. One cost-analysis study showed that, when used with triennial screening, new Pap smear technologies could help generate more life-years at a lower cost than conventional Pap smears taken every 2 years [9]. The authors suggested that cost-effectiveness is improved even further when these

technologies are used in populations with high disease prevalence.

Our study suggests that liquid-based cytologic studies would be useful in improving the detection of high-grade squamous intraepithelial lesions in a rural population with at high prevalence of cervical cancer precursors and no modern system for Pap smear management. ThinPrep was shown to be significantly more likely to detect high-grade squamous intraepithelial lesions than conventional Pap smears ($P=0.011$), in large part because of ThinPrep's ability to eliminate preanalytical problems. We believe that the higher rate of detection reached using ThinPrep correlates with the actual incidence of disease. Analyses of ThinPrep from both the United States and El Salvador have shown the incidence detection of high-grade lesions and above to be 3.2%. Not only is the incidence of cancer precursors in this population exceptionally high, but access to care is inadequate because of a variety of factors that include poverty and poor infrastructure.

An important goal of this study was to prove that the transfer of this technology is possible and relatively simple. Two Salvadoran pathologists were trained to read ThinPrep Pap smears over a week-long training course. The cost of this training was relatively low and the pathologists were quickly able to learn the technique. There were no significant differences in the results of the ThinPrep slides analyzed in San Salvador and those analyzed in the United States.

We realize that a limitation of our study was the lack correlation between biopsy evaluation and histologic diagnosis. Although the women in our study who had lesions low-grade and above were referred to colposcopic studies, it was not possible to control for the examiner or to compare the results of the biopsy with those from the colposcopic studies done in the United States. Since these variables could not control for, it was assumed that the high-grade lesions and above noted in the liquid-based samples correlated with actual disease. A study conducted in a similar population in Guanacaste, Costa Rica, showed that the sensitivity of liquid-based cytology for detecting cervical intraepithelial neoplasia (CIN) 2 or above and squamous cells of undetermined significance (ASCUS) was 92.9% or greater, and that it was 100% for carcinoma [6]. We believe that the positive predictive value of ThinPrep slides is high enough to assume that women with high-grade lesions and above do have significant pathologic studies results.

Another potential problem was overtreatment of low-grade lesions since the women were allowed to be treated according to the normal Salvadoran system. One of the women in our study had CIN 1 and was treated with hysterectomy. It has been argued that the follow-up of rural women is so poor that performing hysterectomy is the only way to ensure adequate treatment. This approach, however, is unlikely to ever be cost-effective, and it can cause considerable morbidity and mortality. We believe that, as is the practice in other countries, it is essential to shift the current algorithm to focus on treatment of high-grade lesions and above before a national screening program can be implemented.

Although cervical cancer is a preventable disease, it causes considerable morbidity and mortality in developing nations. The use of improved screening technology and health fairs are ways to improve screening and detection of treatable precancerous lesions.

References

[1] Robles SC, White F, Peruga A. Trends in cervical cancer mortality in the Americas. Bull Pan Am Health Organ 1996;30:290–301.

[2] Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Matchar DB, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132:810–9.

[3] Coste J, Cochand-Priollet B, Cremoux P, Gales C, Cartier I, Molinie V, et al. Cross-sectional study of conventional cervical smear, monolayer cytology, and human papillomavius DNA testing for cervical cancer screening. BMJ 2000;326:733–8.

[4] Vassilakos P, Schwartz D, deMarvel F, Yousfi L, Broquet G, et al. Biopsy-based comparison of liquid-based, thin-layer preparations to conventional Pap smears. J Reprod Med 2000;45:11–6.

[5] Diaz-Rosario LA, Kabawat SE. Performance of a fluid-based, thin-layer Papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. Arch Pathol Lab Med 1999;123:817–21.

[6] Hutchinson MJ, Zahniser DJ, Sherman ME, Herrero R, Alfaro M, Bratti MC, et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. Cancer Cytopathol 1999;87:48–55.

[7] Roberts JM, Gurley AM, Thurloe JK, Bowditch R, Laverty CR. Evaluation of ThinPrep® Pap test as an adjunct to the conventional Pap smear. MJA 1997;167:466–9.

[8] Shield PW, Nolan GR, Phillips GE, Cummings MC. Improving cervical cytology in a remote, high-risk population. Med J Aust 1999;170:255–8.

[9] Brown AD, Garber AM. Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolaou testing. JAMA 1999;281:347–53.