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Management of Abnormal Cervical Cytology and Histology

Recent evidence has shown that the risk of malignant and premalignant cervical disease and human papillomavirus (HPV) infections varies significantly with age (1, 2). Furthermore, evidence now shows that treatment for cervical disease carries significant risk for future pregnancies (3–7). These factors have led to a re-evaluation of the guidelines for the management of premalignant cervical disease. The purpose of this document is to define strategies for diagnosis and management of abnormal cervical cytology and histology results. In this document, HPV refers to high-risk oncogenic forms of the virus.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Mark Spitzer, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

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Background

Cytology and Histology Findings and Interpretation

The 2001 Bethesda System terminology (see box) is used throughout this document to describe the categories of epithelial cell abnormalities, including atypical squamous cells (ASC), low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL), and glandular cell abnormalities, including atypical glandular cells (AGC) and adenocarcinoma in situ (AIS). Histology diagnoses of abnormalities are reported as cervical intraepithelial neoplasia (CIN) grades 1–3 (8).

The key to developing effective guidelines for the management of cervical abnormalities is to distinguish true cervical cancer precursors from benign cervical abnormalities with little premalignant potential. Both LSIL and CIN 1 reflect the cytologic and pathologic effects of infection with HPV. Most of these lesions will never progress to cancer. However, as many as 28% of women with cytologic LSIL harbor CIN 2 or CIN 3, approximately two thirds of which is identified by colposcopy (9). Cervical intraepithelial neoplasia grade 3 and AIS

The 2001 Bethesda System Terminology

Squamous Cell

- Atypical squamous cells
  - Of undetermined significance
  - Cannot exclude high-grade squamous intraepithelial lesions
- Low-grade squamous intraepithelial lesions—encompassing human papillomavirus, mild dysplasia, and CIN 1
- High-grade squamous intraepithelial lesions—encompassing moderate and severe dysplasia, carcinoma in situ, CIN 2, and CIN 3
- Squamous cell carcinoma

Glandular Cell

- Atypical glandular cells (specify endocervical, endometrial, or not otherwise specified)
- Atypical glandular cells, favors neoplasia (specify endocervical or not otherwise specified)
- Endocervical adenocarcinoma in situ
- Adenocarcinoma

Abbreviation: CIN indicates cervical intraepithelial neoplasia.

Modified from Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. Forum Group Members; Bethesda 2001 Workshop. JAMA 2002;287:2114–9.

are cervical cancer precursors (10). Cervical intraepithelial neoplasia grade 2 lesions are more heterogeneous, and their significance is less clear than that of CIN 3. The reproducibility of a diagnosis of CIN 2 is poor, and many women will have either CIN 1 or CIN 3 (11). Cervical intraepithelial neoplasia grade 2 is more likely to progress to CIN 3 and cancer than CIN 1. However, many CIN 2 lesions will regress without therapy. Many pathologists do not attempt to distinguish between CIN 2 and CIN 3, instead reporting a composite diagnosis of CIN 2,3 or high-grade CIN (CIN 2,3+).

The guidelines discussed in this document follow the 2006 consensus guidelines published by the American Society for Colposcopy and Cervical Pathology (12, 13). These guidelines recognized that a small risk of failing to detect high-grade CIN and even cancer must be accepted. It is unreasonable for patients or clinicians to expect that the risk can be reduced to zero, and attempts to achieve zero risk will result in greater harm than good in the form of overtreatment. When providing care for an individual patient, guidelines define the evidence base for most cases but are not a substitute for clinical judgment because it is impossible to develop guidelines that would apply to all situations (12, 13). Newer data show that cervical treatments, such as ablation or excisional procedures, may have adverse effects on pregnancy, including preterm delivery and low birth weight (7, 14); thus, risk–benefit assessment sometimes favors observation of CIN 2, especially among younger women (12).

Finally, there is increasing recognition that colposcopy is less sensitive than previously thought. A single colposcopy examination in women with positive low-grade cytology results identified only 60% of women with CIN 2,3 lesions and 54% of women with CIN 3 lesions who received their diagnoses within 2 years of study enrollment (9). Some lesions with metaplastic or low-grade features contain CIN 2,3, whereas some lesions with high-grade features contain CIN 1, condylomatous changes, or atypical metaplasia. Recent studies suggest that the correlation between colposcopy impression and biopsy grade is poor (15–17). The sensitivity of colposcopy is significantly greater when two or more biopsy specimens are obtained (18).

Natural History of Cervical Intraepithelial Neoplasia

Carriage of HPV DNA is quite common in the general population, reported in one study to occur at least once over a 3-year period in 60% of young women (19). The lifetime cumulative risk is at least 80% (20). Most women clear the virus or suppress it to levels not associated with CIN 2,3+, and for most women this occurs promptly (21, 22). The duration of HPV positivity is shorter and the likelihood of clearance is higher in younger women (23–25).

The presence of high-risk HPV is a marker for the risk of diagnosis of CIN 2,3+; only 1 in 10 to 1 in 30 HPV infections are associated with abnormal cervical cytology results (26–28), with an even smaller proportion associated with CIN 2,3+ (29). Among women with negative cytology test results and a positive HPV test result, only 15% will have abnormal cytology results within 5 years (30). However, high-risk HPV is necessary for the development and maintenance of CIN 3 (31). Persistent high-risk HPV is a necessary but not sufficient condition for the development of almost all types of invasive cervical cancer (32, 33). Conversely, the risk of cervical cancer in women who do not harbor oncogenic HPV is extremely low (34). The longer high-risk HPV is present and the older the patient, the greater the risk of CIN (35). When HPV is present, smoking doubles the risk of progression to CIN 3 (36).

From a clinical perspective, it is important to distinguish which intraepithelial neoplastic lesions will progress to invasive cancer if left untreated. However,

the diagnostic categories currently available have only modest predictive value, and that value decreases as the lesions become less severe. The likelihood of progression to cancer is higher and the time to progression is shorter as the grade of dysplasia increases (37). Although expression of the presence of HPV as CIN can occur within months of viral acquisition (10), the time course from CIN 3 to invasive cancer averages between 8.1 years and 12.6 years (9, 38, 39). The slow pace of these changes in immunocompetent women means that accurate estimates of progression risk require long follow-up periods. Perhaps more relevant for clinical practice are estimates of regression to normal status. A review of the literature from 1950 to 1992 noted the likelihood of regression to be 60% for CIN 1 and 40% for CIN 2 (40, 41).

Cervical Cytology

Cervical cytology screening programs are associated with a reduction in the incidence of and mortality from invasive squamous cancer. Conventional cytology is reported to be 30–87% sensitive for dysplasia (42). A meta-analysis of conventional cervical cytology studies suggested a sensitivity of 58% when used for population screening (43). Another meta-analysis comparing the performance of ThinPrep® liquid-based cervical cytology screening with conventional cytology screening methods found sensitivity rates, relative to histology, were 68% (conventional) and 76% (ThinPrep®), and specificity rates were 79% (conventional) and 86% (ThinPrep®) (44).

Because the range of sensitivity (30–87%) is so broad, all abnormal cytology results must be evaluated, although the vast majority of results do not represent underlying CIN 2,3+ (25). Reproducibility among observers and among multiple readings by the same observer is quite modest, even under optimal research conditions (45–48). In the ASC-US LSIL Triage Study (ALTS), the quality control reviewer at the National Cancer Institute and the university-based cytopathologist at the study site agreed on an ASC result in 43% of 1,473 cases, on an LSIL result in 68% of 1,335 cases, and on an HSIL result in 47% of 433 cases (45).

Human Papillomavirus Testing

Testing for low-risk HPV types has no role in cervical cancer prevention. Low-risk HPV types are associated with genital warts and with some low-grade intraepithelial lesions of the cervix, vagina, and vulva (49).

For women 30 years and older, high-risk HPV testing can help predict whether CIN 2,3+ will be diagnosed in the next few years despite a normal cytology result (10, 21, 50–52). As new tests are introduced, decisions about clinical practice implementation must be based on clinical sensitivity (relationship of the test result to CIN 2,3+), not analytic sensitivity (ability of the test to detect low levels of HPV).

Human papillomavirus DNA positivity is much more prevalent in women aged 18–22 years (71%) versus those older than 29 years (31%) (88). In the algorithms used in the management of abnormal cervical cytology results or CIN, persistent HPV positivity is used as evidence of persistent HPV infection and, therefore, a marker of disease. However, many adolescents experience multiple sequential HPV infections, so a repetitively positive HPV DNA test in this age group may represent consecutive incident infections rather than a single persistent infection. Consequently, HPV testing should not be used in this age group and if inadvertently performed, a positive result should not influence management.

Colposcopy With and Without Directed Biopsy

Colposcopy with directed biopsy has been the criterion of disease detection and remains the technique of choice for treatment decisions. Evaluation of colposcopy sensitivity has, until recently, focused on populations with identified lesions sufficient to produce abnormal cytology.

Some recent studies have used colposcopy with endocervical curettage and blind four-quadrant ectocervical biopsies or loop electrosurgical excision procedure (LEEP) as the diagnostic criteria (38, 53). This approach permits a more realistic evaluation of the sensitivity of colposcopy with directed biopsy. The presence of CIN 2,3+ was missed on directed biopsy but detected on the random four-quadrant biopsies in 18.6–31.6% of CIN 2,3+ cases (53, 54). These figures may underestimate the prevalence of CIN 2,3+ not diagnosed on colposcopy-directed biopsy because excisions were not performed in the entire population—many women had normal screening test results. Comparing directed biopsy to conization also demonstrates a significant rate of underdiagnosis of CIN 2 and CIN 3 (55, 56).

Similar conclusions are reported in ALTS. Women with a previous LSIL or ASC-US HPV-positive test result and a CIN 1 biopsy were offered LEEP after 2 years of follow-up (38). Of the 189 women with CIN 2,3+ diagnosed during the 2-year study in the "immediate colposcopy" arm of the trial, only 106 (56%) women received the diagnoses on the initial colposcopy. The other cases were identified after HSIL cytology, an exit colposcopy, or LEEP.

Results of these studies indicate that biopsies of all visible lesions are warranted, regardless of colposcopy

impression, and that follow-up should include multiple colposcopy examinations over time for those women with abnormal cytology or histology results who have persistent low-grade abnormalities or persistently test positive for HPV.

Endocervical Sampling

Endocervical sampling may be conducted either with vigorous endocervical brushing or by traditional endocervical curettage with a sharp curette. Compared with curettage, the brush technique is at least as sensitive for endocervical dysplasia (57–61) and returns fewer reports of insufficient specimens (60, 61). The disadvantage is that the result can be equivocal, such as ASC, in which case the patient must be recalled for sharp curettage.

Endocervical sampling is not indicated in the pregnant patient. The following discussion of indications applies to the nonpregnant patient. In the evaluation of an ASC or LSIL cytology result with a satisfactory colposcopy result, endocervical sampling may be considered, although the identification of cancer cases is low (62, 63). Sampling should be performed if colposcopy results are unsatisfactory (64, 65) or if ablative treatment, such as cryotherapy or laser ablation, is contemplated. Higher rates of postablation CIN 2 or CIN 3 and cancer have been reported if pretreatment endocervical assessment is not done (66). Studies of the contribution of endocervical curettage to diagnosis of CIN 2,3+ at colposcopy suggest that its addition to directed biopsy may be expected to add 5–9% to the total number of CIN 2,3+ diagnoses (65, 67–69). This percentage becomes more important as the risk of CIN 2,3+ increases with higher-grade abnormal cytology results. As a consequence, in women with ASC-H, HSIL, AGC, or AIS cytology results, endocervical sampling should be considered as part of the initial colposcopy evaluation (70), unless excision is planned. If an excision is planned, endocervical sampling may be omitted (64), although it may be performed at the time of the procedure after the excision to assess the completeness of the procedure.

Clinical Considerations and Recommendations

▶ ***When the results of cervical cytology screening are normal but a concurrent HPV test result is positive, what is the appropriate follow-up?***

The best management approach for HPV-positive, cytology-negative women 30 years and older is to repeat cytology and HPV testing at 12 months (Figure 1). Women whose HPV result is still positive on repeat testing 12 months later or whose cytology result is ASC or greater should undergo colposcopy, whereas women

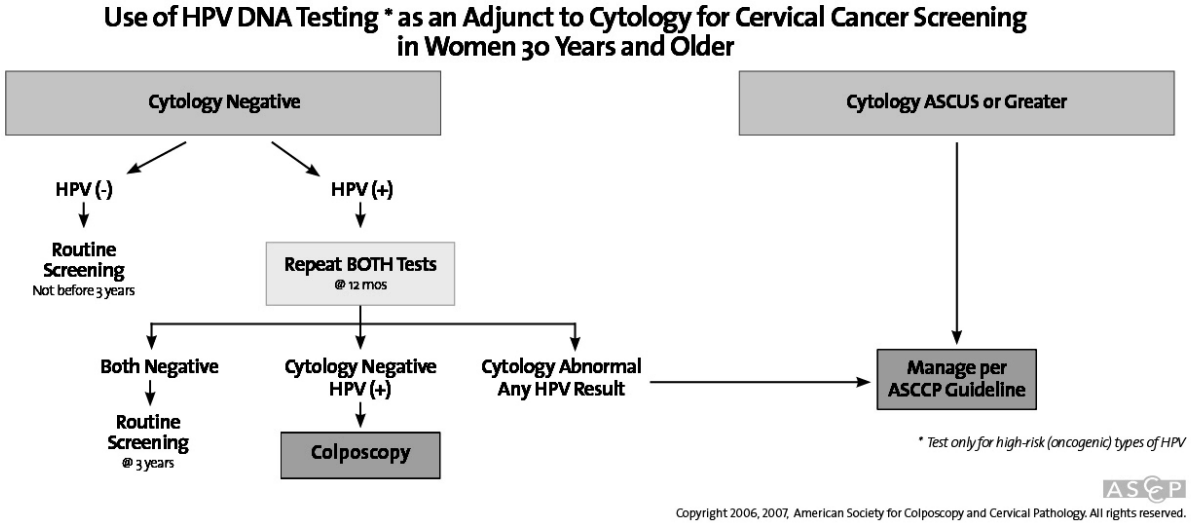

Figure 1. Use of HPV DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years and older. Abbreviations: ASCCP indicates American Society for Colposcopy and Cervical Cytology; ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007; 11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

whose results are negative on both tests can defer screening for 3 years. Incorporating HPV testing into routine screening should be reserved for women aged 30 years and older (71, 72). In screening studies from North America and Europe, the sensitivity using a combination of HPV testing and cytology is significantly higher than that of either test alone with negative predictive values of 99–100% (73). Women who receive negative results from both initial cytology and HPV testing have a less than 1 in 1,000 risk of having CIN 2 or greater (CIN 2+), and prospective follow-up studies in both Europe and the United States have shown that the risk of developing CIN 3 over a 10-year period is less than 2% (71, 74, 75). Modeling studies demonstrate that in women 30 years and older, screening at 3-year intervals using a combination of cytology and HPV testing provides benefits equivalent or greater than those provided by annual screening with conventional cytology (76). Even in women 30 years and older, most HPV-positive women become HPV negative during follow-up (60% in a prospective study from France after a median follow-up of 6 months) (48). In a well-screened population, the risk of CIN 2+ in HPV-positive, cytology-negative women ranges from 2.4% to 5.1% (53, 77, 78).

▶ ***When the results of cervical cytology are reported as atypical squamous cell of undetermined significance, how should they be managed?***

In the Bethesda 2001guidelines, ASC is subcategorized into atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells, cannot exclude HSIL (ASC-H). The difference in the management guidelines for these two cytology findings relates to their inherent risk of CIN 2,3. Atypical squamous cells of undetermined significance is the most common cervical cytology abnormality, accounting for 4.4% of all Pap test results. Although the risk of cancer for any individual patient is very low (0.1–0.2%) (79, 80), and the risk of CIN 2,3+ also is low (6.4–11.9%) (38, 81, 82), because there are so many people with this cytology abnormality, it is the presenting cytology result for approximately one half of the women with CIN 2,3+. The first step in the evaluation of women with ASC-US is to triage those who are at higher risk to more intensive evaluation (colposcopy) and directing the rest to more routine follow-up. Premenopausal women 21 years and older with ASC-US cytology results may undergo immediate colposcopy or may undergo triage testing to determine whether they should be referred to colposcopy. Triage testing may be performed by a single test for high-risk (oncogenic) types of HPV or by repeat cytology screening at 6 months and 12 months. When the index cytology test specimen is obtained by liquid-based cytology or when an HPV specimen is co-collected, "reflex" HPV testing is the preferred approach (Figure 2). Data from ALTS demonstrated that two repeat cytology examinations at 6 months and 12 months at an

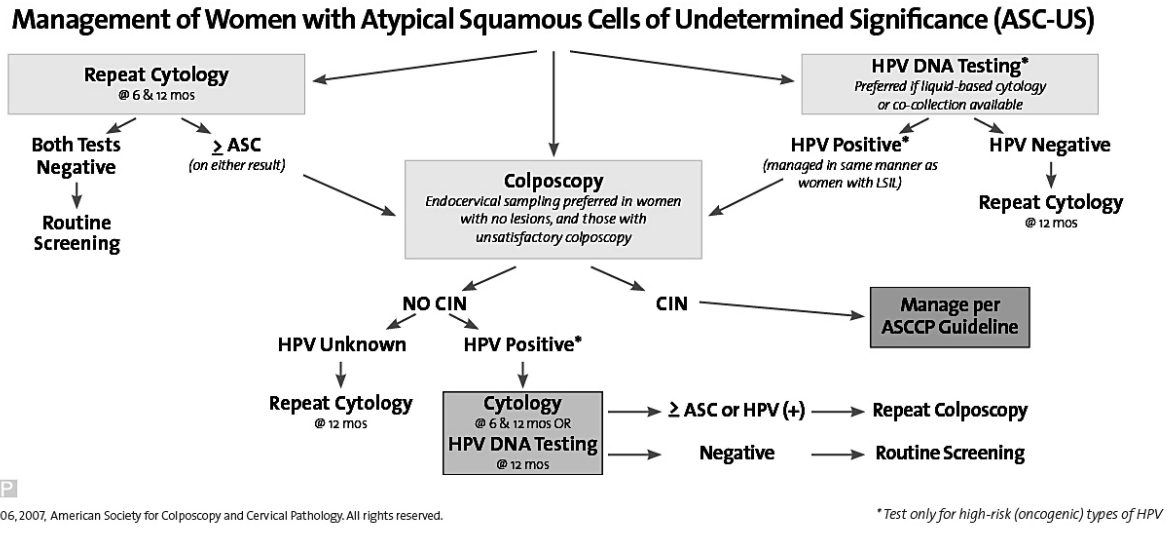

Figure 2. Management of women with atypical squamous cells of undetermined significance (ASC-US). Abbreviations: ASC indicates atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Cytology; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

ASC-US threshold detected 88% of the CIN 2,3+ while referring 63.6% of the women to colposcopy. Human papillomavirus testing alone detected 92.2% of the CIN 2,3+ while referring 55% of the women to colposcopy.

The presence of ASC-US is less common in postmenopausal women, as is the risk of significant pathologic results (2, 83, 84). Human papillomavirus DNA positivity rates also decrease dramatically as women age (85, 86). This means that HPV testing actually is more efficient in older women because it refers a lower proportion of these women to colposcopy (87–89). The prevalence of CIN 2,3 is much higher among women with ASC-H than women with ASC-US, so ASC-H should be considered to represent equivocal HSIL.

▶ *What is the management of ASC-US for women 20 years or younger?*

Invasive cervical cancer is very rare in adolescent women before age 21 years. The National Cancer Institute's SEER program reported that from 1995 to 1999 the incidence rate of invasive cervical cancer was 0 per 100,000 per year for women aged 10–19 years and 1.7 per 100,000 per year for women aged 20–24 years (1). In contrast, minor grade cytology abnormalities (ASC and LSIL) are more common in women aged 15–19 years than in older women (2), and these HPV-associated abnormalities are of little long-term clinical significance (90). Human papillomavirus DNA positivity is much more prevalent in women aged 18–22 years (71%) than those older than 29 years (31%) (85). Thus, using HPV DNA testing to triage adolescents and young women with ASC-US would refer large numbers of women to colposcopy who are at low risk for having cervical cancer. Also, many adolescents experience multiple sequential HPV infections, so a repetitively positive HPV DNA test in this age group may represent consecutive incident infections rather than a single persistent infection. In adolescents with ASC-US, follow-up with annual cytology testing is recommended. Human papillomavirus DNA testing and colposcopy are unacceptable for adolescents with ASC-US, and if HPV testing is inadvertently performed, a positive test result should not influence management. Also, in adolescents, the threshold for referral to colposcopy is different than in adult women (Figure 3). At the 12-month follow-up visit, only the patients with the diagnosis of HSIL or greater on the repeat cytology should be referred to colposcopy. At the 24-month follow-up, the patients with a diagnosis of ASC-US or greater should be referred to colposcopy (Figure 3).

▶ *When the results of cervical cytology are reported as atypical squamous cells, cannot exclude HSIL (ASC-H), how should they be managed?*

Women with ASC-H have a 20–50% risk of having a CIN 2,3 lesion and should be evaluated with immediate colposcopy (Figure 4). Most women with ASC-H are

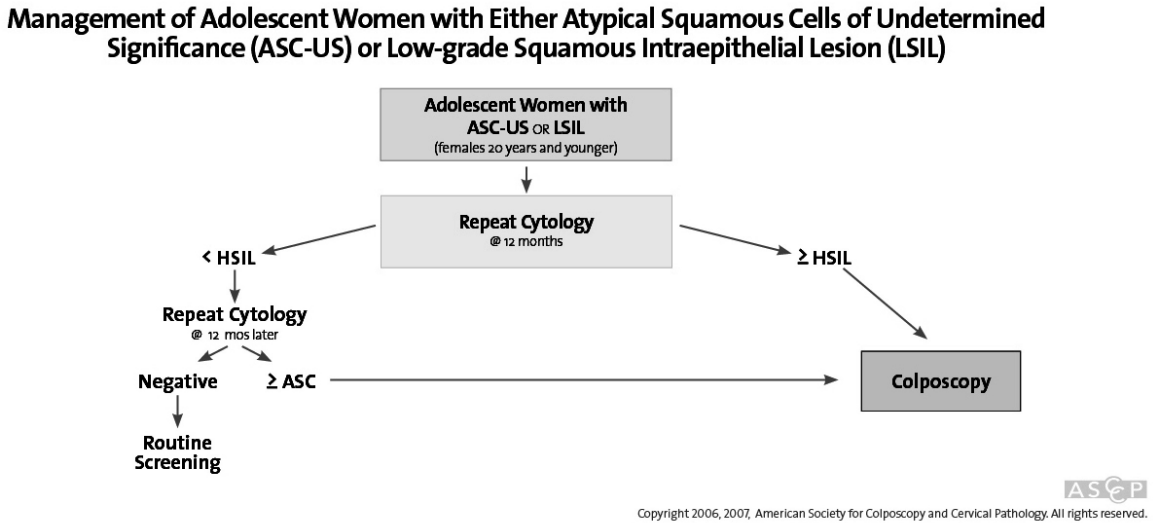

Figure 3. Management of adolescent women with either atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL). Abbreviations: ASC indicates atypical squamous cells; ASC-US; atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

HPV DNA positive (ranging from 67–84%) (91–93), so intermediate triage is inappropriate and HPV testing is not recommended. If CIN 2,3 is not identified by colposcopy, women aged 21 years and older should be monitored in a manner similar to HPV-positive women with ASC-US.

▶ *When the results of cervical cytology are reported as LSIL or ASC-US with HPV positive results, how should they be managed in patient 21 years and older?*

Although a cytology result of LSIL is thought to reflect the cytopathic effects of HPV infection rather than a true premalignant lesion, women with LSIL remain at moderate risk for having CIN 2+. In ALTS, 27.6% of women with LSIL were found to have CIN 2+ either on colposcopically directed biopsies or on close follow-up over the next 2 years (9). This rate is virtually identical to the rate of CIN 2+ in women who presented with HPV-positive ASC-US results in the same population (26.7%). Two thirds of the cases (17.9%) were identified on the initial colposcopy and the remainder at follow-up. Therefore, colposcopy is recommended in premenopausal women aged 21 years and older with ASC-US who are HPV positive, or have two consecutive ASC-US cytology results (Figure 2), or have LSIL (Figure 5).

Many studies have shown that the prevalence of both HPV DNA positivity and CIN 2,3 decreases with age in women with LSIL (94, 95). Well-screened, postmenopausal women with previously negative results are likewise at low risk for invasive cervical cancer (96). This suggests that postmenopausal women with LSIL may be managed using HPV testing for triage in the same protocol as is used in reproductive-aged women with ASC-US.

▶ *When the results of colposcopy performed for the evaluation of ASC-US, ASC-H, or LSIL reveal no CIN 2,3, how should the patient's condition be managed?*

Because a single colposcopy examination can miss significant lesions, women who are referred for colposcopy and found not to have CIN 2,3 require some form of additional follow-up. In ALTS, the initial colposcopy identified only 58% of the CIN 2+ lesions. For the women not found to have CIN 2+ at the initial colposcopy, the rate of CIN 2+ during follow-up (approximately 10–13%) was unaffected by the findings at colposcopy (negative findings not worthy of biopsy, negative biopsy, or CIN 1 biopsy). The ASC-US–LSIL Triage Study evaluated different postcolposcopy follow-up strategies and found that HPV testing performed 12 months after the initial colposcopy and two repeat cytology examinations performed at 6-month intervals were equally effective (97). Because of the additional cost and lack of increased sensitivity, the strategy of

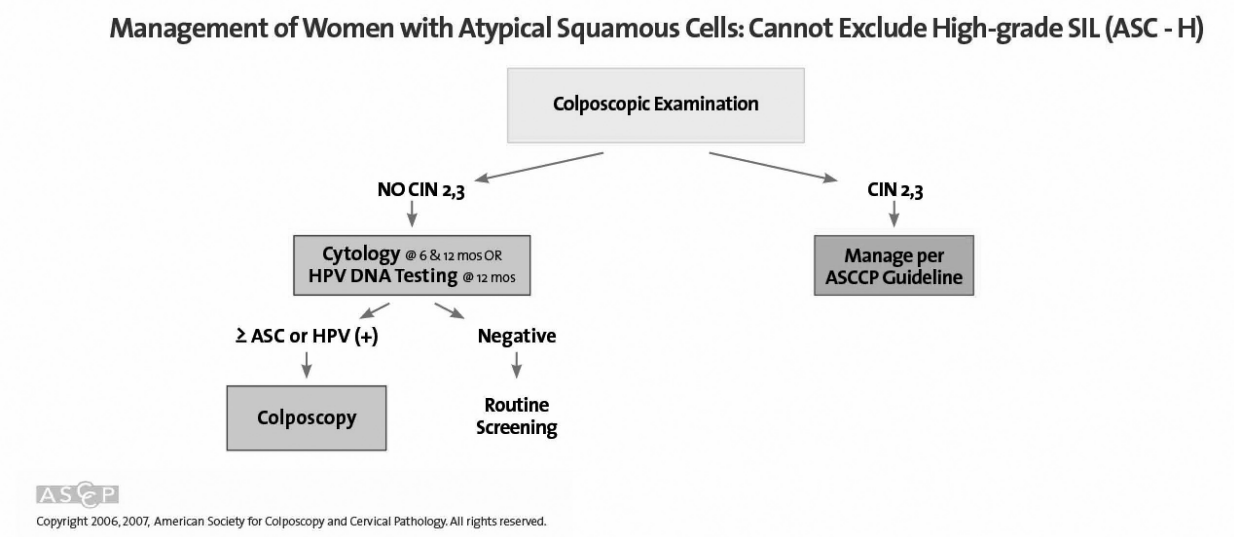

Figure 4. Management of women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H). Abbreviations: ASC indicates atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-H, atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; DNA deoxyribonucleic acid; HPV, human papillomavirus; SIL, squamous intraepithelial lesion. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

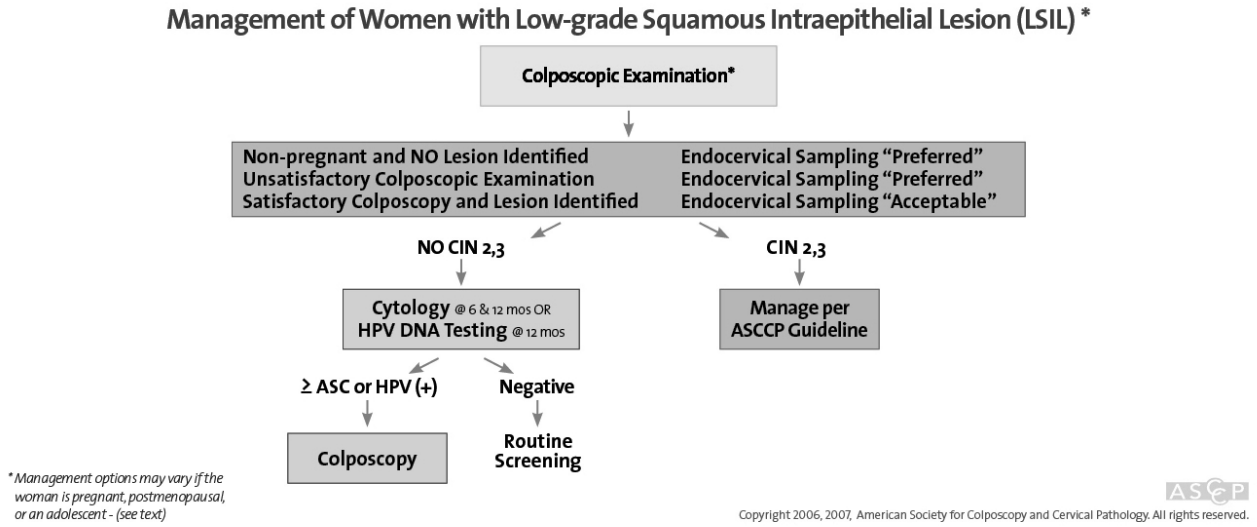

Figure 5. Management of women with low-grade squamous intraepithelial lesion (LSIL). Abbreviations: ASC indicates atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

combined cytology plus HPV testing was discouraged. In the absence of CIN identified histologically, diagnostic excisional or ablative procedures are unacceptable for the initial management of patients with LSIL. Follow-up with either HPV testing at 12 months or cervical cytology at 6 months and 12 months (ASC-US threshold) is acceptable. If the HPV DNA test result is negative or if two consecutive repeat cytology test results are negative, return to routine screening is recommended. If either the HPV DNA test result is positive or if the result of repeat cytology is reported as ASC-US or greater, colposcopy is recommended (Figures 2, 4, and 5).

▶ *When the results of cervical cytology tests are reported as HSIL, how should these be managed in the adult patient?*

The mean reporting rate of HSIL in U.S. laboratories is 0.7% (98). The rate of HSIL varies with age. A cytology result of HSIL carries a high risk of significant cervical disease. A single colposcopy examination identifies CIN 2+ in 53–66% of women with HSIL, and CIN 2+ is diagnosed in 84–97% of women evaluated with LEEP (96, 99, 100). Traditionally, the management of HSIL cytology results has relied on the colposcopy identification of high-grade CIN, followed by treatment when lesions are found (101). This strategy has proved to be highly successful in reducing cervical cancer rates in developed countries. Because colposcopy can miss a significant number of CIN 2,3 lesions and most women with HSIL will eventually undergo a diagnostic excisional procedure, a single-visit strategy (see and treat) is attractive in women in whom future fertility is not an issue (Figure 6). This strategy has been shown to be feasible and cost-effective (102–105). A diagnostic excisional procedure also is recommended for women with HSIL in whom the colposcopy examination is unsatisfactory, except in pregnant women. Because of the limited accuracy of colposcopy generally and of colposcopy grading particularly, colposcopy assessment is no longer required before immediate LEEP. Nevertheless, prudence would suggest that colposcopy is helpful to tailor the excision to the size of the lesion and the limits of the transformation zone.

Some CIN 2,3 lesions will regress spontaneously, especially in adolescents and young adults (11, 106). Therefore, in younger women in whom future fertility is an issue, colposcopy evaluation with endocervical assessment is more appropriate for initial evaluation (90, 107, 108).

▶ *When the initial evaluation of an HSIL cytology result is a diagnosis of CIN 1 or less, how should this condition be managed in the adult patient?*

An important consideration before treatment should be whether the high-grade cytology result is due to a vaginal lesion. Careful examination of the vagina using both 3–5% acetic acid and Lugol's solution may reveal a high-grade vaginal lesion. In such a case, although the cervix has no lesion, the cytology result is correctly pos-

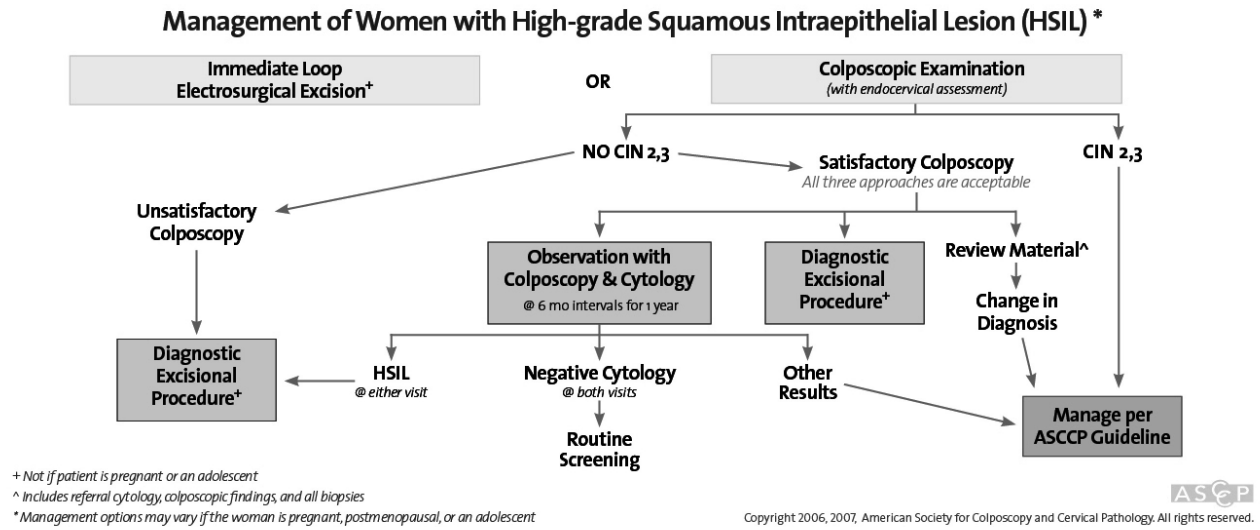

Figure 6. Management of women with high-grade squamous intraepithelial lesion (HSIL). Abbreviations: ASCCP indicates American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

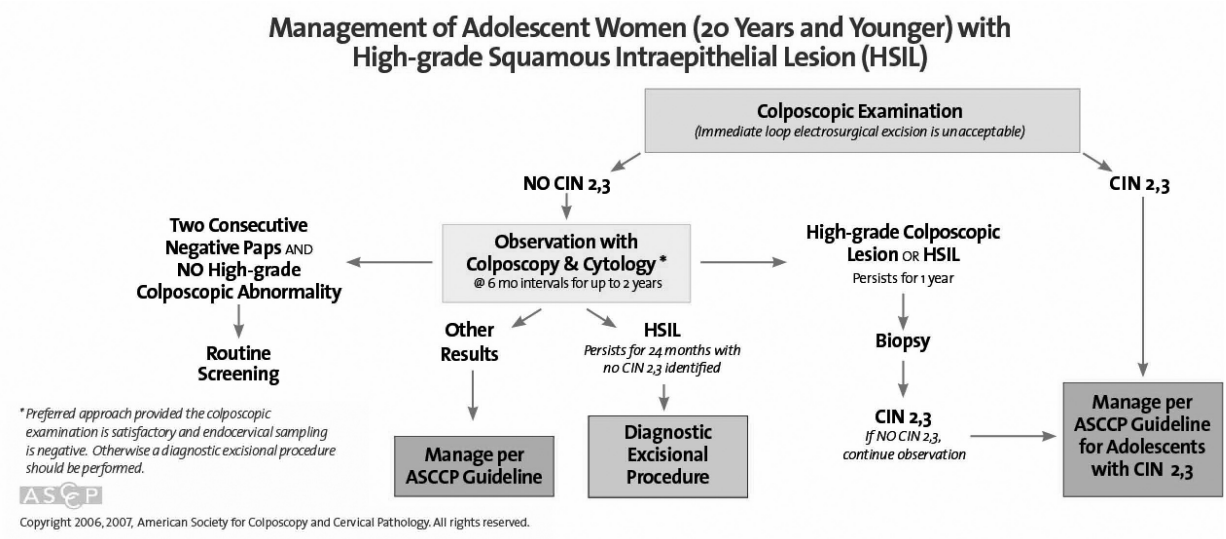

Figure 7. Management of adolescent women (20 years and younger) with high-grade squamous intraepithelial lesion (HSIL). Abbreviations: ASCCP indicates American Society for Colposcopy and Cervicccal Pathology; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

itive, and the patient's disease can be cleared with appropriate therapy. Application of Lugol's solution to the cervix also may identify high-grade lesions not previously appreciated. However, the sensitivity of colposcopy is limited, and these women may harbor an unsuspected high-grade cervical lesion. A British study found that 44% of women with negative evaluations after moderate or severe dyskaryosis (HSIL) had CIN found during follow-up (109), whereas a Swedish study found that 22% of women with an HSIL cytology result had CIN during follow-up after negative colposcopy result (110). Women with an HSIL cytology result remain at significant risk for high-grade CIN not evident on their colposcopy or biopsy. However, the predictive value of

an HSIL cytology result is limited, and some women with HSIL have CIN 1, subclinical HPV infections without colposcopically visible lesions, or even no disease. Finally, cytology interpretation is subjective, and women with HSIL diagnoses may not have HSIL. In a study of the reproducibility of cervical cytology, 27% of women with HSIL were found to have LSIL on review of their slides, whereas 23% had ASC-US, and 3% had negative results (45). Therefore, both the possibility of missed disease and the potential for overtreatment must be considered, and the management must be individualized based on the patient's needs. When CIN 2,3 is not identified histologically, either a diagnostic excisional procedure or observation with colposcopy and cytology at 6 months and 12 months is acceptable, provided in the latter case that the colposcopy examination is satisfactory and endocervical sampling is negative. A diagnostic excisional procedure is more appropriate in women not concerned about future fertility. However, because of the potential effect that treatment for cervical disease may have on future fertility and the possibility that these women may not have CIN 2,3, and that some CIN 2,3 lesions spontaneously regress, especially in adolescents and young adults (11, 106), the option of watchful waiting was added in the 2006 consensus guidelines. In this circumstance it also is acceptable to review the cytology, histology, and colposcopy findings; if the review yields a revised interpretation, management should follow consensus guidelines for the revised interpretation. If observation with cytology and colposcopy is elected, a diagnostic excisional procedure is recommended for women with the results of HSIL on repeat cytology at either the 6-month or 12-month visit. After 1 year of observation, women with two consecutive negative cytology results can return to routine screening. Ablation is unacceptable when CIN 2,3 is not identified histologically or the endocervical assessment identifies CIN of any grade (Figure 6).

▶ *When the results of cervical cytology tests are reported as HSIL in an adolescent (before age 21 years), how should they be managed?*

Because the likelihood of cancer in adolescents is quite small and the window of opportunity for identifying persistent high-grade cancer precursors is consequently longer, immediate excision is inappropriate, and colposcopy with biopsy of visible lesions is the recommended initial management for all adolescents and young women with HSIL cytology (Figure 7). In the 2006 consensus guidelines, the definition of young women was left deliberately vague but among the factors that should be taken into consideration in applying this definition are the number of years since first intercourse and the woman's parity and desire for future fertility. When the colposcopy results are satisfactory, the endocervical sampling is negative and no lesion is identified, or when biopsies show either CIN 1 or no neoplasia, serial Pap testing and colposcopy at 6-month intervals for as long as 2 years are advised. If both Pap test results and colposcopy results are negative at two consecutive visits, then routine annual assessment can resume. Diagnostic excision is recommended when colposcopy results are unsatisfactory or when endocervical sampling yields CIN, but this should be unusual in young women. If during follow-up a high-grade colposcopy lesion is identified or a HSIL cytology result persists for 1 year, biopsy is recommended. However, if HSIL cytology result persists for 2 years, then a diagnostic excisional procedure is recommended. After two consecutive negative Pap test results, adolescents and young women without a high-grade colposcopy abnormality can return to routine screening.

▶ *When the results of cervical cytology tests are reported as AGC or AIS, how should they be managed?*

The results of AGC are relatively uncommon, with a mean reporting rate of only 0.4% in the United States in 2003 (98). Although AGC is frequently caused by benign conditions, such as reactive changes and polyps, it is sometimes associated with a significant underlying neoplasia, such as adenocarcinoma of the cervix, endometrium, ovary, or a fallopian tube. The risk associated with AGC is dramatically higher than that seen with ASC. The risk associated with glandular abnormalities increases as the description in the Bethesda classification system advances from AGC, not otherwise specified (NOS) to AGC, favors neoplasia and, finally, AIS. Recent series have reported that 9–38% of women with AGC have significant neoplasia (CIN 2,3, AIS, or cancer) and 3–17% have invasive cancer (111–113). The rate and type of significant findings in women with AGC varies with age (112). Women younger than 35 years with AGC are more likely to have CIN and less likely to have cancer, whereas in older women the risk of glandular lesions, including malignancies, is higher (111). Human papillomavirus testing, cervical cytology, and colposcopy are all suboptimal at detecting glandular disease (114, 115). Colposcopy with endocervical sampling is recommended for all women with all subcategories of AGC or AIS cytology results. In addition, endometrial sampling is recommended in women 35 years and older or in women younger than 35 years with clinical indications suggest-

ing a risk of neoplastic endometrial lesions (eg, unexplained vaginal bleeding, chronic anovulation, or atypical endometrial cells). In the latter case, colposcopy can be deferred until the results of the initial biopsies are known.

The 2006 consensus guidelines recommend HPV DNA testing at the time of colposcopy in women with atypical endocervical, endometrial, or glandular cells, NOS (Figure 8). Knowledge of the HPV status in these women who do not have CIN 2,3 or glandular neoplasia identified histologically will allow expedited triage. Women with a positive HPV result would have their cytology and HPV test repeated at 6 months, and those with a negative HPV result would receive repeat cytology at 12 months. Those with a positive HPV result or an abnormal cytology result would be referred to colposcopy, and those in whom both tests are negative can return to routine screening. In contrast, if the HPV status is unknown, cervical cytology testing should be repeated every 6 months until there are four consecutive negative test results before the woman can return to routine screening (12). Because the risk of neoplasia (including invasive cancer) is high in women with AGC, favors neoplasia, AIS, or repeat AGC and the sensitivity of available diagnostic tests is poor, diagnostic excisional procedures are recommended for these women. Human papillomavirus testing is not useful in managing these patients (Figure 9). It is recommended that the type of diagnostic excisional procedure used in this setting provides an intact specimen with interpretable margins (12). In pregnant women, the initial evaluation of AGC should be identical to that of nonpregnant women, except that endocervical curettage and endometrial biopsy are unacceptable.

▶ *What is the significance of endometrial cells found in cervical cytology?*

In premenopausal women, benign-appearing endometrial cells or the presence of endometrial stromal cells or histiocytes is rarely associated with significant pathology (116). However, approximately 0.5–1.8% of cervical cytology specimens from women 40 years and older will have endometrial cells (116), and in postmenopausal women they may be associated with significant endometrial pathology (117). Benign-appearing glandular cells derived from small accessory ducts, foci of benign adenosis, or prolapse of the fallopian tube into the vagina are sometimes seen in cytology specimens after total hysterectomy and have no clinical significance.

For asymptomatic premenopausal women with benign endometrial cells, endometrial stromal cells, or histiocytes, no further evaluation is recommended. For postmenopausal women with benign endometrial cells, endometrial assessment is recommended regardless of symptoms. For posthysterectomy patients with a cytology report of benign glandular cells, no further evaluation is recommended.

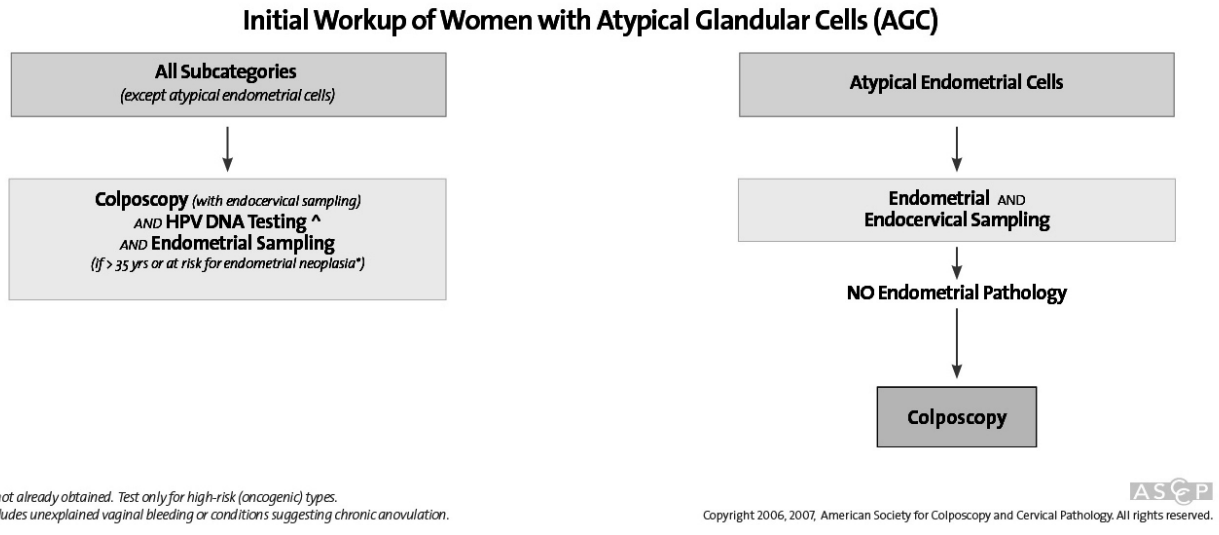

Figure 8. Initial workup of women with atypical glandular cells (AGC). Abbreviation: HPV indicates human papillomavirus. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

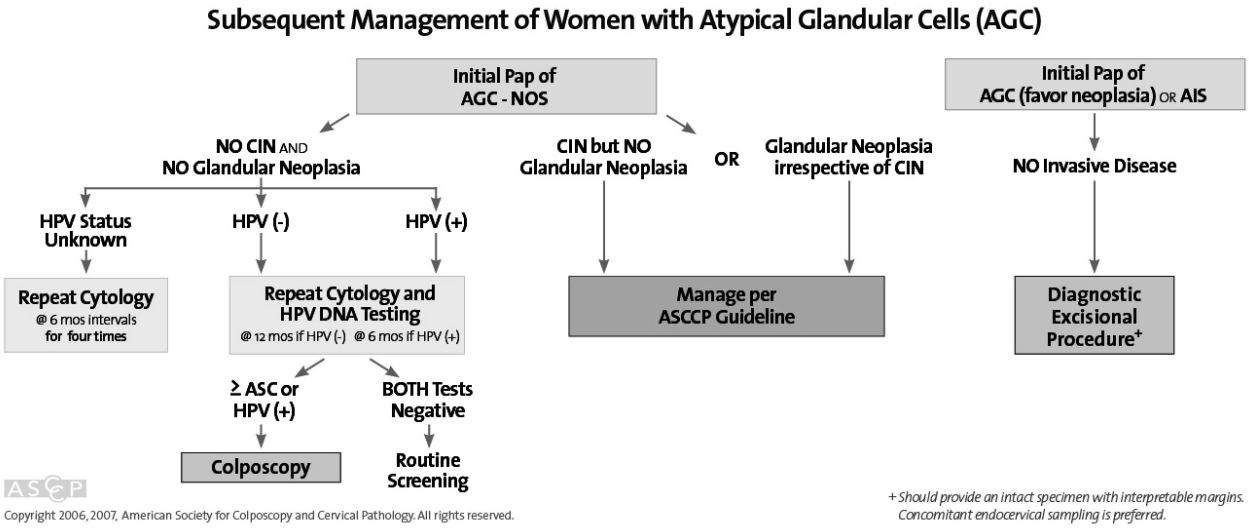

Figure 9. Subsequent management of women with atypical glandular cells (AGC). Abbreviations: AGC indicates atypical glandular cells; AGC-NOS, atypical glandular cells—not otherwise specified; AIS, adenocarcinoma in situ; ASC, atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

▶ *When should endocervical curettage be used in the colposcopy examination?*

The value of routine endocervical curettage (ECC) is controversial. Endocervical sampling is preferred for nonpregnant women in whom no lesions are identified, women with an unsatisfactory colposcopy, and women who have follow-up colposcopy after a conization for CIN 2,3 with a positive endocervical margin. Endocervical curettage is preferred in cases where the results are expected to change the patient's management. Endocervical curettage is especially valuable for women 40 years and older. An analysis of ALTS data showed that ECC identified an additional 2.2% of CIN 2+ in women younger than 40 years, whereas it increased the detection by 13% in women 40 years and older (128). Endocervical curettage is recommended in women with a glandular abnormality on cytology and those who have any abnormal cytology result or HPV test result after cervical treatment. This procedure is unacceptable in pregnant women. However, in nonpregnant women with a satisfactory colposcopy result, a positive ECC result is most likely due to contamination that incorrectly indicates the need for a deeper excisional procedure rather than an ablative procedure or a shallower excision. Endocervical curettage may be especially helpful in such patients if ablative therapy is planned but may not change the management if excisional therapy is planned (119).

▶ *If colposcopy is satisfactory and consistent with the results of cervical cytology, is biopsy necessary?*

Colposcopy assessment may assist the examiner in identifying appropriate biopsy sites, but colposcopy assessment is not sufficiently accurate to eliminate the need for one or more biopsy procedures. A meta-analysis comparing colposcopy impression to colposcopy biopsy reported an average 48% sensitivity of colposcopy impression for separation of CIN 2,3+ from other diagnoses (120). Use of colposcopy impression alone could have caused 18–60% of patients to be treated incorrectly. Recent data suggest that taking additional biopsy specimens in other abnormal areas also may improve detection regardless of the colposcopist's level of experience (16). Biopsy of any visible lesion is an important component of a colposcopy examination, regardless of colposcopy impression. The only exceptions are women for whom a diagnostic excision is planned, and pregnant women without a colposcopically-diagnosed high-grade lesion.

▶ *Is excision or ablation the better treatment for CIN?*

Treatment modalities for CIN should be evaluated based on their effectiveness and appropriateness in treating CIN 2,3. The recommended management of CIN 1 is follow-up without treatment for at least 2 years during

which regression of many of the lesions is expected. After 2 years, the patient may be treated, but continued follow-up is acceptable. Treatment options include cryotherapy, laser ablation, laser conization, knife conization, and loop electrosurgical excision. Although studies in general have been small and may have difficulty in distinguishing subtle differences among treatments, various treatments appear to be similarly efficacious in eradicating preinvasive disease (121–123). Selection of the appropriate treatment modality depends on the operator's experience, equipment availability, lesion size, and other factors. Alternatively, if the lesion extends onto the vagina, laser ablation may be more appropriate than other treatment because it can be tailored to encompass the entire lesion with excellent depth control. When microinvasive cancer or AIS is suspected, then conization provides a histology specimen for assessment.

Ablative treatments (eg, cryotherapy or laser vaporization) should be used only after rigorously excluding invasive cancer. When endocervical assessment shows CIN, the colposcopy result is not satisfactory, cytology or colposcopy examination suggests cancer, or after prior therapy, cancer may be present but unseen and ablative therapy is not appropriate (119, 124). Laser and loop electrosurgical excision minimize blood loss by thermal cautery during excision but may cause thermal artifact that impairs the interpretability of a specimen (125, 126). This may be clinically significant at a focus of possible microinvasion or AIS. In these cases, knife conization may be preferable.

▶ *How should CIN 1 be managed in women who present with HPV-positive ASC-US, ASC-H, or LSIL results?*

Most CIN 1 in ALTS regressed spontaneously and CIN 1 uncommonly progressed to CIN 2,3 (9). In ALTS, 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 colposcopy evaluation (9). The management of women with LSIL is dependent on their risk of CIN 2,3 and cancer that is in turn related to their presenting cytology. Among women enrolled in ALTS who presented with LSIL or HPV-positive ASC-US on cytology and were found to have CIN 1 on initial colposcopy, 13% were subsequently found to have CIN 2,3 (8.9% CIN 3) and none had cancer during the 24-month follow-up period. This rate of CIN 2,3 on follow-up was similar to women whose colposcopy results were completely negative and who had no biopsy (11.3%), and those whose biopsy specimens were negative for CIN (11.7%) (9). The rationale for avoiding treatment in favor of more conservative follow-up is related to the cost, discomfort, and potential morbidity of commonly used treatment modalities. Recent studies have shown a significant risk of premature delivery and preterm premature rupture of membranes in pregnant women previously treated with LEEP (3, 4, 115). This is especially significant in young women with CIN 1, a group for whom future pregnancy complications are a concern and a group very likely to have spontaneous regression (127). Conservative management allows adequate time to identify cases that might have been initially misclassified or to allow identification of those that would progress to higher-grade lesions whereas the risk of developing cancer remains minimal.

Because the finding of CIN 1 on histology does not affect the risk of CIN 2,3 among women with HPV-positive ASC-US, ASC-H, or LSIL cytology results (compared with those in whom no disease was found), women 21 years and older with CIN 1 preceded by these cytology findings should be managed similarly with either HPV DNA testing every 12 months or repeat cervical cytology at 6 months and 12 months. The decision to treat is unaffected by whether the colposcopy result is satisfactory, and treatment during the first 2 years of follow-up is not recommended. Although persistence of CIN 1 beyond 2 years is associated with a higher risk of high-grade dysplasia and the likelihood of regression decreases the longer dysplasia persists, cancer can be effectively prevented with continued follow-up, and there are no data to preclude continued follow-up beyond 2 years. Thus, it is safe to monitor these patients with semi-annual cytology examinations or annual HPV DNA testing with colposcopy for women with positive high-risk HPV DNA testing or cytology of ASC-US or greater. If CIN 1 has not resolved after 2 years, treatment is acceptable with excision or ablation if the colposcopy result remains satisfactory (13).

If the decision has been made to treat the patient and the colposcopy result is unsatisfactory, the endocervical sampling contains CIN, or the patient has been previously treated, ablative procedures are unacceptable and a diagnostic excisional procedure is recommended.

The management of adolescents with CIN 1 is the same as that of adolescents with LSIL. The recommended management of histologically diagnosed CIN 1 in pregnant women is follow-up without treatment. Treatment of pregnant women for CIN 1 is unacceptable.

▶ *How should CIN 1 be managed in women who presented with HSIL or AGC-NOS?*

Either a diagnostic excisional procedure or observation with colposcopy and cytology at 6-month intervals for 1

year is acceptable for women 21 years or older with a histology diagnosis of CIN 1 preceded by an HSIL or AGC-NOS cytology result, provided in the latter case that the colposcopy examination is satisfactory and endocervical sampling is negative. A diagnostic excisional procedure is recommended for women with CIN 1 preceded by an HSIL or AGC-NOS cytology result in whom the colposcopy examination is unsatisfactory, except in pregnancy.

The risk of an undetected CIN 2,3 or an adenocarcinoma in situ lesion is expected to be greater in women with CIN 1 preceded by an HSIL or AGC cytology result than in women with CIN 1 preceded by an ASC or LSIL cytology result. Cervical intraepithelial neoplasia grade 2,3 is identified in 84–97% of women with HSIL cytology results evaluated with a LEEP (96, 99, 100). Therefore, separate recommendations are made for women with CIN 1 preceded by an HSIL or AGC cytology result.

▶ *How should CIN 2 and CIN 3 be managed?*

Cervical intraepithelial neoplasia grade 3 generally is considered to be a cancer precursor, although not all CIN 3 lesions will progress to cancer. The prevalence of CIN 3 peaks between ages 25 years and 30 years, and progression to cancer usually takes at least a decade longer (90). The risk of progression of CIN 3 is unclear because most experts consider the risk too high to justify observation. A biopsy diagnosis of CIN 3 may miss occult invasive cancer and apparent progression after a colposcopy biopsy diagnosis may reflect missed prevalent cancer. One review found that the likelihood of CIN 3 progressing to invasion was 12%, with 33% of patients regressing and the remainder having stable disease (10). Smaller lesions with fewer colposcopy features are more likely to regress, whereas larger lesions with coarse vascular changes are less likely to regress (128). Cervical intraepithelial neoplasia grade 2,3 lesions associated with HPV 16 genotype are less likely to regress, as are those in women with the HLA 201 phenotype (107). The significance of CIN 2 is unclear. The risk of progression to CIN 3 and cancer appears greater for women with CIN 2 than for women with CIN 1. However, many women with CIN 2 will have regression of their lesions without therapy. In one review, CIN 2 progressed to cancer in 5% of patients and to CIN 3 in 20% of patients, persisted in 40% of patients, and regressed in 40% of patients (10). No accepted tests are available to distinguish CIN 2 that reflects an exuberant HPV infection from that with true malignant potential. The cutoff between CIN 1 and CIN 2 and between CIN 2 and CIN 3 is arbitrary. Because of the moderate cancer risk associated with CIN 2, the decision among leaders in colposcopy and cervical cancer prevention in the United States has been to consider CIN 2 the threshold for treatment for most U.S. women.

However, there are exceptions. The risk of progression to invasive cancer is low before age 21 years, and some CIN 2,3 lesions regress, especially in younger women. For this reason, observation of adolescents and young women appears to be a safe and reasonable approach, provided cancer has been ruled out. When a histology diagnosis of CIN 2 is specified, observation is preferred. One study found unsuspected cancerous lesions in 8% of women undergoing hysterectomy for CIN 2,3, which suggests that prior conization is mandatory to exclude malignancy (129). For these reasons, hysterectomy is unacceptable as the primary therapy for CIN 2,3.

▶ *Does management of CIN 2 or CIN 3 differ for women who are HIV positive?*

Standard ablative or excisional treatment is recommended for women who are HIV positive with documented CIN 2 or CIN 3, regardless of HIV viral load. Effective treatment of CIN requires immunologic clearance or suppression of HPV to avoid recurrence (130). Women who are HIV positive have difficulty clearing HPV and, therefore, are at increased risk of recurrent disease in direct relation to their level of immunosuppression (131–134). Treatment of CIN should be pursued despite high recurrence rates (greater than 50% recurrence rate after standard treatment) because it can effectively interrupt progression to invasive cancer (131, 135–138). Women who are HIV positive also appear more likely to have positive surgical margins, which may contribute to increased recurrence rates (139). Because recent studies reported a lower prevalence of high-grade disease and HPV DNA positivity among immunosuppressed women, the 2006 consensus guidelines recommend that the management of these conditions be similar to that in the general population (140–142).

The role of highly active antiretroviral therapy in the management of precancerous cervical lesions remains unclear (143). Therefore, CIN 2 and CIN 3 should be treated similarly in women who are HIV positive regardless of their use of antiretroviral therapy.

▶ *How should AIS be managed? How should patients with AIS be monitored after treatment?*

Although the overall incidence of AIS is increasing, it remains relatively rare compared with CIN 2,3 (144). In 1991–1995, the overall incidence of squamous carcinoma in situ of the cervix among white women in the United States was 41.4 per 100,000, whereas the inci-

dence of AIS was only 1.25 per 100,000 (144). Because cytology screening and colposcopy detection of AIS are so challenging and the clinical behavior of AIS is so different from CIN 2,3, the principles involved in the management of AIS differ from what is the norm for squamous disease. The colposcopy changes associated with AIS can be minimal or unfamiliar to most colposcopists. Adenocarcinoma in situ frequently is multifocal, may have "skip lesions," and frequently extends for a considerable distance into the endocervical canal, making complete excision difficult. Thus, negative margins on a diagnostic excisional specimen do not necessarily mean that the lesion has been completely excised.

Hysterectomy continues to be the treatment of choice for AIS in women who have completed childbearing. However, an excisional procedure is still curative in most of these patients. A comprehensive review of the published literature conducted in 2001 identified 16 studies that included a total of 296 women with AIS who were treated with a diagnostic excisional procedure (145). The overall failure rate was 8% (145). Margin status and endocervical sampling at the time of an excisional biopsy are clinically useful predictors of residual disease (146–149). Excisional biopsy is required in all women with AIS before making any subsequent management decisions. Conservative management is acceptable if future fertility is desired. 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, re-excision to increase the likelihood of complete excision is preferred. These women should be reevaluated at 6 months using a combination of cervical cytology, HPV DNA testing, and colposcopy with endocervical sampling. Long-term follow-up after treatment is recommended for all women with AIS.

▶ *How should inconclusive colposcopic biopsy results for early invasive cancer be managed?*

Colposcopic biopsy results that are inconclusive for cancer should be followed by excision to define whether cancer is present and to permit treatment planning. The management of early invasive cervical cancer depends on the depth of invasion and the presence or absence of lymph and vascular space invasion. Biopsy alone does not adequately provide this information. Cold-knife conization is preferred for this purpose because it maintains tissue orientation in a single specimen, which is essential to permit pathologic evaluation of depth of invasion and other variables that define stage and treatment (150). Loop and laser excisions are acceptable in experienced hands.

▶ *How should a patient's condition be monitored after treatment for CIN?*

Observation after treatment requires long-term surveillance. Although most recurrent or persistent CIN is found within the first 1–5 years, cases of cancer have been found as late as 20 years after initial therapy (151, 152). In one large study of women monitored after treatment for CIN 3, the sensitivity of cytology in identifying recurrent or persistent CIN was only 64%, whereas adding colposcopy improved the sensitivity to 91% but reduced specificity from 95% to 88% (153). The sensitivity of cytology improves with repeated testing, and whereas few women with CIN 2,3 present soon after treatment with invasive cancer, usually there is time for serial cytology assessment 6 months and 12 months after the treatment because the risk for persistence and recurrence is highest during the first year. The outcomes of treatment of recurrent or persistent disease are unaffected by a short delay in diagnosis as long as persistent disease is identified and eradicated before invasion occurs. Human papillomavirus testing alone is highly sensitive, and a single test at 1 year will detect most recurrences. A combination of HPV testing and cytology was only marginally more sensitive but was the least specific and most costly program for identifying persistent or recurrent CIN (154). Colposcopy with endocervical sampling is indicated with cytology results of ASC-US or greater or a positive HPV test result. If the HPV DNA test result is negative or if two consecutive repeat cytology tests yield negative results, routine screening commencing at 12 months is recommended for at least 20 years.

▶ *If LEEP or cone biopsy reveals a positive margin, how should management proceed?*

Most women with positive margins do not have residual disease, so although repeat conization to prevent recurrence is acceptable, it usually is not necessary. Observation without retreatment using cytology with endocervical sampling at 4–6 months after treatment is preferred in these women. Women with CIN 2,3 involving the excision margins of a conization specimen and those with CIN 2,3 at a postprocedure endocervical sampling are at increased risk for persistence of disease compared with those with clear margins (155–160). One center reporting on 5,386 women after conization for CIN 3 (two studies combined) found recurrence in 0.4% of women with clear margins and in 22% of women with involved margins, with cancerous lesions in 7% of recurrences (161, 162). In a meta-analysis of studies describing more than 35,000 women after an excision, the relative risk of CIN 2,3 after incomplete excision

compared with complete excision was 6.09 (163). A positive excision margin is a convenient marker for recurrence, especially when the endocervical margin is involved. However, multiple studies have shown that margin involvement by CIN is not an independent marker for recurrence or persistence (155–157). Risk factors for recurrence or persistence of CIN include older age, larger lesions, and higher-grade disease, with risks as high as 50% for older women with large CIN 3 lesions.

Repeat diagnostic excisional procedures should be discouraged in adolescents because of the potential effect on future fertility. A hysterectomy for this indication is unacceptable in this population.

▶ *When is hysterectomy appropriate in women with CIN 2,3+?*

Hysterectomy in the absence of other indications, such as abnormal bleeding or uterine leiomyomas, usually is not required. However, one indication is in a patient with recurrent disease when the residual cervix is too small to allow safe repeat conization without risk of bladder and vaginal injury. A repeat diagnostic excision or hysterectomy is acceptable for women with a histology diagnosis of recurrent or persistent CIN 2,3. If excision is indicated, it should be performed (where possible) before hysterectomy to rule out invasive cancer. If hysterectomy is performed, the choice of either vaginal or abdominal approach should be dictated by other indications, such as the surgeon's experience and patient characteristics and preferences.

▶ *How do care and follow-up differ for women during pregnancy?*

In pregnancy, the only diagnosis that may alter management is invasive cancer. The presence of cancer may change treatment goals or change the route and timing of delivery. Therefore, colposcopy examination during pregnancy should have as its primary goal the exclusion of invasive cancer.

Management of LSIL and HPV-positive ASC-US results during pregnancy should be the same as in the nonpregnant state, although the evaluation of these conditions may be deferred until after delivery (Figure 10). If colposcopy is performed for LSIL during pregnancy, additional colposcopy examinations are not indicated. The practice of repeating the colposcopy once per trimester in pregnant women with LSIL is unacceptable unless CIN 2,3 is diagnosed. During pregnancy, limiting biopsy to lesions suspicious for CIN 2,3 or cancer is preferred, but biopsy of any lesion is acceptable. Biopsy during pregnancy has not been linked to fetal loss or preterm delivery, whereas failure to perform biopsy during pregnancy has been linked to missed invasive cancer (164–166). Pregnant adolescents should be treated in the same manner as nonpregnant adolescents.

All women with HSIL should undergo colposcopy, including those who are pregnant. The goal of cytology and colposcopy during pregnancy is to identify invasive cancer that requires treatment before or at the time of delivery. However, unless cancer is identified or suspected,

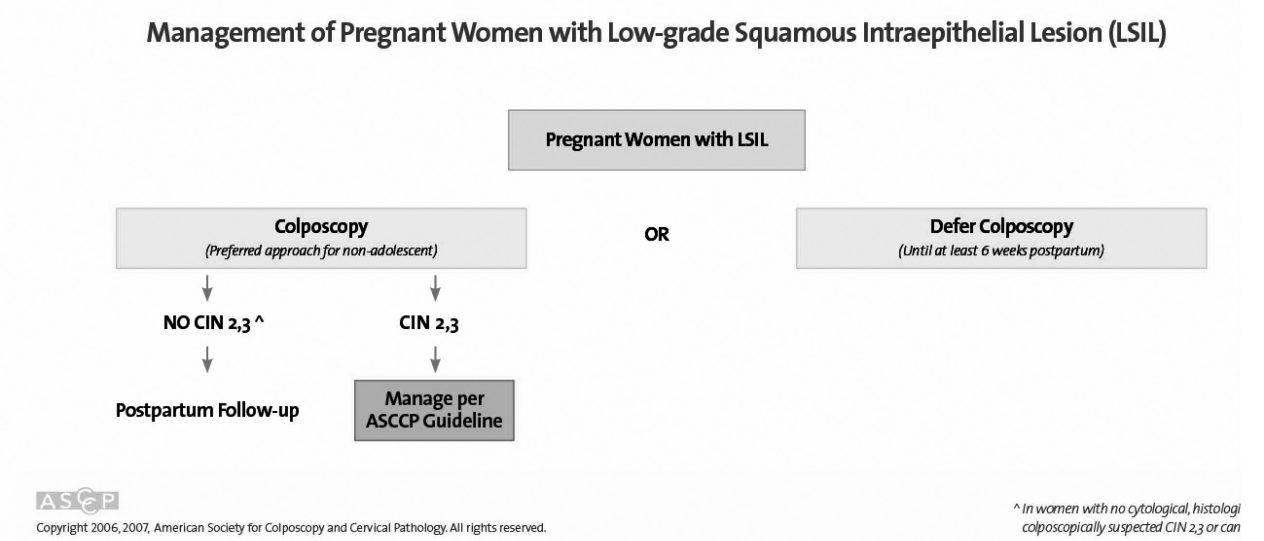

Figure 10. Management of pregnant women with low-grade squamous intraepithelial lesion (LSIL). Abbreviations: ASCCP indicates American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion. Wright TC. Management of cervical cytologic abnormalities. J Low Genit Tract Dis 2007;11:201–22. Reprinted from the Journal of Lower Genital Tract Disease Vol. 11 Issue 4, with the permission of ASCCP © American Society for Colposcopy and Cervical Pathology 2007. No copies of the algorithms may be made without the prior consent of ASCCP.

treatment of CIN is contraindicated during pregnancy. Cervical intraepithelial neoplasia has no effect on the woman or fetus, whereas cervical treatments designed to eradicate CIN can result in fetal loss, preterm delivery, and maternal hemorrhage. Endocervical curettage may result in laceration of the soft cervix with consequent hemorrhage and it also may rupture the amniotic membranes. Endocervical curettage is contraindicated during pregnancy. Colposcopy during pregnancy is challenging because of cervical hyperemia, the development of prominent normal epithelial changes that mimic preinvasive disease colposcopically, obscuring mucus, contact bleeding, prolapsing vaginal walls, and bleeding after biopsy (167). Biopsy is important if the colposcopy impression is high grade, especially in older pregnant women at higher risk of invasive cancer. Once cancer has been excluded, cervical therapy can be deferred until postpartum. Cervical intraepithelial neoplasia may regress during the interval between antenatal cytology and a postpartum examination. In women with biopsy-proven CIN 2 during pregnancy, the risk of microinvasive cancer at the postpartum visit is negligible, whereas the risk after CIN 3 is substantially less than 10%, and deeply invasive cancers are rare (168, 169). For this reason, re-evaluation during pregnancy may prompt needless intervention that may jeopardize current and future pregnancies. Reassessment with cytology and colposcopy no sooner than 6 weeks after delivery is important in tailoring therapy.

Cervical intraepithelial neoplasia 2,3 rarely progresses to invasive cancer during the few months of pregnancy. For these reasons, observation of pregnant women appears a safe and reasonable approach, provided cancer has been ruled out.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Premenopausal women 21 years and older with ASC-US cytology results may undergo immediate colposcopy or may undergo triage testing to determine which of them should be referred to colposcopy. Triage testing may be performed by a single test for high-risk (oncogenic) types of HPV or by repeat cytology screening at 6 months and 12 months. When the index cytology test specimen was obtained by liquid-based cytology or when an HPV specimen was co-collected, "reflex" HPV testing is the preferred approach.
- Colposcopy is recommended in premenopausal women 21 years and older with ASC-US who are HPV positive, those with two consecutive ASC-US cytology results or with LSIL, or women of any age with ASC-H.
- For premenopausal women 21 years and older with an HPV-positive ASC-US, or ASC-H or LSIL cytology result in whom CIN 2,3 is not identified, follow-up without treatment is recommended using either repeat cervical cytology tests at 6 months and 12 months or an HPV test at 12 month-intervals; a repeat colposcopy is indicated for a cytology result of ASC-US or higher-grade abnormality or a positive high-risk HPV test result. After two consecutive negative cytology results or one negative HPV result women can return to routine screening.
- In women 21 years and older with HSIL cytology results, immediate loop electrosurgical excision or colposcopy with endocervical assessment are both acceptable management options. In adolescents and pregnant women with HSIL cytology results, colposcopy is recommended. Immediate excision is not acceptable in adolescents and pregnant women. A diagnostic excisional procedure is recommended for all nonpregnant women with HSIL when colposcopy is unsatisfactory or when CIN of any grade is identified on endocervical assessment.
- Posttreatment management options for women 21 years and older who have CIN 2,3 include a single HPV DNA test at 6–12 months, cytology alone at 6-month intervals or a combination of cytology and colposcopy at 6-month intervals. For adolescents who have undergone treatment, cytology follow-up is preferred. Colposcopy with endocervical sampling is recommended for women who are HPV DNA positive or have a result of ASC-US or greater on repeat cytology. If the HPV DNA test is negative or if two consecutive repeat cytology test results are negative, routine screening commencing at 12 months is recommended for at least 20 years.

The following recommendations are based on limited and inconsistent scientific evidence (Level B):

- Women 21 years or older with ASC-US who test negative for HPV, or whose HPV status is unknown and who test negative for abnormalities using colposcopy, should have a repeat cytology test in 1 year. Women with ASC-US who have two negative results on repeat cytology at 6-month intervals can return to routine screening.

- In adolescents (before age 21 years) with ASC-US or LSIL cytology results, or CIN 1 histology results preceded by ASC-US or LSIL or AGC-NOS cytology results, follow-up is recommended at 12-month intervals. At the first follow-up visit (at 12 months), 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. Human papillomavirus DNA testing is unacceptable for adolescents. If HPV testing is inadvertently performed, a positive result should not influence management.
- In nonpregnant women with ASC and LSIL cytology results who are undergoing colposcopy, endocervical sampling using a brush or curette is preferred for women in whom no lesions are identified and those with an unsatisfactory colposcopy results. Endocervical sampling is acceptable for women with satisfactory colposcopy results and a lesion identified in the transformation zone. Endocervical assessment either with colposcopy or by sampling is recommended for all nonpregnant women with HSIL cytology results. Endocervical curettage is unacceptable in pregnant women.
- The recommended management of pregnant women with a histology diagnosis of CIN 1 is follow-up without treatment. Treatment of pregnant women for CIN 1 is unacceptable.
- In a woman 21 years and older with CIN 1 that has persisted for at least 2 years, either continued follow-up or treatment is acceptable. If treatment is selected and the colposcopy result is satisfactory, either excision or ablation is acceptable. If treatment is selected and the colposcopy examination is unsatisfactory, the ECC is positive, or the woman has been previously treated, excision is recommended and ablative procedures are unacceptable.
- Pregnant women with biopsy-proven CIN 2 or CIN 3 in whom there is no suspicion of invasive cancer may postpone re-evaluation with cytology and colposcopy to no sooner than 6 weeks postpartum. Treatment during pregnancy is unacceptable unless invasion is suspected. When invasion is suspected, a diagnostic excisional procedure is recommended.
- For women 21 years and older, the preferred management of CIN 2,3 identified at the margins of a diagnostic excisional procedure or in an endocervical sample obtained at the end of the procedure is reassessment using cytology with endocervical sampling at 4–6 months following treatment. Performing a repeat diagnostic excisional procedure is acceptable, as is a hysterectomy if a repeat diagnostic procedure is not feasible and for women with a histology diagnosis of recurrent or persistent CIN 2,3.
- In nonpregnant women 21 years and older, both excision and ablation are acceptable treatment modalities in the presence of histology diagnoses of CIN 2,3 and satisfactory colposcopy results. Ablation is unacceptable when colposcopy has not been performed, the endocervical sampling is positive for any grade of CIN, the colposcopy result is unsatisfactory, or a woman has recurrent CIN 2,3.
- Colposcopy with endocervical sampling is recommended and HPV DNA testing is preferred for women with all subcategories of AGC and AIS. In addition, endometrial sampling is recommended in women 35 years and older and in women younger than 35 years with clinical indications suggesting they may be at risk of neoplastic endometrial lesions (eg, unexplained vaginal bleeding, chronic anovulation, or atypical endometrial cells). Colposcopy can be performed either at the initial evaluation or after the results are known. If no endometrial pathology is identified, colposcopy is recommended. Endometrial and endocervical sampling are unacceptable in pregnant women.
- Women 21 years and older with either atypical endocervical, endometrial, or glandular cells NOS who do not have CIN or glandular neoplasia identified histologically should receive repeat cytology testing combined with HPV DNA testing at 6 months if they are HPV DNA positive and at 12 months if they are HPV DNA negative. Referral to colposcopy is recommended for women who subsequently test positive for high-risk HPV DNA or who are found to have ASC-US or greater on their repeat cytology tests. If both tests are negative, women can return to routine cytology testing.
- Women with AGC, favors neoplasia or AIS cytology results should undergo a diagnostic excisional procedure unless invasive disease is identified during the initial colposcopy workup. The diagnostic excisional procedure used in this setting should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred, except in pregnant women.
- Hysterectomy is unacceptable as the primary therapy for CIN.
- Diagnostic ablation or excision is unacceptable as the initial management for ASC or LSIL.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- In nonpregnant women 21 years and older with HSIL in whom CIN 2,3 has not been identified, three management options are acceptable: diagnostic excisional procedure; review of the cytology, histology, and colposcopy findings and management of the patient according to the revised interpretation; or if the colposcopy is satisfactory and endocervical sampling is negative, observation with colposcopy and cytology at 6 month-intervals for 1 year. A diagnostic excisional procedure is recommended for women with repeat HSIL cytology results at either the 6-month or 12-month visit. Women with two consecutive negative cytology results can return to routine screening.
- In adolescents (before age 21 years) with HSIL cytology results, a satisfactory colposcopy result, negative endocervical sampling, and no CIN 2,3 identified on colposcopy biopsy, follow-up is recommended at 6-month intervals with Pap testing and colposcopy for up to 24 months. If during follow-up a high grade colposcopy lesion is identified or HSIL cytology results persist for 1 year, biopsy is recommended. If HSIL persists for 24 months without identification of CIN 2,3, or if the colposcopy result is unsatisfactory, a diagnostic excisional procedure is recommended. After two consecutive negative cytology results, women can return to routine cytology testing.
- For adolescents and young women with a histology diagnosis of CIN 2,3 NOS and a satisfactory colposcopy result either treatment or observation for up to 24 months using both colposcopy and cytology at 6-month intervals is acceptable. When a histology diagnosis of CIN 2 is specified, observation is preferred. When a histology diagnosis of CIN 3 is specified or when the colposcopy result is unsatisfactory, treatment is recommended. If the colposcopy appearance of the lesion worsens or if an HSIL cytology result or a high-grade colposcopy lesion persists for 1 year, repeat biopsy is recommended. After two consecutive negative cytology results, women with normal colposcopy results can return to routine cytology screening. Treatment is recommended if CIN 3 is subsequently identified or if CIN 2,3 persists for 24 months.
- In nonpregnant women 21 years and older with HSIL or AGC-NOS cytology results in whom CIN 1 has been identified on colposcopy three management options are acceptable: diagnostic excisional procedure; review of the cytology, histology, and colposcopy findings and management of the patient according to the revised interpretation; or if the colposcopy is satisfactory and endocervical sampling is negative, observation with colposcopy and cytology at 6-month intervals for 1 year. A diagnostic excisional procedure is recommended for women with repeat HSIL cytology results at either the 6-month or 12-month visit. Women with two consecutive negative cytology results can return to routine cytology screening.
- In women 21 years and older with atypical endocervical, endometrial, or glandular cells NOS, HPV DNA testing is preferred at the time of colposcopy (if not already performed). For women of unknown HPV status who do not have CIN or glandular neoplasia identified histologically, the recommended postcolposcopy management is to repeat cytology testing at 6-month intervals. After four consecutive negative cytology results, women can return to routine cytology testing.
- Women with a cervical biopsy diagnosis of AIS should undergo excision to exclude invasive cancer. A conization technique that preserves specimen orientation and permits optimal interpretation of histology and margin status is recommended. After conization, hysterectomy is preferred for women who have completed childbearing. Conservative management is acceptable if the margins of the specimen and the postprocedure endocervical curettage results are negative and future fertility is desired. If conservative management is planned and the margins of the specimen are involved or the postprocedure endocervical curettage specimen contains CIN or AIS, re-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 after treatment is recommended for all women with AIS.

References

1. Ries LA, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, et al, editors. SEER cancer statistics review, 1975-2005. Bethesda (MD): National Cancer Institute; 2008. Available at: http://seer.cancer.gov/csr/1975_2005. Retrieved July 14, 2008. (Level III)
2. Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. Am J Obstet Gynecol 2004;191:105–13. (Level II-3)
3. Samson SL, Bentley JR, Fahey TJ, McKay DJ, Gill GH. The effect of loop electrosurgical excision procedure on

future pregnancy outcome. Obstet Gynecol 2005;105: 325–32. (Level II-2)

4. Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 2004;291: 2100–6. (Level II-2)
5. 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;367:489–98. (Level III)
6. Bruinsma F, Lumley J, Tan J, Quinn M. Precancerous changes in the cervix and risk of subsequent preterm birth. BJOG 2007;114:70–80. (Level II-3)
7. Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2007;109: 309–13. (Level II-2)
8. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. Forum Group Members; Bethesda 2001 Workshop. JAMA 2002;287:2114–9. (Level III)
9. Cox JT, Schiffman M, Solomon D. 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. ASCUS-LSIL Triage Study (ALTS) Group. Am J Obstet Gynecol 2003;188:1406–12. (Level II-2)
10. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993;12: 186–92. (Level III)
11. Eddy DM. Screening for cervical cancer. Ann Intern Med 1990;113:214–26. (Level III)
12. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. Am J Obstet Gynecol 2007;197:346–55. (Level III)
13. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. Am J Obstet Gynecol 2007;197:340–5. (Level III)
14. Crane JM. Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. Obstet Gynecol 2003;102:1058–62. (Level III)
15. Ferris DG, Litaker MS. Prediction of cervical histologic results using an abbreviated Reid Colposcopic Index during ALTS. ALTS Group. Am J Obstet Gynecol 2006; 194:704–10. (Level II-3)
16. Massad LS, Collins YC. Strength of correlations between colposcopic impression and biopsy histology. Gynecol Oncol 2003;89:424–8. (Level II-3)
17. Jeronimo J, Schiffman M. Colposcopy at a crossroads. Am J Obstet Gynecol 2006;195:349–53. (Level III)
18. Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, et al. Number of cervical biopsies and sensitivity of colposcopy. ASCUS LSIL Triage Study (ALTS) Group. Obstet Gynecol 2006;108:264–72. (Level II-3)
19. Hildesheim A, Schiffman MH, Gravitt PE, Glass AG, Greer CE, Zhang T, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. J Infect Dis 1994;169:235–40. (Level II-2)
20. Herrero R, Munoz N. Human papillomavirus and cancer. Cancer Surv 1999;33:75–98. (Level III)
21. Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr 1998;132: 277–84. (Level II-2)
22. Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. J Infect Dis 1996;174:679–89. (Level II-2)
23. Kotloff KL, Wasserman SS, Russ K, Shapiro S, Daniel R, Brown W, et al. Detection of genital human papillomavirus and associated cytological abnormalities among college women. Sex Transm Dis 1998;25:243–50. (Level II-2)
24. Bauer HM, Ting Y, Greer CE, Chambers JC, Tashiro CJ, Chimera J, et al. Genital human papillomavirus infection in female university students as determined by a PCR-based method. JAMA 1991;265:472–7. (Level II-3)
25. Kinney WK, Manos MM, Hurley LB, Ransley JE. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. Obstet Gynecol 1998;91:973–6. (Level III)
26. Castle PE, Wacholder S, Sherman ME, Lorincz AT, Glass AG, Scott DR, et al. Absolute risk of a subsequent abnormal pap among oncogenic human papillomavirus DNA-positive, cytologically negative women. Cancer 2002;95: 2145–51. (Level II-2)
27. 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. (Level II-2)
28. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12–9. (Level II-3)
29. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. N Engl J Med 2003;348:518–27. (Level II-2)
30. Wright TC Jr, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. N Engl J Med 2003;348:489–90. (Level III)

31. Hopman EH, Rozendaal L, Voorhorst FJ, Walboomers JM, Kenemans P, Helmerhorst TJ. High risk human papillomavirus in women with normal cervical cytology prior to the development of abnormal cytology and colposcopy. BJOG 2000;107:600–4. (Level II-2)

32. Castle PE, Wacholder S, Lorincz AT, Scott DR, Sherman ME, Glass AG, et al. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. J Natl Cancer Inst 2002;94:1406–14. (Level II-2)

33. Barron BA, Richart RM. A statistical model of the natural history of cervical carcinoma based on a prospective study of 557 cases. J Natl Cancer Inst 1968;41:1343–53. (Level III)

34. Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckmann AM, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. N Engl J Med 1992;327:1272–8. (Level II-2)

35. Boyes DA, Fidler HK, Lock DR. Significance of in situ carcinoma of the uterine cervix. Br Med J 1962;1:203–5. (Level III)

36. Dunn JE Jr, Martin PL. Morphogenesis of cervical cancer. Findings from San Diego County Cytology Registry. Cancer 1967;20:1899–906. (Level III)

37. Fidler HK, Boyes DA, Worth AJ. Cervical cancer detection in British Columbia. A progress report. J Obstet Gynaecol Br Commonw 1968;75:392–404. (Level II-3)

38. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. ALTS Study group. J Natl Cancer Inst 2001;93:293–9. (Level I)

39. Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132:810–9. (Level III)

40. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. Am J Epidemiol 1995;141:680–9. (Level III)

41. Kinney W, Sawaya GF, Sung HY, Kearney KA, Miller M, Hiatt RA. Stage at diagnosis and mortality in patients with adenocarcinoma and adenosquamous carcinoma of the uterine cervix diagnosed as a consequence of cytologic screening. Acta Cytol 2003;47:167–71. (Level II-3)

42. Smith AE, Sherman ME, Scott DR, Tabbara SO, Dworkin L, Olson J, et al. Review of the Bethesda System atlas does not improve reproducibility or accuracy in the classification of atypical squamous cells of undetermined significance smears. Cancer 2000;90: 201–6. (Level II-3)

43. Quddus MR, Sung CJ, Steinhoff MM, Lauchlan SC, Singer DB, Hutchinson ML. Atypical squamous metaplastic cells: reproducibility, outcome, and diagnostic features on ThinPrep Pap test. Cancer 2001;93:16–22. (Level III)

44. Abulafia O, Pezzullo JC, Sherer DM. Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. Gynecol Oncol 2003;90:137–44. (Level III)

45. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. JAMA 2001;285:1500–5. (Level III)

46. Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia [published erratum appears in Gynecol Oncol 2002;84:355]. Gynecol Oncol 2001;83:439–44. (Level II-3)

47. Belinson JL, Qiao YL, Pretorius RG, Zhang WH, Rong SD, Huang MN, et al. Shanxi Province cervical cancer screening study II: self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. Int J Gynecol Cancer 2003;13:819–26. (Level II-3)

48. Clavel C, Masure M, Bory JP, Putaud I, Mangeonjean C, Lorenzato M, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. Br J Cancer 2001;84: 1616–23. (Level II-3)

49. Cuzick J, Beverley E, Ho L, Terry G, Sapper H, Mielzynska I, et al. HPV testing in primary screening of older women. Br J Cancer 1999;81:554–8. (Level III)

50. Salmeron J, Lazcano-Ponce E, Lorincz A, Hernandez M, Hernandez P, Leyva A, et al. Comparison of HPV-based assays with Papanicolaou smears for cervical cancer screening in Morelos State, Mexico. Cancer Causes Control 2003;14:505–12. (Level II-3)

51. Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, et al. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. JAMA 2001;286:3106–14. (Level II-2)

52. Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 2001;357:1831–6. (Level II-2)

53. Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003;362:1871–6. (Level I)

54. Kjaer SK, van den Brule AJ, Paull G, Svare EI, Sherman ME, Thomsen BL, et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. BMJ 2002;325:572. (Level II-2)

55. Bonardi R, Cecchini S, Grazzini G, Ciatto S. Loop electrosurgical excision procedure of the transformation zone and colposcopically directed punch biopsy in the diagnosis of cervical lesions. Obstet Gynecol 1992;80:1020–2. (Level III)

56. Buxton EJ, Luesley DM, Shafi MI, Rollason M. Colposcopically directed punch biopsy: a potentially

misleading investigation. Br J Obstet Gynaecol 1991;98: 1273–6. (Level III)

57. Andersen W, Frierson H, Barber S, Tabbarah S, Taylor P, Underwood P. Sensitivity and specificity of endocervical curettage and the endocervical brush for the evaluation of the endocervical canal. Am J Obstet Gynecol 1988;159: 702–7. (Level II-3)
58. Hoffman MS, Sterghos S Jr, Gordy LW, Gunasekaran S, Cavanagh D. Evaluation of the cervical canal with the endocervical brush. Obstet Gynecol 1993;82:573–7. (Level II-3)
59. Klam S, Arseneau J, Mansour N, Franco E, Ferenczy A. Comparison of endocervical curettage and endocervical brushing. Obstet Gynecol 2000;96:90–4. (Level I)
60. Mogensen ST, Bak M, Dueholm M, Frost L, Knoblauch NO, Praest J, et al. Cytobrush and endocervical curettage in the diagnosis of dysplasia and malignancy of the uterine cervix. Acta Obstet Gynecol Scand 1997;76:69–73. (Level I)
61. Tate KM, Strickland JL. A randomized controlled trial to evaluate the use of the endocervical brush after endocervical curettage. Obstet Gynecol 1997;90:715–7. (Level I)
62. Naumann RW, Crispens MA, Alvarez RD, Partridge EE, Shingleton HM, Kilgore LC. Treatment of cervical dysplasia with large loop excision of the transformation zone: is endocervical curettage necessary? South Med J 1996;89:961–5. (Level III)
63. Williams DL, Dietrich C, McBroom J. Endocervical curettage when colposcopic examination is satisfactory and normal. Obstet Gynecol 2000;95:801–3. (Level III)
64. Drescher CW, Peters WA 3rd, Roberts JA. Contribution of endocervical curettage in evaluating abnormal cervical cytology. Obstet Gynecol 1983;62:343–7. (Level III)
65. Moniak CW, Kutzner S, Adam E, Harden J, Kaufman RH. Endocervical curettage in evaluating abnormal cervical cytology. J Reprod Med 2000;45:285–92. (Level III)
66. Fine BA, Feinstein GI, Sabella V. The pre- and postoperative value of endocervical curettage in the detection of cervical intraepithelial neoplasia and invasive cervical cancer. Gynecol Oncol 1998;71:46–9. (Level II-3)
67. Massad LS, Collins YC. Using history and colposcopy to select women for endocervical curettage. Results from 2,287 cases. J Reprod Med 2003;48:1–6. (Level II-3)
68. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepthelial neoplasia II or worse. Am J Obstet Gynecol 2004;191:430–4. (Level II-3)
69. Spitzer M, Chernys AE, Shifrin A, Ryskin M. Indications for cone biopsy: pathologic correlation. Am J Obstet Gynecol 1998;178:74–9. (Level III)
70. Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. Obstet Gynecol 1997;90:1–6. (Level III)
71. Wright TC Jr, Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004;103: 304–9. (Level III)
72. Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. American Cancer Society. CA Cancer J Clin 2002;52:342–62. (Level III)
73. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer 2006;119:1095–101. (Level III)
74. Kjaer S, Hogdall E, Frederiksen K, Munk C, van den Brule A, Svare E, 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;66:10630–6. (Level II-2)
75. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst 2005;97:1072–9. (Level II-3)
76. Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstet Gynecol 2004;103:619–31. (Level III)
77. Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. New Technologies for Cervical Cancer Working Group. J Natl Cancer Inst 2006;98:765–74. (Level I)
78. 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;93:575–81. (Level II-3)
79. Jones BA, Davey DD. Quality management in gynecologic cytology using interlaboratory comparison. Arch Pathol Lab Med 2000;124:672–81. (Level III)
80. Lonky NM, Sadeghi M, Tsadik GW, Petitti D. The clinical significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. Am J Obstet Gynecol 1999;181:560–6. (Level II-3)
81. Cox JT, Lorincz AT, Schiffman MH, Sherman ME, Cullen A, Kurman RJ. Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 1995; 172:946–54. (Level II-3)
82. 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. (Level II-3)

83. Dunn TS, Bajaj JE, Stamm CA, Beaty B. Management of the minimally abnormal Papanicolaou smear in pregnancy. J Low Genit Tract Dis 2001;5:133–7. (Level II-3)

84. Sawaya GF, Kerlikowske K, Lee NC, Gildengorin G, Washington AE. Frequency of cervical smear abnormalities within 3 years of normal cytology. Obstet Gynecol 2000;96:219–23. (Level III)

85. Boardman LA, Stanko C, Weitzen S, Sung CJ. Atypical squamous cells of undetermined significance: human papillomavirus testing in adolescents. Obstet Gynecol 2005;105:741–6. (Level II-3)

86. Sherman ME, Solomon D, Schiffman M. Qualification of ASCUS. A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study. ASCUS LSIL Triage Study Group. Am J Clin Pathol 2001;116:386–94. (Level II-2)

87. Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Natl Cancer Inst 2003;95:46–52. (Level II-2)

88. Eltoum IA, Chhieng DC, Roberson J, McMillon D, Partridge EE. Reflex human papilloma virus infection testing detects the same proportion of cervical intraepithelial neoplasia grade 2-3 in young versus elderly women. Cancer 2005;105:194–8. (Level II-3)

89. Bruner KS, Davey DD. ASC-US and HPV testing in women aged 40 years and over. Diagn Cytopathol 2004; 31:358–61. (Level III)

90. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine 2006;24(suppl 3):S42–51. (Level III)

91. 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;105:457–60. (Level II-3)

92. Srodon M, Parry Dilworth H, Ronnett BM. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion: diagnostic performance, human papillomavirus testing, and follow-up results. Cancer 2006;108:32–8. (Level II-3)

93. 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;108:298–305. (Level I)

94. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study Group. J Natl Cancer Inst 2002;94:102–7. (Level II-3)

95. Evans MF, Adamson CS, Papillo JL, St John TL, Leiman G, Cooper K. Distribution of human papillomavirus types in ThinPrep Papanicolaou tests classified according to the Bethesda 2001 terminology and correlations with patient age and biopsy outcomes. Cancer 2006;106: 1054–64. (Level II-3)

96. Dunn TS, Burke M, Shwayder J. A "see and treat" management for high-grade squamous intraepithelial lesion pap smears. J Low Genit Tract Dis 2003;7:104–6. (Level III)

97. Guido R, Schiffman M, Solomon D, Burke L. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. ASCUS LSIL Triage Study (ALTS) Group. Am J Obstet Gynecol 2003;188:1401–5. (Level II-2)

98. 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;128:1224–9. (Level III)

99. Alvarez RD, Wright TC. Effective cervical neoplasia detection with a novel optical detection system: a randomized trial. Optical Detection Group. Gynecol Oncol 2007;104:281–9. (Level I)

100. Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. Gynecol Oncol 2001;82:516–22. (Level II-3)

101. Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cervical cytology. The 1992 National Cancer Institute Workshop. JAMA 1994;271:1866–9. (Level III)

102. Irvin WP Jr, Andersen WA, Taylor PT Jr, Stoler MH, Rice LW. "See-and-treat" loop electrosurgical excision. Has the time come for a reassessment? J Reprod Med 2002; 47:569–74. (Level III)

103. Numnum TM, Kirby TO, Leath CA 3rd, Huh WK, Alvarez RD, Straughn JM Jr. A prospective evaluation of "see and treat" in women with HSIL Pap smear results: is this an appropriate strategy? J Low Genit Tract Dis 2005;9:2–6. (Level III)

104. Ferris DG, Hainer BL, Pfenninger JL, Zuber TJ. 'See and treat' electrosurgical loop excision of the cervical transformation zone. J Fam Pract 1996;42:253–7. (Level III)

105. 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. (Level I)

106. Tidbury P, Singer A, Jenkins D. CIN 3: the role of lesion size in invasion. Br J Obstet Gynaecol 1992;99:583–6. (Level III)

107. Trimble CL, Piantadosi S, Gravitt P, Ronnett B, Pizer E, Elko A, et al. Spontaneous regression of high-grade cervical dysplasia: effects of human papillomavirus type and HLA phenotype. Clin Cancer Res 2005;11:4717–23. (Level II-2)

108. McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. Obstet Gynecol 1984;64:451–8. (Level II-3)

109. Milne DS, Wadehra V, Mennim D, Wagstaff TI. A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. Br J Obstet Gynaecol 1999;106:38–41. (Level II-2)

110. Hellberg D, Nilsson S. 20-year experience of follow-up of the abnormal smear with colposcopy and histology and treatment by conization or cryosurgery. Gynecol Oncol 1990;38:166–9. (Level III)

111. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI. Dysplasia associated with atypical glandular cells on cervical cytology [published erratum appears in Obstet Gynecol 2005;105:1495]. Obstet Gynecol 2005;105:494–500. (Level II-3)

112. DeSimone CP, Day ME, Tovar MM, Dietrich CS 3rd, Eastham ML, Modesitt SC. Rate of pathology from atypical glandular cell Pap tests classified by the Bethesda 2001 nomenclature. Obstet Gynecol 2006;107:1285–91. (Level II-3)

113. Tam KF, Cheung AN, Liu KL, Ng TY, Pun TC, Chan YM, et al. A retrospective review on atypical glandular cells of undetermined significance (AGUS) using the Bethesda 2001 classification. Gynecol Oncol 2003;91: 603–7. (Level II-3)

114. Derchain SF, Rabelo-Santos SH, Sarian LO, Zeferino LC, de Oliveira Zambeli ER, do Amaral Westin MC, 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;95:618–23. (Level III)

115. Krane JF, Lee KR, Sun D, Yuan L, Crum CP. Atypical glandular cells of undetermined significance. Outcome predictions based on human papillomavirus testing. Am J Clin Pathol 2004;121:87–92. (Level III)

116. 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;10:111–22. (Level III)

117. 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;123:571–5. (Level III)

118. Solomon D, Stoler M, Jeronimo J, Khan M, Castle P, Schiffman M. Diagnostic utility of endocervical curettage in women undergoing colposcopy for equivocal or low-grade cytologic abnormalities. Obstet Gynecol 2007; 110:288–95. (Level II-3)

119. Sevin BU, Ford JH, Girtanner RD, Hoskins WJ, Ng AB, Nordqvist SR, et al. Invasive cancer of the cervix after cryosurgery. Pitfalls of conservative management. Obstet Gynecol 1979;53:465–71. (Level III)

120. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol 1998;91:626–31. (Level III)

121. 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. (Level I)

122. Alvarez RD, Helm CW, Edwards RP, Naumann RW, Partridge EE, Shingleton HM, et al. Prospective randomized trial of LLETZ versus laser ablation in patients with cervical intraepithelial neoplasia. Gynecol Oncol 1994;52:175–9. (Level I)

123. 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. (Level I)

124. Townsend DE, Richart RM, Marks E, Nielsen J. Invasive cancer following outpatient evaluation and therapy for cervical disease. Obstet Gynecol 1981;57:145–9. (Level III)

125. Wright TC Jr, Richart RM, Ferenczy A, Koulos J. Comparison of specimens removed by CO2 laser conization and the loop electrosurgical excision procedure. Obstet Gynecol 1992;79:147–53. (Level II-3)

126. Messing MJ, Otken L, King LA, Gallup DG. Large loop excision of the transformation zone (LLETZ): a pathologic evaluation. Gynecol Oncol 1994;52:207–11. (Level III)

127. Nobbenhuis MA, Helmerhorst TJ, van den Brule AJ, Rozendaal L, Voorhorst FJ, Bezemer PD, et al. Cytological regression and clearance of high-risk human papillomavirus in women with an abnormal cervical smear. Lancet 2001;358:1782–3. (Level II-2)

128. Brewer CA, Wilczynski SP, Kurosaki T, Daood R, Berman ML. Colposcopic regression patterns in high-grade cervical intraepithelial neoplasia. Obstet Gynecol 1997;90:617–21. (Level II-2)

129. Kesic V, Dokic M, Atanackovic J, Milenkovic S, Kalezic I, Vukovic S. Hysterectomy for treatment of CIN. J Low Genit Tract Dis 2003;7:32–5. (Level III)

130. Ahdieh L, Munoz A, Vlahov D, Trimble CL, Timpson LA, Shah K. Cervical neoplasia and repeated positivity of human papillomavirus infection in human immunodeficiency virus-seropositive and -seronegative women. Am J Epidemiol 2000;151:1148–57. (Level II-3)

131. Maiman M, Fruchter RG, Serur E, Levine PA, Arrastia CD, Sedlis A. Recurrent cervical intraepithelial neoplasia in human immunodeficiency virus-seropositive women. Obstet Gynecol 1993;82:170–4. (Level II-2)

132. Maiman M, Watts DH, Andersen J, Clax P, Merino M, Kendall MA. Vaginal 5-fluorouracil for high-grade cervical dysplasia in human immunodeficiency virus infection: a randomized trial. Obstet Gynecol 1999;94: 954–61. (Level I)

133. Massad LS, Collins YC. Using history and colposcopy to select women for endocervical curettage. Results from 2,287 cases. J Reprod Med 2003;48:1–6. (Level II-3)

134. Tate DR, Anderson RJ. Recrudescence of cervical dysplasia among women who are infected with the human immunodeficiency virus: a case-control analysis. Am J Obstet Gynecol 2002;186:880–2. (Level II-2)

135. Adachi A, Fleming I, Burk RD, Ho GY, Klein RS. Women with human immunodeficiency virus infection and abnormal Papanicolaou smears: a prospective study

of colposcopy and clinical outcome. Obstet Gynecol 1993;81:372–7. (Level II-3)

136. 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. (Level II-3)

137. Fruchter RG, Maiman M, Sedlis A, Bartley L, Camilien L, Arrastia CD. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. Obstet Gynecol 1996;87:338–44. (Level II-2)

138. Wright TC Jr, Koulos J, Schnoll F, Swanbeck J, Ellerbrock TV, Chiasson MA, et al. Cervical intraepithelial neoplasia in women infected with the human immunodeficiency virus: outcome after loop electrosurgical excision. Gynecol Oncol 1994;55:253–8. (Level II-3)

139. Boardman LA, Peipert JF, Hogan JW, Cooper AS. Positive cone biopsy specimen margins in women infected with the human immunodeficiency virus. Am J Obstet Gynecol 1999;181:1395–9. (Level II-2)

140. Massad LS, Schneider MF, Watts DH, Strickler HD, Melnick S, Palefsky J, et al. HPV testing for triage of HIV-infected women with Papanicolaou smears read as atypical squamous cells of uncertain significance. J Womens Health 2004;13:147–53. (Level II-3)

141. Kirby TO, Allen ME, Alvarez RD, Hoesley CJ, Huh WK. High-risk human papillomavirus and cervical intraepithelial neoplasia at time of atypical squamous cells of undetermined significance cytologic results in a population with human immunodeficiency virus. J Low Genit Tract Dis 2004;8:298–303 (Level II-3).

142. Massad LS, Seaberg EC, Wright RL, Darragh T, Lee YC, Colie C, et al. Squamous cervical lesions in women with human immunodeficiency virus: long-term follow-up. Obstet Gynecol 2008.111:1388–93.

143. Heard I, Palefsky JM, Kazatchkine MD. The impact of HIV antiviral therapy on human papillomavirus (HPV) infections and HPV-related diseases. Antivir Ther 2004; 9:13–22. (Level II-2)

144. 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;100:1035–44. (Level II-3)

145. Soutter WP, Haidopoulos D, Gornall RJ, McIndoe GA, Fox J, Mason WP, et al. Is conservative treatment for adenocarcinoma in situ of the cervix safe? BJOG 2001;108: 1184–9. (Level III)

146. Lea JS, Shin CH, Sheets EE, Coleman RL, Gehrig PA, Duska LR, et al. Endocervical curettage at conization to predict residual cervical adenocarcinoma in situ. Gynecol Oncol 2002;87:129–32. (Level III)

147. Hwang DM, Lickrish GM, Chapman W, Colgan TJ. Long-term surveillance is required for all women treated for cervical adenocarcinoma in situ. J Low Genit Tract Dis 2004;8:125–31. (Level II-3)

148. Shin CH, Schorge JO, Lee KR, Sheets EE. Conservative management of adenocarcinoma in situ of the cervix. Gynecol Oncol 2000;79:6–10. (Level III)

149. McHale MT, Le TD, Burger RA, Gu M, Rutgers JL, Monk BJ. Fertility sparing treatment for in situ and early invasive adenocarcinoma of the cervix. Obstet Gynecol 2001;98:726–31. (Level III)

150. Orr JW Jr, Orr PJ. Cervical cancer: staging. In: Rubin SC, Hoskins WJ, editors. Cervical cancer and preinvasive neoplasia. Philadelphia (PA): Lippincott Raven; 1996. p. 171–82. (Level III)

151. Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. BMJ 2005;331:1183–5. (Level II-2)

152. Hellberg D, Nilsson S, Valentin J. Positive cervical smear with subsequent normal colposcopy and histology—frequency of CIN in a long-term follow-up. Gynecol Oncol 1994;53:148–51. (Level II-3)

153. Soutter WP, Butler JS, Tipples M. The role of colposcopy in the follow up of women treated for cervical intraepithelial neoplasia. BJOG 2006;113:511–4. (Level II-3)

154. Kreimer AR, Guido RS, Solomon D, Schiffman M, Wacholder S, Jeronimo J, et al. Human papillomavirus testing following loop electrosurgical excision procedure identifies women at risk for posttreatment cervical intraepithelial neoplasia grade 2 or 3 disease. Cancer Epidemiol Biomarkers Prev 2006;15:908–14. (Level II-2)

155. Lu CH, Liu FS, Kuo CJ, Chang CC, Ho ES. Prediction of persistence or recurrence after conization for cervical intraepithelial neoplasia III. Obstet Gynecol 2006; 107:830–5. (Level II-3)

156. Moore BC, Higgins RV, Laurent SL, Marroum MC, Bellitt P. Predictive factors from cold knife conization for residual cervical intraepithelial neoplasia in subsequent hysterectomy. Am J Obstet Gynecol 1995;173: 361–6; discussion 366–8. (Level II-3)

157. Kalogirou D, Antoniou G, Karakitsos P, Botsis D, Kalogirou O, Giannikos L. Predictive factors used to justify hysterectomy after loop conization: increasing age and severity of disease. Eur J Gynaecol Oncol 1997;18: 113–6. (Level II-3)

158. Phelps JY 3rd, Ward JA, Szigeti J 2nd, Bowland CH, Mayer AR. Cervical cone margins as a predictor for residual dysplasia in post-cone hysterectomy specimens. Obstet Gynecol 1994;84:128–30. (Level II-3)

159. Chang DY, Cheng WF, Torng PL, Chen RJ, Huang SC. Prediction of residual neoplasia based on histopathology and margin status of conization specimens. Gynecol Oncol 1996;63:53–6. (Level II-3)

160. Kobak WH, Roman LD, Felix JC, Muderspach LI, Schlaerth JB, Morrow CP. The role of endocervical curettage at cervical conization for high-grade dysplasia. Obstet Gynecol 1995;85:197–201. (Level II-2)

161. Reich O, Pickel H, Lahousen M, Tamussino K, Winter R. Cervical intraepithelial neoplasia III: long-term outcome after cold-knife conization with clear margins. Obstet Gynecol 2001;97:428–30. (Level III)

162. Reich O, Lahousen M, Pickel H, Tamussino K, Winter R. Cervical intraepithelial neoplasia III: long-term follow-up after cold-knife conization with involved margins. Obstet Gynecol 2002;99:193–6. (Level II-3)

163. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol 2007;8:985–93. (Level III)

164. Cristoforoni PM, Gerbaldo DL, Philipson J, Holshneider C, Palmieri A, Bovicelli A, et al. Management of the abnormal Papanicolaou smear during pregnancy: lessons for quality improvement. J Low Genit Tract Dis 1999; 3:225–30. (Level II-3)

165. Benedet JL, Selke PA, Nickerson KG. Colposcopic evaluation of abnormal Papanicolaou smears in pregnancy. Am J Obstet Gynecol 1987;157:932–7. (Level III)

166. Paraskevaidis E, Koliopoulos G, Kalantaridou S, Pappa L, Navrozoglou I, Zikopoulos K, et al. Management and evolution of cervical intraepithelial neoplasia during pregnancy and postpartum. Eur J Obstet Gynecol Reprod Biol 2002;104:67–9. (Level III)

167. Coppleson M, Reid BL. A colposcopic study of the cervix during pregnancy and the puerperium. J Obstet Gynaecol Br Commonw 1966;73:575–85. (Level III)

168. Roberts CH, Dinh TV, Hannigan EV, Yandell RB, Schnadig VJ. Management of cervical intraepithelial neoplasia during pregnancy: a simplified and cost-effective approach. J Low Genit Tract Dis 1998;2:67–70. (Level III)

169. Boardman LA, Goldman DL, Cooper AS, Heber WW, Weitzen S. CIN in pregnancy: antepartum and postpartum cytology and histology. J Reprod Med 2005;50: 13–8. (Level II-3)

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1995 and November 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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