Original Article

Conservative Management of Adolescents With Abnormal Cytology and Histology

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Key Words

Adolescence, squamous metaplasia, human papillomavirus, LSIL, HSIL, CIN I, CIN II, and CIN III

Abstract

Adolescents remain vulnerable to human papilloma virus (HPV) infection because of certain physiologic characteristics inherent in this age group and common sexual behaviors, including lack of condom use. The commonness of HPV in this age group also results in frequent abnormal cytology. Fortunately, most of the infections are transient, with frequent clearance of HPV and the lesion. Current strategies for adolescents with abnormal cytology include conservative management, avoiding invasive procedures. For cytologic atypical squamous cells of undetermined significance or squamous intraepithelial lesions (SIL), management can be obtaining cytology only at 1-year intervals for up to 2 years before referral for colposcopy is necessary. For biopsy-proven cervical intraepithelial neoplasia (CIN) I, management is similar with yearly cytology indefinitely or until high-grade–SIL or CIN II/III develops. CIN II in adherent adolescents can be managed with 6-month cytology and colposcopy. (*JNCCN* 2008;6:101–106)

Because cervical cancers are rare in adolescents (< 21 years), recent American Cancer Society guidelines recommend starting cervical cancer screening at 3 years after the start of sexual activity or 21 years of age, which ever comes first.[1] The strategy was based on the idea that many infections detected in slightly older adolescents would more likely reflect persistent than recently acquired human papilloma virus (HPV) infection, as expected in the recently sexually active. However, natural history studies suggest that HPV acquisition with new infections remains extremely common in most young women probably because of both biologic and behavioral factors. Therefore, abnormal cytology continues to have high prevalence in older adolescents and young women. The good news is most of these "abnormal cytologies" continue to spontaneously clear. New management guidelines consider both the need for surveillance of these women, who may be at risk for HPV persistence and development of significant disease such as carcinoma-in-situ lesions, and allow for conservative follow-up to avoid invasive procedures. This article discusses risk factors and epidemiology of HPV-associated disease and outlines new guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP), for managing abnormal cytology.

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Epidemiology of Squamous Intraepithelial Lesion

Squamous intraepithelial lesion (SIL) is considered a biologic manifestation of HPV. Consequently, its epidemiology is tightly linked to HPV's. HPV begins with infection of basal cells through either a wound or inflammation. HPV is unique in that it requires cell differentiation and maturation to complete its life cycle.[2] Shortly after infection, E6 and E7 proteins are expressed that interfere with cell cycle control, which results in basal cell proliferation and mild changes in the nucleus. E4 expression is seen in the midepithelial layers and is responsible for cytoskeletal changes associated with HPV (i.e., perinuclear halos). The capsid proteins L1 and L2 are not expressed until late and are seen in the mature squamous epithelial cell layer. In this layer, the infectious virion is formed and released with normal desquamating cells. Hence, low-grade–SIL (LSIL) is a pathologic consequence of HPV replication.[3]

Whether all HPV infections result in SIL remains controversial. Certainly, studies have shown that HPV is common in cytologically normal women. Alternatively, the lesion may be present but remain undetected by the insensitive Pap smear. One study in adolescents found that the appearance of LSIL and HPV had different risk factors in the same cohort. HPV acquisition was strongly linked to sexual behavior (i.e., reporting new partners), but LSIL was associated with other factors such as smoking cigarettes.[4] These data suggest that LSIL is manifested in only some HPV-infected women. Conversely, this finding may reflect the size of the lesion. Larger lesions caused by higher HPV loads may be more easily detected, and higher viral loads may be associated with risks such as smoking.

As mentioned, SIL is a manifestation of HPV. How HPV gets to the cervix is thought to be through sexual exposure, primarily through penile–vaginal sex.[4,5] Theoretically, other modes (e.g., finger sex and sex with objects) may also transmit the virus to the cervix. Some researchers speculate that autoinoculation could occur from vulva to cervix with the use of tampons or even from insertion of a speculum. Despite these theories, however, data show that more than 50% of adolescents will acquire HPV shortly after reporting onset of penetrative sex; this figure underscores the ease of sexual transmission.[4–6]

The high rate of acquisition in young women seen in cohort studies is also reflected in worldwide prevalence rates. A recent meta-analysis of HPV throughout the world showed that prevalence peaks in women younger than 21 years at 23%.[7] Not surprisingly, LSIL parallels this pattern, although at a much lower prevalence rate.[8] In some countries, HPV has a second peak in women older than 45 years.[9] Interestingly, LSIL does not mirror this second peak, with rates remaining less than 1%.[8]

Because LSIL is biologically linked to HPV, the natural histories of HPV and LSIL might be expected to parallel each other in adolescents. Natural history studies have shown that both HPV and LSIL are primarily transient in adolescents and young women, with more than 90% clearing infection and 90% showing regression to normal within 3 years, respectively.[10,11] These observations are different than those in adult studies, in which regression is found in approximately 50% to 60% of cases. Most likely, many of the LSILs detected in adults reflect persistent infections with underlying cervical intraepithelial neoplasia (CIN) II or III, helping to explain these differences.

High-grade–SIL (HSIL) is also a manifestation of HPV, but thought to be further along the natural history. Some studies, however, show that HSIL arises as rapidly as LSIL and, in some cases, bypasses detection of LSIL.[12,13] Although HSIL is found at lower rates than LSIL in adolescents, the rate of HSIL in adolescents is similar to that in older women. Mount and Papillo[8] reported that 0.7% of cytologies from 15- to 19-year-old teenagers showed HSIL, compared with 0.8% in women aged 20 to 29 years and 0.7% in those aged 30 to 39 years. Whether these HSIL cases are just "bad" cases of HPV or a truly more aggressive lesion remains unknown in this age group. Certainly, the reproducibility of HSIL is less than desirable.[3] Of adolescents referred for colposcopy for HSIL, 50% have confirmed CIN II or III, which suggests that many HSIL cases are "overcalls."[14] Unfortunately, colposcopic changes can be challenging to detect in adolescents because atypical squamous metaplasia, a common finding in this age group, can be misinterpreted as CIN, misguiding the colposcopist to biopsy.[15]

Natural History of CIN I, II, and III

When interpreting natural history studies, clinicians should remember that cytology is a screening test and, unfortunately, an insensitive one. Colposcopy also has limitations. Experience and number of areas biopsied increase the chance of finding a CIN II or III diagnosis.[16] The reproducibility of CIN I, II, and III is also problematic; often the agreement between pathologists is less than 50%.[3] Data from several studies show that, in all ages, 90% of CIN I is likely to regress.[3] Data from selected studies show that CIN II behaves more similarly to CIN I than CIN III and that CIN III is the least likely to regress and the most likely to progress.[17] A recent chart review study showed that 65% of adolescents with CIN II showed regression over 18 months.[18] Much of the published data in adolescent age groups suggest than CIN II is more likely than CIN III to be present in most HSIL cases.[8,14,19]

Most importantly, invasive cancers are extremely rare in this age group. The incidence of invasive cancer in women younger than 20 years in the United States is 0 to 3 per million.[20] This statistic suggests that progression is not common in adolescence, even with CIN II or III. Conversely, the incidence of invasive

cancer rises at age 25. Interestingly, cancer rates in U.S. adolescents have been stable over the past few decades, despite the lower age of sexual debut.

Biologic Risk Factors and HPV

One question that remains is whether adolescence is a risk for HPV, HPV persistence, or SIL. Some studies show that age of first sexual activity (under 18 years of age) remains a significant risk factor for the eventual development of cervical cancer.[21,22] Whether these are women who will ultimately have a greater number of sexual partners or partners at higher risk for infection or women who as adolescents were somehow biologically at risk for persistence remains another important question.

Most studies that compare age groups are of prevalent infections. Unfortunately, few studies of incident infection compare women of different age groups who have comparable numbers of sexual partners. Munoz et al.[23] examined the incidence of HPV in women of varied ages who were normal cytologically and HPV negative at entry. The incidence of HPV was highest in adolescents from 15 to 19 years of age, with a cumulative incidence of 17% at 1 year and 35.7% at 3 years. The rates gradually declined, with a 3-year incidence rate of 24.1% for women 20 to 24 years, declining to 8.1% in women 45 years and older. The final models showed that age-related risk was independent of recent sexual partners. Although biologic vulnerability is certainly plausible, one explanation may be that the male sexual partners of older women are less likely to carry HPV.

The idea that adolescents are biologically vulnerable is easy to entertain, because the topography of the adolescent cervix is different than that of the adult cervix.[15] The cervix is initially lined by Mullerian columnar epithelium and later replaced by urogenital squamous epithelium from the vagina towards the endocervical os. This replacement is usually incomplete, resulting in an abrupt squamous–columnar junction located on the ectocervix. Many girls enter puberty with the squamo–columnar junction well onto the ectocervix (Figure 1). However, as girls age, the cervix undergoes dramatic changes, predominantly caused by the influence of estrogen.

This process of change is referred to as *squamous metaplasia* and reflects the induction of uncommitted generative cells of the columnar epithelium to change into squamous epithelium. Eventually, the replacement results in a new squamo–columnar junction occurring well into the os. This area of transition is referred to as the *transformation zone*.

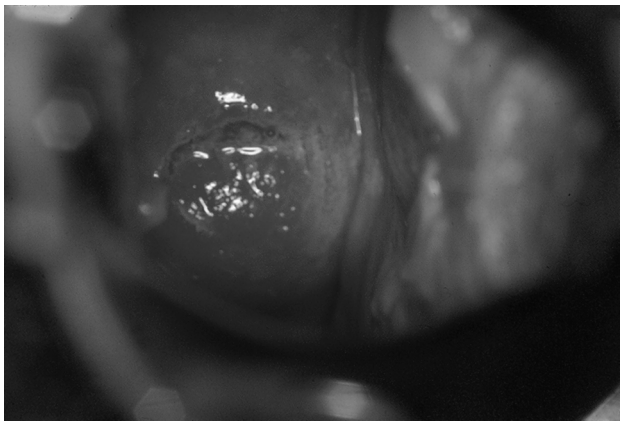

Figure 1 Squamocolumnar junction seen well onto the ectocervix. Cervix is primarily covered by columnar epithelium.

Both columnar and metaplastic epithelium are thought to be vulnerable to HPV infection. The columnar epithelium is 1 cell thick, whereas the squamous epithelium is 60 to 80 cell layers thick. HPV is thought to require access to basal epithelial cells; thus columnar epithelium makes a poor barrier. Metaplastic epithelium is a mixture that includes columnar and metaplastic cells. The transformation zone is important because all squamous cell cancers of the cervix appear to arise within this area.

HPV is a unique infection because it requires host cell replication and differentiation for survival. Both replication and differentiation are hallmarks of squamous metaplasia; thus the process of metaplasia provides fertile ground for HPV infection. The high rates of squamous metaplasia in young women may be in part the explanation for the high rates of LSIL seen in this population.[24]

Other factors may play a role in increasing adolescent vulnerability. *Chlamydia trachomatis*, a common infection in adolescents, was shown in one study to enhance HPV persistence.[25] Cigarette smoking may also enhance persistence and progression and may have an added effect.[26]

Management of Abnormal Cervical Cytology

The ASCCP rationale for managing abnormal cytology in adolescents was based primarily on observed

high rates of HPV and LSIL acquisition and regression and observed low rates of CIN III and cervical cancer in this age group. With HPV clearing and recurring, this strategy is best translated into using "time with surveillance." Historically, cytology is a screening tool used for referral, not treatment. Because most CIN II and III lesions were found in women with a typical squamous cells of undetermined significance (ASCUS) or LSIL, the threshold for referral was ASCUS. Treatment was then based on histologic diagnosis. New guidelines use different thresholds for adolescents based on these natural history studies.

Another rationale for conservative management is the procedure's risk versus perceived benefit. A recent meta-analysis of cervical excisional procedures showed increased risk of preterm delivery, low birth weight, and premature rupture of membranes.[27] One of the greatest concerns in young women is the need for repeat treatments, because development of a lesion is possible with each repeated HPV infection.

HPV Testing

Given that the current FDA-approved test for HPV is not type specific, HPV testing for any reason (ASCUS, LSIL follow-up) is not recommended in adolescents in the ASCCP guidelines. The rationale is that HPV detection in adolescents with or without abnormal cytology at any one time point is likely to reflect a transient infection. Boardman et al.[28] showed that 77% of adolescents with ASCUS are positive for high-risk HPV, calling into question its use for ASCUS triage in this age group. HPV testing strategies that are based on the identification of women with HPV persistence (i.e., 2 time points) may be cost-effective, even in adolescents.[29] Although the importance of HPV persistence in the development of HSIL and invasive cervical cancers is established, the timeframe is variable.[12,13,30] Thus, if HPV testing is used to define persistence, the length of persistence requiring referral in this group has yet to be established.

Triage

ASCUS and LSIL

ASCCP recommendations for ASCUS or LSIL include repeat cytology at 12-month intervals for 2 years. During the 2 years of follow-up, a threshold of HSIL or greater is recommended before referral to colposcopy. After 2 years, a threshold of ASCUS or greater is recommended before referral. HPV testing for follow-up is not recommended.

The rationale for this is that ASCUS and LSIL have similar natural histories; therefore, guidelines for these have been combined. Because HPV testing is not recommended, triage for ASCUS using HPV testing is also no longer recommended in this age group. If HPV testing is inadvertently obtained, patients who test positive for ASCUS or high-risk–HPV are treated the same as those with ASCUS or LSIL. The justification for bypassing histology in adolescents with LSIL is based on natural history studies of cytologic LSIL and histologic CIN I. Prevalence studies of LSIL in adolescents show that these are predominantly CIN I lesions. This is quite different from adult women, in whom LSIL screening shows higher rates of CIN II or III at colposcopy. Follow-up using cytology is recommended for up to 2 years based on the observation that only 60% of LSIL regressed at 1 year and 92% regressed by 3 years.[11]

HSIL and ASCUS Suggestive of HSIL

For HSIL or ASCUS suggestive of HSIL, immediate triage to colposcopy is recommended, similar to management in adults. In the cases of HSIL, if CIN II or III is not diagnosed, ASCCP guidelines suggest screening with colposcopy and cytology at 6-month intervals for up to 2 years. If HSIL persists on cytology or colposcopic persistence is seen, guidelines recommend repeat biopsy during follow-up. If HSIL persists on cytology after 2 years, a diagnostic excisional procedure is recommended.

HSIL or ASCUS suggestive of HSIL in adolescents is initially triaged similarly to that in adults. Because a large proportion of HSIL is consistent with underlying CIN II or III, referral to colposcopy is justified. Although the recommendations for adult women with HSIL include immediate treatment with loop electrocautery excision procedure (LEEP), this approach is not recommended for teens. One study showed that nearly 90% of HSIL referrals in adolescent had no HSIL on the LEEP specimen.[31] This finding may be attributable to either overdiagnosis or small lesions that are treated with biopsy.

Histologic CIN I

ASCCP guidelines suggest that treating CIN I is unwarranted in both adolescents and adults.[32] Instead, follow-up similar to that for ASCUS/LSIL is recommended, with cytology at 12-month intervals. HSIL on repeat cytology at 1 year warrants repeat referral. At 24 months'

follow-up, ASCUS or greater should be referred back to colposcopy. However, as long as CIN I remains the histologic diagnosis, observation is warranted. The rationale for this recommendation is that CIN I is considered benign in all ages.

Histologic CIN II

Because CIN II in adolescents may regress, several treatment options are recommended, including observation. Treatment is usually ablative, using either LEEP or cryotherapy. Some experts suggest that focal LEEPs or cryotherapy is more suitable for adolescents because of the lower rates of complications associated with these procedures. Complications of LEEP include pelvic inflammatory disease, which underscores the importance of screening for sexually transmitted infections before treatment.[33]

Observation can be used with adolescents with CIN II who are believed to be reliable for follow-up, with colposcopy and cytology recommended at 6-month intervals. If CIN II lesions persist on colposcopy or cytology (HSIL) at 1 year, repeat biopsy is recommended. If the lesion progresses to CIN III or greater or CIN II or greater persists at 2 years, treatment is recommended. Treatment is always recommended for patients with CIN III. Unfortunately, histologic diagnoses of CIN II and III are often not distinguished on pathology reports. However, because CIN II lesions are more common than CIN III in adolescent girls, lesions diagnosed as CIN II/III should be treated as CIN II. If the patient's adherence to the observation schedule is doubtful, treatment is the better option. If CIN II/III is treated, recommendations for follow-up of adolescents are similar to those of adults.

The rationale for these recommendations is that CIN II is often an unreliable diagnosis. In adolescents, it may reflect a lesion more similar to CIN I than CIN III. This thought is based on the fact that CIN III lesions and cervical cancers are generally rare in this group. Therefore, close surveillance allows lesions that will spontaneously regress to do so, and lesions that persist, which are unlikely to undergo significant progression, can be treated in a timely manner. However, observation is only an option for adolescent patients whose compliance is assured.

Conclusions

In summary, the new ASCCP management guidelines strongly incorporate observation, based on the high likelihood of regression of HPV-associated lesions and low probability of progression to cancer during adolescence. The guidelines also balance the risks of treatment and risk for progression. Because of the frequent appearance and disappearance of HPV, testing is not recommended in adolescents in any screening or triage strategy. Although HPV vaccination in now widely recommended, vaccinated adolescents should also be counseled about the importance of continued cancer screening.

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