

### Cervicography for triage of women with mildly abnormal cervical cytology results

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**OBJECTIVE:** To estimate the sensitivity and specificity of cervicography in detecting cervical cancer precursor lesions in women participating in the National Cancer Institute's multicenter atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion triage study (ALTS).

**STUDY DESIGN:** Cervigrams were obtained from 3134 women with a referral Papanicolaou smear diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. Cervigram and cervical histology results were compared by using cervical intraepithelial neoplasia (CIN) 2 and CIN 3 disease end points.

**RESULTS:** Of 3134 women, 444 had histologic findings of more than or equal to CIN 2 and 222 had CIN 3. Cervicography interpretation by using a threshold of greater than or equal to atypical had a sensitivity, specificity, and positive and negative predictive values of 79.3%, 61.0%, 13.4%, and 97.5%, respectively, for detecting greater than or equal to CIN 3. Cervicography was more sensitive (80.8% vs 57.1%), but less specific (55.7% vs 81.8%), for detecting CIN 3 in women younger than 35 years compared with women 35 years or older, respectively.

**CONCLUSIONS:** Cervicography functioned moderately well at detecting CIN 2 or CIN 3 in women with atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion Papanicolaou smear results. Cervigram sensitivity was better for younger women. (Am J Obstet Gynecol 2001;185:939-43.)

**Key words:** Cervicography, cervical neoplasia, cervical cytology

Cervicography is a photographic test designed to detect cervical neoplasia.<sup>1, 2</sup> Although intended to be used as an adjunct to cytologic examination for cervical screening, it has also been used as an intermediate triage test for women with Papanicolaou (Pap) smear reports that show atypical squamous cells of undetermined significance (ASCUS) or a low-grade squamous intraepithe-

lial lesion (LSIL).<sup>3-11</sup> One set of guidelines for treating women with minor cytologic abnormalities states that cervicography might be useful as an adjunct to cytologic examination for triage purposes,<sup>12</sup> but because of limited data, those guidelines recommend that its use be limited to research applications until clinicians fully understand the technology and potential utility.

Cervicography is the standardized photography (obtained with a specialized 35-mm camera) of the cervix after application of 5% acetic acid, followed by expert interpretation of its images, as well as quality control measures by a qualified evaluator.<sup>1, 2</sup> Cervigrams are static photographic images of the cervix similar to those seen during low-level magnification colposcopy. Clinicians receive a written evaluation and color print of the cervical image to assist with patient treatment and education and to provide important technical feedback for the operator.

The ASCUS LSIL triage study (ALTS), funded by the National Cancer Institute, was designed to determine the optimal treatment of women with ASCUS and LSIL Pap

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smear results.<sup>13-16</sup> Eligible women with these minor cytologic abnormalities were assigned randomly between 1997 and 1999 to 1 of 3 arms: immediate colposcopic examination, repeated cytologic testing with referral for colposcopy at a threshold of high-grade squamous intraepithelial lesion (HSIL), or repeated cytologic testing with DNA testing for cancer-associated types of human papillomavirus (HPV) at enrollment. During follow-up, Pap smears were obtained from all women every 6 months for 2 years, and cervicography was done during all patient visits as part of a safety net to detect occult cervical cancer.<sup>3</sup> However, we used the data to estimate the performance of cervicography as a triage method; thus, the present analyses refer only to cervical neoplasia detected at enrollment.<sup>15</sup> The purpose was to determine the sensitivity and specificity of cervicography to detect potential cervical cancer precursor lesions in the context of ALTS.

### Patients and methods

After we obtained informed consent from the institutional review boards, patients were enrolled from 4 clinical centers located in Birmingham, Alabama, Oklahoma City, Oklahoma, Pittsburgh, Pennsylvania, and Seattle, Washington. Women eligible for inclusion in this study were nonpregnant, 18 years of age or older, with an intact cervix uteri, no history of prior treatment for neoplasia of the cervix, and a referral Pap smear obtained within the past 6 months demonstrating ASCUS or LSIL. They were assigned randomly by a computer program (accessed by telephoning the central coordinating unit) to the immediate colposcopy, cytology only, or HPV testing plus cytology arm. It was very uncommon ( $n = 6$ ) that patients were sent from triage to undergo colposcopy or biopsy based on "safety net" findings. These findings included a cervigram or digitized cervical image interpretation by the ALTS colposcopy quality control group that indicated possible cervical cancer or a pathology quality control group diagnosis of greater than or equal to CIN 3 in the referral Pap smear, enrollment liquid-based Pap smear, or cervical histology. Excluding these few patients sent from triage because of safety net findings did not change the conclusions. Only women in the immediate colposcopy and HPV testing plus cytology arms were included in this analysis because ascertainment of disease end points at enrollment was complete in these management arms.<sup>16</sup> Women randomly assigned to the less sensitive arm, which depended on high-grade cytology triage alone were excluded because this arm did not readily identify women with high-grade lesions and would have biased the sensitivity and specificity estimates.

Cerviscopes supplied by the manufacturer (National Testing Laboratories, Fenton, Mo) were used by nurse clinicians to obtain cervigrams on all patients during the initial pelvic examination. Before the study, all clinicians

received in-service training in the operation of the cerviscopes and acquisition of cervigrams.<sup>2</sup> Cervigrams were then processed according to the manufacturer's protocol and interpreted in a blinded manner.<sup>6</sup> Only "suspect cancer" diagnoses were reported immediately to the clinical centers; otherwise, cervicography reports were compiled for this analysis.

Cervigram evaluation categories were defined as follows: "technically defective" if the cervigram was uninterpretable; "negative" if no abnormalities were found; "atypical" if an acetowhite lesion was detected outside the transformation zone or within the transformation zone but not considered significant; and "positive" if indicative of cervical intraepithelial neoplasia or cancer. "Positive" interpretations were further divided into 4 subcategories: low-grade squamous intraepithelial lesion (P1); high-grade squamous intraepithelial lesion (P2); cancer (P3); and probably normal, but warning signs of cancer present (P0). However, the last, rare category was defined as normal for our evaluation. The more common terminology of squamous intraepithelial lesion (SIL), rather than P categories, is used for this presentation.

Pap smears were obtained from all women at the enrollment visit by using liquid-based thin-layer cytologic methods (ThinPrep, Cytec Corporation, Boxborough, Massachusetts). Some patients had cervical biopsies taken and underwent an endocervical curettage, if indicated, during subsequent colposcopic examinations. These cytologic and histologic specimens, along with electrosurgical loop excision specimens, were interpreted by clinical center pathologists and the ALTS pathology quality control group. Final diagnoses were determined by the pathology quality control group by using a diagnostic algorithm described previously.<sup>16</sup> Cytologic results were reported by using the Bethesda System. Histologic results were reported by using the CIN classification system.

Distributions of cervigram result categories were compared among study arms and between referral Pap smear groups by means of the  $\chi^2$  statistic. Cervigram performance was evaluated by using 2 cervigram cut points ( $\geq$ atypical and  $\geq$ LSIL) to define positive test results, and 2 histologic disease definitions,  $\geq$ CIN 2 and  $\geq$ CIN 3. Histologic diagnoses were determined by the pathology quality control group. Sensitivity, specificity, positive and negative predictive values, and percent referred were calculated for each test definition. Sensitivity and specificity were compared for different test cut points by using McNemar's test. Exact CIs for sensitivity and specificity were calculated based on the F distribution.

### Results

There were 4961 cervigraphic results available for interpretation from ALTS patients, of which, 1798, 1359, and 1804 were obtained from women in the immediate colposcopy, HPV test, and conservative management

**Table I.** Cervigram compared with referral Papanicolaou smear

Cervigram result	Referral Pap smear		
	ASCUS n (%)	LSIL n (%)	Total n (%)
Normal	1418 (63.0)	409 (46.4)	1827 (58.3)
Atypical	311 (13.8)	166 (18.8)	477 (15.2)
LSIL	483 (21.5)	271 (30.7)	754 (24.1)
HSIL	39 (1.7)	35 (4.0)	74 (2.4)
Cancer	1 (0.1)	1 (0.1)	2 (0.1)
Total	2252 (71.9)	882 (28.1)	3134 (100.0)

$\chi^2 = 76.97, P < .001.$

ASCUS, Atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; Atypical, an acetowhite lesion detected outside the transformation zone or detected within the transformation zone but considered not significant; HSIL, high-grade squamous intraepithelial lesion.

arms, respectively. The reduced number from the HPV testing arm resulted from early closure of this arm among women referred for LSIL cytologic diagnoses because the percentage of cancer-associated HPV positivity was so high (83%).<sup>14</sup> Of the total number of cervigrams, 37 (0.8%) were considered technically defective, and thereafter were excluded from further analyses. The majority of cervigrams (58.0%) were interpreted as negative, whereas 15.5% were atypical, 23.4% low-grade, 2.3% high-grade and 0.1% cancer. As a result of randomization, the 3 study arms demonstrated balance with regard to disease prevalence, including cervicography diagnoses ( $\chi^2 = 8.22, P = .8$ ).

As explained in Patients and methods, only cervigram results from the immediate colposcopy and HPV triage arms were considered in the remaining analyses that follow. Cervigram interpretations were compared with the remaining 2252 ASCUS and 882 LSIL referral Pap smear results (Table I). Cervigram interpretations were not equally distributed for the 2 types of referral Pap smears ( $\chi^2 = 76.9, P < .001$ ). A greater percentage of cervicographic findings were reported as abnormal among the women referred with an LSIL Pap smear. Similarly, the prevalence of underlying CIN was related to the referral diagnoses. Of patients with a referral Pap smear of ASCUS, 11.6% (260/2252) had cervical histologic findings of  $\geq$ CIN 2, and 20.9% (184/882) of patients with LSIL had cervical histologic findings of  $\geq$ CIN 2.

Cervigram interpretations were compared with final diagnoses at 2 histologic levels,  $\geq$ CIN 2 and  $\geq$ CIN 3 (Table II). There were 444 results of patients with  $\geq$ CIN 2 histology and 222 results of patients with  $\geq$ CIN 3 category available for consideration. We considered 2 cervigram positive test thresholds of  $\geq$ atypical and  $\geq$ LSIL to determine variations in cervigram performance. Use of the threshold of  $\geq$ atypical for detection of  $\geq$ CIN 3 would have yielded a sensitivity of 79.3% and would have required the referral of 41.8% of women for colposcopy examina-

tion. If the triage threshold was increased to a low-grade or more severe cervigram finding, the sensitivity for detecting CIN 3 was 65.8%, requiring referral of 26.5% of women to a colposcopy examination.

Cervicography sensitivity and the percent of women referred for colposcopy were also analyzed based on specific referral Pap smear results of ASCUS or LSIL (Table III). The sensitivity of cervicography differed minimally based on the referral Pap smear diagnosis, but comparatively, a greater percentage of women with LSIL would be referred to colposcopy, as might be expected.

Because cervicography may be of decreased utility when the full extent of the cervical transformation zone cannot be appreciated, the results in Table II were stratified by subject age younger than and older than or equal to 35 years (Table IV). For the 2527 women younger than 35 years, the sensitivity of cervicography was 80.8% to detect  $\geq$ CIN 3 by using the threshold of atypical or more severe cervigram to represent positive test results. This would require 47.3% of women to be referred for colposcopy. The sensitivity of cervicography was 57.1% for the remaining 607 women  $\geq$ 35 years and would result in referral of only 19.1% of women for colposcopy.

### Comment

Cervicography functioned moderately well at detecting cervical cancer precursors in women with ASCUS and LSIL Pap smear results. A positive cervigram threshold of greater than or equal to atypical yielded the best sensitivity (79.3%) for detecting cancer precursors resulting in referral of approximately 40% of women for further evaluation by colposcopy. Any additional gains of sensitivity provided by cervicography in relation to the Pap smear may be attributed to it being similar in some respects to a low-magnification static colposcopy examination. However, considerable subjectivity exists in the evaluation of cervical lesions during colposcopy. The same can be said for cervicography, which operates under less ideal circumstances, in comparison.<sup>13</sup> The cervigram interpreter cannot manipulate the cervix, use an endocervical speculum to visualize the transformation zone (main site for cervical neoplasia) or lesion extending into the endocervical canal, appreciate the vasoconstrictive effects of 5% acetic acid, observe the duration of acetic acid effect to predict severity of disease, or determine whether the cervicographic images were taken during the time of maximum acetic acid effect. Cervical alignment, anatomic variation, sufficient acetic acid application, blood, mucus, and inflammation also influence cervigram results.<sup>6</sup> Regardless, less than 1% of the cervigrams in our study were considered technically defective.

A positive cervigram threshold of  $\geq$ LSIL was found to be too insensitive for identifying women with CIN 2 or more severe abnormalities. However, a positive cervigram threshold of greater than or equal to atypical provided similar sensitivity for the detection of greater than or equal to CIN

**Table II.** Performance of cervicography at different positive test result thresholds

Positive cervigram threshold	Positive histology threshold	Sensitivity %	Specificity %	PPV %	NPV %	% Referred
≥Atypical	≥CIN 2	74.1 329/444 (69.8,78.1)	63.5 1708/2690 (61.6,65.3)	25.1	93.7	41.8
	≥CIN 3	79.3 176/222 (73.3,84.4)	61.0 1777/2912 (59.2,62.8)	13.4	97.5	
≥LSIL	≥CIN 2	56.8 252/444 (52.0,61.4)	78.5 2112/2690 (76.9,80.1)	30.4	91.7	26.5
	≥CIN 3	65.8 146/222 (59.1,72.0)	76.5 2228/2912 (74.9,78.0)	17.6	96.7	

PPV, Positive predictive value; NPV, negative predictive value; LSIL, low-grade squamous intraepithelial lesion; Atypical, an acetowhite lesion detected outside the transformation zone, or detected within the transformation zone, but considered not significant; Referred, percent of women referred for colposcopy by using a ≥atypical or ≥LSIL positive cervigram threshold; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, Cervical intraepithelial neoplasia grade 3. (95% CI) for sensitivity and specificity.

**Table III.** Cervicography sensitivity of detecting ≥CIN 3 and percent referred for colposcopy for women with ASCUS and LSIL Pap smear results

Positive cervigram threshold*	Referral Pap smear	Sensitivity %	% Referred†
≥Atypical	ASCUS	78.6	37.1
	LSIL	80.2	53.9
≥LSIL	ASCUS	67.2	23.2
	LSIL	63.7	34.8

\*Threshold of cervigram necessary for triage to colposcopy.

†Percent of women referred for colposcopy.

Atypical, An acetowhite lesion detected outside the transformation zone or detected within the transformation zone but considered not significant; LSIL, low-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance.

2 or greater than or equal to CIN 3 histologic findings when compared with the range of recent estimates of the sensitivity of the Pap smear, but with decreased specificity.<sup>17</sup> Our positive predictive values for detecting high-grade lesions with cervicography were very similar to those of other studies that used cervicography to evaluate women with ASCUS-equivalent Pap smears.<sup>10, 11, 18</sup>

Just as HPV DNA testing and cervical cytology performance results are affected by patient age, so is cervicography. Our study demonstrated the better sensitivity of cervicography when used for younger women in whom the transformation zone is more readily apparent. The visible presence of the transformation zone on the cervigram serves as an adequacy equivalent of columnar and metaplastic cells on Pap smears. Therefore, repeated use of cervicography is not beneficial for postmenopausal women found to have negative or normal cervigram findings with an incompletely visualized transformation zone. HPV DNA testing for oncogenic HPV types may be more suitable for identification of cancer precursors in this

older population,<sup>19</sup> although definite data are lacking. This limitation of cervicography when used as a triage test in older women also applies to the use of cervicography for primary screening.<sup>3</sup> In the Guanacaste study conducted by the National Cancer Institute, cervicography at a referral threshold of greater than or equal to ASCUS had a 54.6% sensitivity for detecting high-grade squamous intraepithelial lesion or more severe lesions in women younger than 50 years of age, but only a 26.9% sensitivity in women older than or equal to 50 years.<sup>19</sup> We used a cut-off of 35 years because our population was younger than that of the study in Guanacaste. Furthermore, most women who are age 50 have an unsatisfactory finding on colposcopy examination, which on an equivalent basis, negatively biases cervicography. A threshold of 35 years of age was therefore considered more appropriate.

Cervicography is one of several Pap smear adjunct techniques designed to complement primary screening for cervical neoplasia or assist in the management of women with mildly abnormal cytologic results. These tests all attempt to enhance the moderate sensitivity of the Pap smear and maintain the excellent levels of specificity of high-grade cytologic diagnoses.<sup>17</sup> The application of cervicography within the context of ALTS is not one of a primary screening adjunct, but rather triage of a population determined to be at increased risk for cervical neoplasia on the basis of a prior ASCUS or LSIL result.

Because we considered ALTS enrollment data only, cervicography at the positive threshold of greater than or equal to atypical achieved reduced sensitivity for detecting CIN 3 (7% to 17% less sensitive than cytology and HPV testing, respectively), resulting in referral of 19% to 21% fewer women for colposcopy when compared with triage by using cytology (86% sensitivity and 58% referred at a ≥ASCUS cut point) or HPV DNA testing (96% sensitivity and 56% referred at a 1-pg positive test threshold).<sup>16</sup>

**Table IV.** Performance of ALTS cervicography for detecting  $\geq$ CIN 3 in women  $<35$  years old and  $\geq 35$  years\*

Age (y)	Sensitivity % <sup>†</sup>	Specificity % <sup>‡</sup>	PPV%	NPV%	% Referred
<35	80.8	55.7	14.1	97.0	47.3
$\geq 35$	57.1	81.8	6.9	98.8	19.1

PPV, Positive predictive value; NPV, negative predictive value; Referred, percent of women referred for colposcopy.

\*For cervigram positive threshold of  $\geq$ atypical.

<sup>†</sup> $\chi^2 = 4.46, P = .035$ .

<sup>‡</sup> $\chi^2 = 134.98, P < .001$ .

Clearly, the performance of cervicography varies whether used as a triage test after abnormal cervical cytologic findings or as a primary adjunct test in a screening population. However, despite the noticeable differences in sensitivity, cervicography, cytology, and HPV testing differed only subtly in terms of positive and negative predictive values in identifying women with  $\geq$ CIN 3 (8% and 99%, 9% and 98%, and 10% and 99%, respectively). Cost-utility analyses will determine whether and when cervicography, compared with other clinical options, is useful in the management of mildly abnormal cervical cytology results.

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