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Management of Abnormal Cervical Cytology and Histology

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.

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.

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

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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. Copyright © 2002, American Medical Association. All rights reserved.

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

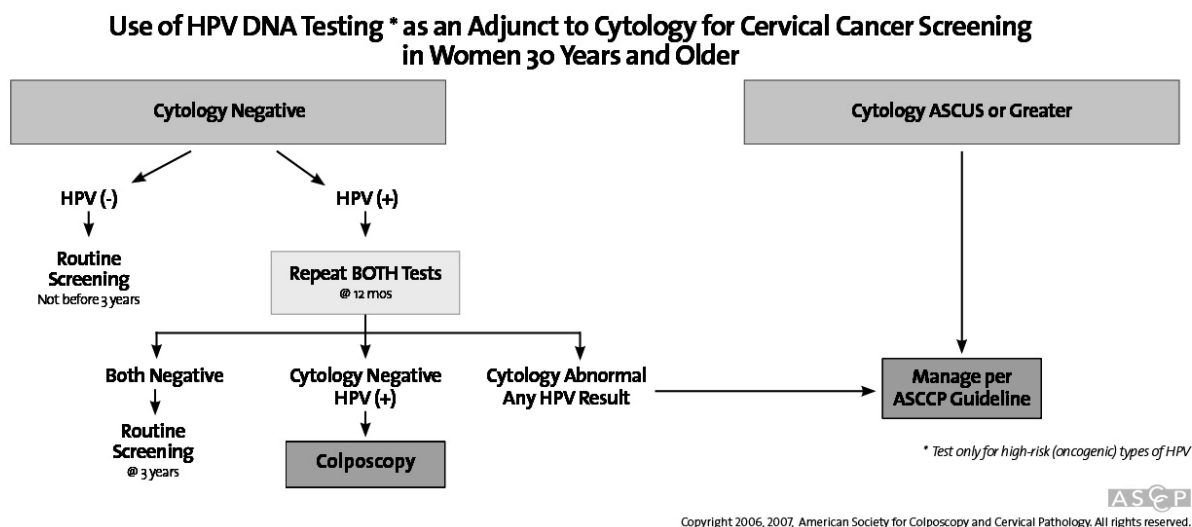


Figure 1. Use of HPV DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years and older. Abbreviations: ASCCP indicates American Society for Colposcopy and Cervical Pathology; ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus. Wright TC. 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 2001 guidelines, 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

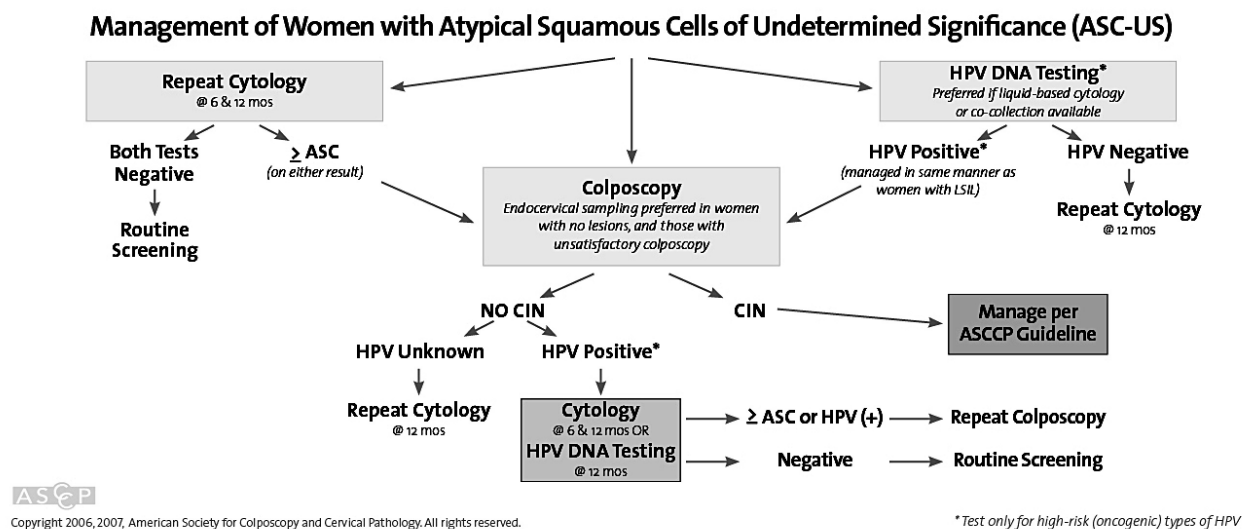


Figure 2. Management of women with atypical squamous cells of undetermined significance (ASC-US). Abbreviations: ASC indicates atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; LSIL, low-grade squamous 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?*

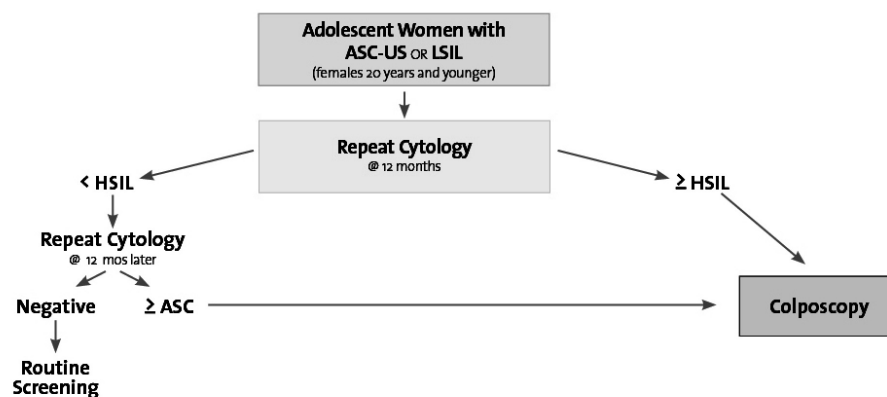
Invasive cervical cancer is very rare in adolescent women before age 21 years. The National Cancer Institute's SEER program reported that from 1995 to 1999 the incidence rate of invasive cervical cancer was 0 per 100,000 per year for women aged 10–19 years and 1.7 per 100,000 per year for women aged 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

Management of Adolescent Women with Either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)



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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).

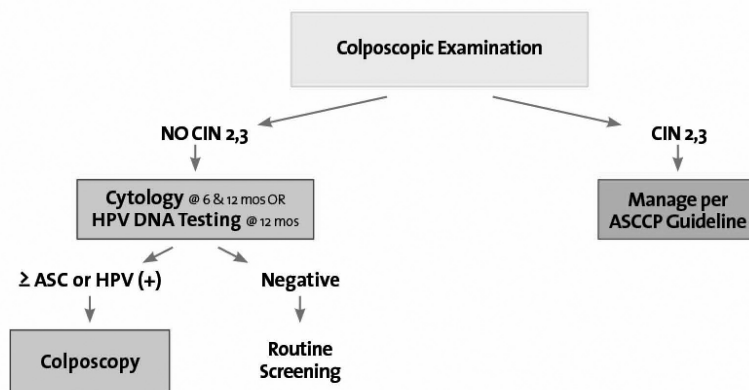
Many studies have shown that the prevalence of both HPV DNA positivity and CIN 2,3 decreases with

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

Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC - H)



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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.

Management of Women with Low-grade Squamous Intraepithelial Lesion (LSIL) *

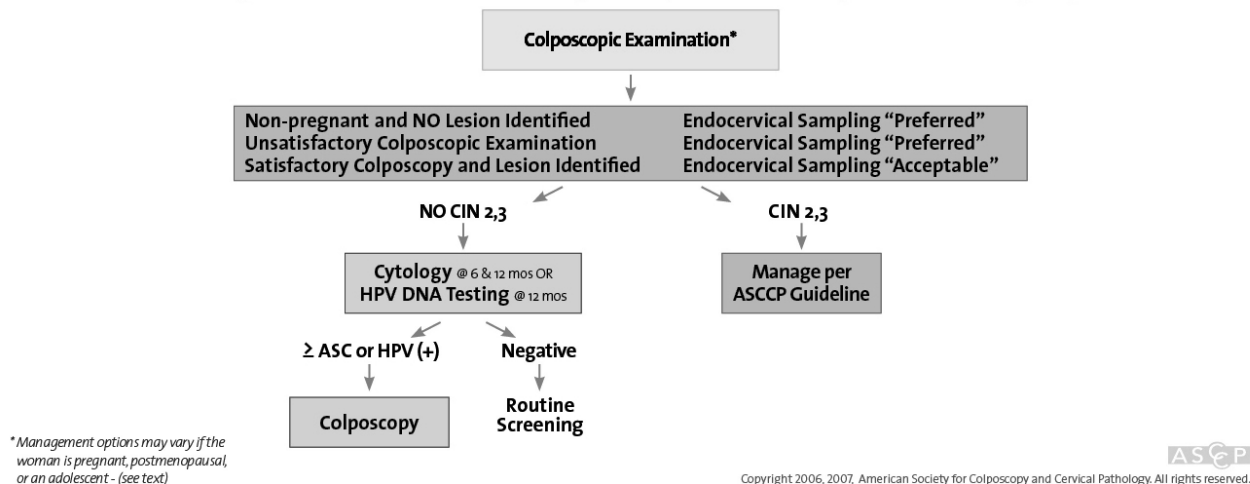


Figure 5. Management of women with low-grade squamous intraepithelial lesion (LSIL). Abbreviations: ASC indicates atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus. Wright TC. Management of cervical 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?*

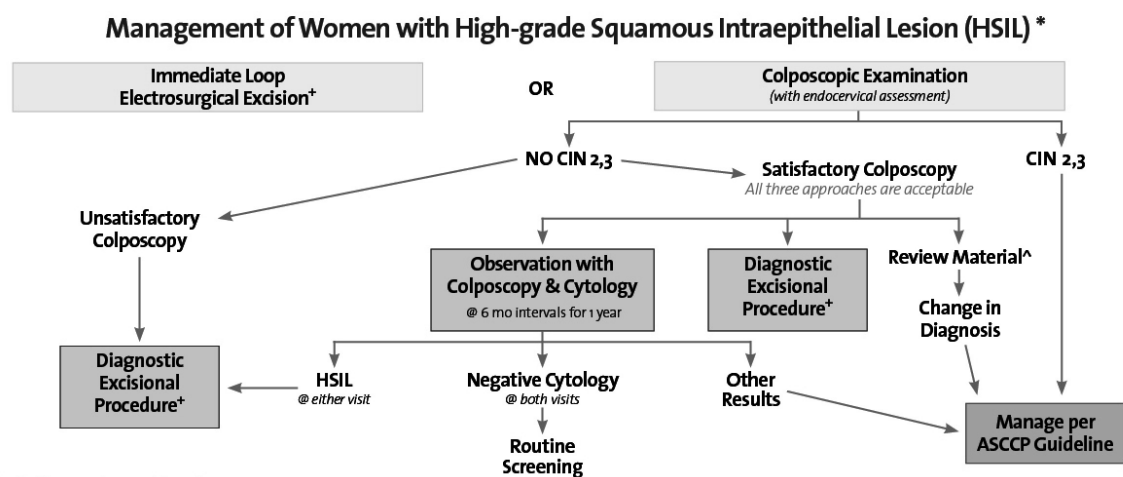
The mean reporting rate of HSIL in U.S. laboratories is 0.7% (98). The rate of HSIL varies with age. A cytology result of HSIL carries a high risk of significant cervical disease. A single colposcopy examination identifies CIN 2+ in 53–66% of women with HSIL, and CIN 2+ is diagnosed in 84–97% of women 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 exci-

sional 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-



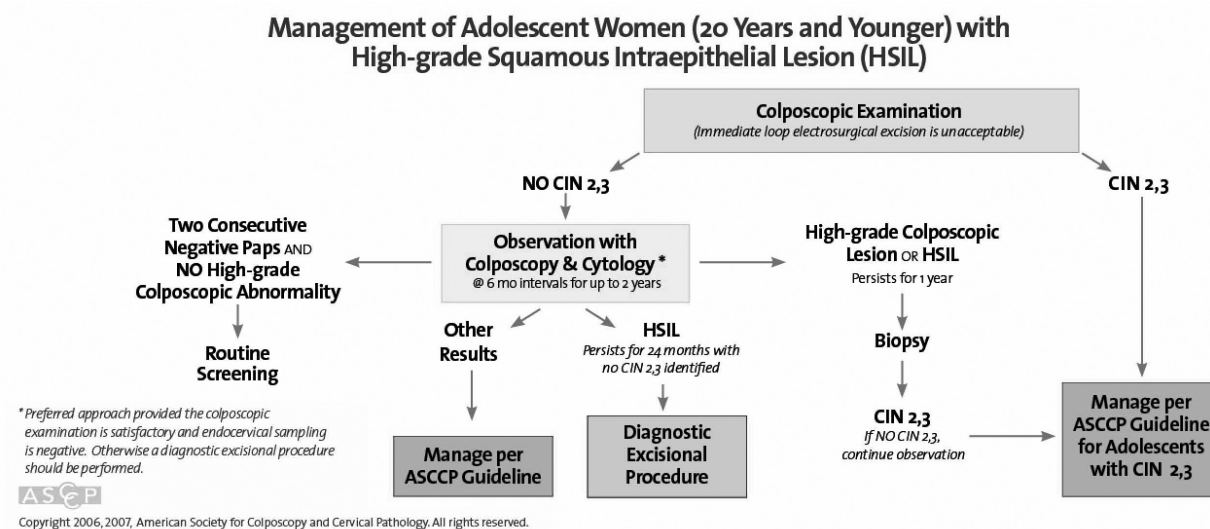
⁺ Not if patient is pregnant or an adolescent

[^] Includes referral cytology, colposcopic findings, and all biopsies

* Management options may vary if the woman is pregnant, postmenopausal, or an adolescent

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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.



* Preferred approach provided the colposcopic examination is satisfactory and endocervical sampling is negative. Otherwise a diagnostic excisional procedure should be performed.

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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 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.

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.

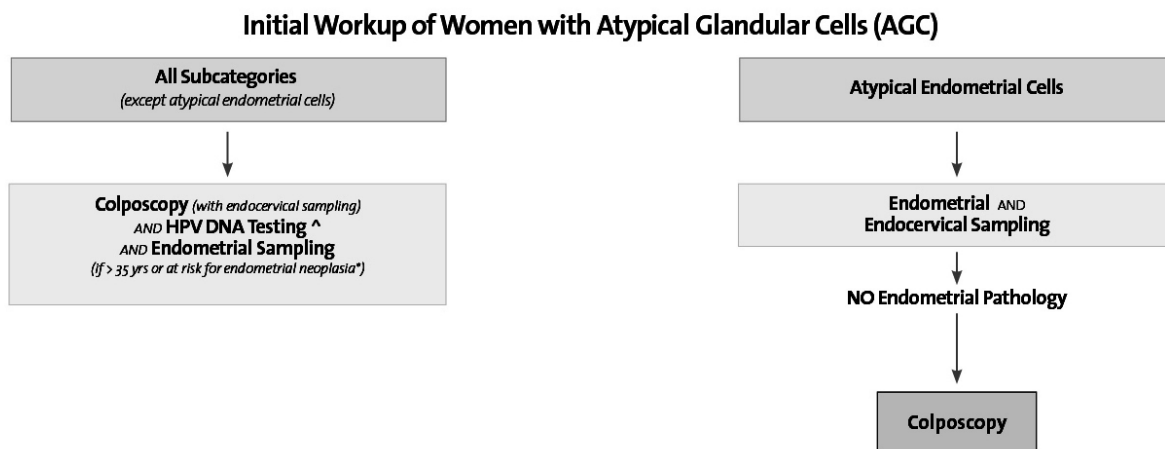
The 2006 consensus guidelines recommend HPV DNA testing at the time of colposcopy in women with atypical endocervical, endometrial, or glandular cells, NOS (Figure 8). Knowledge of the HPV status in these women who do not have CIN 2,3 or glandular neoplasia identified histologically will allow expedited 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 pro-

vides 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.



[^] If not already obtained. Test only for high-risk (oncogenic) types.

^{*} Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.

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.

Subsequent Management of Women with Atypical Glandular Cells (AGC)

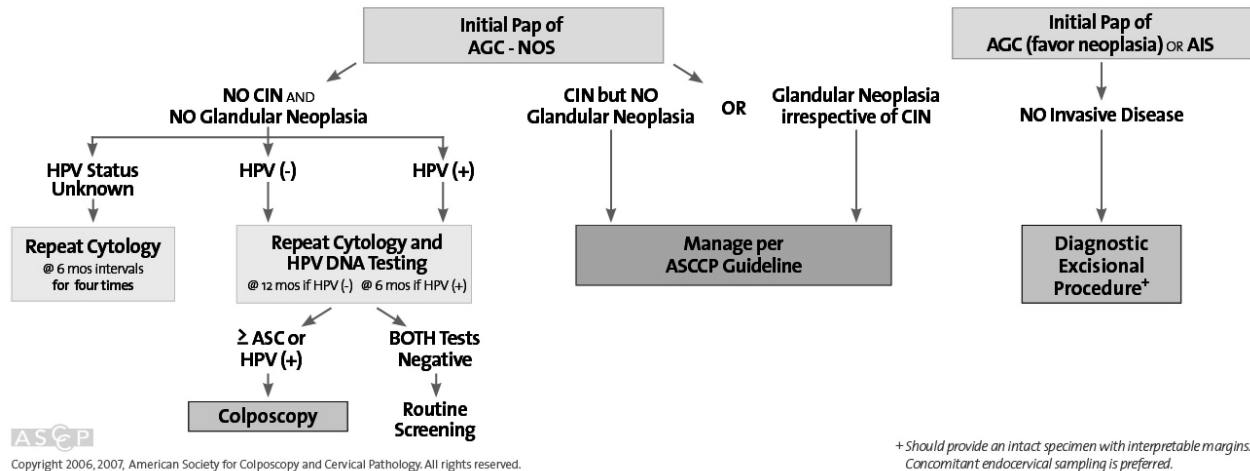


Figure 9. Subsequent management of women with atypical glandular cells (AGC). Abbreviations: AGC indicates atypical glandular cells; AGC-NOS, atypical glandular cells—not otherwise specified; AIS, adenocarcinoma in situ; ASC, atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical 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.

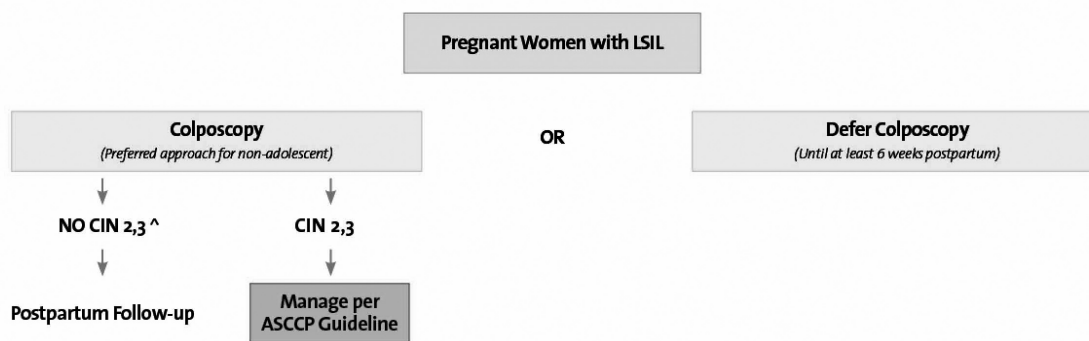
► **How do care and follow-up differ for women during pregnancy?**

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,

Management of Pregnant Women with Low-grade Squamous Intraepithelial Lesion (LSIL)



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^ In women with no cytological, histological, or colposcopically suspected CIN 2,3 or cancer

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.

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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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