

# Management of Histologic Abnormalities of the Cervix

MARK SPITZER, M.D., *New York Methodist Hospital, Brooklyn, New York*

BARBARA S. APGAR, M.D., M.S., *University of Michigan Medical School, Ann Arbor, Michigan*

GREGORY L. BROTZMAN, M.D., *Medical College of Wisconsin, Milwaukee, Wisconsin*

The American Society for Colposcopy and Cervical Pathology sponsored a consensus conference in 2001 to develop evidence-based guidelines for women with histologic abnormalities of the cervix. The options for management of cervical intraepithelial neoplasia 1, 2, and 3 are ranked according to the strength of the recommendation and the quality of the evidence. Follow-up with repeat cytology at six and 12 months or DNA testing for high-risk types of human papillomavirus at 12 months is the preferred management approach for women with cervical intraepithelial neoplasia 1 and satisfactory initial colposcopy. If results from repeat cytology are reported as atypical squamous cells of undetermined significance or greater, or if DNA human papillomavirus testing is positive for oncogenic types of the virus, repeat colposcopy is preferred. When the initial colposcopy is unsatisfactory, a diagnostic excisional procedure is preferred. Follow-up without treatment is acceptable only in women who are pregnant and adolescents with cervical intraepithelial neoplasia 1 who had unsatisfactory colposcopy. Biopsy-confirmed cervical intraepithelial neoplasia 2 and 3 requires treatment except during pregnancy and in compliant adolescents with cervical intraepithelial neoplasia 2 and negative endocervical curettage. When colposcopy is satisfactory, treatment includes ablative or excisional procedures. A diagnostic excisional procedure is recommended in women with biopsy-confirmed cervical intraepithelial neoplasia 2 or 3 and unsatisfactory colposcopy. (*Am Fam Physician* 2006;73:105-12. Copyright © 2006 American Academy of Family Physicians.)

At approximately the same time that results from the National Cancer Institute's atypical squamous cells of undetermined significance (ASC-US) low-grade squamous intraepithelial lesion triage study (ALTS)<sup>1</sup> were published, the American Society for Colposcopy and Cervical Pathology (ASCCP)<sup>2-4</sup> sponsored a consensus conference to develop comprehensive, evidence-based guidelines for women with cytologic and histologic abnormalities of the cervix. The ASCCP developed new options for management of cervical intraepithelial neoplasia (CIN) and ranked them according to the strength of the recommendation and quality of the evidence (*Table 1*).<sup>3</sup> The terminology used in the guidelines is detailed in *Table 2*.<sup>2</sup>

## CIN 1: Overview

There is a high level of intraobserver and interobserver variability in the histologic diagnosis of CIN 1.<sup>5,6</sup> In ALTS, an expert

pathology review committee downgraded 41 percent of CIN 1 diagnoses to normal and upgraded 13 percent of CIN 1 diagnoses to CIN 2-3.<sup>5</sup> Studies<sup>7,8</sup> of women with histologic CIN 1 have found that 23 to 55 percent of patients undergoing loop electrosurgical excision procedures (LEEP) actually have CIN 2-3.

A literature review,<sup>9</sup> meta-analysis,<sup>10</sup> and two-year follow-up data from ALTS<sup>11</sup> found that 10 to 15 percent of CIN 1 lesions progress to CIN 2-3, and that 0.3 percent progress to cancer. It was impossible to ascertain whether CIN 2-3 was present at the beginning of the observation period and discovered later, or whether CIN 1 lesions had progressed. It is difficult to develop management protocols that treat only those women with CIN 1 who have or will develop CIN 2-3 because it is not known which CIN 1 lesions will regress or progress. The consensus guidelines attempt to strike a balance between overtreatment of a nonprogressive human papillomavirus

**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
The preferred treatment for women with CIN 1 and satisfactory colposcopy is repeat cytology at six and 12 months or DNA testing for HPV types at 12 months.	C	3, 4, 18
Endocervical sampling is recommended before any ablative treatment.	C	3, 4
Observation without treatment is acceptable in pregnant women and adolescents with CIN 1 and unsatisfactory colposcopy.	C	3, 4
Observation is unacceptable in women with CIN 2 except during pregnancy and in compliant adolescents with satisfactory colposcopy and negative results on endocervical curettage.	C	3, 4
After treatment for CIN 2-3, acceptable management methods include cytology with or without colposcopy at four- to six-month intervals until three negative evaluations have been obtained, or HPV DNA testing no sooner than six months after treatment.	C	3, 4
The preferred management for CIN identified at the margin of a diagnostic excisional procedure or in postprocedure endocervical sampling is colposcopy and endocervical sampling at the four- to six-month follow-up evaluation.	C	3, 4

*CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.*

*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, see page 17 or <http://www.aafp.org/afpsort.xml>.*

**TABLE 1**  
**Rating System for Consensus Guideline Recommendations**

<i>Rating</i>	<i>Criteria</i>
<b>Strength of recommendation</b>	
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use
B	Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendation may be made on other grounds
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
<b>Quality of evidence</b>	
I	Evidence from at least one randomized controlled trial
II	Evidence from at least one clinical trial without randomization, cohort or case-controlled analytic studies (preferably from more than one center), multiple time-series studies, or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
<b>Terminology</b>	
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

*Adapted with permission from Wright TC Jr, Cox JT, Massad LS, Twigg LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2121.*

(HPV) infection (i.e., CIN 1) and failure to identify and treat lesions with true malignancy potential (i.e., CIN 2-3).

The degree of certainty that the most advanced lesion has been recognized and sampled is an important consideration. When the transformation zone is visualized completely (i.e., satisfactory colposcopy) and endocervical curettage is negative, physicians can be reasonably certain that the histology represents the most serious lesion. However, if the colposcopy is unsatisfactory or the endocervical curettage is positive, unrecognized CIN 2-3 or cancer may be present, and further diagnostic testing is indicated.

Most experts advocate observation without treatment when colposcopy is satisfactory<sup>12</sup> because most cases of CIN 1 spontaneously regress and because most cases of invasive cancer occur in women who are lost to follow-up.<sup>13</sup> The risk of a woman with histologic CIN 1 subsequently developing CIN 2-3 is 9 to 16 percent,<sup>11,13,14</sup> similar to the risk of finding CIN 2-3 in women with ASC-US.<sup>1,11,15,16</sup> This statistic suggests that women with CIN 1 can be followed safely with protocols similar to those for women with ASC-US.<sup>2,3</sup>

In ALTS, repeat cytology at six and 12 months cumulatively detected 85 percent of CIN 3 lesions in women with ASC-US, whereas HPV DNA testing detected 95 percent of CIN 3 lesions over









Figure 6<sup>4</sup>).<sup>3,4</sup> Excisional modalities are preferred in women with recurrent CIN 2-3 (AII recommendation).<sup>3,4</sup> A diagnostic excisional procedure is recommended in women with biopsy-confirmed CIN 2-3 and unsatisfactory colposcopy (AII recommendation).<sup>3,4</sup> Observation of CIN 2-3 without treatment is unacceptable except in special circumstances (EII recommendation).<sup>3,4</sup> Hysterectomy is unacceptable as a primary therapy for women with CIN 2-3 (EII recommendation).<sup>3,4</sup>

### Follow-Up After Treatment for Biopsy-Confirmed CIN 2-3

Acceptable follow-up protocols after treatment of CIN 2-3 include cytology or a combination of cytology and colposcopy at four- to six-month intervals until three negative evaluations have been performed (AII recommendation, Figure 6<sup>4</sup>).<sup>3,4</sup> Annual cytologic follow-up is recommended thereafter (AII recommendation).<sup>3,4</sup> A cytologic result of ASC is the recommended threshold for referral to colposcopy during follow-up (AII recommendation).<sup>3,4</sup> Surveillance with HPV DNA testing performed no sooner than six months after treatment also is acceptable (BII recommendation).<sup>3,4</sup> A positive test for high-risk HPV types is the recommended threshold for referral to colposcopy (BIII recommendation).<sup>3,4</sup> If HPV testing is negative, annual cytologic screening is recommended (BIII recommendation).<sup>3,4</sup> Repeat conization or hysterectomy based on a single positive HPV test that is not corroborated by other findings (e.g., cytology, colposcopy, histology) is unacceptable (DIII recommendation).<sup>3,4</sup>

If CIN is identified at the margin of a diagnostic excisional procedure or on a postprocedure endocervical curettage, it is preferred that endocervical sampling be added to one of the previous follow-up protocols (BII recommendation).<sup>3,4</sup> When CIN 2-3 is identified at the endocervical margin or in the endocervical sampling obtained after the diagnostic excisional procedure, a repeat diagnostic excisional procedure is acceptable (AII recommendation).<sup>3,4</sup> Hysterectomy is acceptable when repeat diagnostic excision is not feasible (BII recommendation)<sup>3,4</sup> or for women with recurrent or persistent CIN 2-3 (BII recommendation).<sup>3,4</sup>

### Follow-Up After Treatment for Biopsy-Confirmed CIN 2-3: Special Circumstances

In compliant adolescents with histologic CIN 2, satisfactory colposcopy, and negative endocervical curettage, observation with colposcopy and cytology at four- to six-month intervals for one year is acceptable (BII recommendation).<sup>3</sup> Ablation or excision is required for adolescents with CIN 3 (BIII recommendation).<sup>3,4</sup>

### The Authors

MARK SPITZER, M.D., is professor of clinical obstetrics and gynecology at Weill Medical College of Cornell University, New York, and chairman of the Department of Obstetrics and Gynecology at New York Methodist Hospital, Brooklyn. He received his medical degree from Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, and completed a residency in obstetrics and gynecology at affiliated hospitals.

BARBARA S. APGAR, M.D., M.S., is clinical professor of family medicine at the University of Michigan Medical School, Ann Arbor. Dr. Apgar received her medical degree from Texas Tech University Health Sciences Center School of Medicine, Lubbock, where she also completed a family practice residency. She received a master's degree from the University of Michigan and completed a faculty development fellowship at Michigan State University College of Human Medicine, East Lansing. Dr. Apgar is an associate editor of *American Family Physician*.

GREGORY L. BROTZMAN, M.D., is professor of family and community medicine at the Medical College of Wisconsin in Milwaukee. Dr. Brotzman received his medical degree from Southern Illinois University School of Medicine, Springfield, where he completed a family practice residency.

Address correspondence to Mark Spitzer, M.D., Dept. of Obstetrics and Gynecology, New York Methodist Hospital, 506 Sixth St., Brooklyn, NY 11215 (e-mail: mas9096@nyp.org). Reprints are not available from the authors.

Author disclosure: Dr. Brotzman is on the speakers bureau for Digene Corp. and Merck & Co., Inc. Dr. Spitzer is on the speakers bureau for Quest Diagnostics and Merck & Co., Inc.

### REFERENCES

- Solomon D, Schiffman M, Tarone R; ALTS Study group. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93:293-9.
- Wright TC Jr, Cox JT, Massad LS, Twigg LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287:2120-9.
- Wright TC Jr, Cox JT, Massad LS, Carlson J, Twigg LB, Wilkinson EJ; American Society for Colposcopy and Cervical Pathology. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003;189:295-304.
- Wright TC Jr, Cox JT, Massad LS, Carlson J, Twigg LB, Wilkinson EJ. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *J Low Genit Tract Dis* 2003;7:154-67.
- Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. *JAMA* 2001;285:1500-5.
- Hopman EH, Voorhorst FJ, Kenemans P, Meyer CJ, Helmerhorst TJ. Observer agreement on interpreting colposcopic images of CIN. *Gynecol Oncol* 1995;58:206-9.
- Spitzer M, Chernys AE, Shifrin A, Ryskin M. Indications for cone biopsy: pathologic correlation. *Am J Obstet Gynecol* 1998;178:74-9.
- Massad LS, Halperin CJ, Bitterman P. Correlation between colposcopically directed biopsy and cervical loop excision. *Gynecol Oncol* 1996;60:400-3.
- Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;12:186-92.
- Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol* 1998;92:727-35.

## Cervical Abnormalities

- Cox JT, Schiffman M, Solomon D, 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;188:1406-12.
- Shafi MI, Luesley DM, Jordan JA, Dunn JA, Rollason TP, Yates M. Randomised trial of immediate versus deferred treatment strategies for the management of minor cervical cytological abnormalities. *Br J Obstet Gynaecol* 1997;104:590-4.
- Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. *Obstet Gynecol* 1986;67:665-9.
- Weaver MG, Abdul-Karim FW, Dale G, Sorensen K, Huang YT. Outcome in mild and moderate cervical dysplasias related to the presence of specific human papillomavirus types. *Mod Pathol* 1990;3:679-83.
- Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999;281:1605-10.
- Wright TC, Sun XW, Koulos J. Comparison of management algorithms for the evaluation of women with low-grade cytologic abnormalities. *Obstet Gynecol* 1995;85:202-10.
- Guido R, Solomon D, Schiffman M, Burke L. Comparison of management strategies for women diagnosed as CIN 1 or less postcolposcopic evaluation: data from the ASCUS and LSIL Triage Study (ALTS), a multicenter randomized trial. *J Lower Gen Tract Dis* 2002;6:176.
- Nobbenhuis MA, Walboomers JM, Helmerhorst TJ, Rozendaal L, Remmink AJ, Risse EK, et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet* 1999;354:20-5.
- Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst* 1999;91:252-8.
- Brotzman G, Spitzer M, Apgar B. Colposcopy image library CD-ROM 2003. St. Louis: SABK Inc., 2003.
- Shafi MI, Luesley DM. Management of low-grade lesions: follow-up or treat? *Baillieres Clin Obstet Gynaecol* 1995;9:121-31.
- Mitchell MF, Tortolero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstet Gynecol* 1998;92:737-44.
- Nuovo J, Melnikow J, Willan AR, Chan BK. Treatment outcomes for squamous intraepithelial lesions. *Int J Gynaecol Obstet* 2000;68:25-33.
- Giacalone PL, Laffargue F, Aligier N, Roger P, Combecal J, Daures JP. Randomized study comparing two techniques of conization: cold knife versus loop excision. *Gynecol Oncol* 1999;75:356-60.
- Mitchell MF, Tortolero-Luna G, Wright T, Sarkar A, Richards-Kortum R, Hong WK, et al. Cervical human papillomavirus infection and intraepithelial neoplasia: a review. *J Natl Cancer Inst Monogr* 1996;21:17-25.
- Wright TC Jr, Gagnon S, Richart RM, Ferenczy A. Treatment of cervical intraepithelial neoplasia using the loop electrosurgical excision procedure. *Obstet Gynecol* 1992;79:173-8.
- Duggan BD, Felix JC, Muderspach LI, Gebhardt JA, Groshen S, Morrow CP, et al. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. *Am J Obstet Gynecol* 1999;180:276-82.
- Felix JC, Muderspach LI, Duggan BD, Roman LD. The significance of positive margins in loop electrosurgical cone biopsies. *Obstet Gynecol* 1994;84:996-1000.
- Gardeil F, Barry-Walsh C, Prendiville W, Clinch J, Turner MJ. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstet Gynecol* 1997;89:419-22.
- Spitzer M, Chernys AE, Seltzer VL. The use of large loop excision of the transformation zone in an inner-city population. *Obstet Gynecol* 1993;82:731-5.
- Economos K, Perez Veridiano N, Delke I, Collado ML, Tancer ML. Abnormal cervical cytology in pregnancy: a 17-year experience. *Obstet Gynecol* 1993;81:915-8.
- Yost NP, Santoso JT, McIntire DD, Iliya FA. Postpartum regression rates of antepartum cervical intraepithelial neoplasia II and III lesions. *Obstet Gynecol* 1999;93:359-62.
- Connor JP. Noninvasive cervical cancer complicating pregnancy. *Obstet Gynecol Clin North Am* 1998;25:331-42.
- Robinson WR, Webb S, Tirpack J, Degefu S, O'Quinn AG. Management of cervical intraepithelial neoplasia during pregnancy with LOOP excision. *Gynecol Oncol* 1997;64:153-5.
- National Cancer Institute. Surveillance, epidemiology, and end results (SEER). Accessed online Aug. 3, 2005, at: <http://seer.cancer.gov>.
- American College of Obstetricians and Gynecologists 50th anniversary meeting. April 28-May 2, 2001. Chicago, Illinois, USA. Abstracts. *Obstet Gynecol* 2001;97(suppl 4):1S-90S.
- Holcomb K, Matthews RP, Chapman JE, Abulafia O, Lee YC, Borges A, et al. The efficacy of cervical conization in the treatment of cervical intraepithelial neoplasia in HIV-positive women. *Gynecol Oncol* 1999;74:428-31.
- Lopes A, Mor-Yosef S, Pearson S, Ireland D, Monaghan JM. Is routine colposcopic assessment necessary following laser ablation of cervical intraepithelial neoplasia? *Br J Obstet Gynaecol* 1990;97:175-7.
- Paraskevaides E, Kitchener H, Adonakis G, Parkin D, Lolis D. Incomplete excision of CIN in conization: further excision or conservative management? *Eur J Obstet Gynecol Reprod Biol* 1994;53:45-7.
- Strand A, Wilander E, Zehbe I, Rylander E. High risk HPV persists after treatment of genital papillomavirus infection but not after treatment of cervical intraepithelial neoplasia. *Acta Obstet Gynecol Scand* 1997;76:140-4.
- Jain S, Tseng CJ, Horng SG, Soong YK, Pao CC. Negative predictive value of human papillomavirus test following conization of the cervix uteri. *Gynecol Oncol* 2001;82:177-80.
- Nagai Y, Maehama T, Asato T, Kanazawa K. Persistence of human papillomavirus infection after therapeutic conization for CIN 3: is it an alarm for disease recurrence? *Gynecol Oncol* 2000;79:294-9.
- Brown JV, Peters WA, Corwin DJ. Invasive carcinoma after cone biopsy for cervical intraepithelial neoplasia. *Gynecol Oncol* 1991;40:25-8.