Update on ASCCP Consensus Guidelines for Abnormal Cervical Screening Tests and Cervical Histology

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New data have emerged since publication of the American Society for Colposcopy and Cervical Pathology's 2001 consensus guidelines for management of abnormal cervical cytology and histology. The 2006 guidelines include recommendations for special populations (i.e., adolescents and pregnant women). Human papillomavirus testing is now included for management of atypical glandular cytology, for follow-up after treatment for cervical intraepithelial neoplasia, and in combination with cytologic screening in women 30 years and older. The preferred management of atypical squamous cells of undetermined significance in adult women is reflex human papillomavirus DNA testing. Colposcopy is recommended for adult women with low-grade squamous intraepithelial lesion, atypical glandular cells, high-grade intraepithelial neoplasia, and atypical squamous cells–cannot exclude high-grade intraepithelial neoplasia. Cervical intraepithelial neoplasia, grade 1 can be managed conservatively in adult women, but treatment for cervical intraepithelial neoplasia, grades 2 and 3 is recommended. Immediate treatment is an option for adult women but not for adolescents with high-grade squamous intraepithelial lesion. Conservative management of adolescents with any cytologic or histologic diagnosis except specified cervical intraepithelial neoplasia, grade 3 and adenocarcinoma in situ is recommended. Colposcopy is preferred for pregnant women with low-grade squamous intraepithelial lesion and high-grade squamous intraepithelial lesion, but evaluation of the former may be deferred until no earlier than six weeks postpartum. Treatment during pregnancy is unacceptable unless invasive carcinoma is identified. (*Am Fam Physician*. 2009;80(2):147-155. Copyright © 2009 American Academy of Family Physicians.)

▶ **See related editorial on page 131.**

▶ **Patient information:** A handout on HPV and Pap testing, written by the authors of this article, is available at http://www.aafp.org/afp/20090715/147-s1.html.

Since publication of the 2001 American Society for Colposcopy and Cervical Pathology (ASCCP) consensus guidelines for management of abnormal cervical cytology[1,2] and histology,[3,4] new data have emerged. Updated guidelines published in October 2007 place greater emphasis on testing for high-risk human papillomavirus (HPV).[5-8] New algorithms focus on special populations (i.e., adolescents and pregnant women).[6,8] Immunosuppressed women are no longer classified separately. The management of abnormal cytologic and histologic findings has been updated. Management algorithms and information on strength of recommendations and quality of evidence can be found at http://www.asccp.org and in the publications that featured the updated guidelines.[5-8] Cytologic and histologic terminology is described in *Table 1*,[5-8] and additional terminology used in the consensus guideline recommendations is defined in *Table 2*.[5-8]

Screening in Women 30 Years and Older

The relationship of cervical intraepithelial neoplasia, grades 2 and 3 (CIN 2,3) and cervical cancer to HPV infection is well established.[9] The use of annual conventional cervical cytology has reduced the incidence of cervical cancer,[10] but these rates may be plateauing or even slightly increasing.[11] Screening for cervical cancer may be improved by applying HPV testing, given the limited sensitivity of cytology.[12] HPV testing refers only to a U.S. Food and Drug Administration–approved HPV DNA test (Hybrid Capture 2) for high-risk HPV types.[5,6]

Although HPV testing is more sensitive than cytology for detecting CIN 2,3,[13] it is less specific when used alone.[14] A single negative HPV test result carries a negligible risk for CIN 3.[15] Conversely, a single positive HPV test result with normal cytology is substantially predictive of CIN 2,3.[15] These data suggest that HPV testing can be used

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Colposcopy is the recommended management of HPV DNA–positive ASC-US, ASC-H, HSIL, and LSIL in adult women.	C	5, 6
The preferred management of ASC-US in adult women is reflex HPV DNA testing.	C	5, 6
Colposcopy with endocervical sampling is recommended for all women with AGC and AIS. Reflex HPV DNA testing or repeat cytology is unacceptable for the initial triage of AGC and AIS.	C	5, 6
HPV DNA testing at 12 months or repeat cytology at six and 12 months is recommended in adult women with CIN 1 preceded by ASC-US, ASC-H, or LSIL.	C	6, 7
Immediate excision ("see and treat") instead of colposcopy is acceptable for adult women with HSIL, but is unacceptable in adolescents.	C	5-8
Colposcopic biopsy of lesions suspicious for cancer or CIN 2,3 is preferred in pregnant women, but biopsy of other lesions is acceptable. Endocervical curettage is unacceptable.	C	5, 6

NOTE: *References 5 through 8 are American Society for Colposcopy and Cervical Pathology consensus guidelines, expert review.*

AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells–cannot exclude HSIL; ASC-US = atypical squamous cells of undetermined significance; CIN 1 = cervical intraepithelial neoplasia, grade 1; CIN 2,3 = cervical intraepithelial neoplasia, grades 2 and 3; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

to stratify the risk of developing high-grade cervical lesions.[16]

HPV infection is most prevalent among women 20 to 24 years of age, with a gradual decline in prevalence through 59 years of age.[17] Among women who are HPV positive but cytologically negative, about 60 percent become HPV negative within six months. However, even with negative cytology, older women who are HPV positive have a greater risk of developing CIN 3 within 10 years, compared with younger women (21.0 versus 13.6 percent, respectively).[16] Alternatively, negative cytology with a concurrent negative HPV test result in women older than 30 years carries a high long-term negative predictive value (NPV), indicating the absence of significant disease.[18] Therefore, combination screening should be performed no more than every three years if the results of both tests are negative.[5,6]

Women with a positive HPV test and negative cytology can have conservative follow-up with repeat combination testing at 12 months.[5,6] Colposcopy is recommended if HPV test results remain positive or cytology shows atypical squamous cells of undetermined significance (ASC-US) or greater cytologic abnormality[5,6] *(Figure 1[6])*. Cytology alone is an acceptable screening method in women 30 years and older.[6]

Table 1. Cervical Cytologic and Histologic Terms

Cytology	
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells–cannot exclude HSIL
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
AGC	Atypical glandular cells
AIS	Adenocarcinoma in situ
Histology	
CIN 1	Cervical intraepithelial neoplasia, grade 1
CIN 2	Cervical intraepithelial neoplasia, grade 2
CIN 3	Cervical intraepithelial neoplasia, grade 3
AIS	Adenocarcinoma in situ

Information from references 5 through 8.

Abnormal Cervical Cytology in Adult Women

ATYPICAL SQUAMOUS CELLS

Approximately 4 percent of cytologic smears exhibit ASC-US.[19] Additional triage is recommended for nonadolescent women because the risk of CIN 2 or more serious abnormality is 9.7 percent.[20] Reflex HPV DNA testing is the preferred triage option, with colposcopic evaluation for women who are HPV positive.[5,6] Repeat cytology at six and 12 months or immediate colposcopy is also an acceptable initial management option.[5,6] If colposcopy is negative, follow-up includes repeat cytology at six and 12 months, or HPV testing at 12 months, with colposcopic reevaluation if HPV testing is positive or cytology is ASC-US or greater[5,6] *(Figure 2[6])*.

In women with atypical squamous cells–cannot exclude high-grade squamous intraepithelial lesion (ASC-H), the prevalence of CIN 2,3 is as high as 50 percent.[21] Therefore, colposcopy is recommended.[5,6] Although HPV testing for ASC-H is not included in the guideline, a negative test reassures of the absence of disease.[22] Postcolposcopy

Table 2. Terminology Used in ASCCP Consensus Guideline Recommendations

Term	*Description*
Terminology used for recommendations	
Acceptable	One of multiple options when data indicate another approach is superior or when no data favor any single option
Preferred	Best option (or one of the best) when multiple options are available
Recommended	Good data to support use when only one option is available
Unacceptable	Good data against use
Definition of terms	
Adolescent female	20 years and younger (from 13th to 21st birthday)
Diagnostic excisional procedure	Obtaining a histologic specimen of the transformation zone and endocervical canal by laser or cold-knife conization or loop electrosurgical excision or conization
Endocervical assessment	Evaluating the endocervical canal for neoplasia by colposcopy or endocervical sampling
Endocervical sampling	Obtaining a cytologic sample with a cytobrush or histologic specimen by a cytobrush or endocervical curette
Endometrial sampling	Obtaining a specimen for histologic evaluation by endometrial biopsy, dilatation and curettage, or hysteroscopy
HPV DNA testing	Refers only to an HPV DNA test (Hybrid Capture 2) approved by the U.S. Food and Drug Administration for high-risk HPV types
Satisfactory colposcopy	Margin of any visible lesion and entire squamocolumnar junction are visible

ASCCP = American Society for Colposcopy and Cervical Pathology; HPV = human papillomavirus.

Information from references 5 through 8.

management of women with ASC-H is the same as that of women with ASC-US.[5,6]

LSIL

Colposcopy is recommended for adult women with low-grade squamous intraepithelial lesion (LSIL), because 28 percent will harbor CIN 2,3 over a two-year period[5,6,23] *(Figure 3[6])*. Use of HPV testing is not recommended, because 86 percent of women with LSIL will be HPV positive.[24] If colposcopy results are negative or unsatisfactory, endocervical assessment using a cytobrush or endocervical curette is preferred.[5,6]

Twelve percent of women with LSIL will develop CIN 2,3 or worse within two years, regardless of

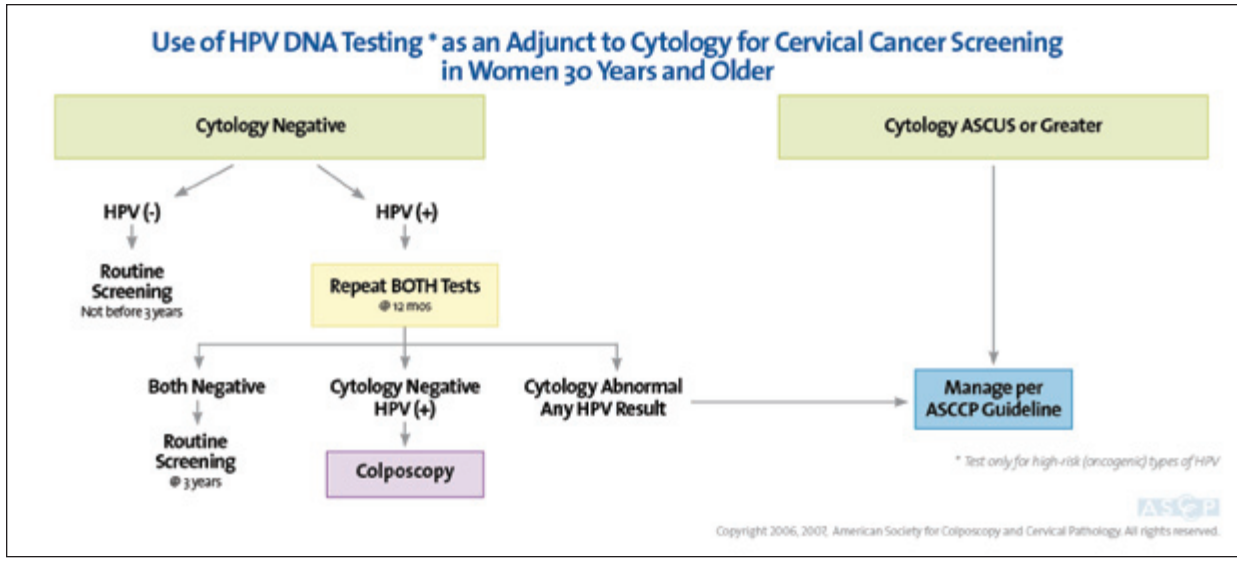

Figure 1. Use of human papillomavirus DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years and older.

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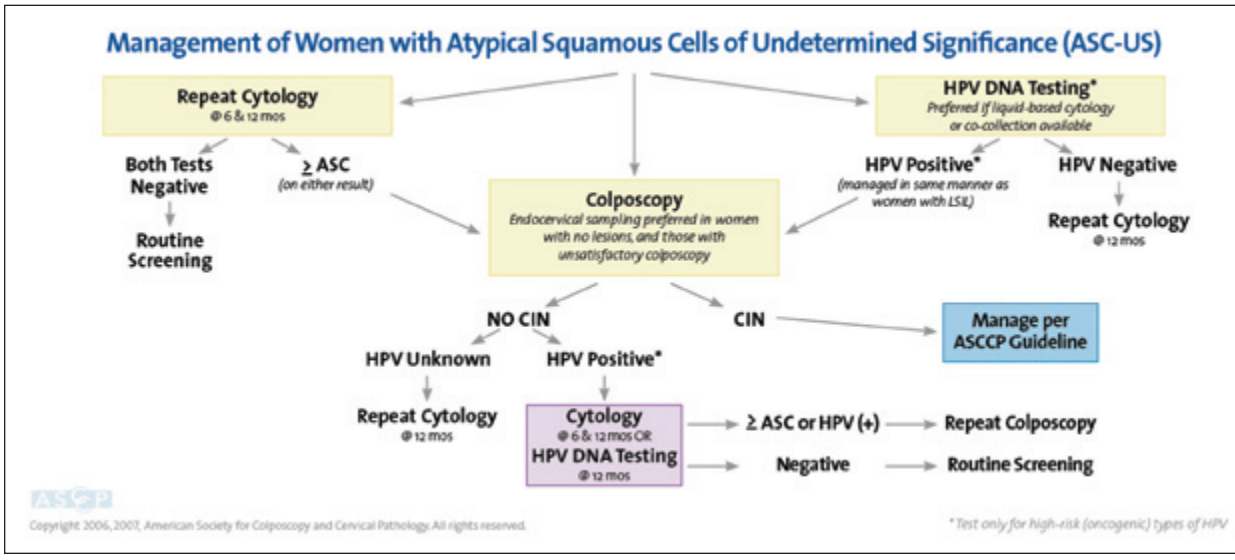

Figure 2. Management of women with atypical squamous cells of undetermined significance.

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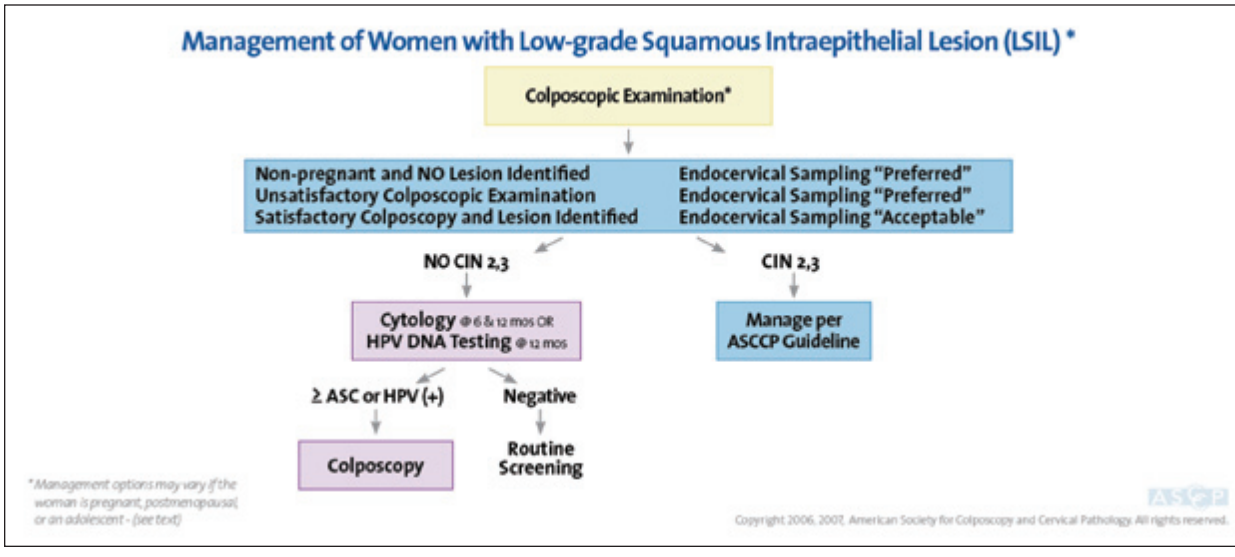

Figure 3. Management of women with low-grade squamous intraepithelial lesion.

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whether they have a negative biopsy result or CIN 1.[23] Therefore, if no CIN 2,3 is found at colposcopy, HPV testing in 12 months or cytology at six and 12 months is acceptable.[5] If this testing is negative, routine screening may resume.[5,6]

HSIL

Only 0.5 percent of cytologic samples demonstrate high-grade squamous intraepithelial lesion (HSIL).[25] Of women with HSIL, 70 to 75 percent will have CIN 2,3 and 1 to 4 percent will have invasion.[25,26] Initial evaluation may include *either* an immediate diagnostic excisional procedure, especially for women at risk of not returning for further evaluation or those who have completed childbearing, *or* colposcopy with endocervical assessment[5,6] *(Figure 4[6])*. If satisfactory colposcopy does not identify CIN 2,3 and endocervical sampling is negative, management may include a diagnostic excisional

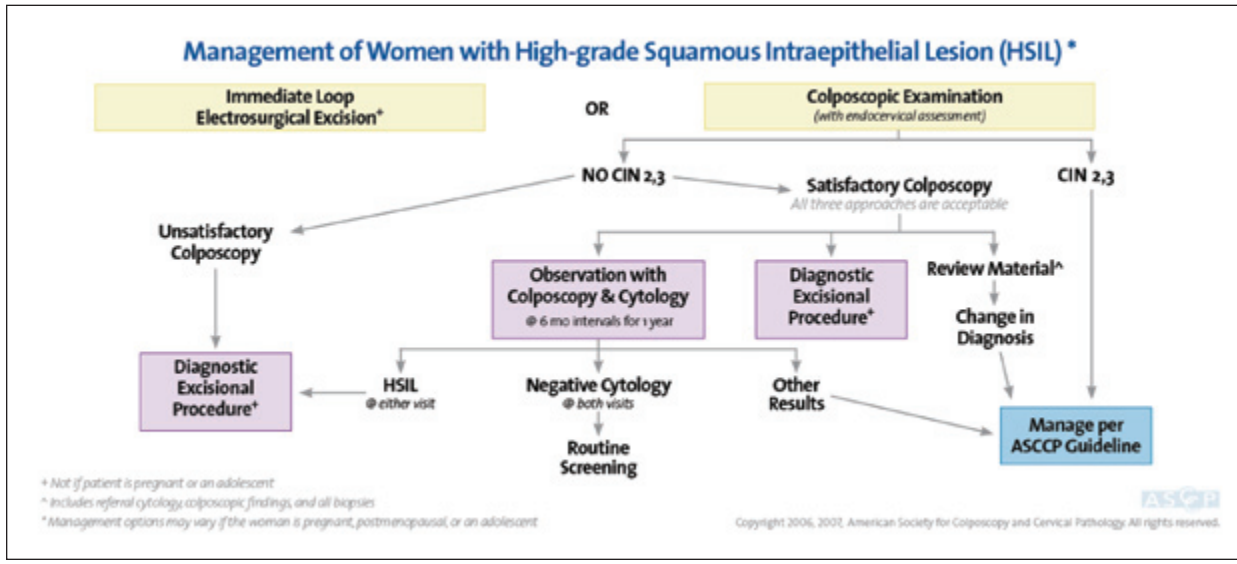

Figure 4. Management of women with high-grade squamous intraepithelial lesion.

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procedure or cytology and colposcopy every six months until both are negative twice.[5,6] If HSIL persists at six or 12 months, excision is recommended.[5,6]

ATYPICAL GLANDULAR CELLS

Only 0.2 percent of cytologic smears exhibit atypical glandular cells (AGC).[19] Although benign lesions are the most common underlying cause, AGC can indicate a significant squamous or glandular lesion up to 38 percent of the time.[27] Because CIN is the most common pathology, especially for women younger than 35 years,[28] initial evaluation includes colposcopy with endocervical sampling and HPV DNA testing for all subcategories of AGC and AIS.[5,6] Endometrial sampling is also recommended in women 35 years and older or in younger women with risk factors for endometrial cancer.[5,6] Reflex HPV DNA testing or repeat cytology is unacceptable as initial triage of atypical glandular cells–not otherwise specified (AGC-NOS), AGC–favor neoplasia, or adenocarcinoma in situ (AIS).[5,6]

HPV positivity has a high positive predictive value for significant cervical disease, with 20 percent of women having CIN 3 or cancer on biopsy.[29] If the initial evaluation of AGC is unremarkable, cytology and HPV testing should be repeated in six months if HPV testing is positive, and at 12 months if HPV testing is negative.[5,6] If HPV testing and cytology are both negative on reevaluation, annual cytologic testing may resume.[5,6] If HPV DNA status is unknown, retesting at six-month intervals for a total of 24 months is recommended[5,6] *(Figure 5[6])*. If initial cytology is AGC–favor neoplasia or AIS instead of AGC-NOS, an excisional procedure may be required for full evaluation despite initial negative testing[5,6] *(Figure 5[6])*.

ENDOMETRIAL CELLS

Endometrial cells are found on 0.5 to 1.8 percent of Papanicolaou tests of women 40 years and older.[30] For asymptomatic premenopausal women, benign endometrial cells do not require evaluation because they are rarely associated with underlying pathology.[5,6] However, endometrial assessment is recommended for postmenopausal women with benign endometrial cells, because 7 percent will have significant endometrial pathology.[5,6,31]

Abnormal Cervical Histology in Adult Women

CIN 1

If original cytology demonstrated ASC-US, ASC-H, or LSIL, follow-up with cytology at six and 12 months or HPV DNA testing at 12 months is recommended because of the low risk of cancer in women with CIN 1 on biopsy.[7,8] If CIN 1 persists for at least two years, continued observation is still an option, as is treatment.[7,8] Excision is preferred for women with unsatisfactory colposcopy, positive endocervical sampling, or previous treatment.[7,8]

For women with CIN 1 preceded by HSIL or AGC-NOS, closer follow-up is warranted because 84 to

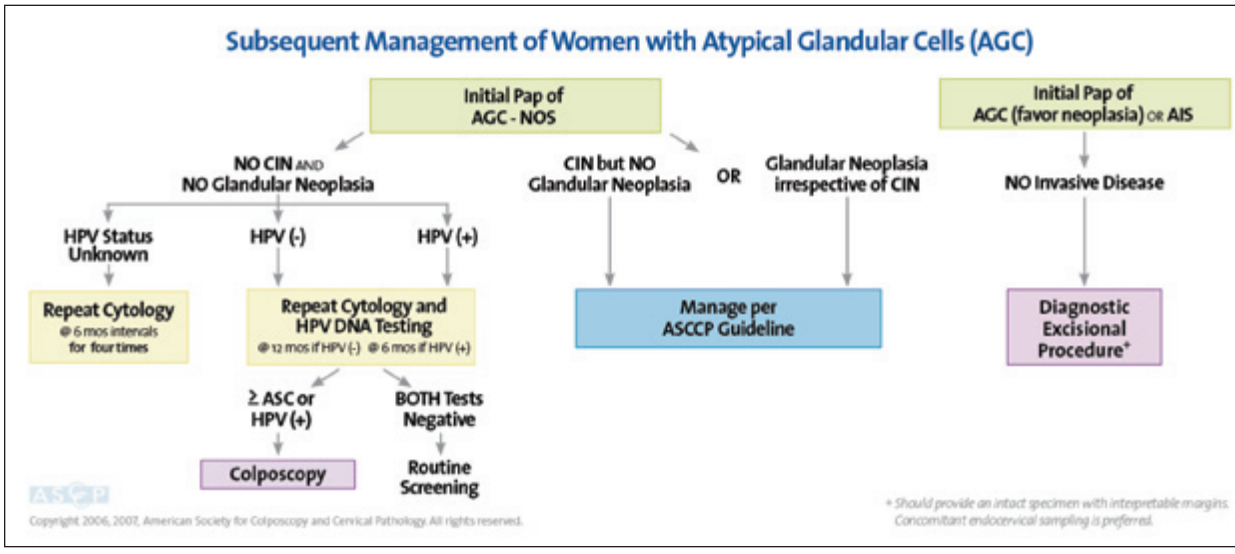

Figure 5. Subsequent management of women with atypical glandular cells.

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97 percent of these women will have at least CIN 2 on excision.[26] Either a diagnostic excision or cytology and colposcopy every six months for 12 months are acceptable, provided colposcopy is satisfactory and the endocervical sampling is negative.[7,8] Excision is recommended if the colposcopy is unsatisfactory or if HSIL repeats.[7,8]

CIN 2,3

CIN 3 is considered a cancer precursor. About 12 percent of cases of CIN 3 progress to invasive cancer, 33 percent regress, and the rest remain CIN 3.[32] For women with CIN 2,3 and satisfactory colposcopy, ablation or diagnostic excision is acceptable.[7,8] Unless the woman is pregnant or an adolescent, observation is unacceptable.[7,8] If colposcopy is unsatisfactory or if CIN 2,3 recurs, a diagnostic excision is recommended.[7,8]

Women who remain HPV positive after treatment for CIN 2,3 are at increased risk of recurrent or residual CIN.[33] HPV-negative women rarely have recurrent or residual lesions (NPV of 98 percent).[34] This is higher than the NPV of negative resection margins (91 percent) or cervical cytology (93 percent).[34] Therefore, HPV testing may be used to monitor post-treatment status.[34] Cytology alone or combined with colposcopy at six-month intervals is also an option.[7,8]

AIS

AIS is a high-grade glandular lesion that is relatively rare (0.3 to 1.25 per 100,000 woman-years) but with an increasing incidence.[35] Evaluation should include HPV testing, colposcopy, and endocervical sampling when appropriate. Colposcopy is often unremarkable when AIS is present, because it can extend deep into the endocervical canal with noncontiguous lesions. Therefore, if the initial cytology is AGC–favor neoplasia or AIS and no invasion is identified, an excisional procedure is still recommended.[7,8] If histologic AIS is confirmed, hysterectomy is preferred.[7,8] Because of the high likelihood of missing an AIS lesion or of an incomplete excision, reexcision for positive margins or positive endocervical sampling is preferred if conservative management is planned.[7,8,36,37] Conservative management includes reevaluation with cytology, HPV testing, and colposcopy with endocervical sampling in six months.[7,8] Long-term follow-up is recommended for all women diagnosed with AIS who do not undergo hysterectomy.[7,8]

Special Populations

ADOLESCENTS

Most HPV infections occur in adolescents shortly after first intercourse,[38] with a prevalence up to 54 percent.[38,39] Cervical cancer rates are no more than three per 1 million adolescents.[40] However, intercourse before 18 years of age carries a two- to fourfold increased risk of subsequently developing invasive cancer.[41]

Because up to 90 percent of HPV infections in adolescents are transient or cleared spontaneously within two years,[42,43] the guidelines have been modified to avoid unnecessary testing and treatment. Cytologic screening should be initiated three years after first intercourse, or

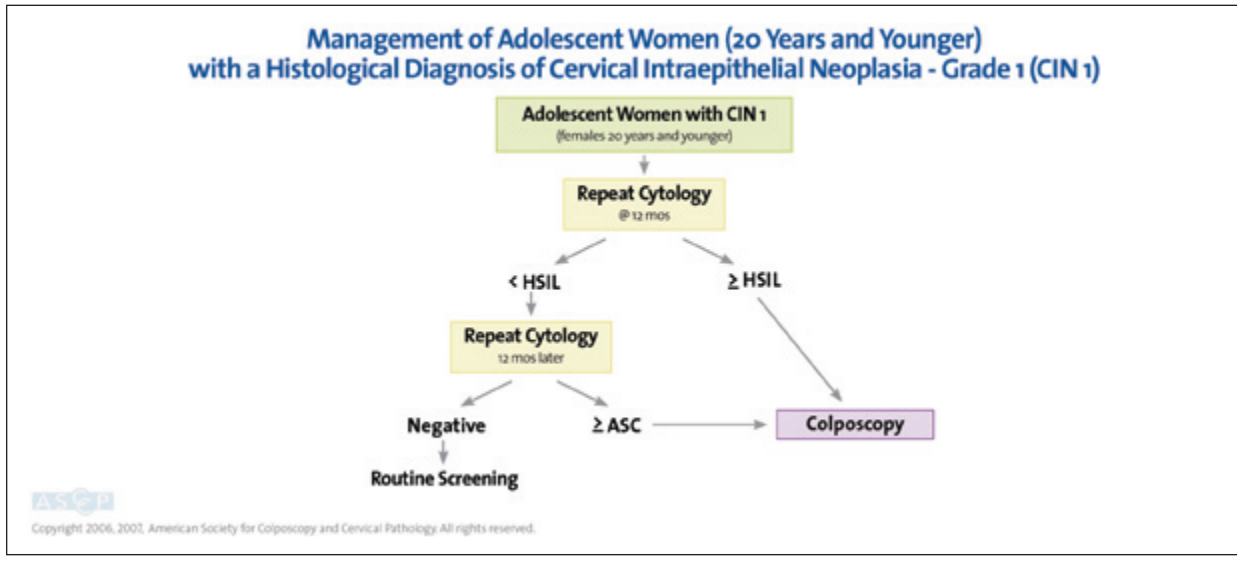

Figure 6. Management of adolescent women (20 years and younger) with a histologic diagnosis of cervical intraepithelial neoplasia, grade 1.

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at 21 years of age, whichever comes first.[10] Because of the high incidence of HPV infection, HPV DNA testing is not clinically useful for adolescents.[44]

ASC-US and LSIL are common in adolescents[45,46] and are considered reactive changes to transient HPV infections. Repeat cytology in 12 months is recommended to allow these changes to resolve.[5,6] Colposcopy should be performed if cytology progresses to HSIL or if any cytologic abnormality persists for 24 months.[5,6]

Adolescents with CIN 1 are managed with repeat cytology at 12 and 24 months.[7,8] Colposcopy is recommended only if HSIL is present at 12 months or ASC-US or greater is present at 24 months[7,8] *(Figure 6*[8]*)*.

The incidence of HSIL in adolescents is 0.7 percent, nearly identical to that of older women,[47] and colposcopy is recommended.[5,6] Immediate excision ("see and treat") is not recommended for adolescents with HSIL. If CIN 2,3 is not found, cytology and colposcopy are preferred every six months for one year with biopsy if high-grade lesions are identified or if HSIL persists on subsequent cytology.[5,6] Adolescents may return to annual cytologic screening after two consecutive normal cytologies if colposcopy does not show high-grade findings.[5,6] An excisional procedure is acceptable only if HSIL persists for 24 months and no CIN 2,3 is found.[5,6]

Some pathologists are beginning to separate CIN 2 and 3 by histologic criteria. If histology indicates CIN 2,3–not otherwise specified, adolescents may undergo colposcopy and cytology every six months up to 24 months, or treatment with excision or ablation.[7,8] When CIN 2 is specified, observation is preferred.[7,8] If CIN 3 is specified or colposcopy is unsatisfactory, treatment is recommended.[7,8] It is unacceptable to perform an excisional procedure without histologic confirmation to avoid potential obstetric complications.[48]

PREGNANT WOMEN

Pregnancy does not accelerate cervical lesions, and cervical cancer occurs in only five of 100,000 pregnancies.[49] The rate of CIN 2,3 is only 3.7 percent on postpartum follow-up for women with prenatal ASC-US or LSIL.[49] Postpartum regression is common in women with CIN 1 (36 percent) and CIN 2,3 (48 to 70 percent).[50,51] Management of nonadolescent women with ASC-US or LSIL is the same as for nonpregnant women[5,6]; however, because of the low risk of cancer, the initial colposcopic evaluation can be deferred until at least six weeks postpartum.[5,6] When necessary to rule out invasion, colposcopy and directed biopsies are safe in pregnancy,[52] but endocervical curettage is unacceptable.[5,6] Because cervical changes in pregnancy can mimic CIN, colposcopy should be performed by experienced colposcopists.[5,6] Treatment is unacceptable without confirmation of cancer[7,8] because of the risk of complications such as hemorrhage or fetal loss.[53]

Pregnant women with HSIL should undergo prenatal colposcopy[5,6] with biopsy of lesions suspicious for CIN 2,3 or cancer.[5,6] Colposcopy should be repeated no

earlier than six weeks postpartum if no CIN 2,3 is found.[5,6] For pregnant women with CIN 2,3, repeat cytology and colposcopy may be performed every 12 weeks with repeat biopsy if the lesion worsens or cytology suggests invasion.[7,8]

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REFERENCES

1. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ, for the ASCCP-Sponsored Consensus Conference. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA*. 2002;287(16):2120-2129.
2. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ, for the 2001 ASCCP-sponsored Consensus Conference. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *J Low Genit Tract Dis*. 2002;6(2):127-143.
3. Wright TC Jr, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ, for the American Society for Colposcopy and Cervical Pathology. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol*. 2003;189(1):295-304.
4. Wright TC Jr, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ, for the 2001 ASCCP-sponsored consensus workshop. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *J Low Genit Tract Dis*. 2003;7(3):154-167.
5. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, for the 2006 American Society for Colposcopy and Cervical Pathology-sponsored consensus conference. 2006 Consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*. 2007;197(4):346-355.
6. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, for the 2006 ASCCP-sponsored consensus conference. 2006 Consensus guidelines for the management of women with abnormal cervical screening tests [published correction appears in *J Low Genit Tract Dis*. 2008;12(3):255]. *J Low Genit Tract Dis*. 2007;11(4):201-222.
7. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, for the 2006 American Society for Colposcopy and Cervical Pathology-sponsored consensus conference. 2006 Consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol*. 2007;197(4):340-345.
8. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, for the 2006 American Society for Colposcopy and Cervical Pathology-sponsored consensus conference. 2006 Consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ [published correction appears in *J Low Genit Tract Dis*. 2008;12(1):63]. *J Low Genit Tract Dis*. 2007;11(4):223-239.
9. Schiffman M, Herrero R, Desalle R, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology*. 2005; 337(1):76-84.
10. U.S. Preventive Services Task Force. Screening for cervical cancer. Rockville, Md.: Agency for Healthcare Research and Quality; January 2003. http://www.ahrq.gov/clinic/uspstf/uspscerv.htm. Accessed March 30, 2009.
11. Vizcaino AP, Moreno V, Bosch FX, et al. International trends in incidence of cervical cancer: II. Squamous-cell carcinoma. *Int J Cancer*. 2000;86(3):429-435.
12. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med*. 2000;132(10):810-819.
13. Schneider A, Hoyer H, Lotz B, et al. Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. *Int J Cancer*. 2000;89(6):529-534.
14. Mayrand MH, Duarte-Franco E, Coutlée F, et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). *Int J Cancer*. 2006;119(3):615-623.
15. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst*. 2003;95(1):46-52.
16. Kjaer S, Høgdall E, Frederiksen K, et al. The absolute risk of cervical abnormalities in high-risk human papillomavirus-positive, cytologically normal women over a 10-year period. *Cancer Res*. 2006;66(21): 10630-10636.
17. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA*. 2007;297(8):813-819.
18. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. *Br J Cancer*. 2005;93(5):575-581.
19. Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE, Mody DR. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med*. 2004;128(11):1224-1229.
20. Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine*. 2006;24(suppl 3):S78-S89.
21. Sherman ME, Castle PE, Solomon D. Cervical cytology of atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H): characteristics and histologic outcomes. *Cancer*. 2006;108(5):298-305.
22. Liman AK, Giampoli EJ, Bonfiglio TA. Should women with atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion, receive reflex human papillomavirus-DNA testing? *Cancer*. 2005;105(6):457-460.
23. Cox JT, Schiffman M, Solomon D, for the ASCUS-LSIL Triage Study (ALTS) Group. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *Am J Obstet Gynecol*. 2003;188(6):1406-1412.

24. ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol.* 2003;188(6):1393-1400.
25. Jones BA, Novis DA. Cervical biopsy-cytology correlation. A College of American Pathologists Q-Probes study of 22,439 correlations in 348 laboratories. *Arch Pathol Lab Med.* 1996;120(6):523-531.
26. Massed LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. *Gynecol Oncol.* 2001;82(3):516-522.
27. DeSimone CP, Day ME, Tovar MM, Dietrich CS III, Eastham ML, Modesitt SC. Rate of pathology from atypical glandular cell Pap tests classified by the Bethesda 2001 nomenclature. *Obstet Gynecol.* 2006; 107(6):1285-1291.
28. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI. Dysplasia associated with atypical glandular cells on cervical cytology [published correction appears in *Obstet Gynecol.* 2005;105(6):1495]. *Obstet Gynecol.* 2005;105(3):494-500.
29. Derchain SF, Rabelo-Santos SH, Sarian LO, et al. Human papillomavirus DNA detection and histological findings in women referred for atypical glandular cells or adenocarcinoma in situ in their Pap smears. *Gynecol Oncol.* 2004;95(3):618-623.
30. Greenspan DL, Cardillo M, Davey DD, Heller DS, Moriarty AT. Endometrial cells in cervical cytology: review of cytological features and clinical assessment. *J Low Genit Tract Dis.* 2006;10(2):111-122.
31. Simsir A, Carter W, Elgert P, Cangiarella J. Reporting endometrial cells in women 40 years and older: assessing the clinical usefulness of Bethesda 2001. *Am J Clin Pathol.* 2005;123(4):571-575.
32. Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol.* 1993;12(2):186-192.
33. Verguts J, Bronselaer B, Donders G, et al. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conisation. *BJOG.* 2006;113(11):1303-1307.
34. Zielinski GD, Bais AG, Helmerhorst TJ, et al. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. *Obstet Gynecol Surv.* 2004;59(7):543-553.
35. Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. *Cancer.* 2004;100(5):1035-1044.
36. Soutter WP, Haidopoulos D, Gornall RJ, et al. Is conservative treatment for adenocarcinoma in situ of the cervix safe? *BJOG.* 2001; 108(11):1184-1189.
37. Azodi M, Chambers SK, Rutherford TJ, Kohorn EI, Schwartz PE, Chambers JT. Adenocarcinoma in situ of the cervix: management and outcome. *Gynecol Oncol.* 1999;73(3):348-353.
38. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students [published correction appears in *Am J Epidemiol.* 2003;157(9):858]. *Am J Epidemiol.* 2003;157(3):218-226.
39. Moscicki AB, Ellenberg JH, Vermund SH, et al. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: impact of infection with human immunodeficiency virus. *Arch Pediatr Adolesc Med.* 2000;154(2):127-134.
40. SEER Cancer Statistics Review 1975-2003. Bethesda, Md.: National Cancer Institute; 2006.
41. Green J, Berrington de Gonzalez A, Sweetland S, et al. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20-44 years: the UK National Case-Control Study of Cervical Cancer. *Br J Cancer.* 2003;89(11):2078-2086.
42. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338(7):423-428.
43. Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis.* 1995;171(4):1026-1030.
44. Boardman LA, Stanko C, Weitzen S, Sung CJ. Atypical squamous cells of undetermined significance: human papillomavirus testing in adolescents. *Obstet Gynecol.* 2005;105(4):741-746.
45. Sadeghi SB, Hsieh EW, Gunn SW. Prevalence of cervical intraepithelial neoplasia in sexually active teenagers and young adults. Results of data analysis of mass Papanicolaou screening of 796,337 women in the United States in 1981. *Am J Obstet Gynecol.* 1984;148(6):726-729.
46. Bjørge T, Gunbjørud AB, Langmark F, Skare GB, Thoresen SO. Cervical mass screening in Norway—510,000 smears a year. *Cancer Detect Prev.* 1994;18(6):463-470.
47. Mount SL, Papillo JL. A study of 10,296 pediatric and adolescent Papanicolaou smear diagnoses in northern New England. *Pediatrics.* 1999;103(3):539-546.
48. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet.* 2006;367(9509):489-498.
49. Dunn TS, Bajaj JE, Stamm CA, Beaty B. Management of the minimally abnormal Papanicolaou smear in pregnancy. *J Low Genit Tract Dis.* 2001;5(3):133-137.
50. Paraskevaidis E, Koliopoulos G, Kalantaridou S, et al. Management and evolution of cervical intraepithelial neoplasia during pregnancy and postpartum. *Eur J Obstet Gynecol Reprod Biol.* 2002;104(1):67-69.
51. Yost NP, Santoso JT, McIntire DD, Iliya FA. Postpartum regression rates of antepartum cervical intraepithelial neoplasia II and III lesions. *Obstet Gynecol.* 1999;93(3):359-362.
52. Economos K, Perez Veridiano N, Delke I, Collado ML, Tancer ML. Abnormal cervical cytology in pregnancy: a 17-year experience. *Obstet Gynecol.* 1993;81(6):915-918.
53. Robinson WR, Webb S, Tirpack J, Degefu S, O'Quinn AG. Management of cervical intraepithelial neoplasia during pregnancy with LOOP excision. *Gynecol Oncol.* 1997;64(1):153-155.