CE 2.5 CONTACT HOURS

# HPV & age-appropriate cervical cancer prevention for adolescents

***Abstract: Over the last decade, new information about human papillomavirus infection has increased the healthcare community's understanding of the natural history of the disease and cervical cancer. Advances in screening, management, and diagnosis continue to refine clinicians' efforts to prevent cervical cancer in adolescent females.***

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Adolescents have the highest rates of cervical disease as a result of initial human papillomavirus (HPV) exposure and infection. More than 90% of adolescent HPV infections and early precancerous lesions are cleared by the immune system within as little as 6 to 9 months of infection.[1] High-grade disease detected in adolescents is also different from that found in adult women, since it may regress spontaneously more often in adolescents. Although HPV infection is common in adolescents, cervical cancer is very rare regardless of the age of first intercourse.[2] Using current guidelines and recommendations when caring for adolescent females decreases over-response and over-treatment of transient HPV infection and disease.

## Cervical cancer

New recommendations from the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), The American Society for Colposocpy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) state that Pap testing should begin at the age of 21, regardless of the age of sexual debut or sexual history.[3,4] Delaying this initial Pap to age 21 allows young women who have a significant prevalence of HPV infection and associated neoplasia to clear their infections and cervical intraepithelial neoplasia (CIN) before screening begins. Adolescents have a high incidence of HPV infection and a low incidence of cervical cancer.

According to data from the Surveillance Epidemiology and End Results Program of the National Cancer Institute (NCI), from 2003 to 2007, the median age at diagnosis for cancer of the cervix was 48 years old.[5] Only 0.2% of cervical cancers were diagnosed in young women under age 20.[5] Delayed screening supports a decrease in the over-response and over-treatment of the cervix in young women. The purpose of cervical screening is to detect precancer or high-grade cervical lesions that have the potential to progress to invasive cancer. The current guidelines for cervical screening, which delay the age of initiation to 21, will prevent the detection of low-grade lesions that generally reflect transient HPV infection and have low potential to progress to cancer. Cervical treatment by ablative or excisional methods has the potential for morbidity. Data have shown that the loop electrosurgical excision procedure (LEEP) can lead to fertility complications including preterm birth, low birth

Pap smear photo by Spike Walker/Getty Images ©

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weight, and premature rupture of membranes.[6] While many practitioners have adopted the new screening guideline for starting cervical screening at 21 years of age, many young women were screened earlier and will present for care with a history of abnormal cytology or CIN. The Consensus Guidelines for Management of Abnormal Cytology and CIN have been updated to include a specific approach to screening adolescents that addresses the natural history of HPV in young women and promotes a follow-up approach rather than invasive evaluations and procedures in this low-risk population.[7]

## History

HPV is a nonenveloped, double-stranded DNA virus.[1] Over 100 genotypes have been identified and of those, 14 have been identified as high-risk or oncogenic.[8] Oncogenic genotypes have the potential to cause neoplasia and cancer and include genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.[9,10] Low-risk or nononcogenic genotypes include: 6, 11, 40, 42, 43, 44, 54.[9] Nononcogenic genotypes 6 and 11 may cause benign changes and mild cellular abnormality, and are associated with external genital warts or condylomata.[8] Infection with oncogenic HPV genotypes is the most significant risk factor in cervical cancer etiology.[11] Almost all cases of high-grade Cervical Intraepithelial Neoplasia (CIN 2, 3), invasive cancer of the cervix, and most other anogenital (vagina, vulva, and anus/anal canal) tract cancers are associated with high-risk HPV genomes 16, 18, 31, and 45.[9,12] HPV 16 and 18 are responsible for approximately 70% of cervical cancer cases and CIN 3, and approximately 50% of CIN 2.[9] HPV 16 and 18 are responsible for approximately 35% to 50% of all low-grade CIN 1.

***At least 50% of sexually active individuals will have genital HPV at some time in their lives.***

## Prevalence

In 2008, the CDC reported that 3.2 million, or one in four adolescents, ages 14 to 19 had a sexually transmitted infection (STI).[13] HPV is the most common STI in the United States.[14] It is estimated that each year there are as many as 20 million active infections and 6.2 million new HPV infections in women and men.[13,15] It is important for clinicians to recognize that infection with HPV is not necessarily associated with promiscuity and/or deviance in sexual behavior.

### Transient vs. persistent infection

At least 50% of sexually active individuals will have genital HPV at some time in their lives. The majority of those infections (90%) will be cleared by the immune system mounting a cellular immune response.[16] HPV is a skin cell virus, which resides in the basal layer in epithelial cells, so the virus is not easily recognized by the immune system. The time it takes the immune system to recognize the virus contributes to the variability in immune response. Once recognized, the virus can be cleared (transient infection), can become a persistent infection (not cleared), and, if persistent, will integrate into the human genome and cause cellular transformation, leading to carcinogenesis.[17]

### Transformation zone (TZ)

In the lower genital tract, the area at greatest risk for the development of neoplasia and cancer when oncogenic HPV persists is the metaplastic epithelium of the TZ of the cervix. The TZ is an area where one type of epithelium (glandular cells from the endocervical canal) meets another (stratified squamous cells of the ectocervix). A gradual replacement of glandular cells to stratified squamous cells occurs here in a process known as metaplasia. The line where squamous and glandular epithelium meet is called the squamo-columnar junction (SCJ). The line is continually moving towards the cervical canal and eventually into the canal. This area is represented in the Pap test sample as the endocervical component. The Pap test is a screening test that requires a subjective interpretation by the cytotechnologist or pathologist about the appearance of the cells. When a colposcopy and biopsy are performed, the histology of the submitted tissue is considered diagnostic. The histology of cervical lesions is reported as CIN, and is classified as low-grade (CIN 1) or high-grade (CIN 2 and CIN 3). A colposcopy exam is satisfactory when SCJ is seen, and when a lesion is present, it is considered satisfactory when the upper margin of the lesion is completely visualized. Conversely, if the SCJ has already migrated up into the endocervical canal or if a lesion extends into the endocervical canal, a higher-grade process or cancer may be present, but is out of range for visualization. Management guidelines address the safety of following CIN, and are determined by the degree of CIN and whether or not colposcopy is satisfactory.

## Cervical cancer screening

The Pap test is the evaluation of a sample of cells that are collected from the cervix using devices such as spatulas, brooms, and brushes. The sample can be placed onto a slide

and fixed. This method is known as a conventional or dry slide. Another method of collection involves putting the cellular material into a liquid transport medium, which is sent to the lab where a slide is prepared from the liquid sample. The liquid sample allows for additional testing to be performed from the residual solution after the Pap has been prepared. This includes testing for HPV DNA using one of multiple FDA approved tests. HPV DNA testing may also be performed on a separate sample that is collected by turning a brush in the endocervical canal and sent to the lab separate from the Pap.

### Pap test reporting

The Pap test is a screening test that looks for cellular changes caused by HPV. The test result is reported according to the 2001 Bethesda System of cytologic classification and determines whether a woman will require routine follow-up or further evaluation by accelerated repeat Pap testing, HPV DNA testing, or colposcopy.[18] The test is reported as: Negative for Intraepithelial Lesion or Malignancy, Atypical Squamous Cells of Undetermined Significance (ASC-US), Atypical Squamous Cells: Cannot Exclude High-Grade Squamous Intraepithelial Lesion, Low-Grade Intraepithelial Lesion (LSIL), High-Grade Intraepithelial Lesion (HSIL), Atypical Glandular Cells-Not Otherwise Specified (AGC-NOS), Atypical Glandular Cells-favor neoplasia (AGC-favor neoplasia), or Adenocarcinoma in Situ (AIS).

### HPV DNA testing

HPV DNA testing is utilized in the triage of the ASC-US Pap test in women 21 and older. The majority of women with an ASC-US Pap test do not have neoplasia. However, women with an ASC-US Pap test who have oncogenic HPV infection may have or may develop neoplasia and should be referred for colposcopy. Additionally, HPV testing is approved for screening in all women age 30 and older along with the Pap test for improving the accuracy of screening and triaging for cancer risk.[4,19] Women under 30 have a high prevalence of HPV infection that is generally cleared by an immune response in a short time.[4] Screening young women under 30 by HPV DNA testing detects most transient HPV infections that would likely be cleared in a relatively short time. As women age, the prevalence of HPV decreases and the detection of oncogenic HPV is more significant for persistent infection and the possibility of neoplasia that has been missed by the Pap test. Women 30 and older who test positive for oncogenic HPV with a negative Pap test will require diligent follow-up activity, as they are at risk for the development of neoplasia as long as the HPV infection persists.[19]

### Neoplastic changes

HPV-related cancers include cervical squamous cell carcinoma and cervical adenocarcinoma. Oncogenic potential is attributed to HPV oncogenes (E6 and E7). Expression of HPV oncoproteins in primary human epithelial cells leads to genomic instability. Molecular processes involved in genomic destabilization are essential for the development of cancer. These processes include E6 and E7, which block the ability of the normal human antioncogenes (p53 and retinoblastoma genes) to either repair human cells or destroy them when they begin to accumulate mutations that lead to carcinogenesis. HPV-related cancers appear to maintain and express HPV viral oncogenes for years or even decades.[20,21]

Whether or not an HPV infection clears or persists is determined by a variety of factors such as host immunocompetence and smoking.[22] Other co-factors related to the persistence or clearing of an HPV infection are not well understood at this time. Additionally, disease severity can range from minimal to severe and treatment response can vary. Persistent, oncogenic, HPV infection is necessary for the development and maintenance of high-grade lesions and cancer. The co-factors may play a role in cervical carcinogenesis.

***The paradigm of an "annual" visit is being replaced by a new paradigm called the "periodic well woman" visit.***

## Diagnosis and management

The most recent estimate for new cases of diagnosed invasive cervical cancer in the United States is 12,170 women.[23] Of the 12,170 newly diagnosed women, it is estimated that 4,220 will die (approximately 12 women each day).[23] Equally important are the projected 1.4 million new cases of low-grade cervical dysplasia (CIN 1) and 330,000 new cases of high-grade (CIN2/3) cervical dysplasia.[24]

The ASC-US/LSIL Triage Study (ALTS) sponsored by the National Cancer Institute (NCI) provided much of the data that supports current evidence-based guidelines for appropriate management for all women, including special populations such as adolescents.[25] The first guidelines were published in 2001 and later updated in 2005. In 2005, a meeting was convened for the purpose of discussing the clinical implications of the new evidence. One hundred and

forty six experts, including representatives from professional organizations, federal agencies, and national and international health organizations were in attendance. This collaboration led to the development of the 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Screening Tests and the 2006 Consensus Guidelines for the Management of Women with CIN or AIS.[7,19] The most significant change in the current guidelines was the approach to adolescents who were defined as young females age 13 to 20 years.[19]

### Management guidelines for abnormal cytology in adolescents[19]

The risk for cervical cancer in adolescents with ASC-US and LSIL are similar and the management algorithm has been combined.[19] The ASC-US Pap result represents a change that is considered inconclusive. The majority of women with an ASC-US Pap test result do not have neoplasia. The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines prefer the use of an HPV test for oncogenic types to the use of triage for women who are 21 and older with ASC-US when the test can be performed off of the residual solution of the Pap vial. Women testing positive for high risk HPV may have a disease that is can be found when the Pap is read ASC-US. Women with an ASC-US Pap and are HPV positive should be referred for colposcopy. The adolescent guidelines specifically state that an HPV test should not be used to triage this Pap test result as adolescents have a high prevalence of HPV but the risk for cervical cancer is low. The LSIL Pap test result in adolescents usually represents transient HPV infection. The guidelines recommend observation of these women with a Pap test repeated in 12 months. If an HPV test is inadvertently performed and is positive for oncogenic HPV, knowing the information does not change management and should be ignored.[25] At the 12-month follow-up, an abnormal Pap less severe than HSIL, leads to another repeat Pap in 12 months. If the 24 month follow-up Pap is ASC or greater, the woman should receive colposcopy. At the 12-month follow-up, if the Pap is HSIL or greater, colposcopy should be performed. This algorithm keeps the adolescent who has been screened and who has a minor cytologic abnormality under surveillance, but without invasive testing or treatment (see *Management of adolescent women 20 years and younger with ASC-US or LSIL algorithm)*.

***HPV-related cancers appear to maintain and express HPV viral oncogenes for years or even decades.***

All adolescents with a HSIL Pap should receive a colposcopic evaluation, and the findings determine whether there should be follow-up at regular intervals or treatment. The guidelines recommend that an adolescent should never proceed directly to an immediate excisional procedure with LEEP, which may be considered in women 21 years and older.[25] If the colposcopy is unsatisfactory, treatment is recommended. If the colposcopy is satisfactory and there is not any CIN 2,3 the patient can be observed with Pap and colposcopy every 6 months, for 24 months. Two consecutive negative Pap tests and no high-grade abnormality indicates that the woman may return to routine screening (see *Management of adolescent women (20 years and younger) with high-grade squamous intraepithelial lesion [HSIL] algorithm*).

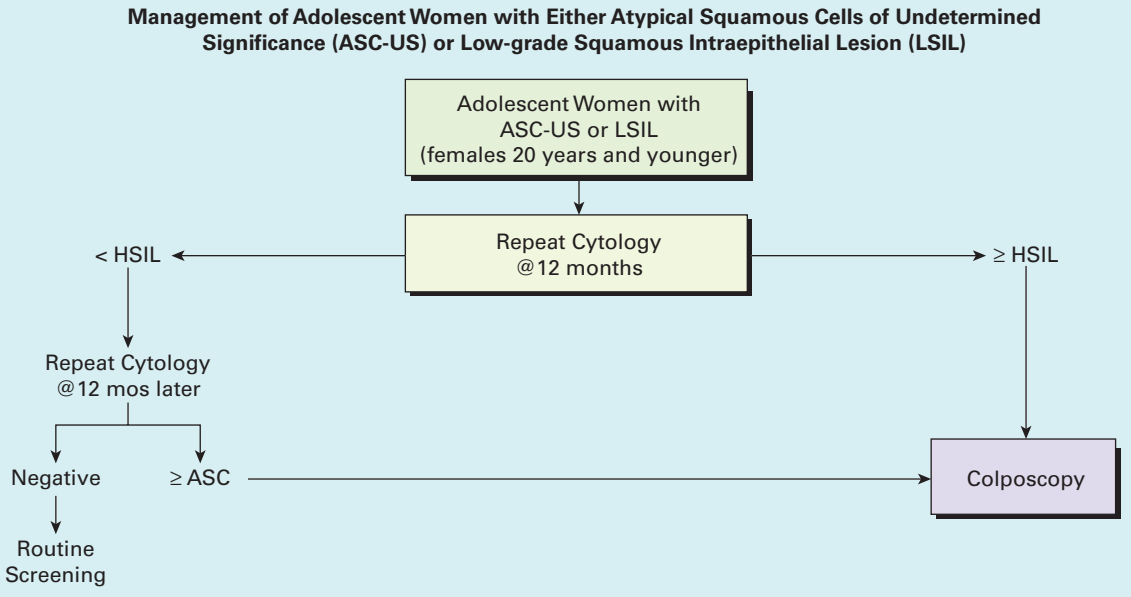
### Management guidelines for CIN grade 1 in the adolescent[19]

Perhaps the most significant change in the guidelines from 2001 to 2006 is in the approach to the adolescent with CIN 1. Treatment is not recommended in this population and the approach is an annual Pap test. Low-grade lesions have a high rate of regression in this population. In a study by Moscicki et al., 91% of adolescents and young women with LSIL spontaneously cleared their lesions within 36 months, regardless of which type of HPV was present.[1] According to the algorithm, at the 12-month follow-up those adolescents with HSIL or greater should be referred to colposcopy. At the 24-month follow-up, those with an ASC-US or greater should be referred to colposcopy. The use of HPV DNA testing is not recommended for management decisions (see *Management of adolescent women (20 years and younger) with histological diagnosis of cervical intraepithelial neoplasia grade 1 [CIN1]*).

### Management guidelines for CIN grade 2 or 3 in the adolescent[19]

The guidelines recommend two different approaches to management of adolescents for histologic confirmed CIN 2 or 3. Treatment or observation with Pap test and colposcopy every 6 months for up to 24 months is recommended. If CIN 2 or 3 is specified, treatment may be performed but observation is preferred. CIN 3 is the best marker for invasive cancer risk. If CIN 3 is specifically diagnosed, treatment is recommended. Treatment is also recommended if the colposcopic exam is not satisfactory (see *Management of adolescent and young women with a histological diagnosis of cervical intraepithelial neoplasia - grade 2,3 [CIN 2,3]*). The

**Management of adolescent women 20 years and younger with ASC-US or LSIL algorithm**






guidelines provide recommendations that are evidence-based and allow adolescent women to receive appropriate care without unnecessary screening and subsequent invasive procedures. While some practitioners are reluctant to change practice by delaying the onset of cervical screening or by doing less colposcopy, it is in the best interest of the young patient. Utilization of primary prevention by HPV vaccine is underutilized and is an excellent tool for offering protection to young women. The quadrivalent and bivalent vaccines both offer immunogenicity for HPV 16 and 18 that cause approximately 70% of cervical cancers.[26] The use of the HPV vaccines also decreases the incidence of abnormal Pap tests and cervical precancer in women.

## The adolescent periodic well women visit

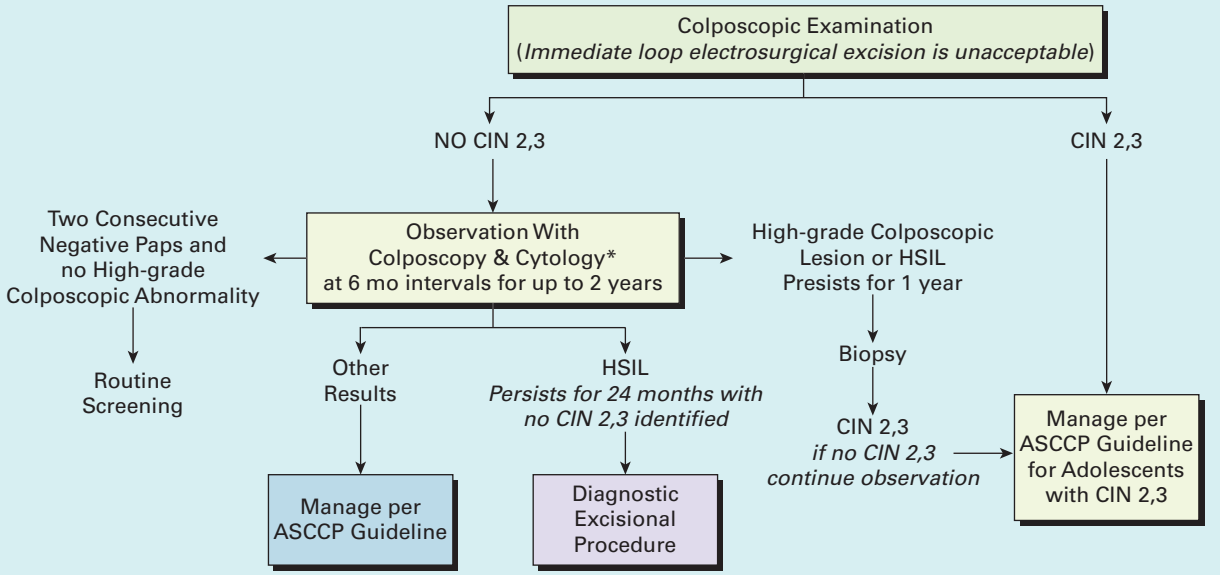
The paradigm of an "annual" visit is being replaced by a new paradigm titled the "periodic well woman" visit.[27] The periodic well woman visit during the adolescent years does not necessitate a Pap smear exam. The first Pap smear exam should occur at age 21 unless the woman has had a previous abnormal Pap test.[27] The focus of a periodic well woman visit is to complete a history and physical exam, provide health guidance and screening, and offer preventive healthcare services and counseling.[27] The American College of Obstetricians and Gynecologists (ACOG) recommends that the first visit to clinician for screening and provision of preventive healthcare services and guidelines begin between the ages of 13 and 15 years.[27] It is critical for clinicians to educate adolescents that although a Pap test may not be indicated, evaluation of the lower genital tract remains important.

## Contraception and sexual health

Data from 1995 to 2008 demonstrate that virtually all sexually active adolescents have used some method of contraception.[28] Data also demonstrates a Pap test is not needed prior to combined oral contraceptive (COC) initiation for an asymptomatic, nonsexually active adolescent woman.[28,29] In addition, starting COCs for the treatment of dysmenorrhea or menstrual cycle control does not require a Pap test.[27] A bimanual pelvic exam is included in the ACOG recommendations for adolescent woman aged 13 to 19 years of age when indicated by medical history.[27,29] In sexually active adolescent women, under the age of 25 years a visual inspection of the external genitalia, vaginal speculum exam (without cytology), and screening for STIs may be indicated by medical history.[27]

Sexual identity and sexual behaviors and practices are also important aspects of an adolescent's sexual health. STIs continue to be a major public health burden in the United States.[30] STI rates are disproportionally higher among adolescents than in any other age group.[30] Globally, HPV is one of the most common STIs; estimated at 24.9 million women aged 14 to 59 years.[30] Between the age of 14 and 19 years one in four (26% or 3.2 million) adolescent women are

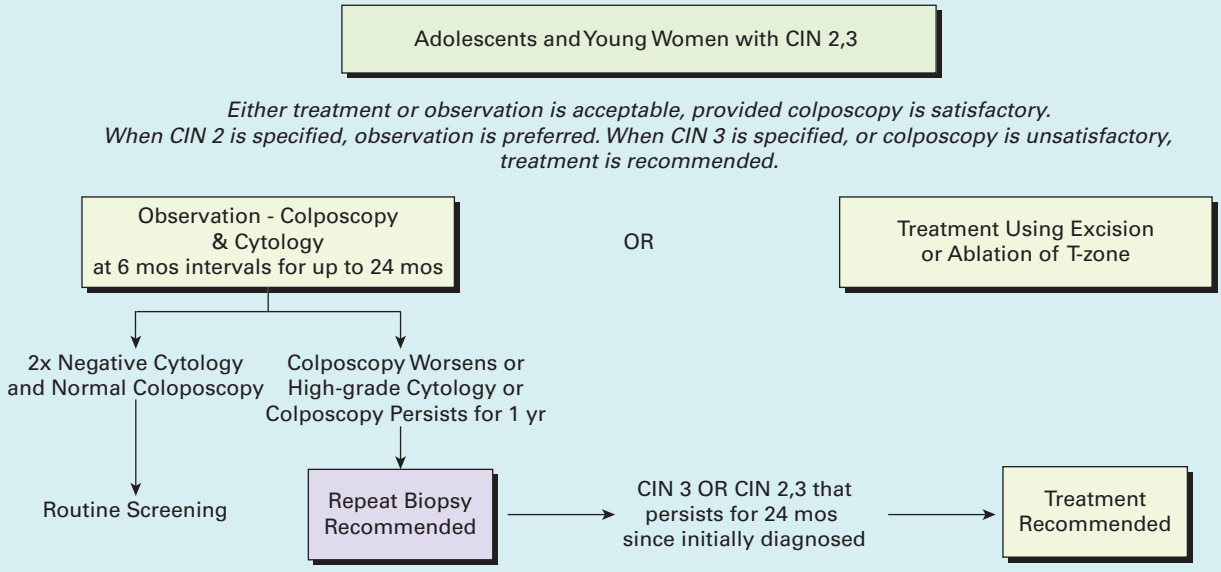
## Management of adolescent women (20 years and younger) with high-grade squamous intraepithelial lesion [HSIL] algorithm



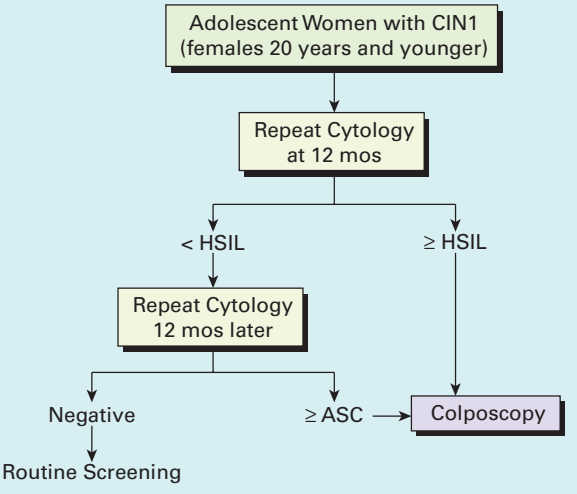

*Preferred approach provided the colposcopic examination is satisfactory and endocervical sampling is negative. Otherwise a diagnostic excisional procedure should be performed.



## Management of adolescent and young women with a histological diagnosis of cervical intraepithelial neoplasia - grade 2,3 (CIN 2,3)



### Management of adolescent women (20 years and younger) with histological diagnosis of cervical intraepithelial neoplasia grade 1 (CIN1)






### General guidelines to STI testing

- History of multiple sexual partners or sexual partner with multiple contacts
- History of repeated episodes of STIs
- Annual screening for *chlamydia* infection for all sexually active women aged 25 years or younger
- Annual screening for gonorrheal infection for all sexually active adolescents
- Testing for syphilis for sexually active adolescents who exchange sex for drugs or money, use I.V. drugs, are entering a detention facility, or live in a high-prevalence area.

Adapted from: American College of Obstetricians and Gynecologists. Primary and preventive care: periodic assessments. ACOG Committee Opinion No. 452. *Obstet Gynecol.* 2009;114(6):1444-1451.[22]

infected with at least one of the most common STIs.[31] Based on these high rates, STI screening should be based on history, risk behavior, and national guidelines (see *General guidelines to STI testing*).

## Nutritional health

Screening adolescents for eating disorders and obesity should occur annually. Weight issues should be determined by weight, height, stature, and body mass index (BMI). Positive behaviors, such as good nutrition, a normal BMI (18.5 to 24.9), balanced meal intake, and exercise should be reinforced. Nutritional health includes of healthy eating patterns and good dietary habits, which can lead to safe weight management. Poor nutrition, low weight, and BMI less than 18.5 can affect bone health and should be discouraged. Adolescent behavior, such as smoking, can also negatively affect bone health. Adolescent years are a prime time for building bone mass. Smokers may not develop maximum bone mass.

## Conclusion

Delivery of gynecologic health services to adolescent women differs from that of adult women. Clinical management should be guided and delivered according to medical history, appropriate assessment, and evidence-based guidelines in order to maximize patient safety and well-being. In regards to HPV infection, the majority of adolescent women will become naturally inoculated with HPV and resolve their infection. Adolescents would be better served if clinicians directed their efforts at primary prevention through education and vaccination, rather than secondary prevention efforts such as cytology, colposcopy, biopsy, and treatment.[32] NP

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