

Young woman with HPV?

# DIFFERENT RISKS.



## Management of cervical cytological and histological abnormalities in adolescents

**y**our adolescent patient's abnormal cervical cytology and histology can largely be managed conservatively, according to the Consensus Guidelines published in October 2007.<sup>1,2</sup> These updated guidelines include specific recommendations for young women, emphasizing that the unique features of human papillomavirus (HPV) infection in this population warrant a modified approach to management and treatment.

In revising their earlier guidelines, the National Institutes of Health and the American Society for Colposcopy and Cervical Pathology considered new data from the ASC-US/LSIL Triage Study (ALTS)<sup>3</sup> and the accumulating evidence of the utility of HPV testing. Adherence to these recommendations should decrease the number of unnecessary diagnostic procedures and the long-term obstetrical risks of excisional or ablative treatment. The key changes and rationale behind these recommendations are reviewed here.

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## KEY POINT

Fewer than 10% of HPV infections persist at 2 years in young women.

### How adolescents are different

Adolescents, defined as young women aged 20 years and younger, represent a unique population of patients. Incident oncogenic HPV infection and transient mild cytologic abnormalities are commonly seen in this group. Although at risk to develop high-grade disease, many adolescents will experience regression of both cytologic and histologic disease.

Despite the high incidence of HPV infection among sexually active women (SIDEBAR), such infections in adolescents are often transient. Approximately 50% of HPV infections in young women persist in the short term (6 months), but fewer than 10% remain at 24 months.<sup>4-6</sup>

HPV-related low-grade cytologic abnormalities, in particular, are frequently detected in sexually active adolescents.<sup>7</sup> These lesions, similar to HPV infection, have also been shown to be transient, with high reported rates of regression. In a cohort of 1075 sexually active teens (aged 15 to 19 years) with normal cytology and negative HPV tests at recruitment, 407 (38%) became HPV positive over the 3-year study period, and 246 (23%) developed abnormal cervical cytology (atypical squamous cells of undetermined significance [ASC-US] or greater).<sup>8</sup> Similar rates of incident HPV infection were documented in a longitudinal cohort study of more than 500 college-aged women in Washington State.<sup>9</sup> The 36-month cumulative incidence of squamous intraepithelial lesions in this population was 47%. Of the 112 women who developed incident low-grade squamous intraepithelial lesions (LSIL), 96 (87%) became cytologically normal while enrolled in the study.<sup>10</sup> Finally, Moscicki et al demonstrated very high rates of resolution of LSIL among teens and young women, with regression rates over 60% at 12 months of follow-up and 91% at 36 months.<sup>11</sup>

Regression has also been noted in young women with high-grade squamous intraepithelial lesions (HSIL), as well as biopsy-proven cervical intraepithelial neoplasia (CIN) 2. Over a median follow-up period of 18 months, Moore et al found regression in 65% of a cohort of young

women (aged 20 years and younger) with CIN 2.<sup>12</sup> In another retrospective study of expectantly managed adolescents and young women (aged 21 years and younger) with CIN 2, Fuchs demonstrated that 50% of CIN 2 lesions regressed within 2 years, and 75% regressed within 3 years.<sup>13</sup> Progression to CIN 3 occurred in 13% of the first cohort and 8% of the second; invasive cancer was not found in any of the young women who were followed.

### When to begin screening

Cervical cancer screening should begin approximately 3 years after initiation of sexual intercourse but no later than 21 years of age, according to the 2002 American Cancer Society Guidelines for the Early Detection of Cervical Neoplasia and Cancer.<sup>14</sup> Prior recommendations had been to begin screening by age 18 years, but this was revised based on several factors. First, cervical cancer in women younger than 20 years is rare. Between 2000 and 2004, the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program reported that the incidence rate of invasive cervical cancer was 0/100,000 per year for adolescents and young women aged 10 to 19 years.<sup>15</sup> Second, the risk of developing a high-grade lesion (either HSIL, CIN 2, or CIN 3) within 3 to 5 years following initial HPV exposure is low.<sup>10,16</sup>

### The 2006 Consensus Guidelines: What is new?

ASC-US and LSIL in adolescents are now managed similarly and more conservatively than in adult women. As with the first Consensus Guidelines, young women aged 20 years and younger are considered to be adolescents.

**Recommendation 1:** Don't test for HPV infection in adolescents with ASC-US.

**In the past:** Management of ASC-US called for reflex high-risk HPV testing in all women, regardless of age.<sup>17</sup>

**Rationale behind the change:** Adolescents with ASC-US have a high rate of oncogenic HPV infection, so HPV DNA testing is not indicated. In a secondary analysis of the ALTS data, Sherman demonstrated that among women with ASC-US, 71% of the cohort aged 18 to 22 years tested positive for high-risk HPV, compared with 31% of women older than 29 years.<sup>18</sup>

Dr Boardman reports that she serves on the speakers' bureau of Merck & Co., Inc. Dr Fuchs reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

## Sidebar

## How Many Patients Are Infected?

Genital human papillomavirus (HPV) infection is extremely common among sexually active adolescent women. At enrollment in a longitudinal study of 60 adolescents ranging in age from 14 to 17 years, 28% were HPV positive and 22% were positive for high-risk HPV subtypes; after a mean follow-up period of 2.2 years, this number grew to 82% (with 77% positive for oncogenic strains).<sup>1</sup>

Young age (<25 years) and increasing numbers of sexual partners are risk factors for infection,<sup>2</sup> which occurs relatively rapidly following sexual initiation. In a cohort of sexually inexperienced college students, 40% of students were infected with HPV within 2 years of first coitus; at 5 years' follow-up, 60% were positive.<sup>3</sup>

Among all sexually active women, the cumulative lifetime risk of HPV infection is approximately 80%. Current estimates from the Centers for Disease Control and Prevention indicate that over 6.2 million sexually active women become infected with HPV annually, with approximately 20 million women currently infected.<sup>4</sup>

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Similarly, Boardman et al found oncogenic HPV infection in 77% of women 19 years of age and younger with ASC-US, in contrast to 59% of women older than 25 years.<sup>19</sup> If HPV typing is inadvertently performed, the results should not be used to determine subsequent management.

Of note, this recommendation is similar to that for LSIL, in which HPV DNA was found in more than 75% of women tested.<sup>3</sup> It has been estimated that the cost of HPV testing of all women with LSIL would outweigh the savings gained from avoiding colposcopy in the 20% to 27% who would be found negative. Based on this estimate and the high prevalence rate, HPV testing was not recommended for the management of LSIL in the 2001 Consensus Guidelines.<sup>17</sup>

**Recommendation 2:** Repeat annual cytologic testing—not colposcopy—should be performed for adolescents with ASC-US or LSIL.

**In the past:** No specific recommendation existed for adolescents with ASC-US, whose follow-up might have included repeat cervical cytologic testing, colposcopy, or DNA testing for high-risk types of HPV. The recommendation for adolescents with LSIL (as opposed to adult women with LSIL) included not only colposcopic triage, but also repeat cytologic testing or HPV DNA testing 12 months after the index Papanicolaou test.

**Rationale behind the change:** The revision was made to avoid unnecessary colposcopic evaluation of low-grade cytologic abnormalities, which are likely to regress in young women. If a repeat cytology test at 12 months reveals HSIL or worse, the young woman should be referred for colposcopy. Otherwise, for young women with ASC-US or LSIL, the cytology test should be repeated again at 24 months from the initial abnormal test. At 24 months, any cytologic abnormality (ie, ASC-US or greater) warrants colposcopic evaluation.<sup>20</sup>

Immediate colposcopic examination continues to be advised for all women, including adolescents, with atypical squamous cells, cannot exclude HSIL (ASC-H), HSIL, and atypical glandular cells on cervical cytologic testing.

**Recommendation 3:** “Wait and see” for adolescents with CIN 2 and satisfactory colposcopy—repeat colposcopy and cytologic testing at 6-month intervals rather than performing an ablative or excisional procedure.

**In the past:** Conservative management with repeat colposcopy and cytology at 4- to 6-month intervals had been reserved for young women of reproductive age with cytologically confirmed HSIL if biopsy did not confirm CIN 2,3. The authors of the 2001 Guidelines also expressed the opinion that observation

## KEY POINT

Given the high rate (77%) of oncogenic HPV in adolescents with ASC-US, it is safe to skip the HPV test.



## KEY POINT

Excisional or ablative therapy may pose obstetrical risks, so observation of CIN 2 lesions for up to 2 years is recommended before performing a procedure.

## Timeline of Key Publications

In 2001, the first Consensus Conference on the Management of Women with Cervical Cytological and Histological Abnormalities (NIH/ASCCP) was held in Bethesda, Maryland. The conference's goal was to establish national guidelines to help clinicians navigate the rapidly evolving literature in this area of women's health care.<sup>1</sup>

A second Consensus Conference was held in September 2006 to incorporate new data and outline significant revisions in the management of abnormal cervical cytology and histology. At this conference, the Committee on Young Women was established to focus on the new recommendations with respect to this population.

The revised guidelines were published in October 2007.<sup>2,3</sup>

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3. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol*. 2007;197:340-345.

is appropriate for adolescents with CIN 2 who are considered to be reliable for follow-up.<sup>21</sup>

**Rationale behind the change:** New findings that excisional or ablative therapy poses long-term obstetrical risks are particularly salient in adolescents, many of whom have not yet begun or completed child-bearing. Cervical conization, including loop electrosurgical excision procedures (LEEP), has been shown to increase the risk of pregnancy complications such as preterm, premature rupture of the membranes<sup>22</sup> and preterm delivery.<sup>23,24</sup> Treatment with LEEP has been estimated to result in a roughly 2- to 3-fold increased risk of premature delivery.<sup>23,24</sup> This risk was found to be significant in deliveries

occurring only after 34 weeks of gestation, although a trend toward increased preterm deliveries at earlier gestational ages was noted.<sup>23</sup> Cryotherapy, often suggested as an alternative to excisional procedures in young or nulliparous women, has also been found in a recent study to be associated with an increase in preterm delivery rates, although the magnitude of this effect was less pronounced.<sup>24</sup>

Colposcopy and cytologic testing at 6-month intervals has been—and remains—the preferred management option for young women with HSIL whose histologic assessment does not confirm high-grade disease (ie, those with normal findings or CIN 1) and whose colposcopic evaluation is satisfactory. Clinicians may proceed to immediate treatment if, for example, compliance is an issue. If managed conservatively and repeat cytology testing and colposcopic impression and/or biopsy remains normal over the next year, patients may then return to annual cytologic assessment. For those with persistent HSIL or persistent or worsening lesions on colposcopy, repeat biopsy is recommended and should be triaged accordingly. If HSIL is still detected at 2 years, treatment should be offered.

The revised guidelines now recommend as preferred management that clinicians also observe the lesions for up to 24 months in adolescents with CIN 2 and satisfactory colposcopy. As with HSIL, those adolescents with normal cervical cytology and colposcopy on 2 subsequent exams can then be followed with annual cytology testing. Patients with either HSIL on cytology tests for 1 year or with a persistent or worsening lesion on colposcopy should undergo repeat biopsy. Patients with CIN 2 that persists on biopsy for 1 to 2 years should be treated; 2 years is preferred.<sup>25</sup>

Treatment guidelines remain unchanged for adolescents with biopsy-proven CIN 3 or with biopsy-proven CIN 2 and unsatisfactory colposcopy. In both cases, treatment with either ablation (only if the examination is satisfactory and the lesion is small) or an excisional procedure is recommended.

## Conclusions

The 2006 Consensus Guidelines stress conservative management of both cytological and histological abnormalities in

young women. Important changes include the removal of reflex oncogenic HPV testing in the context of ASC-US and delayed colposcopic evaluation of young women with ASC-US or LSIL until persistence is demonstrated. In terms of treatment, women aged 20 years and younger with HSIL and non-confirmatory biopsies or with CIN 2 and adequate colposcopy should be followed closely with colposcopy and repeat cytology testing at 6-month intervals. Excisional procedures are only recommended for adolescents with CIN 3 or for those with CIN 2 and unsatisfactory colposcopy or positive endocervical specimens. For young women with HSIL or CIN 2 that persists for 2 years, treatment is recommended.

Adherence to these guidelines should help to not only decrease the number of unnecessary diagnostic procedures in this specific population of women, but also to reduce the anxiety associated with colposcopy and the long-term obstetrical risks of excisional or ablative therapy. ■

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#### KEY POINT

New guidelines encourage the conservative management of cytological and histological abnormalities in adolescents.