Cervicography: An Intermediate Triage Test for the Evaluation of Cervical Atypia

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Background. A substantial number of abnormal Papanicolaou (Pap) smears are reported as demonstrating "cytologic atypia." This finding may actually represent premalignant cervical disease. Some of these patients may not be able to afford definitive colposcopic examinations, and simply repeating cytologic testing may result in missed treatable disease. The purpose of this study was to evaluate the use of cervicography as an intermediate triage test for women with atypical cervical cytology.

Methods. Women with a recent smear demonstrating cytologic atypia were evaluated using colposcopy, biopsy, and cervicography.

Results. Colposcopically directed cervical biopsies were obtained from 224 of 685 women with cytologic atypia. The histologic specimens confirmed evidence of cervical dysplasia for 166 women. Of these women, cervicography detected 74.7% of those who had mild dysplasia, 87.5% of those who had moderate dysplasia, 75% of those who had severe dysplasia, and the one patient who had cervical cancer. Most (93%) of the women with dysplasia that was undetected by cervicography had mild dysplasia.

Conclusions. Cervicography may be an effective intermediate triage test for the evaluation of young women with Pap smears demonstrating cytologic atypia.

Key words. Cervix dysplasia; cervix neoplasms; cytological techniques; cytology; cervicitis; photography.
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Of the abnormal Papanicolaou (Pap) smears collected from young women, 56% are reported as demonstrating cytologic atypia, or, more specifically, atypical squamous cells of undetermined significance (ASCUS).[1] The reason for this high rate of reported atypia is multifactorial. Closer scrutiny of smears by cytotechnologists, prompted by the Clinical Laboratory Improvement Amendment of 1988,[2] may be one explanation. The new Bethesda System of cervical cytology classification has also modified the morphologic categorizations of interpretation of the cytology smear.[3] Benign cellular changes of infection, inflammation, repair, and atypia, once known collectively as a class II Pap smear, are now reported as separate entities.

Approximately 15% to 25% of women with a Pap smear report of cytologic atypia actually have significant premalignant cervical disease.[4] Therefore, although there is no consensus, many physicians suggest that women with cytologic atypia should have a colposcopic examination. Such an aggressive, unselective threshold for colposcopy evaluation of minor abnormalities strains clinical capabilities and resources. Frequently, delays in colposcopy scheduling exacerbate patient anxiety over the abnormal Pap smear report. These emotional concerns are typically compounded by the expense of expert colposcopic examination.

A less aggressive management option is to obtain subsequent Pap smears at more frequent intervals. This option, however, involves serial office visits for the patient. Furthermore, this means continuing to monitor the

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abnormality by means of a screening test that is relatively insensitive compared with colposcopy. A more moderate management option or intermediate triage test to evaluate women with atypical cervical cytology, one that was technically uncomplicated, quick, inexpensive, and sensitive, could be useful.

Cervicography (National Testing Laboratories, Fenton, Mo) is a rapid and relatively inexpensive test used to detect cervical abnormalities.[5,6] Cervicography is most commonly used as a Pap smear adjunct to increase the sensitivity of detecting premalignant and malignant cervical disease.[7,8] Cervicography is based on colposcopic principles, and includes a photographic examination of the cervix after the application of acetic acid. The "cervigram," or photographic slide, is taken by suitably trained clinicians and interpreted by expert evaluators. A written evaluation, along with the cervigram, is returned to the clinician and included in the medical record. Cervicography has been shown to be more sensitive but less specific than the Pap smear in detecting premalignant cervical disease.[8–11]

The purpose of this investigation was to evaluate the use of cervicography as an intermediate triage test for women with atypical cervical cytology smear reports.

Methods

Subjects were recruited from the Family Medicine Center and Student Health Service, Medical College of Georgia, Augusta, Georgia; the Student Health Service, University of Georgia, Athens, Georgia; and the Student Health Center, Humboldt State University, Arcata, California. The inclusion criteria were that the woman be at least 18 years of age with a recent Pap smear indicating cytologic atypia.[3] The exclusion criteria were clinically apparent cervicitis, menses, surgical absence of the cervix uteri, and cytologic evidence of a low-grade or high-grade squamous intraepithelial lesion (mild to severe dysplasia).

Cervigrams were taken by manufacturer-trained clinicians according to the specified technique. The cervix was gently swabbed twice with a solution of 5% acetic acid. It was clearly visualized, focused through the cerviscope (camera), and two cervigrams were taken. The film was returned to the manufacturer for processing and then interpreted by certified evaluators as follows: "negative" if normal; "atypical" if there was evidence of an acetowhite lesion outside the transformation zone, or inside the transformation zone but of doubtful significance, or of atypical immature squamous metaplasia; "positive" if there was evidence of minor or major grade lesion or cancer; and "technically defective" if the film was technically uninterpretable. Cervigram and histologic evaluators were mutually blinded to the results.

Colposcopy was performed, and colposcopically directed biopsies were obtained by traditional methods.[12] Only subjects with colposcopically significant cervical changes of the abnormal transformation zone had a tissue biopsy. Histologic specimens were evaluated at each clinical site reference laboratory by certified pathologists.

Statistical Methods

For data analyses, atypical cervigrams were considered as positive tests, since frequently the findings are indicative of minimally significant premalignant change. "High-risk" patients were defined as those having a current or prior human papillomavirus infection of the lower genital tract; having a history of an abnormal Pap smear; or being older than 50 years of age.

The proportion of patients in each dysplasia category who were correctly classified as atypical or positive by cervigram was calculated as a measure of the effectiveness of cervicography as a triage test. Ninety-five percent confidence intervals (CI) for the proportions were calculated, based on the F-distribution. The Mantel-Haenszel chi-square statistic was used to test the statistical significance of the association of cervigram category and histology category, incorporating the ordinal nature of the classifications. Kendall's tau statistic was calculated as a measure of the strength of association.

Results

A total of 1449 subjects were screened by a Pap smear and cervicography. Pap smears detected cytologic atypia in 685 women. The majority of these women received an examination by colposcopy; however, some subjects refused colposcopy, opting for management by repeat Pap smears. Occasionally women received colposcopy examinations by another clinician whose findings were unavailable. Evaluation and treatment for some women were also managed by the clinicians, based on the appearance of the cervigram.

Colposcopically directed cervical biopsies were obtained from 224 women. Cervical dysplasia was histologically confirmed in 166 of the 685 (24%) women with atypical cytology. Cervigrams were technically adequate for 220 of 224 (98%) subjects. Obscuring cervical mucus was noted on the remaining four cervigrams.

Demographic data, based on those women who had a cervical biopsy, revealed a mean subject age of 23.8 years. No subjects were pregnant, and 86% were nulliparous. A history of previous human papillomavirus in-

Cervicography Use for Triage of Atypical Papanicolaou Smear Reports* (N = 224)

Histology	Cervicography			Totals
	Negative†	Atypical‡	Positive§	
Negative	2	7	3	12
Atypia	11	13	21	45
Mild dysplasia	37	48	61	146
Moderate dysplasia	2	5	9	16
Severe dysplasia	1	0	3	4
Cancer	0	0	1	1
Totals	53	73	98	224

**Mantel-Haenszel chi-square = 1.425; P = .233 for association of cervigram and histology. Kendall's tau = .06 for measure of association.*
†Normal.
‡Acetowhite lesion outside the transformation zone, inside the transformation zone but of doubtful significance, or atypical immature squamous metaplasia.
§Minor or major grade lesion or cancer.

fection was indicated by 55 of 224 (25%) subjects. Previous cervical biopsies or cervical therapy, or both, were noted by 27 of 224 (12%) subjects.

A comparison between the cervicography and biopsy results for women with atypical Pap smears is given in the Table. Cervicography detected 75% (95% CI, 67.3 to 82.0) of women with mild dysplasia, 88% (95% CI, 61.6 to 98.4) with moderate dysplasia, 75% (95% CI, 19.4 to 99.4) with severe dysplasia, and the one patient with cervical cancer. Cervicography thus detected 126 of 166 (76%) women with dysplasia when an atypical cervigram was considered as a positive finding.

The majority (93%) of the 40 women with dysplasia that was not detected by cervicography had mild dysplasia. Each of the 3 women with high-grade squamous intraepithelial lesions undetected by cervicography had a cervigram on which the complete squamocolumnar junction and transformation zone had not been visualized. Of the remaining 37 women with low-grade squamous intraepithelial lesions missed by cervicography, the squamocolumnar junction and transformation zone were inadequately visualized in 26 (70%).

The ability of cervicography to detect premalignant disease in high-risk and low-risk subjects was evaluated. Cervicography detected 86 of 112 (77%) low-risk subjects with dysplasia and detected 41 of 55 (75%) high-risk subjects with dysplasia. There was no statistically significant difference between the rates of detection for these two groups. The three subjects with high-grade disease undetected by cervicography were considered high-risk subjects.

When the exclusion of high-risk patients and the limitation of nonvisible transformation zone are considered, only 8 of 166 (5%) women with dysplasia were missed by cervicography. It must be remembered that the Pap smear failed initially to detect dysplasia in all of those 166 subjects. Of the 166 women with histologic evidence of dysplasia from the original 685 with cytologic atypia, only 1.2% remained undetected by cervicography.

Discussion

The results of this study indicate that cervicography, used as an intermediate triage test to evaluate women with cervical cytologic atypia, detected 76% of women with previously undetected histologic evidence of dysplasia. With the exclusion of high-risk patients, only 16% of subjects with dysplasia remained undetected. Moreover, when those patients with a nonvisible transformation zone were excluded, only 5% of women with dysplasia undetected by Pap smear were also undetected by cervicography. Of those few women undetected by cervicography, 93% had only mild dysplasia. At least 50% of patients with mild dysplasia will experience disease regression,[13] and less than 10% of patients will progress to cervical intraepithelial neoplasia (CIN) grade III.[14] More important, provided the cervigram demonstrated adequate visualization of the transformation zone of the cervix, no women with moderate to severe dysplasia were undetected by cervicography. Therefore, triage with cervicography minimized the need for colposcopy, identified all cases of high-grade disease (when the transformation zone was visible), and was capable of detecting more premalignant disease than initial Pap smear.

Colposcopy with directed biopsy is the current diagnostic method of choice for the evaluation of premalignant or malignant cervical disease. Management options, however, should not be limited to using either a less sensitive screening technique (ie, repeat Pap smear) or an expensive technique (ie, colposcopy) when evaluating minimally abnormal cytology, when serious disease of the ectocervix is readily identified by cervicography.[8–11] However, cervicography is not a diagnostic test. The limitations of cervicography are the inability to evaluate the endocervical canal and the absence of a histologic specimen. Otherwise, there are many similarities between colposcopy and cervicography. Because it combines features of both screening and diagnostic testing, cervicography is well suited for the role of an intermediate test.

The clinical significance of cervical cytologic atypia is unclear and controversial.[15] In theory, the cellular changes of atypia are minimal but discernible. The atypical cells are neither normal squamous epithelial cells nor premalignant squamous cells. Whether atypical cells represent true cervical cancer precursor cells is debatable. That approximately 15% to 25% of women with atypical cervical cytology actually have histologic evidence of premalignant cervical disease is not controversial.[4] In our population of young women, 24% of women with cytologic atypia had histologic evidence of cervical dysplasia, which was primarily mild and virally induced.

The threshold for performing colposcopy for cytologic atypia varies among physicians.[16] Some clinicians colposcopically evaluate women with a single atypical smear; others wait for two successive atypical smears; and some await a smear demonstrating high-grade premalignant changes.[17] Yet the actual risk for premalignant disease is equivalent for women with one or more atypical smears. Using colposcopy to detect 15% to 25% of patients with disease is expensive, emotionally traumatic, and unnecessary for the 75% to 85% of patients with normal findings. Certainly, limiting colposcopy to those women at high risk for disease is preferable. Thus, cervicography appears to be an appropriate triage test to minimize unnecessary colposcopy.

The essence of this study was to evaluate an alternative, practical clinical approach to women with atypical (ASCUS) Pap smears. Based on the retrospective data analysis, we propose an algorithm for triage by cervicography (Figure). Further prospective studies may be useful to examine the follow-up interval cytology recommendations, but only for the negative cervigram arm of the triage.

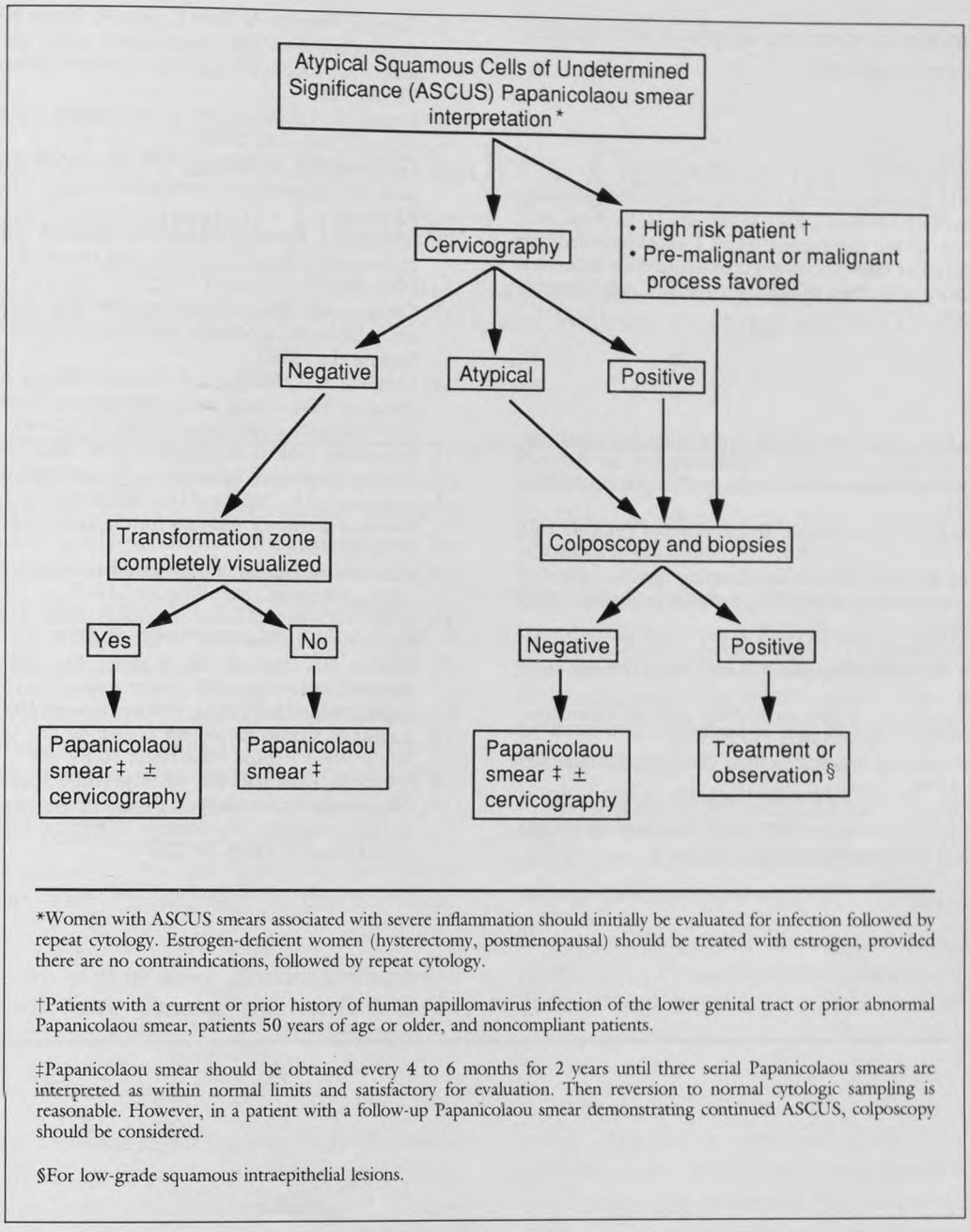
Women found to have an atypical or positive cervigram should be examined by colposcopy, and, when appropriate, cervical biopsies should be obtained. Although our data indicate that cervicography is nearly as effective in detecting premalignant disease in high-risk women (75%) as in low-risk women (77%), high-risk or noncompliant patients may be best evaluated initially by colposcopy. All women with negative cervicography findings and cytologic atypia should still be considered at greater risk than women with normal cervical cytology. Women with a negative cervigram interpretation and fully visualized transformation zone should be scheduled for a Pap smear and possibly cervicography in 4 to 6 months. Women with a negative cervigram but an incompletely visualized transformation zone should have a repeat Pap smear every 4 to 6 months until three serial Pap smears are interpreted as being within normal limits and satisfactory for evaluation. Women found to have mildly abnormal cervical cytology may be monitored in the future by serial computerized colposcopy.[18]

Women 50 years of age or older with evidence of atypical cytology should be examined by colposcopy. The rationale for this recommendation is that these women have a greater risk for actually having significant premalignant cervical disease than younger women. Also, it is less likely that the squamocolumnar junction and transformation zone will be adequately visualized by cervicography.

Other investigators have documented the utility of cervicography as an intermediate triage test. In a comparative study of 681 patients with atypical cervical cytology, August[19] demonstrated that cervicography and colposcopy were superior to repeat cytology or human papillomavirus (HPV) DNA testing for the 14% of patients subsequently found to have cervical intraepithelial neoplasia. Cervicography detected 85% of patients with cervical intraepithelial neoplasia, colposcopy 52%, HPV DNA testing 43%, and repeat cytology 10%. Cervicography failed to detect only nine cases of cervical intraepithelial neoplasia (eight CIN I, one CIN II). As in our study, most represented low-grade disease.

Jones et al[4] evaluated 236 patients with atypical Pap smears by colposcopy, cervicography, and repeat Pap smear. Of 58 patients (25%) with actual CIN, 97% were detected by colposcopy, 81% by cervicography, and only 17% by repeat Pap smear. In a comparative study of similar design, Spitzer et al[20] demonstrated that in 97 patients with atypical cervical cytology a repeat Pap smear identified 58% of the patients with colposcopically identified CIN, whereas cervicography detected 89% correctly. In our study, 76% of patients with dysplasia were identified by cervicography, similar to the rates of 81% to 89% reported in the previous studies.

The conclusions of this study must be accepted with the knowledge of potential limitations. First, the study



*Women with ASCUS smears associated with severe inflammation should initially be evaluated for infection followed by repeat cytology. Estrogen-deficient women (hysterectomy, postmenopausal) should be treated with estrogen, provided there are no contraindications, followed by repeat cytology.

†Patients with a current or prior history of human papillomavirus infection of the lower genital tract or prior abnormal Papanicolaou smear, patients 50 years of age or older, and noncompliant patients.

‡Papanicolaou smear should be obtained every 4 to 6 months for 2 years until three serial Papanicolaou smears are interpreted as within normal limits and satisfactory for evaluation. Then reversion to normal cytologic sampling is reasonable. However, in a patient with a follow-up Papanicolaou smear demonstrating continued ASCUS, colposcopy should be considered.

§For low-grade squamous intraepithelial lesions.

Figure. Intermediate triage of cervical cytologic atypia.

included a small number of women with actual high-grade cervical disease. Also, subject enrollment selection bias occurred, which may have influenced the outcome data. Furthermore, no pregnant patients were included. The study population also consisted of young women, who, in general, are less likely to have significant cervical disease. When present, however, cervical disease and the transformation zone would typically be ectocervical in location and easily visualized. Thus, cervicography may be the ideal intermediate triage test for this population. A cost-benefit analysis of intermediate triage of atypical smears by cervicography would help clarify the financial implications of this approach.

In summary, cervicography may be used as an effective, inexpensive intermediate triage test for the evaluation of women with Pap smears demonstrating cytologic atypia. Cervicography detected 76% of women who had histologically proven dysplasia with an initial atypical cytologic cervical smear. Provided the transformation zone was adequately visualized on the cervigram, all

women with moderate to severe dysplasia were suitably recognized by cervicography.

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