Trials That Matter: Liquid-Based Cervical Cytology: Disadvantages Seem to Outweigh Advantages

Liquid-based cytology is a technique for preserving and preparing cells for cytologic study. As applied to cervical cytology, cells are obtained by scraping the external cervix uteri with a spatula and by rotating a cytobrush in the endocervix. Instead of being spread onto a glass slide and fixed, the samples are suspended in a vial of liquid preservative. In the laboratory, processing removes debris and places a thin layer of cells onto slides that are stained and read similarly to conventional cytology. Systematic reviews have concluded that the quality of the evidence about liquid-based cytology has not been good enough to judge its performance relative to conventional cytology (1, 2). The lack of large randomized studies comparing the 2 techniques is an important evidence gap (1, 3). In 2003, the U.S. Preventive Services Task Force (USPSTF) found the evidence insufficient to make a recommendation about using liquid-based cytology (4).

What Did This Landmark Trial Show?

Ronco and colleagues made a head-to-head comparison of conventional and liquid-based cytology (5). More than 45 000 women undergoing a new round of periodic cervical cancer screening were randomly assigned to conventional or liquid-based cytology in each of 9 sites. The same cytologists read both types of slides, and a supervisor or a panel of cytologists checked abnormal results. All centers participated in a program to monitor quality and to promote uniform interpretation among the centers.

The authors used a standard nomenclature to classify cytology results. The principal outcome was a histologic diagnosis of cervical intraepithelial neoplasia or worse (CIN+) on a biopsy done during colposcopy (the reference standard test) and read by pathologists blinded to study group and cytology results. Researchers referred patients in the liquid-based cytology group for colposcopy if cytology showed atypical cells of undetermined significance or worse. They referred patients in the conventional cytology group according to the same protocol as used for liquid-based cytology in 7 of the 9 centers but used a higher referral threshold in 2 centers, which probably resulted in an overall lower rate of CIN+ detection in the conventional cytology group. Because patients with normal cytology did not have colposcopy, the authors could not directly calculate the sensitivity and specificity of cytology. However, because of the randomized design, the number of patients who had CIN+ should have been the same in both groups. Therefore, the ratio of the rates of CIN+ results in the 2 groups should reflect the sensitivity of one test relative to the other.

The researchers found that the frequency of abnormal cytology results was greater with liquid-based cytology than with conventional cytology (6.3% vs. 3.8%). Because the prevalence of CIN+ should be the same in both study groups, the increased rate of abnormal cytology results in the liquid-based cytology group could have resulted from more false-positive results in the liquid-based cytology group or from more false-negative results in the conventional cytology group. In sum total, detection rates of CIN grade 2 or worse and grade 3 or worse were similar in both study groups, suggesting that the frequency of false-negative results and sensitivity were the same for both methods. However, the probability of CIN+ histology after a positive test was lower in the liquid-based cytology group, indicating that more false-positive results had occurred with the liquid-based technique. Therefore, liquid-based cytology had lower specificity than the conventional technique. The rate of unsatisfactory specimens was lower with liquid-based cytology, which the authors cited as the main advantage of this technique.

How Does the Trial Advance Knowledge?

Many people will be surprised to learn that liquid-based cytology was not more sensitive than conventional cytology, especially since the U.S. Food and Drug Administration allows the manufacturer of the technology used in this trial to claim that it is "significantly more effective" than conventional cytology for detecting cervical abnormalities (6). In fact, it seems that the main effect of liquid-based cytology was to increase the number of false-positive results, which resulted in needless referrals for colposcopy. Concerns about false-positive results with the liquid-based technique are not new: The American Cancer Society suggests that women screened with liquid-based cytology have biennial rather than annual testing to avoid increases in minimally abnormal cytology findings that lead to unnecessary colposcopy and treatment (7). We now have firmer evidence to inform this policy. The other major finding was fewer unsatisfactory tests with liquid-based cytology, which conflicts with results from a previous randomized study that reported more wholly unsatisfactory tests with the liquid-based technique (8).

What Should Clinicians Do?

Despite the lack of high-quality studies, many clinicians have adopted liquid-based cytology (9, 10). In some cases, clinicians have converted to facilitate management of atypical squamous cells of undetermined significance, a common and vexing cytologic abnormality. Current guidelines (11, 12) suggest 3 options for women with such cells: immediate colposcopy; repeated cytology in 6 months, with referral for colposcopy if cytologic abnormalities per-

sist; or testing for oncogenic types of human papillomavirus (HPV), with referral to colposcopy if results are positive. A good case can be made for any of these 3 strategies (13), but clinicians often prefer HPV testing after liquid-based cytology because they can test for HPV by using fluid from the vial, avoiding a return visit to obtain another specimen. Unsatisfactory cytology tests also require repeated testing. The evidence supporting fewer unsatisfactory tests with the liquid-based technique, however, is conflicting. Nevertheless, both of these potential advantages of liquid-based cytology are unlikely to outweigh the disadvantage of increased overall colposcopy referral rates because of more frequent false-positive results with liquid-based cytology.

In other settings, the clinical laboratory itself has converted to liquid-based cytology to make readings less labor-intensive and time-consuming. Although technology-related considerations are important, the welfare of patients clearly has priority. We seriously doubt that the benefits to the cytology laboratory outweigh the invasive procedures and needless worry that more women will experience with liquid-based cytology because of the increased rate of false-positive results.

Users of liquid-based cytology should reconsider their decision to adopt this technology and ponder whether the harms to patients outweigh the benefits to the clinical laboratory. Those who use this technique for primary cervical cancer screening in women older than 30 years of age because it is easy to combine with HPV testing (7) should realize that the USPSTF considers the evidence to be insufficient to endorse this strategy (4). Finally, clinicians who use the conventional technique should not feel that their patients are receiving substandard care; indeed, current best evidence suggests the opposite conclusion.

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