

The Effectiveness and Safety of Two Cervical Cytologic Techniques During Pregnancy

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BACKGROUND. There have been few studies documenting the optimal cervical cytologic technique in pregnancy. This study was initiated to investigate the effectiveness and safety of two standard techniques.

METHODS. Two hundred twenty-two new obstetrical patients at a family practice residency program signed informed consent, were enrolled, and were randomized for cervical cytologic screening using either Zelsmyr Cytobrush and Ayre spatula or Dacron swab and Ayre spatula. The pathologists were blinded to the study, and results were reported with standard Bethesda System nomenclature. Patients were asked about complications at follow-up visits. Statistical analysis was performed using Fisher's exact test and the two-sample *t* test, with statistical significance set at $P < .05$.

RESULTS. The Cytobrush-spatula technique yielded 95.6% (108/113) smears with adequate endocervical cells, as compared with 69.7% (76/109) of smears obtained with the Dacron swab and spatula ($P = <.0001$, odds ratio 9.38). Cytologic atypia, defined as noninflammatory cellular abnormalities, was uncovered on 15.9% (18/113) of the smears obtained with the Cytobrush and spatula technique and on 13.8% (15/109) of the smears obtained with the Dacron swab and spatula ($P = .7082$). The complication rate, which included spot bleeding and spontaneous abortion, occurred in 6.5% (7/108) of the smears obtained with the Cytobrush and 3.8% (4/105) of the smears obtained with the Dacron swab ($P = .54$).

CONCLUSIONS. The Cytobrush-spatula technique significantly increased endocervical cell yield, did not increase detection of cytologic atypia, and did not increase the risk of adverse maternal or fetal outcomes when used for cervical cytologic screening during pregnancy. These results support the use of the Cytobrush-spatula technique over the swab and spatula for obtaining cervical cytologic smears in pregnancy.

KEY WORDS. Vaginal smears; cervical smears; cytological techniques; pregnancy. (*J Fam Pract* 1997; 45:159-163)

The Papanicolaou smear has been used for cervical cytologic screening since the 1940s.¹ Subsequently, the techniques and instruments used for collecting cervical cytologic samples have evolved, resulting in an increased sensitivity of the test.^{2,8} The pathologic investigation of cervical cytologic samples has also undergone evolution, with a greater emphasis being placed on the presence of endocervical cells for adequate pathologic interpretation.^{6,9-11}

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This has been codified in the Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses.¹² During the same period, several studies documented that pregnancy significantly increases the likelihood of suboptimal smears as defined by a lack of endocervical cells.^{13,14}

The Cytobrush has emerged as an important tool for increasing endocervical cell yields in nonpregnant women of reproductive age and in postmenopausal women.¹⁵⁻²² Recent studies verify a similar effect with pregnant women; however, none of the studies demonstrate that use of the Cytobrush leads to enhanced detection of cytologic atypia.²³⁻²⁷ There has been some concern over potential maternal-fetal complications associated with the use of the Cytobrush, which has led the manufacturer to list pregnancy as a contraindication to its use. Presumably, this warning is based on potential com-

plications such as cervical bleeding, amniotomy, premature labor, and spontaneous abortion. These potential problems have hampered the number of investigations involving pregnant women. At this time there are only five such studies in US medical literature,²³⁻²⁷ and all of them have failed to identify complications significant enough to warrant a contraindication for the use of the Cytobrush in pregnancy.

Since optimal techniques and safety in pregnancy have been examined in only a small number of studies, this study was initiated to investigate endocervical cell yield, detection of cytologic atypia, and complication rates of two standard cervical cytologic techniques.

METHODS

The study group consisted of all new obstetric patients seen from February 1993 to February 1995 at the three family practice centers of the Carilion Health Systems-Roanoke Memorial Hospital Family Practice Residency in Roanoke, Virginia. Patients signed a consent form approved by the Institutional Review Board of Roanoke Memorial Hospital. There were no exclusion criteria for entrance into the study. A total of 222 patients were enrolled, evaluated, and followed by family practice residents and faculty. Physicians were not blinded to the method, but were instructed in the proper techniques for the performance of a Papanicolaou (Pap) smear by each method. Demographic data obtained at the time of the initial examinations were considered potential confounding variables, and included age, gravidity, parity, gestational age, and history of abnormal Pap smear.

The patients signing informed consent were randomized by alternate assignment to the two methods being studied based on chronological presentation to each office. The methods evaluated were (1) Dacron swab and Ayre spatula, and (2) Zelsmyr Cytobrush (Medscand [USA], Hollywood, Fla) and Ayre spatula. The cervical cytologic collection technique for both methods was the same. The Dacron swab and Cytobrush were inserted into the endocervical canal and rotated 90° one to three times. The Ayre spatula was rotated circumferentially over the ectocervix; the number of rotations was operator dependent. Smears were placed in pairs on a single glass slide, with a swab-spatula specimen on one half

of the surface and a Cytobrush-spatula specimen on the other. The slide was immediately fixed with 95% alcohol spray.

Cytologic interpretation of the smears was performed by pathologists at Roanoke Memorial Hospital. The pathologists were blinded to the method of cell harvest. The Bethesda System of reporting was used for all smears, and specimen adequacy was designated "satisfactory for evaluation," "satisfactory but limited," or "unsatisfactory" based on standard criteria.¹² The results were likewise described with standard Bethesda System nomenclature. For the purposes of this study, cytologic atypia was defined as cytologic abnormalities including nonspecific inflammation, atypical squamous cells of undetermined significance (ASCUS), low-grade or high-grade squamous intraepithelial lesion, and squamous cell carcinoma. Smears with infectious causes such as trichomonas, *Candida*, herpes simplex virus, and bacterial abnormalities were not included in the smears considered to have cytologic atypia.

All patients were seen for follow-up in a maximum of 4 weeks after the initial examination. Data were collected on the incidence of spontaneous abortion, premature rupture of membranes, vaginal bleeding, and premature labor, as well as other problems identified by the patient. Patients with inadequate follow-up were excluded from the study. Inadequate follow-up was defined as no office follow-up within 4 weeks of obtaining the smear. A total of 9 patients met this definition and were excluded.

Statistical analysis was performed using Fisher's exact test and the two-sample *t* test, with statistical significance set at $P < .05$. Where statistically significant differences were detected, the odds ratio was calculated. A power analysis was performed with regard to complications; to achieve a power of .8 would require 420 patients and a complication rate difference of 5%.

RESULTS

The two groups were balanced with respect to demographic means and frequencies regarding age, gravidity, parity, gestational age, and previous abnormal Pap smear (Table 1). Because of the symmetry between the two groups, the demographic variables were not considered confounding factors, and consequently, were not used in the analysis.

TABLE 1

Patient Demographic Data and Gestational Age at Entry into Study of Two Methods of Collecting Cervical Cytologic Samples

Variables	Cytobrush and Spatula, n=113	Dacron Swab and Spatula, n=109	P Value
Age, mean (\pm SD)	23.28 (5.59)	23.05 (5.24)	.74*
Gravidity, mean (\pm SD)	2.59 (1.14)	2.58 (1.69)	.94*
Parity, mean (\pm SD)	1.04 (1.04)	0.98 (1.08)	.66*
History of abnormal Pap, no. (%)	6 (5)	7 (6)	.78†
First trimester, no. (%)	71 (63)	70 (64)	.89†
Second trimester, no. (%)	33 (29)	30 (28)	.88†
Third trimester, no. (%)	9 (8)	9 (8)	1.0†

* Using two-sample *t* test.

† Using Fisher's exact test.

In the study, 95.6% (108/113) of the smears obtained with the Cytobrush and 69.7% (76/109) of the smears obtained with the swab yielded adequate numbers of endocervical cells. This difference was statistically significant, with $P < .0001$ and an odds ratio of 9.38. The odds ratio of 9.38 implies that there is a ninefold increased chance of obtaining adequate numbers of endocervical cells using the Cytobrush technique.

Cytologic atypia was obtained from 15.9% (18/113) of the smears harvested by the Cytobrush technique and from 13.8% (15/109) of the smears

obtained by the Dacron swab. The differences between the two methods were not statistically significant ($P = .7082$). If only the smears considered adequate for interpretation were evaluated, however, the swab uncovered cytologic atypia at a rate of 19.7% (15/76) as compared with the Cytobrush rate of 16.7% (18/108). Again, this finding was not statistically significant. ($P = .6969$).

The complication rate with the Cytobrush was 6.5% (7/108) as compared with the swab at 3.8% (4/105). The difference between these complication rates was not statistically significant ($P = .2418$). The complications included spotting for less than 1 week in nine patients, spotting for less than 10 days in one patient, and one spontaneous abortion. The spontaneous abortion occurred in a patient who had a history of recurrent

spontaneous abortions; she was in her first trimester, and she aborted 4 days after her cervical cytologic smear with swab and spatula (Table 2). Other than these complications, there were no adverse fetal or maternal complications in the study.

DISCUSSION

Many factors are involved in choosing the proper technique for cervical cytologic smears during pregnancy, but three of the most important are endocervical cell yield, detection of cytologic atypia, and complications.

The presence of adequate numbers of endocervical cells or squamous metaplastic cells is a criterion for cervical cytologic adequacy^{6,11,12}; this is due primarily to a recognition of the importance of the transformation zone as the source of 90% to 95% of cervical cytologic atypia. The endocervical cells obtained by the cervical cytologic smear serve as evidence that the transformation zone or a portion of the transformation zone has been adequately sampled. It has been suggested that the smear be repeated if an adequate number of endocervical cells is not present.¹² This criterion, coupled with the high frequency of inadequate smears due to decreased endocervical cell yields during the gravid state, has led one author to question the cost-effectiveness of cervical cyto-

TABLE 2

Complication Rates of Endocervical Cell Sampling in Pregnancy by Two Methods

Complication	Cytobrush and Spatula, n=108	Swab and Spatula, n=105	P Value
	No. (%)	No. (%)	
Spotting ≤1 week	7 (6.5)	2 (2)	0.17*
Spotting >1 week	0 (0)	1 (1)	0.49*
Spontaneous abortion	0 (0)	1 (1)	0.49*
Total	7 (6.5)	4 (3.8)	0.54*

*Using Fisher's exact test.

logic smears in pregnancy.²⁸

There are several factors involved in obtaining endocervical cells by a cervical cytologic smear, including the location of the squamocolumnar junction, the tenacity of the cervical mucus, the presence of cervical inflammation, the cervical cytologic method and technique used, and the fertility state of the patient. It is postulated that in the gravid patient the decreased endocervical cell yield is due primarily to thickened cervical mucus, increased vascularity, and inflammatory changes.¹³

This study is consistent with and supports the findings of several recent reports that demonstrate that the Cytobrush is the optimal instrument for obtaining adequate endocervical cells from Pap smears in pregnant women²³⁻²⁷ (Table 3). The results of this study suggest that the Cytobrush-spatula technique has a ninefold increased chance of yielding an adequate number of endocervical cells over the swab and spatula. This represents a finding with both clinical and fiscal significance.

Detection of cytologic atypia, particularly precancerous or cancerous cells, is the primary purpose of cervical cytologic smears. Whether endocervical cells are present is not significant as long as cytologic atypia is detected when it is present. When evaluating cervical cytologic techniques, the detection of cytologic atypia should be the critical element. The technique with the greatest sensitivity for cytologic atypia would be the most desirable.

In this study, the Cytobrush enhanced detection of cytologic atypia (15.9% vs 13.8%) for all smears; however, if only the smears with an adequate number of endocervical cells are included, the swab improves detection of cytologic atypia (19.7% vs 16.7%). In both cases this is notable, but not statistically significant, indicating that the techniques are equal at detecting cytologic atypia. This is a finding consistent with four other studies in which there was no difference in the detection of cytologic atypia between the two techniques.^{23,24,26,27} To date, no study has documented a statistically significant improvement of cytologic atypia detection with the Cytobrush in pregnancy. This study suggests a trend in favor of the Cytobrush enhancing detection of cytologic atypia; however, an increased number of participants would be required for it to reach statistical significance. Further investigations on this subject should be undertaken.

The manufacturer of the Cytobrush identifies

TABLE 3

Percentages of Adequate Endocervical Cell Yield from Two Methods of Sample Collection for Papanicolaou Smears in Pregnancy as Reported in Six Studies

Study/Cite	Spatula and Cytobrush, %	Spatula and Swab, %
Orr et al ²⁵	86.0	21.0
Rivlin et al ²⁴	70.9	41.9
McCord et al ²³	77.6	64.9
Paraiso et al ²⁶	90.7	70.8
Smith-Levitin et al ²⁷	98.5	84.0
Current study	95.6	69.7

pregnancy as a contraindication to its use even though there are no published data to support this position. It is presumed that this is a cautionary stance based on potential complications. There have been only a few studies investigating the safety of the Cytobrush in pregnancy (Table 3).²⁵⁻²⁷ Orr and colleagues²⁵ documented that this technique did not adversely affect pregnancy outcome in a series of 300 patients. Paraiso et al²⁶ reported no difference in the complication rates between the techniques, but did not publish the numbers, nor were they statistically analyzed. Smith et al²³ reported no statistically significant difference in complication rates within 2 weeks of smear collection using three collection techniques including cotton swab and Cytobrush. Morrison²⁹ commented on the safety of the Cytobrush based on unpublished data.

This is the first study to document the major and minor complications and to statistically analyze them. The difference in complication rates was not statistically significant, and there were no adverse maternal or fetal outcomes with the Cytobrush. These findings are consistent with the findings of four other studies with a combined population of almost 1000 patients.²³⁻²⁶ These results should give clinicians reassurance as to the safety of the Cytobrush, despite the manufacturer's warning.

There are several limitations to this study. First, it was a relatively small study; a larger study group would have been necessary to result in statistically significant differences in complication rates and detection of cytologic atypia. Even though the sample size was not sufficient to detect a 5% increase in complications, it was sufficient to detect a 20%

increase. The complications experienced were relatively minor, indicating relative safety. The sample size was not large enough, however, to detect smaller differences in rare but important complications such as amniotomy and preterm delivery.

Second, the wide variation in experience between first-year residents and faculty physicians could potentially affect the consistency in technique. There were no safeguards to ensure that the same technique was used by each physician.

Finally, because low-grade squamous intraepithelial lesions were the highest grade lesions identified in the study, our study population tended to be low risk.

CONCLUSIONS

The use of the Cytobrush-spatula technique for obtaining cervical cytologic smears in pregnant women significantly increased the endocervical cell yield, yet did not significantly enhance the detection of cytologic atypia. Also, the study did not find an increased risk of adverse maternal or fetal outcomes, suggesting that the Cytobrush-spatula technique is relatively safe. Our findings support the findings of prior studies concerning endocervical cell yield, raise some questions concerning the detection of cytologic atypia, and suggest the safety of the procedure in pregnancy. These results support the use of the Cytobrush-spatula as the optimal technique for obtaining endocervical cells in pregnancy. While the numbers are small, the results of this and other studies suggest safety of this device. The Cytobrush should be considered, especially in those pregnant patients at high risk for dysplasia, when the presence of endocervical cells in the sample is particularly important.

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