ONCOLOGY

# 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ

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A group of 146 experts representing 29 organizations and professional societies met Sept. 18-19, 2006, in Bethesda, MD, to develop revised evidence-based, consensus guidelines for managing women with abnormal cervical cancer screening tests. The management of low-grade cervical intraepithelial neoplasia (CIN) grade 1 has been modified significantly. Previously, management depended on whether colposcopy was satisfactory and treatment using ablative or excisional was acceptable for all women with CIN 1. In the new guidelines, cytological follow-up is the only recommended management option for women with CIN 1 who have low-grade referral cervical cytology, regardless of whether the colposcopic examination is satisfactory. Treatment is particularly discouraged in adolescents. The basic management of women in the general population with CIN 2,3 underwent only minor modifications, but options for the conservative management of adolescents with CIN 2,3 have been expanded. Moreover, management recommendations for women with biopsy-confirmed adenocarcinoma in situ are now included.

**Key words:** adenocarcinomas in situ of the cervix, cervical intraepithelial neoplasia, cryotherapy, loop electrosurgical excision procedure, treatment

The appropriate management of women with cervical intraepithelial neoplasia (CIN) is as critical a component of cervical cancer prevention programs as screening and managing abnormal screening test results. CIN is a relatively common problem, especially in women of reproductive age. Laboratory surveys from the mid-1990s from the College of American Pathologists suggest that more than 1 million women are diagnosed each year with low-grade cervical intraepithelial lesions, referred to as CIN 1, and that approximately 500,000 are diagnosed with high-grade cervical cancer precursor lesions, referred to as CIN 2,3.[1] More recent data from the Kaiser Permanente Northwest health plan indicate a somewhat lower rate, with a projected annual incidence per 1000 women of 1.2 for CIN 1 and 1.5 for CIN 2,3.[2] Improper management of CIN can increase the risk of cervical cancer on the one hand and complications from overtreatment on the other. Approximately 5 years ago the American Society for Colposcopy and Cervical Pathology (ASCCP) joined other professional societies and federal and international organizations to develop the 2001 Consensus Guidelines for Managing Women with Cervical Intraepithelial Neoplasia.[3] The goal was to minimize risks by weighing the best available evidence.

Since 2001, considerable new information has become available on the natural history of CIN, particularly in adolescents and young women, and the impact of treatment for CIN on future pregnancies.[4,5] Our understanding of how to manage women with cervical adenocarcinoma in situ (AIS), a human papillomavirus (HPV)-associated precursor to invasive cervical adenocarcinoma, also has progressed. Therefore, in 2005 the ASCCP and its partner organizations (listed in Appendix A), began the process of revising the 2001 consensus guidelines. This culminated in a consensus conference held at the National Institutes of Health in September 2006. This report provides the recommendations developed with respect to managing women with CIN and AIS. Recommendations for managing women with abnormal cervical cancer screening tests appear in an accompanying article.[6] A more comprehensive discussion of the recommendations and their supporting evidence, algorithms, and a glossary of terms are available on the ASCCP website (www.asccp.org).

## Guideline Development Process

The process used to develop the 2006 guidelines was similar to that for the 2001 guidelines and is described in depth in other publications.[3,6] Guidelines were developed through a multistep process. Working groups initially defined ques-

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tions and performed literature reviews of articles published since 2000 and conducted Internet-based discussions open to the professional community at large. The terminology utilized in the new guidelines is identical to that used previously, as is the 2-part rating system and is provided in the accompanying article.[6] The terms "recommended," "preferred," "acceptable," and "unacceptable" are used to describe various interventions. The letters A through E are used to indicate "strength of recommendation" for or against the use of a particular option. Roman numerals I-III are used to indicate the "quality of evidence" for a given recommendation. The "strength of recommendation" and "quality of evidence" are provided in parenthesis after each recommendation.

## 2006 Consensus Guidelines

### General comments

The histological classification incorporated into these guidelines is a 2-tiered system that applies the terms CIN 1 to low-grade lesions and CIN 2,3 to high-grade precursors. Cytological low-grade squamous intraepithelial lesion (LSIL) is not equivalent to histological CIN 1 and cytological high-grade squamous intraepithelial lesion (HSIL) is not equivalent to histological CIN 2,3.

It is important to recognize that these guidelines should never substitute for clinical judgment. Clinical judgment should always be used when applying a guideline to an individual patient because it is impossible to develop guidelines that apply to all situations.

### Treatment methods

Both ablative treatment methods that destroy the affected cervical tissue in vivo and excisional modalities that remove the affected tissue are utilized for treating CIN lesions.[7] Ablative methods include cryotherapy, laser ablation, electrofulguration, and cold coagulation. Excisional methods that provide a tissue specimen for pathological examination include cold-knife conization, loop electrosurgical excision procedures (widely referred to as LEEP or LLETZ), laser conization, and electrosurgical needle conization. Although there are only a limited number of randomized trials comparing these different treatment modalities, it appears that all of the ablative and excisional modalities listed above have a similar efficacy with respect to eliminating CIN and reducing a woman's risk of future invasive cervical cancer.[7-11]

It has been recognized for some time that cold-knife conization increases a woman's risk of future preterm labor, a low birthweight infant, and cesarean section.[12] Other treatment methods were thought to have no adverse effects on future pregnancies. This is no longer the case. Several large retrospective series have now reported that women who have undergone a loop excision procedure or a laser conization are also at increased risk for future preterm delivery, a low birthweight infant, and premature rupture of membranes.[8,13-16] Although in most studies ablative methods have not been shown to be associated with a similar adverse effect on pregnancy outcome, it is difficult to measure small effects on pregnancy outcome, and therefore, it is possible that ablative methods have an adverse effect on future pregnancies.[13,15-17]

There are no accepted nonsurgical therapies for CIN.[18] Several topical agents have been either evaluated or are in clinical trials, but none has been proven as effective as excision or ablation. Similarly, although there is considerable interest in therapeutic HPV vaccines, none have been proven effective.[19]

These considerations indicate that the decision as to which therapeutic option to use in an individual patient depends on considerations such as patient age; parity; desire for future child-bearing; preferences; prior cytology and treatment history; and history of default from follow-up, operator experience, and nonvisualization of the transformation zone.

### Posttreatment follow-up

The treatment failure rate for CIN using either ablative or excisional methods has varied between 1% and 25%.[7,9,20-22] Systematic reviews indicate overall pooled failure rates of 5-15% for the different modalities with no significant difference between the modalities.[9] Most failures occur within 2 years after treatment.[20,23] In addition to developing recurrent/persistent CIN, women who have been treated for CIN 2,3 remain at increased risk for developing invasive cervical cancer for a protracted period of time.[11,24] A recent systematic review reported that the incidence of invasive cervical disease in treated women remains about 56 per 100,000 for at least 20 years after treatment, substantially greater than that in the general US population (5.6 per 100,000 women-years).[11,25] Therefore, follow-up is essential.

A number of follow-up protocols have been recommended.[26,27] These include cytology, colposcopy, combinations of cytology and colposcopy, and HPV deoxyribonucleic acid (DNA) testing at a variety of intervals. None of the follow-up protocols have been evaluated in randomized clinical trials, and because the various follow-up approaches are so different, it is difficult to compare them.[23] Systematic reviews of the performance of HPV DNA testing for posttreatment follow-up have found that its performance is quite good and exceeds that of cytological follow-up.[23,27] Overall, the pooled sensitivity of HPV testing for identifying recurrent/persistent CIN reaches 90% by 6 months after treatment and has been shown to remain at this level for at least 24 months. In contrast, the pooled sensitivity of cytology is approximately 70%.[23] In some studies, but not others, use of a combination of HPV testing and cytology resulted in an increased sensitivity.[23]

### Special populations

Adolescents (aged 13-20 years) and young women are considered a special population. There is a very low risk for invasive cervical cancer in this group, but CIN lesions are common.[2,28] CIN in adolescents also has a very high rate of spontaneous regression of CIN lesions.[29]

Pregnant women are another special population. The risk of progression of CIN 2,3 to invasive cervical cancer during pregnancy is minimal, and the rate of spontaneous regression postpartum is relatively high.[30,31] Treatment of CIN

during pregnancy is associated with complications and a high rate of recurrence or persistence.[32] Therefore, the only indication for therapy of cervical neoplasia in pregnant women is invasive cancer.

## CIN 1

Literature cited at the time of the 2001 Consensus Conference recognized that CIN 1 represents a heterogeneous group of lesions.[33] This heterogeneity is due in large part to the poor reproducibility of a histological diagnosis of CIN 1.[34] Less than half of lesions diagnosed as CIN 1 by individual pathologists are classified as CIN 1 when reviewed by a panel of pathologists.[34] Although most of CIN 1 lesions are associated with high-risk types of HPV, the distribution of high-risk types in CIN 1 lesions is different from that seen in CIN 2,3 lesions.[35] In addition, CIN 1 lesions can be associated with non–high-risk types of HPV.[35] CIN 1 lesions are also heterogeneous with respect to ploidy status and other markers of neoplasia.[36]

There is a very high rate of spontaneous regression of low-grade cervical lesions in the absence of treatment. For example, a prospective study of Brazilian women with a cytological result of LSIL found that more than 90% regressed within 24 months.[37] Another study from The Netherlands found that over 4 years all women with LSIL who were infected with non–high-risk types of HPV regressed to normal cytology as did 70% of those infected with high-risk types of HPV.[38] Even higher rates of regression occur in adolescents and young women. Moscicki et al[29] found that 91% of adolescents and young women with LSIL spontaneously cleared their lesions with 36 months, irrespective of associated HPV type.

Recent data suggest that CIN 1 uncommonly progresses to CIN 2,3, at least within the first 24 months. In the ASCUS/LSIL Triage Study, many of the CIN 2,3 lesions subsequently identified in women diagnosed with CIN 1 appeared to represent lesions that were missed during the initial colposcopic evaluation.[39] Risk for having a CIN 2,3 lesion identified during the subsequent 2 years after initial colposcopy was nearly identical in women with a histological diagnosis of CIN 1 (13%) and in women whose initial colposcopy and biopsy were negative (12%).[39]

It should be noted that the risk of having an undetected CIN 2,3 or adenocarcinoma in situ lesion is expected to be greater in women with CIN 1 preceded by a HSIL or atypical glandular cells (AGC) cytology result than for women with CIN 1 preceded by an ASC or LSIL cytology result. CIN 2,3 is identified in 84-97% of women with HSIL cytology evaluated using a loop electrosurgical excision procedure.[40-42] Therefore, in the 2006 guidelines, separate recommendations are made for women with CIN 1 preceded by an HSIL or AGC cytology result.

## Recommended management of women with CIN 1

**CIN 1 preceded by atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells, cannot exclude HSIL, ASC-H, or LSIL cytology.** The recommended management of women with a histological diagnosis of CIN 1 preceded by an ASC-US, ASC-H, or LSIL cytology is follow-up with either HPV DNA testing every 12 months or repeat cervical cytology every 6 to 12 months. (BII) If the HPV DNA test is positive or if repeat cytology is reported as ASC-US or greater, colposcopy is recommended. If the HPV test is negative or 2 consecutive repeat cytology tests are "negative for intraepithelial lesion or malignancy," return to routine cytological screening is recommended. (AII)

If CIN 1 persists for at least 2 years, either continued follow-up or treatment is acceptable. (CII) If treatment is selected and the colposcopic examination is satisfactory, either excision or ablation is acceptable. (AI) A diagnostic excisional procedure is recommended if the colposcopic examination is unsatisfactory, the endocervical sampling contains CIN, or the patient has been previously treated. (AIII)

Treatment modality should be determined by the judgment of the clinician and should be guided by experience, resources, and clinical value for the specific patient. (A1) In patients with CIN 1 and an unsatisfactory colposcopic examination, ablative procedures are unacceptable. (EI) Podophyllin- or podophyllin-related products are unacceptable for use in the vagina or on the cervix. (EII) Hysterectomy as the primary and principal treatment for histological diagnosed CIN 1 is unacceptable. (EII)

## CIN 1 preceded by HSIL or AGC-NOS cytology

Either a diagnostic excisional procedure or observation with colposcopy and cytology at 6 month intervals for 1 year is acceptable for women with a histological diagnosis of CIN 1 preceded by HSIL or atypical glandular cells–not otherwise specified (AGC-NOS) cytology, provided in the latter case that the colposcopic examination is satisfactory and endocervical sampling is negative. (BIII) In this circumstance it is also acceptable to review the cytological, histological, and colposcopic findings; if the review yields a revised interpretation, management should follow guidelines for the revised interpretation. (BII)

If observation with cytology and colposcopy is elected, a diagnostic excisional procedure is recommended for women with repeat HSIL or AGC-NOS cytological results at either the 6- or 12-month visit. (CIII) After 1 year of observation, women with 2 consecutive "negative for intraepithelial lesion or malignancy" results can return to routine cytological screening. A diagnostic excisional procedure is recommended for women with CIN 1 preceded by a HSIL or AGC-NOS cytology in whom the colposcopic examination is unsatisfactory, except in special populations (eg, pregnant women). (BII)

## CIN 1 in special populations

**Adolescent women.** Follow-up with annual cytological assessment is recommended for adolescents with CIN 1. (AII) At the 12 month follow-up, only

adolescents with HSIL or greater on the repeat cytology should be referred to colposcopy. At the 24 month follow-up, those with an ASC-US or greater result should be referred to colposcopy. (AII) Follow-up with HPV DNA testing is unacceptable. (EII)

**Pregnant women.** The recommended management of pregnant women with a histological diagnosis of CIN 1 is follow-up without treatment. (BII) Treatment of pregnant women for CIN 1 is unacceptable. (EII)

## CIN 2,3

CIN 2,3 includes lesions previously referred to as moderate dysplasia (ie, CIN 2) and severe dysplasia/carcinoma in situ (ie, CIN 3).[36] Although CIN 2 lesions are more heterogenous and more likely to regress during long-term follow-up than are CIN 3 lesions, histological distinction between CIN 2 and CIN 3 is poorly reproducible.[43-45] Therefore, CIN 2 is utilized as the threshold for treatment in the United States to provide an added measure of safety, and recommendations for the management of women with histologically diagnosed CIN 2 and CIN 3 are combined in the 2006 Consensus Guidelines.[36]

## Recommended management of women with CIN 2,3

**Initial management.** Both excision and ablation are acceptable treatment modalities for women with a histological diagnosis of CIN 2,3 and satisfactory colposcopy, except in special circumstances (see following text). (AI) A diagnostic excisional procedure is recommended for women with recurrent CIN 2,3. (AII) Ablation is unacceptable and a diagnostic excisional procedure is recommended for women with a histological diagnosis CIN 2,3 and unsatisfactory colposcopy (AII). Observation of CIN 2,3 with sequential cytology and colposcopy is unacceptable, except in special circumstances (see following text). (EII) Hysterectomy is unacceptable as primary therapy for CIN 2,3. (EII)

## Follow-up after treatment

Acceptable posttreatment management options for women with CIN 2,3 include HPV DNA testing at 6-12 months. (BII) Follow-up using either cytology alone or a combination of cytology and colposcopy at 6 month intervals is also acceptable. (BII) Colposcopy with endocervical sampling is recommended for women who are HPV DNA positive or have a repeat cytology result of ASC-US or greater. (BII) If the HPV DNA test is negative or if 2 consecutive repeat cytology tests are "negative for intraepithelial lesion or malignancy," routine screening for at least 20 years commencing at 12 months is recommended. (AI) Repeat treatment or hysterectomy based on a positive HPV DNA test is unacceptable. (EII)

If CIN 2,3 is identified at the margins of a diagnostic excisional procedure or in an endocervical sample obtained immediately after the procedure, reassessment using cytology with endocervical sampling at 4-6 months after treatment is preferred. (BII) Performing a repeat diagnostic excisional procedure is acceptable. (CIII) Hysterectomy is acceptable if a repeat diagnostic procedure is not feasible.

A repeat diagnostic excision or hysterectomy is acceptable for women with a histological diagnosis of recurrent or persistent CIN 2,3. (BII)

## CIN 2,3 in Special Populations

### Adolescent and young women

For adolescents and young women with a histological diagnosis of CIN 2,3 not otherwise specified, either treatment or observation for up to 24 months using both colposcopy and cytology at 6 month intervals is acceptable, provided colposcopy is satisfactory. (BIII)

When a histological diagnosis of CIN 2 is specified, observation is preferred but treatment is acceptable. When a histological diagnosis of CIN 3 is specified or when colposcopy is unsatisfactory, treatment is recommended. (BIII)

If the colposcopic appearance of the lesion worsens or if HSIL cytology or a high-grade colposcopic lesion persists for 1 year, repeat biopsy is recommended. (BIII) After 2 consecutive "negative for intraepithelial lesion or malignancy" results, adolescents and young women with normal colposcopy can return to routine cytological screening. (BII)

Treatment is recommended if CIN 3 is subsequently identified or if CIN 2,3 persists for 24 months. (BII)

### Pregnant women

In the absence of invasive disease or advanced pregnancy, additional colposcopic and cytological examinations are acceptable in pregnant women with a histological diagnosis of CIN 2,3 at intervals no more frequent than every 12 weeks. (BII) Repeat biopsy is recommended only if the appearance of the lesion worsens or if cytology suggests invasive cancer. (BII) Deferring reevaluation until at least 6 weeks postpartum is acceptable. (BII) A diagnostic excisional procedure is recommended only if invasion is suspected. (BII) Unless invasive cancer is identified, treatment is unacceptable. (EII) Reevaluation with cytology and colposcopy is recommended no sooner than 6 weeks postpartum. (CIII)

## AIS

AIS is much less commonly encountered than is CIN 2,3. In 1991-1995 the overall incidence of squamous carcinoma in situ of the cervix in white women in the United States was 41.4 per 100,000, whereas the incidence of AIS was only 1.25 per 100,000.[25] Although the overall incidence of AIS remains rather low, the incidence increased by approximately 6-fold from the 1970s to 1990s.[25]

Management of women with AIS is both challenging and controversial. Many of the assumptions that are used to justify conservative management approaches in women with CIN 2,3 lesions do not apply to AIS. For example, the colposcopic changes associated with AIS can be minimal, so it can be difficult to determine the extent of a lesion. AIS frequently extends for a considerable distance into the endocervical canal making complete excision difficult. AIS is also frequently multifocal and frequently has

"skip lesions" (ie, lesions which are not contiguous). Thus negative margins on a diagnostic excisional specimen do not necessarily mean that the lesion has been completely excised.

Because of these considerations hysterectomy continues to be the treatment of choice for AIS in women who have completed child-bearing. However, AIS often occurs in women who wish to maintain their fertility. A number of studies have now clearly demonstrated that an excisional procedure is curative in the majority these patients. The failure rate after an excisional procedure (eg, recurrent/persistent AIS or invasive adenocarcinoma) ranges from 0% to 9%.[46-50] A comprehensive review of the published literature conducted in 2001 identified 16 studies that included a total of 296 women with AIS who had been treated with a diagnostic excisional procedure.[49] The overall failure rate was 8%.[49] Margin status is one of the most clinically useful predictors of residual disease.[51-54] Recent data suggest that endocervical sampling at the time of an excisional biopsy is also predictive of residual disease.[51] Some, but not all, studies have suggested that there is an increased recurrence rate as well as an increase in positive margins when a loop excision procedure as opposed to cold-knife conization is used.[48,49,55] Irrespective of conization method, clinicians should remember that margin status and interpretability of the margins are important for future treatment planning and management. Moreover, it should be emphasized that an excisional biopsy is required in all women with AIS prior to making any subsequent management decisions.

## Recommended management of women with AIS

Hysterectomy is preferred for women who have completed child-bearing and have a histological diagnosis of AIS on a specimen from a diagnostic excisional procedure. (CIII) Conservative management is acceptable if future fertility is desired. (AII) If conservative management is planned and the margins of the specimen are involved or endocervical sampling obtained at the time of excision contains CIN or AIS, reexcision to increase the likelihood of complete excision is preferred. Reevaluation at 6 months using a combination of cervical cytology, HPV DNA testing, and colposcopy with endocervical sampling is acceptable in this circumstance. Long-term follow-up is recommended for women who do not undergo hysterectomy. (CIII) ■

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## APPENDIX A
## Participating organizations

American Academy of Family Physicians; American Cancer Society; American College Health Association; American College of Obstetricians and Gynecologists; American Social Health Association; American Society for Clinical Pathology; American Society for Colposcopy and Cervical Pathology; American Society of Cytopathology; Association of Reproductive Health Professionals; Centers for Disease Control and Prevention, Division of Viral and Rickettsial Disease; Centers for Disease Control and Prevention, Division of Cancer Prevention and Control; Centers for Disease Control and Prevention, Division of Laboratory Systems; Centers for Medicaid and Medicare Services; College of American Pathologists; Food and Drug Administration; International Academy of Cytology; International Federation for Cervical Pathology and Colposcopy; International Federation of Gynecology and Obstetrics; International Gynecologic Cancer Society; International Society of Gynecological Pathologists; National Cancer Institute; National Association of Nurse Practitioners in Women's Health; Papanicolaou Society of Cytopathology; Pan American Health Organization; Planned Parenthood Federation of America; Society of Canadian Colposcopists; Society of Gynecologic Oncologists; Society of Gynecologic Oncologists of Canada; and Society of Obstetricians and Gynaecologists of Canada.

Note: A full listing of participants of the 2006 Consensus Conference is available online ( www.asccp.org).