Management of Cervical Cytology with HPV Test

[Announcer] This podcast is presented by the Centers for Disease Control and Prevention. CDC – safer, healthier people.

[Dr. Saraiya] Welcome to this CDC program on the management of cervical cytology. I'm your host, Dr. Mona Saraiya and my guest today is Dr. Stewart Massad. Dr. Massad is a professor in the Division of Gynecologic Oncology at Washington University in Saint Louis, where his academic interests focus on cervical cancer prevention and medical education. He's also a board member of the American Society for Colposcopy and Cervical Pathology, and was on the steering committee that developed the ASCCP's 2006 Consensus Guidelines on the management of abnormal cytology and histology. He's also an advisor to the Illinois Breast and Cervical Cancer Screening Program. Welcome, Dr. Massad.

[Dr. Massad] Thanks, Dr. Saraiya. I'm excited to be helping the CDC better educate clinicians on this very important subject.

[Dr. Saraiya] Dr. Massad, the 2006 ASCCP guidelines have a lot on the management of abnormal Paps and abnormal histology. Talk to us a little about the overarching theme in these guidelines.

[Dr. Massad] We have a better understanding now than a decade ago, that most cervical lesions are manifestations of transient HPV infections, with minimal oncogenic potential, especially over the span of only six to 12 months. Early cancer prevention studies showed how treating CIN interrupts progression to cancer. But since most CIN1 and many CIN2 lesions resolve spontaneously, treatment may hurt more than it helps. Over the past two decades we've lowered the threshold for colposcopy with the introduction of Bethesda diagnoses of atypia and low-grade squamous intraepithelial lesions. Cotesting lowers the threshold even further.

We're finding disease earlier, when it's harder to find colposcopically and more likely to regress or remain stable. This means that many women with early disease can be safely watched instead of treated. So across most grades of abnormality, the guidelines recommend or at least offer the option of less aggressive management.

[Dr. Saraiya] What do the guidelines say in general about treatment?

[Dr. Massad] Until recently, we thought that there were few risks associated with treatment. Now, it appears that all cervical disease treatments — cone biopsy, loop excision, laser ablation, even cryotherapy — increase risk for preterm delivery for women who subsequently conceive. Excisional treatments — conization and loop excision — carry the highest risks, and risks seem to increase with the amount of cervix destroyed. The absolute risk is small — on the order of five to 10 percent — so doubling that background risk still means most pregnancies will deliver at term. Most preterm births found in these studies were between 34 and 37 weeks, so many preterm births resulting from CIN treatment still do well, but there is a clear increase in very early preterm birth with attendant neonatal morbidity.

[Dr. Saraiya] So would you say that the guidelines seem to emphasize watchful waiting?

[Dr. Massad] HPV infections are detected in more than 20 percent of sexually active women in their teens and early twenties, and many of these women have minor cytologic abnormalities. These HPV infections clear spontaneously in up to 90 percent of young women.

On the other hand, cancer risk in teens is vanishingly small — barely three per million — so observation carries little risk of missing a cancer. And treatment is most likely to adversely impact these young women, with most of their reproductive lives ahead of them.

[Dr. Saraiya] Why are younger women being discouraged from HPV DNA testing in the guidelines? And by young, I mean ages 20 and younger.

[Dr. Massad] HPV infection is an almost universal event among sexually active youth, and for many young women it's a recurring event, as new sexual partners introduce new HPV types. But for those with intact immune systems, these HPV infections almost always resolve without intervention. HPV is a sexually transmitted infection, and a positive test results in stigma, anxiety, anger, and disrupted relationships. Most women and many of their clinicians don't understand how transient HPV infections are for most teens. Once they find it, they want to do something about it. But while treatment may speed HPV regression, it doesn't change the overall natural history of disease that's fated to regress. What clinicians should be looking for in young women is the high-grade lesion that's persisted across time and may result in cancer over the coming decade or longer. HPV testing doesn't help in that regard. Serially positive HPV tests — even serially positive high-risk HPV tests — may reflect serial infection with new HPV types rather than persistent infection. To avoid that, ASCCP guidelines recommend cytology for screening young women, not HPV DNA testing.

[Dr. Saraiya] What about low-risk HPV DNA testing? Do you think there’s any rationale for that?

[Dr. Massad] No. Low-risk is really a misnomer, since these types haven't been associated with cancer. So there's no cancer prevention benefit to testing for low-risk types. There's no role for testing in the evaluation of genital warts, which are usually caused by low risk HPV types, or in STD screening, since there's no known effective treatment and no benefit from partner notification. It's not useful in deciding whether to offer HPV vaccination, since women with negative results may have been previously infected.

[Dr. Saraiya] Dr. Massad, now I’m going to be asking you about reflex testing and cytologic abnormalities, such as LSIL. Can you provide any comments on that?

[Dr. Massad] In ALTS, the pivotal national multicenter study, more than 80 percent of women with Low SIL had high-risk HPV, so HPV testing didn't really help in the triage of Low SIL by avoiding colposcopy, as it did for ASCUS. The one exception may be among postmenopausal women. As women age, HPV rates fall. Menopausal women also may have atrophic changes that cytologically resemble LSIL but are not HPV-related and certainly are not preneoplastic. So for

postmenopausal women, HPV testing can be used as a triage test when deciding on colposcopy, following the same criteria used for ASCUS triage for younger women.

[Dr. Saraiya] What about reflex testing for HSIL?

[Dr. Massad] Not a good idea. For women with High SIL, the risk of false-negative HPV testing just seems too high. For safety, those women go to colposcopy or treatment. There is the option in adult women to treat High SIL with immediate loop excision without intervening colposcopy, an advantage for clinicians at clinics with high rates of dropout.

[Dr. Saraiya] Dr. Massad, tell us about the atypical glandular cells on a Pap test. Is this the same as the atypical squamous cells?

[Dr. Massad] They are not the same. Many clinicians fail to appreciate the distinction between the two results. An AGC result occurs in only about 0.2 percent of Pap tests, but up to 40 percent of women with AGC have CIN2, 3 or cervical adenocarcinoma in situ, and 5 to 10 percent have cancer, most often endometrial cancer. AGC is an extremely serious finding that merits aggressive evaluation, including, in most cases, sampling of the endometrium.

[Dr. Saraiya] What about HPV testing with AGC?

[Dr. Massad] There is no role for HPV triage for AGC. Associated endometrial cancers are always HPV negative and endocervical lesions may be missed by HPV testing, so it can be falsely reassuring. However, for women with AGC, there is a role for HPV testing in truncating follow-up when colposcopy and endometrial assessment are negative. If the HPV test is negative, then only one additional Pap test is needed before returning to annual testing. If it's positive, then closer surveillance is needed. If the HPV test isn't done, then four additional Pap tests over two years must be done, a significant logistical and compliance challenge. But in either scenario, negative findings on colposcopy with negative endocervical curettage, and in most cases, negative endometrial sampling are all prerequisites to observation.

[Dr. Saraiya] Tell us about the newer uses of the HPV DNA test for post-treatment follow-up of women.

[Dr. Massad] HPV testing is a sensitive way to identify residual disease after treatment. Randomized trials have shown that most cervical therapies — cryotherapy, laser ablation, loop excision, and cold knife conization — have cure rates of 90 percent or better. Predictors of persistence or recurrence after treatment are age, unsatisfactory colposcopy, higher lesion grade, and larger lesion size. Regardless of risk factors, all women treated for CIN merit careful surveillance, though at six-month intervals rather than the three- to four-month intervals we used to use. Most recurrences will be found using Pap surveillance alone, but HPV testing may shorten time to detection. There remains a trade-off between sensitivity and specificity, and some HPV tests that are positive after treatment reflect new HPV infections rather than persistent disease. So ASCCP guidelines offer clinicians the option of HPV testing. In some cases that would be the preferred course, although, cytology surveillance remains an option too. Cotesting

in post-treatment surveillance improves sensitivity even further, but the cost seems to be prohibitive.

[Dr. Saraiya] Are there any caveats clinicians should keep in mind when using HPV testing?

[Dr. Massad] There's currently only one HPV test that's FDA-approved. I'm not a fan of monopoly, but the FDA approval process does mean that we know what the sensitivity and specificity of the test are, and we know the implications that follow for clinical practice.

The guidelines we've discussed apply only to tests with similar accuracy. Some labs have peer-reviewed publications documenting that degree of accuracy for HPV tests they've developed. But others are using kits that aren't FDA-approved or peer-reviewed. The accuracy of these tests is unknown. Clinicians can't expect results using assays of unknown accuracy to yield the same results found in trials like ALTS. We all hope that additional HPV tests, including genotyping tests, by the way, will work their way rapidly through the approval pipeline. Maybe we can do another session like this when that happens.

[Dr. Saraiya] Well we sure would like that. Dr. Massad, thank you again for your time today. If you are interested in learning more about the guidelines that Dr. Massad shared today, you can go to asccp.org.

[Announcer] For the most accurate health information, visit www.cdc.gov or call 1-800-CDC-INFO, 24/7.