

## Mini-Reviews

# Guidelines for Screening and Treatment of Cervical Disease in the Adolescent

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**Abstract.** *Background:* The last decade has seen a significant increase in our knowledge of HPV infection and its natural history. The advent of liquid-based cytology and HPV testing has changed the way we approach patients with abnormal Pap tests. The objective is to summarize some of the key evidence that lead to the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for the management of abnormal cytology and histology and the American Cancer Society (ACS) cervical cancer screening guideline as they pertain to adolescents.

*Methods:* The critical publications responsible for the recent ASCCP guidelines as well as the ACS recommendations for cervical cancer screening were reviewed.

*Results:* Sexually active adolescents are frequently infected by HPV. The natural history of these infections is one with a high rate of resolution. The typical HPV infection will resolve in approximately one year. The ACS has recommended that Pap test screening begin at 21, or 3 years after the onset of sexual activity. The ASCCP guidelines for the management of CIN 1 conclude that observation is the preferred therapy. These recommendations reflect our improved understanding of the natural history of HPV infection.

*Conclusions:* Adolescents frequently experience transient HPV infections. As our understanding of the natural history of these infections has improved major national organizations have changed the recommendations for the screening of cervical disease and treatment of low-grade cervical abnormalities. The health care community servicing adolescents should incorporate these recommendations into daily practice.

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**Key Words.** Pap test—Cervical cancer screening—HPV

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*Synopsis:* This review discusses our understanding of HPV infections, the new recommendations for screening for cervical disease, and the ASCCP guidelines for managing abnormal cytology and histology as they pertain to adolescents.

## Introduction

The introduction of the Papinicolaou (Pap) test as a routine screening test has resulted in a 70% reduction in the incidence of cervical cancer in the United States over the last five decades. In 2003 over 50 million women will undergo cervical cancer screening, resulting in close to 2.5 million abnormalities. Screening is provided by a variety of health care providers in various specialties.

The last decade has seen a remarkable increase in a fund of knowledge of the natural history of cervical dysplasia, the role of Human Papilloma Virus (HPV) in cervical cancer, and the development of new technologies for cervical cancer screening, specifically HPV testing and liquid-based cytology. The new information has prompted the ACS, the ASCCP, and the NIH to develop new guidelines pertaining to cervical cancer screening, cytologic terminology, and treatment of cytologic abnormalities.

As our understanding of the natural history of HPV has improved there has been a shift away from aggressive therapy of low-grade abnormalities to appropriately monitored observation. This is particularly true for the adolescent patient. The ASCCP and ACS guidelines reflect this change. This article will summarize some of the important data that has led to this change, and highlight the present recommendations as they pertain to the adolescent.

## 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. The development of accurate tests for HPV, Hybrid Capture II™ and polymerase chain reaction (PCR), 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 85 different types of HPV viruses. The genital tract represents one of the major sites of HPV infection. 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, and squamous cell cancers of the cervix, vagina, and vulva.

The transmission of HPV is strongly associated with sexual activity. 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 that are sexually active. Studies that have followed a specific cohort of young sexually active women over time have demonstrated that over 50–60% of the population will be positive for HPV.<sup>1</sup> 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- and hetero-inoculation through close non-sexual contact, and possibly indirect transmission via fomites.<sup>2,3</sup>

The majority of women infected with HPV will be asymptomatic. Those that 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 13 months. The majority of patients with an intact immune system will resolve an HPV infection within 24 months.<sup>1</sup> Further evidence for the resolution of HPV infection comes from the high resolution rate of CIN 1 and CIN 2, 70% and 50% respectively.<sup>4,5</sup> 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.

### Cervical Cancer Screening Test

Cervical cancer screening programs based on the Pap smear 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.<sup>6</sup>

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 two techniques have been approved by the FDA for cervical cancer screening; ThinPrep® (Cytoc, Boxborough, MA), and SurePath™ (TriPath, Burlington, NC).<sup>7</sup>

ThinPrep® requires that the cervix is 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 (Meds-cand, 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 as well as high grade cervical abnormalities.<sup>7</sup> ThinPrep® prevents air drying effect, has increased sensitivity for the detection of cervical abnormalities, 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.<sup>8</sup>

### 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.<sup>9</sup> 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

**Table 1.** Bethesda 2001

**SPECIMEN TYPE:** Indicate conventional smear (Pap smear) vs. liquid-based vs. other

**SPECIMEN ADEQUACY**

- Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, e.g., 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 (e.g. 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
- Adenocarcinoma
  - endocervical
  - endometrial
  - extrauterine
  - not otherwise specified (NOS)

**OTHER MALIGNANT NEOPLASMS:** (specify)

**EDUCATIONAL NOTES AND SUGGESTIONS** (optional)

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

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 lab may comment with regards to the presence of obscuring inflammation. The presence of endocervical or metaplastic cells on a Pap test is considered 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 one-sentence summary of the results of the cytology for easier triage. The sample is either “negative for intraepithelial lesions or malignancy” or an “epithelial cell abnormality” is present.

The “Epithelial Cell Abnormality” interpretation has a number of important changes. The cytologic abnormality “Atypical Squamous Cells of Undetermined Significance (ASCUS)” has been renamed and subdivided. The new abnormality is “Atypical Squamous Cells (ASC)” and is subdivided into “of undetermined significance (ASC-US)” and “cannot exclude HSIL (ASC-H).” This change mirrors 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.<sup>4</sup> The more dysplastic changes associated with HSIL (High Grade Squamous Intraepithelial Lesions) 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 followup.<sup>10</sup>

The Low Grade Squamous Intraepithelial Lesion (LSIL) and the HSIL categories remain unchanged from the 1991 Bethesda system. These diagnoses are generally reproducible and in many ways reflect the dichotomous division in the squamous intraepithelial lesions.

There have been numerous changes in the description of glandular cell abnormalities in the new Bethesda system. The previous system included the diagnosis Atypical Glandular Cells of Undetermined

Significance (AGUS), which was frequently confused with ASCUS, yet represented a more significant diagnosis. Glandular cell abnormalities are now separated into four separate categories: (1) Atypical glandular cells (AGC); (2) Atypical glandular cells-favor endocervical; (3) Endocervical adenocarcinoma in situ (AIS); and (4) Adenocarcinoma. The first two groups should when possible characterize the cell of origin, endocervical vs. endometrial. The new system better describes the cellular abnormalities and is best suited for use by clinicians.

The final changes to the new Bethesda system are the addition of automated review and 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.** The American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) have recently published evidence based guidelines that cover a variety of issue relating to cervical cancer screening. In some cases these recommendations represent a significant departure from previous guidelines.<sup>11,12</sup>

**Onset of Screening.** The change in the onset of screening for cervical disease in the adolescent is somewhat controversial. The adolescent has 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 SIL, there are virtually no cancers reported before age 19, and there is a significant cost for the evaluation and treatment of low-grade cervical disease in population.

Traditionally cervical cancer screening has been initiated at age 18 or the onset of sexual activity. This time period corresponds to a period during which young women are very likely 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 that acquire HPV demonstrate that 36 months are required to develop an HSIL Pap test.<sup>1</sup> Finally, squamous cell cancer in women <21 years of age is exceedingly rare.<sup>13</sup> Therefore the American Cancer Society and ACOG recommend the initiation of cervical cytology no later than age 21, or 3 years after the onset of sexual activity.

The change in screening recommendations will require numerous changes on the part of clinicians. The sexual history will become even more important, as the onset of sexual activity must be specifically identified and noted on the chart. Many clinicians are concerned that due to the delay in the onset of Pap testing fewer adolescents will seek care. Sexually active adolescents have many reasons to seek care, specifically STD screening and contraceptive counseling. 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 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 that 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 15–30%.<sup>7</sup> Therefore its success in part depends on repeated test that reduce the rate of false negative test 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. Both societies agree that screening intervals may be increased to every 2 to 3 years for women over the age of 30 who have three consecutive, technically satisfactory normal exams. Women who are HIV positive, have a history of in utero exposure to DES, or are immunosuppressed should continue with annual examinations.

### Screening in HIV-positive Women

HIV positive women represent an at risk population due to the impairment of their cellular immunity. With the advent of highly effective antiviral therapy, this population may have a relatively normal immune response to HPV. All women who are HIV positive should have two sequential Pap tests at 6 month intervals when initially diagnosed with HIV. If both tests are normal the patient should have regular cytologic screening at 12-month intervals.<sup>14</sup> Women that have a low CD4 count (<200 cells/mL) are at increased risk for cervical disease and should have Pap test every 6 months, especially if there is a history of abnormal Pap test, HPV infections, or have recently been treated for cervical dysplasia.

### Triage for Cytologic Abnormalities

#### ASCCP Guidelines

The American Society for Colposcopy and Cervical Pathology (ASCCP) held a consensus workshop in

September 2001 to develop evidence-based guidelines for the management of both cytologic and histologic abnormalities of the cervix. 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 when possible evidence based.<sup>12,15</sup> These guidelines represent the first well-organized, nationally accepted management strategies for treating cytologic and histologic abnormalities.

#### ASCCP Triage Study and Its Role in the ASCCP Guidelines

The first Bethesda system included the new cytologic category ASCUS. See Fig. 1. The net result was an increase in the number of colposcopies performed in the United States. In an effort to develop an effective method for the triage of low grade cytologic abnormalities the National Cancer Institute funded a multi-center, randomized trial to determine if HPV testing could be used to separate those women at true risk for developing CIN/2,3 or cancer. The working hypothesis was that women that are positive for high risk HPV using the Hybrid Capture II technique are at greater risk. The ASCUS/LSIL Triage Study (ALTS) provided critical information regarding the role of HPV testing in both the triage as well as followup of women with ASCUS and LSIL cytology.<sup>16–20</sup> Table 2 summarizes the important findings of the ALTS trial.

The following paragraphs and tables summarize the ASCCP consensus guidelines, and highlight the key points for consideration. The ASCCP guidelines have specific guidelines related to adolescents for some but not all cytologic and histologic diagnoses.

Highlights of management triage. See Fig. 1.

- Three separate triage methods exist: colposcopy, repeat cytology, and HPV testing

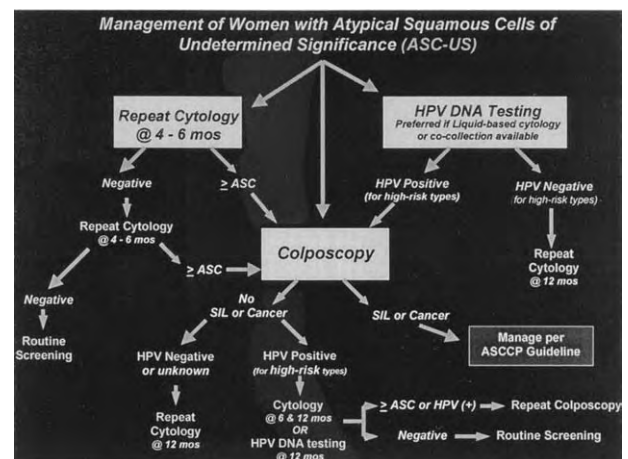


Fig. 1. Management of ASC-US.

**Table 2.** Key Findings of the ALTS Trial

- Women with a LSIL diagnosis are frequently positive for HPV (82.9%) and this technique is not useful in the triage of women with this diagnosis.
- Triage of women with ASC-US using HPV testing is effective. The cytologic diagnosis harbors HPV in 50% of cases.
- HPV testing is a very sensitive method for the initial detection of CIN 2, 3 (>90%).
- HPV testing or repeat cytology using an ASC-US threshold (testing every 6 months) are similarly sensitive for the detection of CIN 2,3.
- Women with ASC-US who are HPV positive and those with an LSIL cytology have very similar clinical outcomes.

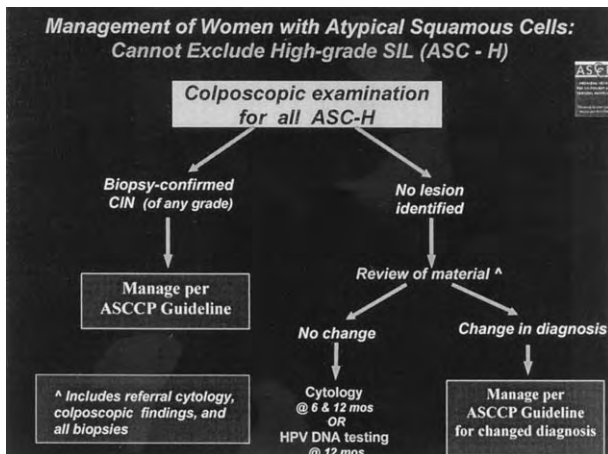
- If liquid-based cytology is used, HPV triage (sent from the residual fluid) is the preferred management option.
- A negative HPV test allows a patient to return to routine annual screening.
- During serial cytologic followup any abnormality will warrant a repeat colposcopic examination
- A single HPV test (without a Pap test) can be used for follow-up of women found to be histologically normal or without an obvious lesion on colposcopy.

Management of ASC-US in special circumstances

- **Postmenopausal patients:** An alternative acceptable option for postmenopausal women with an ASC-US diagnosis who suffer from estrogen deficiency is treatment with vaginal estrogen for 1 month. If a repeat cytologic examination 1 week following the estrogen therapy is normal then the patient may be followed by Pap tests at 6-month intervals without a colposcopic examination.
- **Pregnancy:** Pregnant patient are to be managed in a similar fashion as those that are not pregnant.
- **Immunosuppressed patients:** All immunosuppressed patients should be referred for colposcopy.

Highlights of ASC-H. See Fig. 2.

- ASC-H are frequently >80% positive for HPV.
- ASC-H require immediate colposcopy and close follow-up.



**Fig. 2.** Management of ASC-H.

Highlights of LSIL management. See Fig. 3.

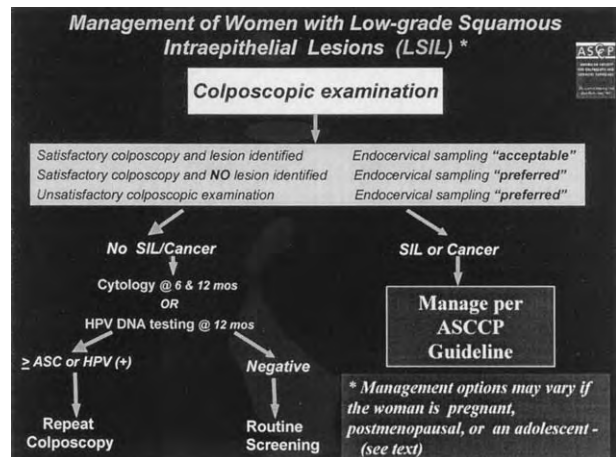
- LSIL requires immediate colposcopy.
- Endocervical sampling is referred in cases without a lesion or unsatisfactory colposcopy.
- Follow-up strategies reflect the high rate of HPV infection and risk for the detection of subsequent disease over a 2-year period.

Management of LSIL in the adolescent patient. See Fig. 4.

- Due to high rate of HPV in this population and the lack of cervical cancer screening, colposcopy may be delayed. A repeat Pap test conducted 6 months following the initial Pap test or a HPV test alone 12 months from the incident Pap are acceptable alternatives to colposcopy. If the Pap test is normal on two subsequent Pap tests the adolescent may return to annual screening. It should be noted that the HPV test performed at 12 months is conducted without a Pap test. The addition of a Pap test does not increase the sensitivity of detecting a high-grade lesion, yet increases the number of patients that require colposcopy.<sup>20</sup> The delay in obtaining the HPV test for 12 months is designed to allow enough time for the resolution of the HPV infection.

Highlights of HSIL. See Fig. 5.

- 70–75% of patients with HSIL will be found to have CIN 2,3



**Fig. 3.** Management of LSIL.

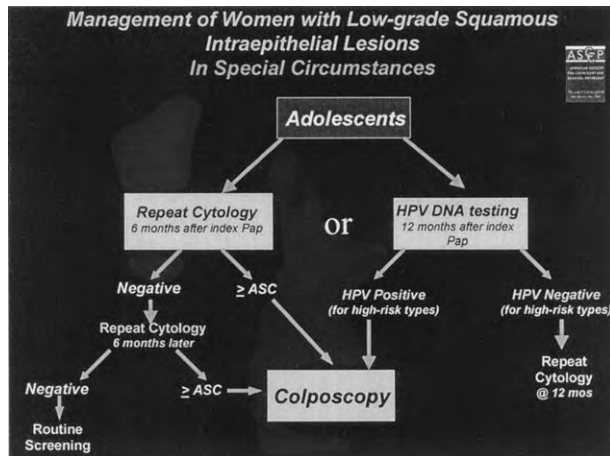


Fig. 4. Management of LSIL in the adolescent patient.

- Endocervical sampling is preferred in all patients with HSIL
- Diagnostic excisional procedures are frequently used when the source of the abnormal cytology is not identified.

Management of HSIL in Special Circumstances

- **Adolescents:** When biopsy confirmed CIN 2,3 is not identified in an adolescent, repeat cytology every 4–6 months for a year is an acceptable option in a compliant patient.
- **Pregnancy:** Management should be conducted by individuals with considerable colposcopic experience. Treatment is reserved for invasive disease only.

Highlights of Atypical Glandular Cells. See Fig. 6.

- This group of abnormalities carries a much higher rate of dysplasia, endocervical abnormalities, and endometrial abnormalities than atypical squamous cells.

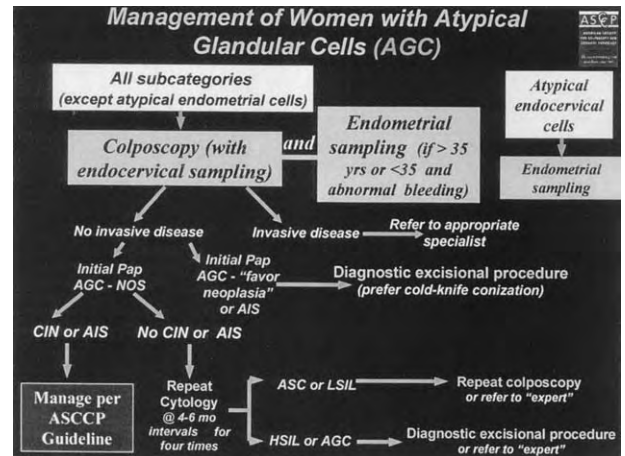


Fig. 6. Management of glandular abnormalities.

- AGC represent a small percentage of Pap test abnormalities in the adolescent population. Review of all cytology and histology should be undertaken before an excisional cone procedure is conducted in this population
- When an endometrial abnormality is suggested the initial evaluation is typically an endometrial biopsy. The adolescent is highly unlikely to have an endometrial cancer. Obese adolescents, or those with diseases that produce states of anovulation may experience unopposed estrogen and be at risk for endometrial hyperplasia. Irregular endometrial shedding in due to combination or progestin only contraceptives may result in endometrial cells being present on a Pap test. Care should be individualized in the case of endometrial abnormalities in the adolescent.
- Referral to an experienced clinician may be required in this group of abnormalities.
- This group of abnormalities is subdivided into AGC-NOS (not otherwise specified and AGC-Favor dysplasia. The clinical management of the two entities varies, with AGC-NOS having a less aggressive management.

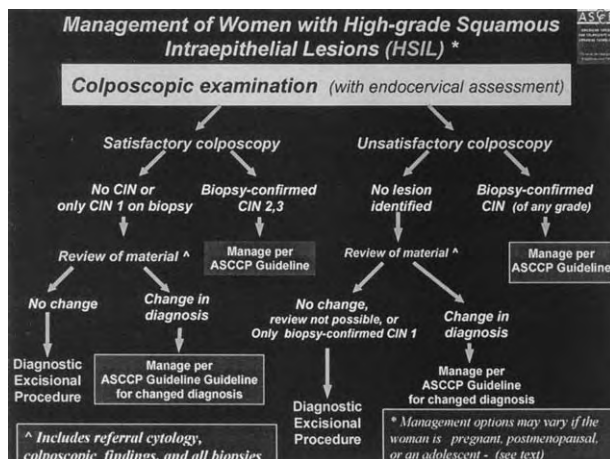


Fig. 5. Management of HSIL.

Post-Colposcopy Management

The ASCCP has published recommendations for the management of biopsy proven CIN. These guidelines were developed during the 2001 workshop and represent in many cases evidence-based treatment guidelines.<sup>15</sup>

The management of CIN 1 has changed drastically over the last 10 years. See Fig. 7. Treatment has evolved from one where all individuals were treated with ablative therapies, to the majority of women being eligible for close follow-up. The rationale for the use of observation is the high rate of spontaneous resolution of CIN 1. In the adolescent population the rate of

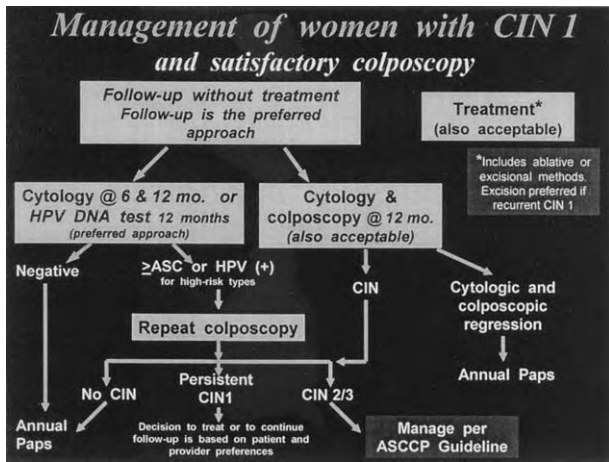


Fig. 7. ASCCP guidelines on management of CIN 1.

resolution approaches 90%, whereas in the older population the resolution is generally felt to be 70%.<sup>21</sup>

When an individual is followed with observation there are two methods for follow-up, cytology every 6 months or HPV testing alone at 12 months. These recommendations were developed from the ALTS trial in which HPV testing and serial cytology were shown to have similar sensitivities for the detection of CIN 2,3 (93%) with reasonable rate of referral to colposcopy. The addition of a repeat cytology to the HPV test at 12 months only marginally increases sensitivity with a significant increase in colposcopic referrals and is not recommended.<sup>20</sup>

**Treatment of CIN 2 and CIN 3**

CIN 2 and CIN 3 are generally accepted as cancer precursors and should be treated except in special circumstances. See Fig. 8. The treatments are divided into ablative therapies and excision therapies. The treatment methods available for ablation include cryotherapy, laser therapy, and LEEP. There are no significant differences in the success rates of the three

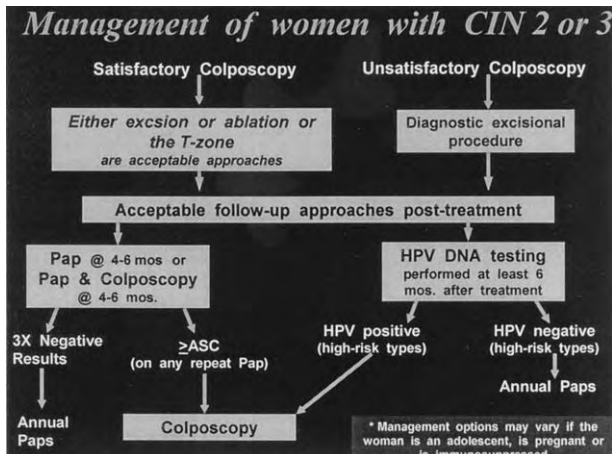


Fig. 8. ASCCP Management of women with CIN 2,3.

therapies, and treatment decisions are at the discretion of the clinician. The following criteria must be met to use an ablative therapy: (1) The lesion is on the outside of the cervix and does not extend significantly into the cervical canal. (2) There should be agreement between the cytology and the histology. (3) The endocervical sampling should be negative. (4) Ablative therapy is not acceptable for the treatment of Adenocarcinoma in Situ, Adenocarcinoma, and Squamous cell carcinoma.

Following the treatment for CIN 2,3, the patient should undergo a series of cytologic examination to confirm the appropriate treatment of the dysplasia. Following three normal cytologic examinations the patient may return to routine annual Pap tests. There is growing evidence that an HPV test done 6 months following the therapy may substitute for the serial cytologic examinations. A patient with a negative HPV test at 6 months can return to routine screening.

Adolescents are the only group in which the ASCCP offers observation for the treatment of CIN 2. The resolution rate of CIN 2 is 50%, and in this population that is low risk for the development of invasive cancer CIN 2 can be observed without therapy in the properly selected compliant patient.<sup>22</sup>

During pregnancy CIN 2 and CIN 3 are not treated due to the high risk of adverse pregnancy outcome. Close observation with repeated colposcopic examinations during the pregnancy (each trimester) followed by post-partum colposcopy and appropriate treatment is recommended.

**HPV Vaccines**

The future for the prevention of cervical cancer lies in the reduction of the spread of HPV via vaccines. The most promising vaccines use the outer shell of the HPV virus, the Virus Like Particle (VLP), which presents an antigen to the host immune response that is specific to an individual or group of HPV types. The first large scale randomized study of VLP for HPV 16 demonstrated complete protection against abnormal cytology and over 90% immunogenic response to the VLP.<sup>23</sup> There are numerous efforts presently ongoing to develop a commercially available, multivalent HPV vaccine. The wide spread use of such a vaccine has the potential to reduce the rate of cervical cancer across the globe.

Presently the majority of HPV vaccine trials have been conducted in the adult population. The key to prevention of cervical disease may very well be to rely on the vaccination of the adolescent. The next decade will be very important for the care of adolescent patients as a commercially available vaccine will likely come to fruition. The issues of when and who to vaccinate will need to be determined. Davis et al recently surveyed 550 parents of adolescents to determine their

knowledge of HPV and potential barriers to the use of such a vaccine. They concluded that a brief educational intervention significantly improved parent's acceptance of the HPV vaccine. The negative impact of an HPV vaccine perceived as condoning early initiation of sexual intercourse appeared to be minimal.<sup>23</sup>

The vaccination of a large section of the population may alter Pap test screening guidelines. The ultimate goal of these advancements is to reduce the burden of cervical dysplasia and cervical cancer in the entire population.

## Conclusion

The last decade has seen a tremendous increase in our fundamental understanding of the role of HPV in the process of dysplasia. The natural history of the disease is better understood as primarily a transient infection. The treatment of all women, and adolescents in particular, has been altered by our understanding of the disease process. The screening of young women for cervical cancer has been changed to no later than age 21, or 3 years after the onset of sexual activity. The new ASCCP guidelines recommend observation for the treatment of CIN 1 in all women, and for CIN 2 in the appropriate adolescent. Finally, the rapid development of the HPV vaccines give us great hope for the reduction of the number of patients with cervical cancer and its precursors world-wide.

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