

## Grand Rounds: How, when, and why to manage cervical dysplasia in adolescents

HPV infection is on the rise in teens and typically transient—yet it still raises the risk of dysplasia. The authors offer evidence-based yet practical guidelines for this management challenge.

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Since cervical cancer screening with the Papanicolaou smear has become widespread, the incidence of invasive cervical cancer in developed countries has dramatically decreased. At the same time, the detection of cervical dysplasia has dramatically increased. Diagnosis, management, and follow-up of preinvasive cervical lesions are now a major public health challenge. With teens becoming sexually active earlier, the incidence of cervical dysplasia in adolescents has risen in the past decade. For these young women, the benefits of detecting and eradicating cervical dysplasia must be balanced against the long-term complications of treatment and the low incidence of cervical cancer.

### The role of HPV

To date, more than 100 types of small, double-stranded DNA viruses known as human papillomaviruses (HPV) have been isolated. Approximately 40 of these HPV types are believed to infect the human genital tract.<sup>1</sup> The papillomaviruses have been divided into low- and high-risk subgroups, based upon their oncogenic potential. Low-risk viruses—most commonly HPV 6 and 11—are associated with anogenital condyloma. The high-risk viruses—HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82—are associated with cervical dysplasia and cancer.<sup>2</sup> More than 99% of invasive cervical neoplasms are associated with HPV.<sup>3</sup>

At any given time, the prevalence of HPV in the general population is 14% to 35%.<sup>4</sup> The rate of HPV positivity is highly variable and depends on the demographics of the population being studied. HPV is even more prevalent among adolescents and young women, according to longitudinal sampling studies.<sup>5-8</sup> In Woodman and colleagues' study of 1,075 women aged 15 to 19, the 3-year incidence of HPV infection was 44%. After 5 years of follow-up, 60% of the women had tested positive for HPV.<sup>5</sup> Despite the high frequency of HPV infections, most infections are transient. The median duration of infection among college-aged women is 8 months.<sup>8</sup> Spontaneous viral clearance is more common for low-risk viral infections and in younger women.<sup>9</sup> The subset of patients who do have persistent viral infections are at substantial risk for developing cervical dysplasia.<sup>10</sup> Despite the high incidence of HPV infection in young women, only a fraction of HPV-positive women develop cytologic abnormalities. In a series of 312 adolescents, nearly 52% of those who were HPV positive had normal cervical cytology.<sup>11</sup>



How HPV replicates in cervical epithelial cells.  
(Kevin Somerville)

### When to screen?

The goal of cervical cancer screening is to identify significant preinvasive lesions and prevent development of

invasive cervical cancer. Age 18 has traditionally been accepted as the time to start cytologic screening, but recent consensus panels have recommended initiating screening later. The benchmark now is 3 years after the onset of sexual activity, but not later than age 21.<sup>12-14</sup> This recommendation is based on the natural history of HPV infection and the rarity of cervical cancer in adolescents. The incidence of cervical cancer is 0 per 100,000 per year in girls aged 10 to 14 and 1.7 per 100,000 for those aged 15 to 19, according to the Surveillance, Epidemiology, and End Results database.<sup>15</sup> Earlier screening is unlikely to add additional benefit and may lead to overtreatment of lesions that would spontaneously regress.

**TABLE 1**  
**When should you start cervical cancer screening?**

Organization	Guideline
American Cancer Society	3 years after the onset of vaginal intercourse, no later than age 21. Screen annually with conventional cytology or every 2 years using liquid-based cytology before age 30.
American College of Obstetricians and Gynecologists	3 years after the onset of vaginal intercourse, no later than age 21. Cytologic screening may be initiated earlier at the discretion of the clinician. Annual cytologic screening should be recommended for women younger than age 30.
US Preventive Services Task Force	3 years after the onset of sexual activity or age 21 (whichever comes first) and screening at least every 3 years.

Table 1: When should you start cervical cancer screening?

The American Cancer Society, American College of Obstetricians and Gynecologists, and the US Preventive Services Task Force all recommend screening at 1- to 3-year intervals (Table 1). Routine gynecologic care, counseling, and health maintenance should not be postponed until a teen is eligible for cervical cancer screening. While data in support of initiating screening at age 21 are limited, mathematical models support this strategy.<sup>12</sup> Screening should be initiated earlier in adolescents who have HIV or who are immunocompromised. Women with HIV should undergo cytologic screening twice in the first year after their diagnosis and annually thereafter.

### How to manage abnormalities?

Population-based studies indicate that the incidence of cervical cytologic abnormalities among adolescents is increasing. Of more than 190,000 women aged 15 to 19 evaluated in 1981, 1.9% had dysplasia.<sup>16</sup> In 1999, Mount and colleagues examined Pap test results from 10,296 adolescents and found squamous intraepithelial lesions (SIL) in 4% and atypical squamous cells of undetermined significance (ASC-US) in 10%.<sup>17</sup> Adolescents have an ASC-US rate of 7% to 16%, a 3% to 13% rate of low-grade (LSIL), and a 0.2% to 3% rate of high-grade squamous intraepithelial lesions (HSIL).<sup>17-19</sup> Longitudinal studies of adolescents have shown that these women commonly develop cytologic abnormalities.<sup>5,7,20</sup> In Woodman and colleagues' study, 28% of the adolescents developed cytologic abnormalities and 33% of those who were HPV positive developed cervical dysplasia.<sup>5</sup>

**The ASC-US conundrum.** In adult populations, ASC-US is associated with a significant risk of underlying pathology. Five to 17% of adults with ASC-US have CIN 2 or 3 upon further investigation.<sup>21</sup> The largest series of adolescents and young women with ASC-US reported on follow-up of 398 patients aged 10 to 19. Overall, 67% of the women had normal follow-up, 16% had persistent ASC-US, 11% had low-grade lesions (LSIL or CIN 1), and 9% had high-grade abnormalities (HSIL, CIN 2 or 3).<sup>19</sup> These findings suggest that adolescents have a risk of underlying cervical dysplasia similar to that of adults. Of note, no cases of invasive cancer were identified. While spontaneous regression would be expected in a high percentage of the women,<sup>19</sup> the 9% incidence of high-grade abnormalities highlights the need for careful follow-up and evaluation.

Current guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP) do not specifically address management of ASC-US in adolescents. Strategies for management include reflex high-risk HPV testing, immediate colposcopy, and repeat cytology (Table 2). Reflex HPV testing is the management approach of choice in adults. Young women who are HPV positive should undergo colposcopy, whereas repeat cytology in 1 year is appropriate for those who are HPV negative.<sup>21</sup>

**TABLE 2**  
**ASCCP guidelines for managing cytologic abnormalities**

Cytology	Recommended management
ASC	Reflex DNA testing with referral for colposcopy for HPV-positive women preferred. Acceptable alternatives include immediate colposcopy or repeat cytology. If repeat cytology is chosen, it should be performed at 4- to 6-month intervals until two negative samples are obtained.
LSIL	Repeat cytology at 6 and 12 months with referral for colposcopy if ASC or greater is identified.
HSIL	Colposcopy. If biopsy-confirmed CIN 2 or 3 is not identified, patient may be observed with colposcopy and cytology at 4- to 6-month time points for 1 year if colposcopy results are satisfactory.
ASC-H	Colposcopy

ASCCP—American Society for Colposcopy and Cervical Pathology  
ASC—atypical squamous cells of undetermined significance  
LSIL—low-grade squamous intraepithelial lesion  
HSIL—high-grade squamous intraepithelial lesion  
ASC-H—atypical squamous cells, cannot exclude HSIL

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**LSIL.** Biopsy will confirm CIN 2 or 3 in 15% to 30% of adults with LSIL, whereas LSIL has a high rate of regression in adolescents and young women. Moscicki and colleagues' prospective evaluation of 187 women with LSIL found a 61% probability of regression by 12 months, and by 24 months, 91% of the subjects had regression.<sup>22</sup> The median time to the first negative Pap test was 8.1 months. Of note, 55% of the women who underwent biopsy had normal histology. In a separate cohort of 477 adolescents age 18 or younger with LSIL, 18% ultimately were found to have high-grade cervical abnormalities (HSIL, CIN 2 or 3). By 36 months the cumulative rate of regression was 62%.<sup>18</sup> No cases of cervical cancer were identified among any of the women.

These trials underscore the fact that in most young women, LSIL will regress without treatment. However, a portion—particularly those with persistent LSIL—will have underlying CIN 2 or 3. While conservative management is appropriate, these young women should be closely followed to ensure regression. Whether

histologically verified high-grade CIN is biologically different in adolescents than in older women remains unknown.

The ASCCP consensus guidelines specifically address management of LSIL in adolescents. For adults with LSIL, colposcopy is recommended, whereas repeat cytology is appropriate for adolescents. Cytology should be repeated at 6 and 12 months, and colposcopy performed on any patient who is found to have ASC or higher-grade disease.<sup>21</sup>



Figure 1. Algorithm for managing adolescent cervical dysplasia

**HSIL.** Data on the outcome of HSIL in adolescents is limited. Of 50 young women with HSIL who underwent biopsy at the time of follow-up, 13 were found to have CIN 2, 13 had CIN 3 identified and 1 patient had adenocarcinoma in-situ.<sup>18</sup> These findings highlight the fact that young women with HSIL are at substantial risk of harboring high-grade CIN. According to the ASCCP, young patients with HSIL should undergo colposcopy with directed biopsy of any suspicious lesions. Adolescents with biopsy-confirmed CIN 3 should undergo ablation or excision. Young women with CIN 2 who can be relied upon to return for follow-up can be counseled and observed with follow-up cytology. Adolescents with HSIL whose biopsies are negative for CIN 2 or 3 and have negative endocervical samples can be offered conservative follow-up with colposcopy and cytology every 4 to 6 months for 1 year (Figure 1).<sup>21,23</sup>

## Conclusion

Rising rates of sexual activity among young women have led to an increased incidence of cervical dysplasia in adolescents. Because HPV infection tends to be transient and adolescents have an exceedingly low incidence of invasive cervical cancer, screening can be deferred in most young women until age 21 or 3 years after they become sexually active. When you do encounter a cytologic abnormality in a teen, be aware that most of them are from transient viral infections that will spontaneously regress without treatment. Follow young patients closely to ensure regression, however, as they still are at risk of underlying pathology. Use cervical ablation and excision sparingly in adolescents, as their long-term consequences in this group are not well understood. More data clearly are needed on the biology of biopsy-confirmed CIN in adolescents to further refine management guidelines.

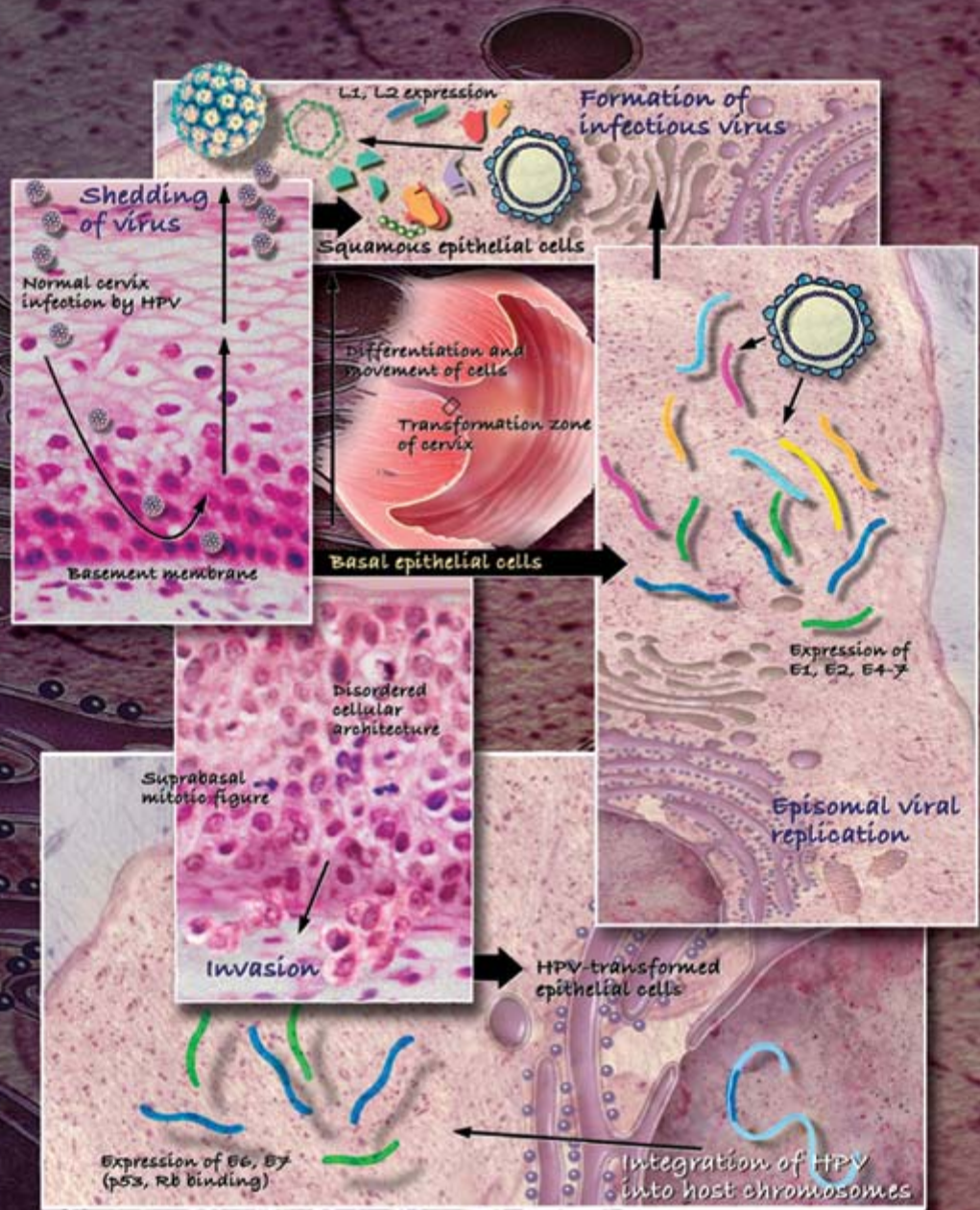
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## How HPV replicates in cervical epithelial cells

Human papillomavirus (HPV) is probably most infectious to cells that are close to the cervix's transformation zone (A), the area of transition from columnar to squamous epithelium. After entering the vagina, HPV infects the cervix's basal epithelial cells and replicates episomally (B). The result is expression of the viral genes E1, E2, E4, E5, E6, and E7 (C). As the infection progresses, the basal cells are disrupted and continue to differentiate and migrate to the epithelial surface. Productively infected cells express the viral capsid proteins L1 and L2 (D). Infection with high-risk HPV subtypes can result in dysplasia, cervical intraepithelial neoplasia (CIN), and eventually invasive cervical cancer (E, F).



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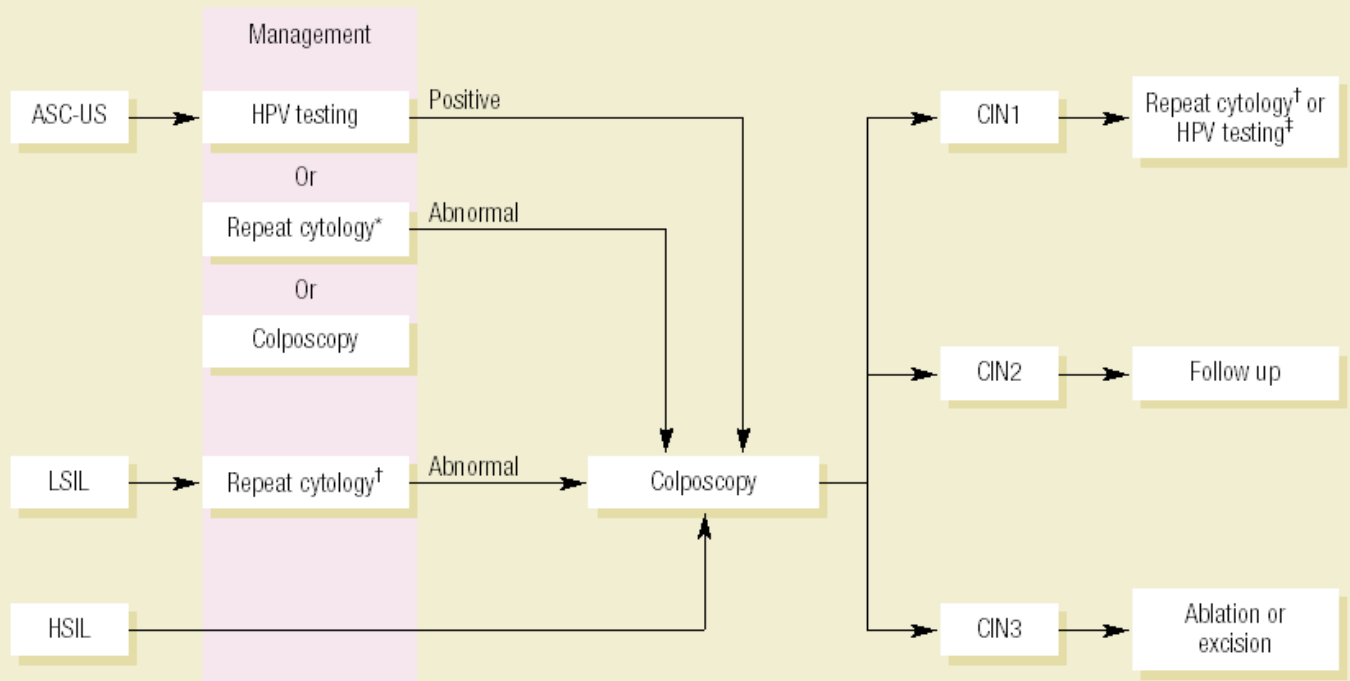
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**FIGURE 1. Algorithm for managing adolescent cervical dysplasia**



\* Repeat cytology every 4 to 6 months.

† Repeat cytology every 6 months until negative times two.

‡ HPV testing at 1 year.

ASC-US—Atypical squamous cells of undetermined significance

LSIL—Low-grade squamous intraepithelial lesions

HSIL—High-grade squamous intraepithelial lesions