Evidence-Based Medicine Versus Liquid-Based Cytology

George F. Sawaya, MD

In this issue, Arbyn et al (see p. 167) update the evidence about the accuracy of liquid-based cytology compared with conventional cytology, and the results are not encouraging.[1] In summary, best evidence suggests that liquid-based cytology does not lead to more disease detection and appears to increase false-positive testing, sobering news given that over 80% of U.S. obstetrician–gynecologists surveyed[2,3] report using this screening method.

The review reveals a surprising lack of high-quality studies performed in screening settings. The recent landmark Italian randomized trial, however, is an exception and deserves focused attention.[4] Over 45,000 women aged 25–60 years were randomized to either liquid-based or conventional cytology. Colposcopy was performed in all women with atypical squamous cells of undetermined significance or worse. In comparing these techniques head-to-head, two important clinical questions were answered. First, liquid-based tests were more likely to be interpreted as abnormal and equivocal. Second, despite more positive tests, liquid-based cytology did not lead to detection of more high-grade cervical intraepithelial neoplasia (CIN). In other words, all extra-positive tests appeared to be falsely positive. Arbyn's meta-analysis of summary data showed similar results.

How could a technology be so widely implemented before the appropriate studies have been performed to assess benefits and harms? Reasons are myriad. Many clinicians likely converted to liquid-based cytology to facilitate human papillomavirus (HPV) testing for management of atypical squamous cells of undetermined significance (ASC-US) tests, a strategy designed to decrease unnecessary colposcopy by identifying women at low risk of high-grade CIN (ie, those with negative HPV tests). Does liquid-based cytology combined with HPV testing for ASC-US management decrease uncertainty and overall colposcopy rates compared with conventional cytology with either repeat cytology or HPV testing for ASC-US management? On the basis of results from the Italian trial,[5,6] the answer is not obviously "yes." In that trial, 3.84% of women randomized to liquid-based cytology would have undergone colposcopy for atypical cytology/HPV-positivity or low-grade squamous intraepithelial lesion or worse. In the conventional cytology arm, colposcopy in everyone with ASC-US or worse triaged a near-identical proportion of women to colposcopy (3.81%). Note, however, that colposcopy rates in traditional practice would be lower since the majority of clinicians would not perform colposcopy for a single ASC-US result.[2] The reasoning that HPV triage of ASC-US unequivocally justifies use of liquid-based cytology, therefore, is contestable.

Some clinicians may have been enticed by claims of fewer unsatisfactory tests with liquid-based cytology. Evidence from randomized trials

See related article on page 167.

Dr. Sawaya is from the Department of Obstetrics, Gynecology and Reproductive Sciences and the Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California; e-mail: sawayag@obgyn.ucsf.edu.

Financial Disclosure
The author has no potential conflicts of interest to disclose.

ISSN: 0029-7844/07

concerning the effect of liquid-based cytology on unsatisfactory tests, however, is mixed, with one reporting more with liquid-based cytology[7] and another reporting less.[4] These conflicting results may be due to variations in the criteria by which unsatisfactory tests were judged. As Arbyn points out, the potential benefit of fewer unsatisfactory tests with liquid-based cytology is unlikely to justify its use, especially in light of concurrent false-positive testing.[1]

Others may have converted to liquid-based cytology due to factors seemingly beyond their control: the laboratory simply stopped reading conventional tests. How the clinical laboratory has held such sway with clinical practice is enigmatic and disheartening, given current evidence. Although laboratory personnel may prefer reading liquid-based tests, this benefit certainly does not outweigh the decrements in quality of life experienced by women who have undergone needless invasive procedures due to false-positive testing with liquid-based cytology.

What should we do with this new information? First, we should weigh the benefits of liquid-based cytology for the laboratory against harms for patients. Second, we should seriously question the balance of benefits and harms of liquid-based cytology in women in younger age groups since equivocal diagnoses are doubled[5] and HPV triage of ASC-US tests sends large proportions to colposcopy for little benefit in return.[8] Lastly, as advocates for best practices in women's health, we must simply be more skeptical about claims of superiority of new tests and treatments. Such claims are often based on flawed scientific methodology and amount to little more than advertising. Although navigating the ever-mounting morass of new information is daunting, clinicians should be aware that help is available. For example, the U.S. Preventive Services Task Force systematically reviews evidence and issues recommendations that are designed to maximize benefits and minimize harms. Of note, the Preventive Services Task Force considers evidence about liquid-based cytology and HPV testing to be insufficient to make a recommendation.[9] However, evidence from large-scale randomized trials using HPV testing for screening is emerging.

If nothing else, Arbyn's review suggests that the saga of liquid-based cytology be added to the list of cautionary tales in women's health. In our new age of direct-to-consumer advertising, clinicians now have a new role as arbiters between rational, evidence-based care and marketing exuberance. We all have the power and responsibility to make wise choices, and our patients certainly deserve no less.

REFERENCES

1. Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. Obstet Gynecol 2008;111:167–77.
2. Noller KL, Bettes B, Zinberg S, Schulkin J. Cervical cytology screening practices among obstetrician-gynecologists. Obstet Gynecol 2003;102:259–65.
3. Saint M, Gildengorin G, Sawaya GF. Current cervical neoplasia screening practices of obstetrician/gynecologists in the US. Am J Obstet Gynecol 2005;192:414–21.
4. Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. BMJ 2007;335:28.
5. Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L, et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol 2006;7:547–55.
6. Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst 2006;98:765–74.
7. Obwegeser JH, Brack S. Does liquid-based technology really improve detection of cervical neoplasia? A prospective, randomized trial comparing the ThinPrep Pap Test with the conventional Pap Test, including follow-up of HSIL cases. Acta Cytol 2001;45:709–14.
8. Sawaya GF. A 21-year-old woman with atypical squamous cells of undetermined significance. JAMA 2005;294:2210–8.
9. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force. Screening for cervical cancer. Available at: http://www.ahrq.gov/clinic/uspstf/uspscerv.htm. Retrieved November 5, 2007.