



Human Papillomavirus and Cervical Disease in Adolescents

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Abstract: The addition of the human papillomavirus vaccination and the 2006 national guidelines for the management of abnormal cervical cytology have led to significant changes in the management of cervical disease among adolescents. This article reviews recommendations for prevention, screening, diagnosis, and management of cervical disease.

Key words: HPV, vaccination, cytology, colposcopy, adolescent

Introduction

The management of cervical disease in the adolescent population is an area of clinical medicine that has undergone significant changes with the addition of the human papillomavirus (HPV) vaccination and the 2006 national guidelines for the management of abnormal cervical cytology. This chapter will discuss the prevention, screening, and management of cervical disease in the adolescents. The chapter will highlight the overriding consensus that the objective of care of this

population is one of prevention and minimal intervention.

Natural History of HPV

Over 90% of all cervical cancer patients have evidence of HPV DNA present in the cancer cells, specifically high-risk HPV.¹ The development of accurate tests for HPV, Hybrid Capture II, and polymerase chain reaction, has drastically improved our understanding of the pathophysiology of cervical cancer and cervical dysplasia.

HPV is a group of common DNA viruses that infect squamous epithelium and are associated with a broad range of clinical manifestations. There are over 100 different types of HPV viruses. The genital tract represents one of the major sites of HPV infection.² The majority of infections of the genital tract are asymptomatic in both men and women. Clinically apparent HPV is associated with genital warts, cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia, vulvar intraepithelial neoplasia,

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and squamous cell cancers of the cervix, vagina, and vulva.

The transmission of HPV is strongly associated with sexual activity. HPV is primarily transmitted by skin-to-skin genital contact. Natural history studies of HPV-negative adolescent with normal pap test who become sexually active clearly demonstrate the sexual acquisition of HPV. HPV is detectable in <2% of sexually inexperienced women yet detectable in 45% of those who are sexually active. Studies that have followed a specific cohort of young sexually active women over time have demonstrated that over 50% to 60% of the population will be positive for HPV.³ The link between sexual activity and HPV infection is further strengthened by the identification of similar HPV types among sexual partners. Sexual transmission is the primary means of acquiring HPV but evidence of non-sexual transmission does exist. Although rare, there is some evidence for in utero infection, perinatal infection, auto-inoculation and hetero-inoculation through close nonsexual contact, and possibly indirect transmission via fomites.^{4,5}

The majority of adolescents infected with HPV will be asymptomatic. Those who are detected, either by an abnormal pap test, HPV test, or the presence of clinically evident genital warts will most likely resolve the infection without treatment. In natural history studies of adolescents with newly acquired HPV infection, the average length of infection of detectable HPV is 8 months. The majority of patients with an intact immune system will resolve an HPV infection within 24 to 30 months.^{6,7} Further evidence for the resolution of HPV infection comes from the high resolution rate of CIN 1 and CIN 2, 70% and 50%, respectively.^{8,9} Unfortunately, some individuals are susceptible to persistent HPV infection. In these individuals, the HPV may be present for years, and may put them at high risk for the development of cervical cancer.

During adolescence, the number of sexual exposures may be high. Recurrent infections are therefore common. Consequently, prevalence data for HPV have been reported in up to 40% of adolescents at any 1 point in time.¹⁰ Despite the increased exposures to HPV, most (90%) adolescents infected with HPV will resolve without treatment. Surveillance Epidemiology and End Result (SEER) data demonstrate that the rate of cervical cancer in the adolescent <20 years of age is 0.3/100,000.¹¹ These facts are the cornerstone to the adoption of less aggressive screening and treatment programs for the adolescents.

Prevention of HPV

The best method for preventing the effects of HPV disease is to not acquire the infection. Because the HPV virus is acquired by skin-to-skin contact, acquisition of HPV can occur without penetrating intercourse. Recent studies have demonstrated that the use of condoms will reduce the incidence of HPV acquisition by 70%. In women who consistently use condoms, the incidence of genital HPV infection was 37.8 per 100 patient-years at risk among women whose partners used condoms for all instances of intercourse, as compared with 89.3 per 100 patient-years at risk in women whose partners used condoms less than 5% of the time.¹²

The addition of HPV vaccination to the armamentarium of prevention is one of the most significant advancement in the history of cancer prevention. The groundwork for the use of a virus like particle (VLP) began with a canine model for oral carcinoma induced by HPV.¹³ This model clearly demonstrated that a VLP could produce immunity against the native virus that is type specific. Subsequent research has lead to the human studies.

VLPs are produced via the synthesis and self-assembly of the L1 capsid protein.

The L1 protein is type specific and demonstrates morphologic and antigenic properties that are identical to the native virion. Presently, there are 2 HPV vaccines, Gardasil (Merck and Co), which is a quadrivalent vaccine against types 6, 11, 16, and 18, and Cervarix, which is a bivalent vaccine against type 16 and 18. Gardasil has been Food and Drug Administration (FDA) approved since June 2006 whereas Cervarix is presently under review by the FDA.

Gardasil is composed of purified L1 VLPs of HPV 6, 11, 16, and 18 at 20, 40, 40, and 20 $\mu\text{g}/\text{dose}$ levels. The vaccine is supplied as 0.5 mL for intramuscular injections that is administered at 0, 2, and 6 month intervals. There have been numerous clinical trials for FDA approval of the vaccine. The vaccine is 100% effective in producing an immune response against type-specific HPV. Villa et al¹⁴ studied 552 women of age 16 to 23 in a randomized, placebo controlled, multicenter prospective study of Gardasil. The study demonstrated a 96% reduction in the combined incidence of HPV-related 6/11/16/18 persistent infection or disease.¹⁵

The Females United to Unilaterally Reduce Endo/Ectocervical Disease (Future II) study was a large, randomized, placebo controlled multicenter trial of over 12,000 women, which further demonstrated the effectiveness of the vaccine. The quadrivalent HPV vaccine was 98% (86% to 100%) effective in reducing CIN 2 or 3 associated with HPV 16 and 18.¹⁶

The Future II and other studies have clearly demonstrated a persistent effectiveness of the vaccine. The development and deployment of the vaccine included smaller studies to test for the immune response and safety data for the younger population. On the basis of these data, the FDA approved Gardasil for use in girls and women from ages 9 up to and including age 26.

The bivalent vaccine, Cervarix is presently under review by the FDA. This vaccine, developed by GlaxoSmithKline Biologicals (Rixensart, Belgium) is a bivalent HPV vaccine that includes types 16 and 18. The vaccine consists of purified L1 VLPs of HPV type 16/18 at 20/20 $\mu\text{g}/\text{dose}$. The vaccine incorporates an ASO4 adjuvant consisting of aluminum hydroxide 500 μg . The proprietary adjuvant is designed to increase the immune response to the vaccine. The vaccine is administered as 0.5 mL intramuscular injection at 0, 1, and 6 months.

Clinical trials with Cervarix have demonstrated excellent immunogenicity and effectiveness in reducing HPV-related cervical dysplasia. In a large, multicenter, placebo controlled trial of 776 subjects, the vaccine was 96.9% effective against HPV-16/18 infections and 100% effective in preventing 12-month persistent infection.¹⁷

The American College of Obstetrics and Gynecology (ACOG) recommends the routine vaccination of girls of age 11 to 12 years. On the basis of the data provided to the FDA, ACOG recommends continued screening of women for cervical disease by cytology as per the ACOG guidelines. Receiving the vaccine does not reduce or eliminate the need for the cytologic screening. Young women who have had prior exposure to the HPV virus may still be vaccinated, despite the fact that the benefit from the vaccination may not be as significant as for those who are HPV naive.¹⁸

CERVICAL CANCER SCREENING TEST

Cervical cancer screening programs based on the pap test have been highly effective in reducing the rate of cervical cancer in countries that have widespread screening programs. The system, however, is not without problems. The most common cause for a missed diagnosis of cervical cancer is the lack of screening. Despite the

widespread availability of pap test in the United States, 17% of women report not having a pap test in the previous 3 years.¹¹

Until the development of a reliable liquid-based pap test, the only available cervical cytology screening method was the conventional pap smear. This test is an excellent screening test but it does have numerous limitations. The overall sensitivity of the pap smear is believed to be 70%. The missed cases of cervical disease are more often due to the lack of transfer of the cells from the cervix to the smear rather than an oversight by the cytologist. The development of liquid-based cytology was in part developed to overcome the shortcomings of the traditional pap smear. Presently, 2 techniques have been approved by the FDA for cervical cancer screening; ThinPrep (Cytoc, Boxborough, MA) and SurePath (TriPath, Burlington, NC).¹⁹

ThinPrep requires that the cervix be sampled with either a broom-type device (eg, Wallach Papette, Wallach Surgical Devices Inc, Milford, CT) or a combination of a plastic spatula and a Cytobrush (Medscand, Hollywood, FL). The spatula is then vigorously swirled in the collection medium and the cytobrush is rubbed against the side of the collection vial to remove as many cells as possible from the device. The broom is vigorously compressed against the base of the vial 10 times to separate the cells from the device.

The cervical cells are retrieved from the liquid medium via an automated device. The fluid is first agitated and then suctioned up through a filter that separates the cells from the liquid. The medium itself is both mucolytic and hemolytic and therefore the resulting monolayer sample is free of many of the obscuring problems that are present in a traditional pap smear. This technology has demonstrated an increased sensitivity for low-grade and high-grade cervical abnormalities.¹⁹ ThinPrep prevents air drying effect, has increased sensitivity for the detection of cervical abnormal-

ities, and is FDA approved for the ancillary testing of residual fluid, specifically for HPV. Liquid-based cervical screening is now the most common method used in the United States. SurePath is FDA approved as an equivalent technique for cervical cancer screening and is in the process of seeking FDA approval for ancillary testing for HPV.²⁰

BETHESDA 2001

The Bethesda system is designed to standardize the reporting of cervical cytology, improve quality assurance, and ultimately assist clinicians in the management of patients with an abnormal pap test. Originally developed in 1988, the system has undergone its most recent changes in 2001. The entire classification is presented in Table 1.²¹ Bethesda 2001 has numerous changes, which not only make the system easier for the clinician to use but also reflect the importance of new technologies in the evaluation of cytologic abnormalities of the cervix.

Specimen adequacy is one of the most important components of the cytologic report. This aspect of the report has been simplified by eliminating the previously confusing category of "satisfactory but limited by." The specimen is now either "satisfactory for evaluation" or "unsatisfactory for evaluation." Minimum standards for the presence of endocervical and squamous cells have been established, and the cytology laboratory may comment with regard to the presence of obscuring inflammation. The presence of endocervical or metaplastic cells on a pap test is considered as evidence that the entire transformation zone has been sampled.

The presence of these cells is preferred; however their absence has not been shown to decrease the sensitivity for the detection of high-grade cytologic abnormalities.

The report includes a "general categorization" section, which is optional, but provides a 1-sentence summary of the

TABLE 1. Bethesda 2001**SPECIMEN TYPE**

Indicate conventional smear (Pap smear) versus liquid-based versus other

SPECIMEN ADEQUACY

Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, eg, partially obscuring blood, inflammation, etc.)

Unsatisfactory for evaluation ... (*specify reason*)

Specimen rejected/not processed (*specify reason*)

Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

GENERAL CATEGORIZATION (optional)

Negative for Intraepithelial Lesion or Malignancy

Epithelial Cell Abnormality: See Interpretation/Result (*specify 'squamous' or 'glandular' as appropriate*)

Other: See Interpretation/Result (eg, endometrial cells in a woman + 40 years of age)

AUTOMATED REVIEW

If case examined by automated device, specify device and result

ANCILLARY TESTING

Provide a brief description of the test methods and report the result so that it is easily understood by the clinician

INTERPRETATION/RESULT

Negative for Intraepithelial Lesion or Malignancy (when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether or not there are organisms or other non-neoplastic findings)

ORGANISMS:

Trichomonas vaginalis

Fungal organisms morphologically consistent with *Candida* spp

Shift in flora suggestive of bacterial vaginosis

Bacteria morphologically consistent with *Actinomyces* spp.

Cellular changes consistent with Herpes simplex virus

OTHER NON-NEOPLASTIC FINDINGS (Optional to report; list not inclusive):

Reactive cellular changes associated with

Inflammation (includes typical repair)

Radiation

Intrauterine contraceptive device (IUD)

Glandular cells status post hysterectomy

Atrophy

OTHER

Endometrial cells (in a woman + 40 years of age) (Specify if 'negative for squamous intraepithelial lesion')

EPITHELIAL CELL ABNORMALITIES**SQUAMOUS CELL**

Atypical squamous cells

Of undetermined significance (ASC-US)

Cannot exclude HSIL (ASC-H)

Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/CIN 1

High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, CIS/CIN 2, and CIN 3

With features suspicious for invasion (*if invasion is suspected*)

Squamous cell carcinoma

GLANDULAR CELL

Atypical

Endocervical cells (NOS or *specify in comments*)

Endometrial cells (NOS or *specify in comments*)

Glandular cells (NOS or *specify in comments*)

Atypical

Endocervical cells, favor neoplastic

Glandular cells, favor neoplastic

Endocervical adenocarcinoma in situ

TABLE 1. (continued)

Adenocarcinoma
Endocervical
Endometrial
Extrauterine
Not otherwise specified (NOS)
OTHER MALIGNANT NEOPLASMS: (<i>specify</i>)
EDUCATIONAL NOTES AND SUGGESTIONS (<i>optional</i>)
Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included)

results of the cytology for easier triage. The sample is either “negative for intraepithelial lesions or malignancy” or an “epithelial cell abnormality” is present.

Atypical squamous cells (ASC) is a category of cytologic abnormalities that is subdivided into “of undetermined significance (ASC-US)” and “cannot exclude HSIL (ASC-H).” These 2 categories reflect the general understanding of cervical disease being subdivided into low and high-grade abnormalities. The bulk of scientific data suggest that the majority of minor cytologic abnormalities (ASC-US and low-grade squamous intraepithelial lesions) represent clinical manifestation of various stages of HPV infection.⁸ The more dysplastic changes associated with high-grade squamous intraepithelial lesions (HSIL) represent a significant risk for the development of cervical cancer.

The ASC-H subcategory represents a modest fraction (5%) of all ASC diagnosis and is characterized by a small number of moderate to severely dysplastic cells on entire specimen. This group has been shown to harbor high-risk HPV in greater than 80% of samples and may be found to have moderate to severe dysplasia in 40% of cases within a 2-year period. As such, this diagnosis requires more extensive evaluation and close follow-up.²²

The low-grade squamous intraepithelial lesion (LSIL) and the HSIL categories have remained unchanged from the 1991 Bethesda system. These diagnoses are generally reproducible and in many ways

reflect the dichotomous division in the squamous intraepithelial lesions.

Glandular cell abnormalities are separated into 4 separate categories: (1) atypical glandular cells (AGC); (2) AGC-favor dysplasia; (3) endocervical adenocarcinoma in situ; and (4) adenocarcinoma. The first 2 groups when possible characterize the cell of origin, endocervical versus endometrial. The system describes the cellular abnormalities and is best suited for use by clinicians.

The Bethesda system includes a statement regarding the use of an automated review, ancillary testing, and educational notes. This information gives the clinician information about the use of computerized cytologic analysis, ancillary test (such as HPV testing), and provides the opportunity for the cytologist to comment about the validity and significance of an interpretation. Ultimately all these changes reflect the advancement in the technology used in the preparation and interpretation of cytologic specimens.

SCREENING GUIDELINES

ACOG and the American Cancer Society (ACS) have published evidence-based guidelines that cover a variety of issues relating to cervical cancer screening. In some cases, these recommendations represent a significant departure from previous guidelines.^{23–25}

ONSET OF SCREENING

The onset of screening for cervical disease in adolescents is consistent with our

understanding of the nature of HPV of the cervix. The adolescents have many characteristics that make them at high risk for cervical disease. They have multiple sexual partners; have a high rate of squamous intraepithelial lesions and HPV infections, in addition to the larger transformation zone associated with early menarche. Yet despite the risk factors associated with this population they have a high rate of resolution of both HPV and squamous intraepithelial lesions, there are virtually no cancers reported before the age of 19, and there is a significant cost for the evaluation and treatment of low-grade cervical disease in this population. Recent studies have highlighted the significant impact of treatment on the reproductive health of women, demonstrating that women who have undergone a loop electro-surgical excision procedure (LEEP) or laser conization procedure are at increased risk for preterm deliveries, premature rupture of membranes, and low birthweight babies.²⁶⁻²⁸

Traditionally, cervical cancer screening has been initiated at the age of 18 or at the onset of sexual activity. This time period corresponds to a period during which young women are very likely to have exposure to HPV infection. The majority of HPV infections in this population are transient yet they can produce cytologic abnormalities that prompt a colposcopic examination. Longitudinal studies of HPV-negative adolescents who acquire HPV demonstrate that 36 months are required to develop an HSIL pap test.³ Finally, squamous cell cancer in women <21 years of age is exceedingly rare.²⁹ Therefore, ACS and ACOG recommend the initiation of cervical cytology no later than age of 21, or 3 years after the onset of sexual activity.

The screening recommendations for adolescents require that the onset of sexual activity must be specifically identified and noted on the chart. Many clinicians are concerned that owing to the delay in

the onset of pap testing fewer adolescents will seek care. Sexually active adolescents have many reasons to seek care, specifically sexually transmitted disease (STD) screening and contraceptive counseling and HPV vaccination. Clinicians should not change their practice patterns regarding the frequency of visits; rather they will no longer be required to obtain a pap test until 3 years after the onset of sexual activity or until 21 years of age, whichever comes first.

There are a variety of special circumstances that would warrant the early onset of pap testing. Those adolescents who are known or suspect of being sexually abused and those with diseases or medical treatments that compromise the immune system warrant early pap testing.

FREQUENCY OF SCREENING

The optimal screening frequency for women is difficult to identify. Cytology, by its very nature, has a false negative rate of 15% to 30%.¹⁹ Therefore, its success in part depends on repeated tests that reduces the false negative rate to an acceptable level. ACOG and the ACS recommend annual cytologic screening with traditional pap smears and screening every 2 years if a liquid-based system is used.

TRIAGE FOR CYTOLOGIC ABNORMALITIES

ASCCP GUIDELINES

The American Society for Colposcopy and Cervical Pathology (ASCCP) held the second consensus workshop in September 2006 to revise the national evidence-based guidelines for the management of both cytologic and histologic abnormalities of the cervix based on new evidence. The meeting included representation from 29 professional organizations, federal agencies, and national and

international health organizations. The resulting clinical guidelines are the result of this workshop and are evidence based when possible.^{30,31} These guidelines represent a well organized, nationally accepted management strategies for treating cytologic and histologic abnormalities.

There were numerous modifications to the guidelines, but by far the changes to the management of the adolescent were the most significant. Summarized in the following sections are the most recent recommendations for the management of cytologic abnormalities in adolescents.

Management of Abnormal Cervical Cytology

ASC-US/LSIL

The 2006 consensus guidelines for the management of abnormal cervical cytology include significant changes in the management of ASC-US and LSIL pap tests for adolescents. The high prevalence of HPV in adolescents and young women (<21) and the very similar clinical outcome of young women with these 2 cytologic abnormalities has prompted ASCCP to recommend a similar management scheme for both of these diagnosis. Data from the ASC-US LSIL Triage Study (ALTS) trial have clearly demonstrated that women with ASC-US who are HPV positive and women with LSIL diagnosis have similar risk of having incident CIN 2+ at the time of colposcopy. This group of patients also carries the same risk of developing CIN 2+ during a 2-year follow-up period if their initial colposcopic evaluation did not demonstrate CIN 2+.³² The rationale for triaging these 2 groups in a similar manner is also based on the fact that the rate of detecting HPV in adolescents with ASC-US and LSIL are very similar (~80%).

HPV triage is no longer recommended for the management of adolescents and

young women with ASC-US. Unlike the adult population where HPV positive rates are typically 50%, the younger population has a much higher rate of HPV, which minimizes the triage utility of this test. The consensus guidelines specifically state that HPV testing is not to be used in the management of young women with ASC-US, and if the information is obtained inadvertently it is to be ignored.

The present recommendation for the management of adolescents and young women with ASC-US and LSIL is to repeat cytology at 12-month intervals for a period of 2 years. Adolescents are only to undergo a colposcopic evaluation for a follow-up cytologic diagnosis of HSIL at any time, or the persistence of ASC-US or LSIL for a period of 2 years. This recommendation is based on natural history studies of ASC-US and LSIL that demonstrate a high rate of resolution of the disease rather than randomized-controlled trials of this triage method.³³ Figure 1 summarizes the management guideline.

ASC and ASC-H

ASC-H represents a small proportion of cervical cytology results. Multiple studies have demonstrated that women with a ASC-H diagnosis frequently have an ongoing HPV infection (~80%), and are at increased risk for CIN 2, 3 in a 2-year period.²² Because there are limited data on ASC-H in adolescents, the management of ASC-H in adolescents is the same as that for adults, immediate colposcopy. In women where no CIN 2, 3 is identified, the subsequent management is cytologic evaluation at 6-month intervals. If any cytologic abnormality is found (\leq ASC), the patient should undergo a repeat colposcopy. When the patient has 2 consecutive normal pap test they can return to annual evaluations. HPV testing is not recommended for follow-up in this

Management of Adolescent Women with Either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

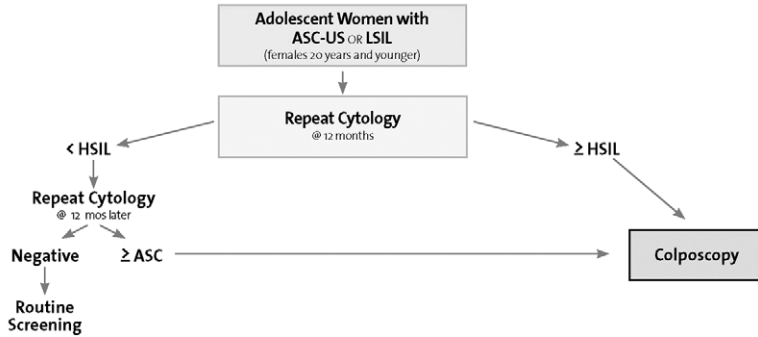


FIGURE 1. Management of adolescent women with either atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL). Used with permission from *J Low Genit Tract Dis.* 2007;11:201–222. The color version of this figure is available online by accessing the ASCCP guidelines at <http://links.lww.com/A408>; please refer to Figure 2, page 206.

population owing to the high prevalence of HPV in the adolescent. Figure 2 summarizes the management of ASC-H for all women.

HSIL

The adolescent with HSIL requires an immediate colposcopic evaluation with

endocervical sampling for adolescents where the SCJ is not well visualized. The 2006 ASCCP consensus guidelines allow for “see and treat LEEP” for adults with HSIL cytology. This, however, is not recommended for adolescents. Although adolescents with an HSIL cytologic diagnosis may have biopsy proven CIN 2 or

Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC - H)

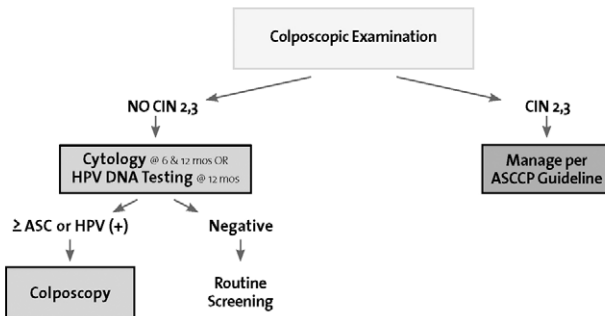


FIGURE 2. Management of women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H). Used with permission from *J Low Genit Tract Dis.* 2007;11:201–222. The color version of this figure is available online by accessing the ASCCP guidelines at <http://links.lww.com/A408>; please refer to Figure 3, page 207.

CIN 2/3 identified, immediate treatment is not recommended in the compliant adolescent. The primary reasons for less intervention in the adolescent population is the high rate of resolution of CIN 2 in the adolescent population and the increased relative risk of preterm labor and premature rupture of membranes in women undergoing LEEP.

There are number of aspects to the care of the adolescent with HSIL that are worthy of discussion. During the colposcopic examination, adolescents are frequently identified as having a large transformation zone, and an easily visualized squamocolumnar junction. It is recommended that all individuals undergo an endocervical sampling when HSIL is diagnosed. An argument can be made that because adolescents are more likely to have CIN 2 than CIN 3, and that the management of CIN 2 in adolescents includes an option for observation without treatment, performing an endocervical curettage could result in a false positive result, and an unnecessary excisional procedure. There is little or no evidence to strongly recommend for or against endocervical curettage in an adolescent with a

visible lesion with an adequate colposcopy.

The 2006 consensus guidelines do provide an alternative to an excisional procedure for the patient with a HSIL pap and where no visible lesion is identified. This is particularly important for the adolescent. The adolescent with HSIL where there is no evidence of CIN 2, 3 will be managed with repeat cytologic and colposcopic evaluation at 6-month intervals. During the follow-up, in keeping with the cytologic follow-up recommended for the ASC-US and LSIL patient, an adolescent with either of these diagnoses in follow-up can be monitored with continued cytology. If HSIL persists for 24 months without identification of CIN 2, 3, a diagnostic excisional procedure is recommended. Figure 3 outlines the present recommendations for the management of patients with HSIL.

AGC

The Bethesda 2001 system for reporting cytologic abnormalities separates AGC into “not otherwise specified” and “favor

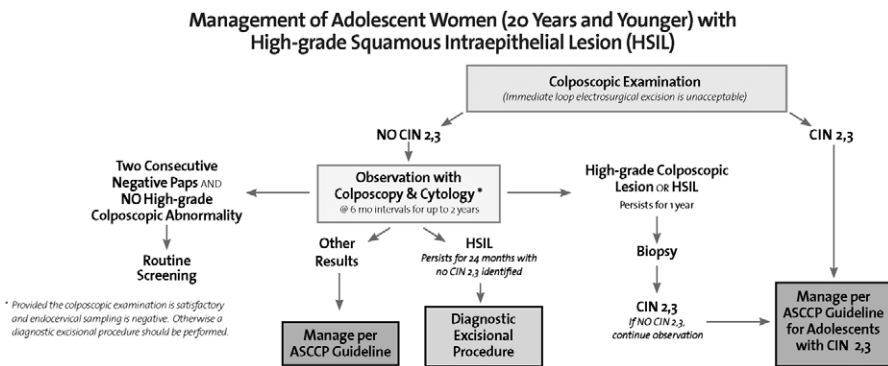


FIGURE 3. Management of adolescent women (20 y and younger) with high-grade squamous intraepithelial lesion (HSIL). Used with permission from *J Low Genit Tract Dis.* 2007;11:201–222. The color version of this figure is available online by accessing the ASCCP guidelines at <http://links.lww.com/A408>; please refer to Figure 7, page 211.

dysplasia.” The cytology report further classifies the abnormalities based on the probable location of the cell of origin (endocervix, endometrium, or unknown). The prevalence of AGC cytology in the adolescent population is very low, and most of these abnormalities will arise from the squamous component of the cervix.²⁹ Because of the rare nature of this diagnosis, a gynecologist with expertise in managing cervical dysplasia should manage cases of AGC cytology in the adolescents. The adolescents with AGC should undergo a colposcopy and endocervical sampling.

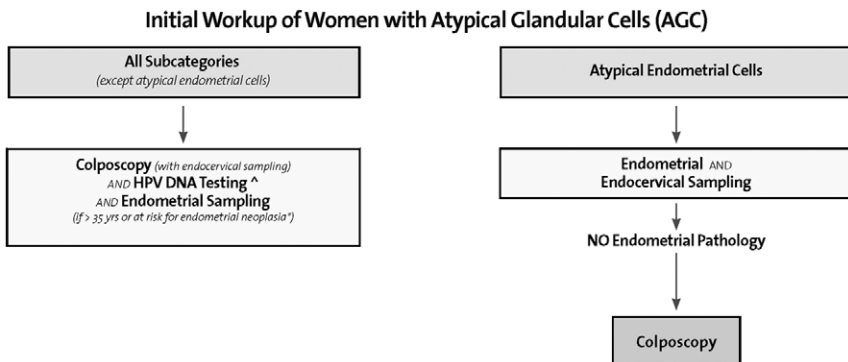
The 2006 consensus guidelines for the management of AGC now incorporate the use of HPV testing for adults. This is based on data from a series of studies that demonstrate high sensitivity for the detection of cervical dysplasia in patients with AGC.³⁴ The present guidelines, do not specifically address the use of HPV in the postcolposcopy triage of the adolescent population with AGC. As this cytologic diagnosis is rare, and there are no specific data to argue against using HPV in the management of adolescent,

the preferred method of management of the adolescent population would be similar to the adult (Fig. 4). Because the adolescent population has a higher rate of HPV infection than the adult population they are more prone to require subsequent colposcopic evaluation during the monitoring of their AGC cytology.

The adolescent with AGC suggestive of an endometrial abnormality is rare. Endometrial sampling would not be used in most adolescents unless they are morbidly obese, they have abnormal uterine bleeding or oligomenorrhea, or there is a suspicion of endometrial cancer (Fig. 4).

CIN 1

Assuming that CIN 2 or greater has been ruled out by colposcopy, prospective studies of an adult population with CIN 1 demonstrate that the risk of CIN 2 or greater developing over a 2-year period is 10%.³² In the adolescent population, the rate of resolution of CIN 1 is extremely high (>90%) and the rate of progression is estimated to be 3%.³³



[^] If not already obtained. Test only for high-risk (oncogenic) types.

^{*} Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.

FIGURE 4. Initial workup of women with atypical glandular cells (AGC). Used with permission from *J Low Genit Tract Dis*. 2007;11:201–222. The color version of this figure is available online by accessing the ASCCP guidelines at <http://links.lww.com/A408>; please refer to Figure 8, page 213.

Therefore, initial management of CIN 1 without therapy is the recommended management option.

The 2006 ASCCP consensus guideline for the follow-up of an adolescent with CIN 1 mirrors those recommendations for the management of an ASC-US or LSIL cytologic diagnosis, namely the use of repeat cytology at 12-month intervals. Only adolescents with a cytologic diagnosis of HSIL should be referred for colposcopic evaluation. If the adolescent continues to have a cytologic abnormality (\geq ASC) at 24 months, she should be referred for colposcopy. HPV testing is not recommended for the adolescent being followed for a diagnosis of CIN 1.

The management of an adolescent with persistent CIN 1 (> 24 mo) should be individualized. It is very reasonable, and strong consideration should be given to, continued monitoring of such patient owing to the frequency of new sexual partners in this population. The 2006 consensus conference recommendation for an adult with 2 years of persistent

disease is either treatment or continued observation. The adolescent would be best served by HPV education and counseling about the risk and benefits of treatment of dysplasia if she request treatment for CIN 1. The clinician must be sensitive to the physical and psychologic burden of the continued pap testing, and colposcopy that the adolescent experiences when she requires continued follow-up (Fig. 5).

CIN 2, 3

The histologic difference between CIN 2 and CIN 3 is very subtle, and numerous studies have demonstrated a lack of reproducibility of these diagnosis.³⁵ The 2006 consensus guidelines provide a recommendation for the combined diagnosis, with knowledge that the clinician will frequently get a diagnosis that specifically classifies the cervical biopsy as either CIN 2 or CIN 3.

The management of the adolescents with CIN 2, 3 not otherwise specified is either treatment, or observation for up to 24 months using both colposcopy and

Management of Adolescent Women (20 Years and Younger) with a Histological Diagnosis of Cervical Intraepithelial Neoplasia - Grade 1 (CIN 1)

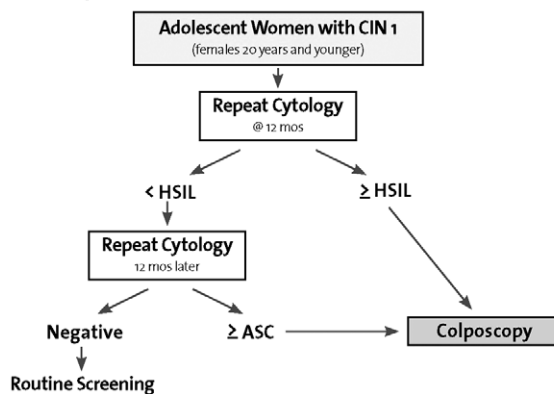


FIGURE 5. Management of adolescent women (20 y and younger) with a histologic diagnosis of cervical intraepithelial neoplasia-grade 1 (CIN 1). Used with permission from *J Low Genit Tract Dis.* 2007;11:223–239. The color version of this figure is available online by accessing the ASCCP guidelines at <http://links.lww.com/A409>; it is Figure 3, page 230.

cytology at 6-month intervals provided colposcopy is satisfactory. If during a period of observation, the colposcopic appearance worsens or the HSIL pap test persist for a year then repeat biopsy should be conducted to assess for worsening of disease. The adolescent can return to annual screening when she has 2 negative pap test. Treatment is recommended for adolescents with persistent CIN 2, 3 by histology for a 24-month period.

A variety of studies, including the ALTS trial, have demonstrated that CIN 2 lesion may have a significant rate of resolution (up to 40%) in adults. This rate of resolution is suspected to be higher in adolescence. The 2006 consensus guidelines preferred management of adolescents with the specific diagnosis of CIN 2 is observation with colposcopy and

cytology at 6-month intervals as described for the management of CIN 2,3. The care of the adolescent who specifically has CIN 2 for 24 months should be individualized, taking into account the reproductive impact of treatment and the ability of the adolescent/young women to continue in the frequent follow-up schedule.

The management of the adolescents with CIN 3 is treatment. CIN 3 is typically a stable lesion, and one that infrequently resolves. Treatment modalities for CIN 3 include cryotherapy, laser, or LEEP. The outcomes of all 3 therapies are comparable, and the actual mode of treatment should be determined by the geometry of the lesion, the clinician's abilities, and with a conscious effort to minimize the treatment area to that required to treat the disease (Fig. 6).

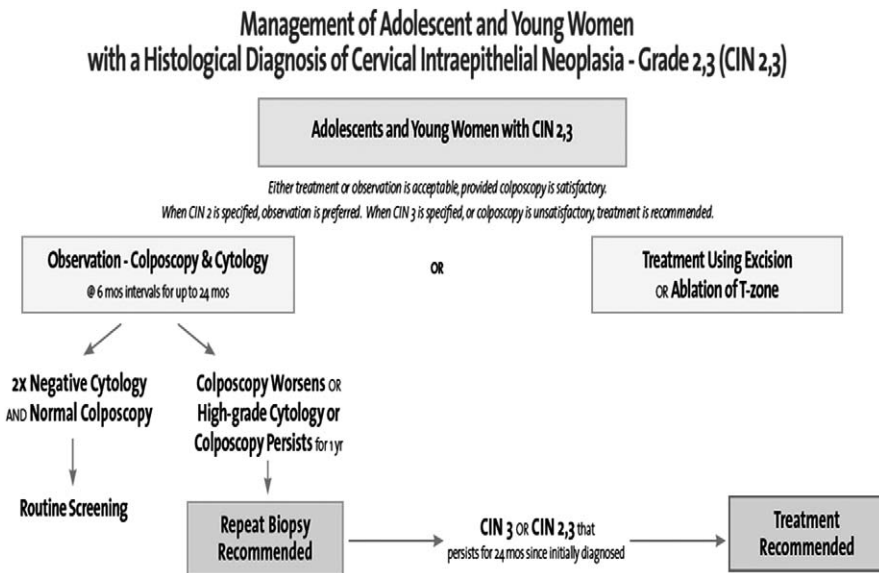


FIGURE 6. Management of adolescent and young women with a histologic diagnosis of cervical intraepithelial neoplasia-grade 2, 3 (CIN2, 3). Used with permission from *J Low Genit Tract Dis.* 2007;11:223–239. The color version of this figure is available online at *J Low Genit Tract Dis.* 2008;12:63. The ASCCP guidelines may be accessed at <http://links.lww.com/A409>; it is Figure 5, page 232. Please note: Figure 5 in the original guidelines has been corrected. The correct figure is linked above.

Special Considerations for Colposcopy in the Adolescents

All adolescents who have an abnormal pap test are allowed to undergo a confidential evaluation of the abnormality as it relates to an STD. It is preferred to involve the patient's parent when performing a colposcopic examination, but is not required. The care provider should respect the privacy of the adolescents if they do not wish to engage their parent in their care.

The issues regarding parental consent for biopsy or therapy for cervical dysplasia are more complicated. The need for consent depends on whether the biopsy or therapy is considered part of STD evaluation and treatment and on the specifics of state law. Even if the minor legally can consent, the law may not ensure confidentiality. Some states allow minors to consent for STD care but give the healthcare provider discretion to disclose information to parents, particularly if it is necessary to protect the minor's health.

Biopsy and therapy for cervical dysplasia are more invasive than a colposcopic examination and carry a higher risk of complication. They also are likely to generate a bill, which can compromise confidentiality. These issues need to be considered when determining whether parental consent should be obtained, even if it is not legally required, before providing biopsy or therapy for a minor. Medical care providers throughout the United States provide such care without parental consent under the umbrella of the treatment of STDs. Any healthcare provider who delivers such care should be fully informed of their state laws and established local standards of care.

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