Diagnosis and Management of Adenocarcinoma in Situ

A Society of Gynecologic Oncology Evidence-Based Review and Recommendations

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This publication represents an extensive literature review with the goal of providing guidelines for the evaluation and management of cervical adenocarcinoma in situ (AIS). The authors drafted the guidelines on behalf of the Society of Gynecologic Oncology, and the guidelines have been reviewed and endorsed by the ASCCP. These guidelines harmonize with the ASCCP Risk-Based Management Consensus Guidelines and provide more specific guidance beyond that provided by the ASCCP guidelines. Examples of updates include recommendations to optimize the diagnostic excisional specimen, AIS management in the setting of positive compared with negative margins on the excisional specimen, surveillance and definitive management after fertility-sparing treatment, and management of AIS in pregnancy. The increasing incidence of AIS, its association with human papillomavirus–18 infection, challenges in diagnosis owing to frequent origin within the endocervical canal, and the possibility of skip lesions all make AIS a unique diagnosis whose management needs to be differentiated from the management of the more prevalent squamous cell dysplasia.

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This evidence-based review and recommendations have been endorsed by ASCCP. Each author has confirmed compliance with the journal’s requirements for authorship.

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The incidence of cervical adenocarcinoma in situ (AIS) is rising, and though an increase in the number of diagnoses of in situ squamous cell carcinoma has been associated with a concomitant decrease in the incidence of invasive squamous cell carcinoma owing to earlier diagnosis and treatment, a similar decrease in subsequent invasive adenocarcinoma has not occurred.1 This suggests delayed diagnosis of AIS, a shorter interval of disease progression from clinically evident AIS to invasive adenocarcinoma, or both. Although other cervical cancer screening management guidelines provide specific algorithms for initial screening and management,2–5 they do not provide detailed recommendations for management and surveillance of AIS, especially when conservative management is desired. The purpose of these guidelines is to provide clinicians with information and recommendations for diagnosis and management of cervical AIS.

BACKGROUND

Epidemiology

The incidence of cervical AIS has increased over the past few decades, especially among individuals aged 30–40 years.1,6 The mean age at diagnosis is 35–37 years,6,7
and the current incidence rate is approximately 6.6 per 100,000 persons, increasing to 11.2 per 100,000 persons at the peak age of 30–39 years. The average interval between a diagnosis of clinically detectable AIS and early invasive cancer is at least 5 years. Additionally, approximately 55% of patients with AIS have a coexisting squamous lesion.

**Etiology and Risk Factors**

Human papillomavirus (HPV) infection, particularly infection with HPV-16, -18, or both, is the primary risk factor for AIS and associated cervical cancer. Although HPV-18 is associated with only 8% of all high-grade dysplasia (cervical intraepithelial neoplasia [CIN] 2 or worse and AIS) diagnoses (compared with 46–58% for HPV-16), it is associated with 38–50% of AIS diagnoses and 50% of all invasive cancer diagnoses (squamous cell carcinoma plus adenocarcinoma). Therefore, factors that inhibit suppression of HPV are additional risk factors for AIS, such as immunosuppression (eg, rheumatologic disease on two or more immunosuppressants, human immunodeficiency virus [HIV], solid organ transplant) and smoking. Some studies also suggest oral contraceptive pill use as a risk factor for AIS. Conversely, vaccination against HPV is anticipated to be protective, with early evidence of this demonstrated by a decrease in incidence rate of AIS in the first 8 years of the HPV Vaccine Impact Monitoring Project among women aged 21–24 years, despite stable incidence rates in women aged 25–29 years and increases in women aged 30–39 years.

**GUIDELINE QUESTIONS**

This clinical practice guideline addresses the following clinical questions: 1) What clinical evaluation and diagnostic tests should be performed for individuals with suspected cervical AIS? 2) How should diagnostic or therapeutic excisional procedures be performed? 3) What are the recommendations for patients undergoing definitive surgical management with positive compared with negative excisional biopsy margins? 4) Which patient and disease criteria should be used to identify individuals who are eligible for fertility-sparing therapy? 5) What is the recommended surveillance after treatment of AIS? 6) How should AIS be managed during pregnancy? (Fig. 1).

**METHODS**

**Guideline Development Process**

The authors reviewed the available evidence, contributed to the development of the guidelines, provided critical review of the guidelines, and finalized the guideline recommendations. The guidelines were also reviewed and approved by the Society of Gynecologic Oncology (SGO) Clinical Practice Committee, SGO Education Committee, SGO Publications Committee, and the SGO board members before submission for publication.

The recommendations were developed by a panel of gynecologic oncologists who were members of the SGO Clinical Practice and Education Committees. Panelists reviewed and considered evidence from current cervical cancer screening and dysplasia management guidelines, observational studies, and meta-analyses; phase III randomized clinical trials for management of AIS do not currently exist. A list of the MeSH terms searched are included in Appendix 1, available online at http://links.lww.com/AOG/B790.
The terminology used in these guidelines was adopted from the American Society for Colposcopy and Cervical Pathology (ASCCP) management guidelines using a two-part rating system to grade the strength of recommendation and quality of evidence (Table 1). The rating for each recommendation is given in parentheses. Similar to the ASCCP guidelines, the terms “recommended,” “preferred,” “acceptable,” “unacceptable,” and “not recommended” are used to describe interventions.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

Clinical Question 1
What clinical evaluation and diagnostic tests should be performed for patients with suspected cervical AIS?

Recommendation 1.1
Evaluation of abnormal cytology or a positive HPV test result or both is recommended per the ASCCP Risk-Based Management Consensus Guidelines (BII), and colposcopic examination should be performed using the ASCCP colposcopy standards (Table 2). Atypical glandular cells (AGC) and HPV-16 and -18 are associated with AIS and should be evaluated with colposcopy, endocervical sampling, and endometrial biopsy, as recommended by the ASCCP Risk-Based Management Consensus Guidelines (http://www.asccp.org/consensus-guidelines). Given the association of HPV-18 with AIS, endocervical sampling in the setting of a positive HPV-18 test result regardless of colposcopy findings is acceptable (CIII).

Recommendation 1.2
A diagnostic excisional procedure is recommended for all patients with AIS diagnosed on cervical biopsy, as well as all patients whose cervical biopsy and endocervical curettage results are negative in the setting of cytology results showing AIS or AGC-favor neoplasia. For persistent AGC-not otherwise specified, refer to ASCCP Risk-Based Management Consensus Guidelines. A diagnostic excisional

Table 1. Rating the Recommendations

| Strength of recommendation*  | Good evidence for efficacy and substantial clinical benefit support recommendation for use. |
|------------------------------|------------------------------------------------------------------------------------------|
| A                            | Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use. |
| B                            | Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds. |
| C                            | Moderate evidence for lack of efficacy or adverse outcome supports a recommendation against use. |
| D                            | Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. |
| Quality of evidence*          | Evidence from at least one randomized, controlled trial. |
| I                            | Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments. |
| II                           | Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. |
| Terminology used for recommendations† | Good data to support use when only one option is available. |
| Recommended                  | Option is the best (or one of the best) when there are multiple options. |
| Preferred                    | One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option. |
| Acceptable                   | Weak evidence against use and marginal risk for adverse consequences. |
| Not recommended              | Good evidence against use. |
| Unacceptable                 |                                                                                           |

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† The assignment of these terms represents an opinion ratified by vote during the 2012 consensus conference.
procedure is recommended to rule-out an invasive adenocarcinoma, even when definitive hysterectomy is planned (AII).

**Literature Review**

Nearly all AIS lesions are asymptomatic and thus are diagnosed during cervical cancer screening examinations. A cytologic diagnosis of AGC results in a diagnosis of AIS in 3–4% of cases and invasive cervical adenocarcinoma in 2%. However, any degree of cytologic atypia can be indicative of AIS, and one study showed AIS diagnosis is most often preceded by a low-grade cytologic abnormality (atyypical squamous cells of undetermined significance, low-grade

### Table 2. ASCCP Risk-Based Colposcopy Standards and Atypical Glandular Cells Evaluation

| Precolposcopy Test Results | Colposcopic Finding* | Recommendation(s) |
|---------------------------|-----------------------|-------------------|
| Low risk: cytology less than HSIL and HPV-16 and -18-negative | Normal | No biopsies |
| Intermediate risk: cytology HSIL, ASC-H, or HPV-16– or -18-positive | Acetowhitening, metaplasia, other abnormality | 2–4 targeted biopsies of acetowhite, metaplastic, or abnormal lesions |
| High risk: combination of 2 of the following: HSIL HPV-16– or -18-positive High-grade colposcopic impression | Acetowhitening, metaplasia, other abnormality | 2–4 targeted biopsies of acetowhite, metaplastic, or abnormal lesions |
| Refer to The ASCCP Risk-Based Management Consensus Guidelines for other history-test result combinations that have a 50% or greater risk of high-grade dysplasia AGC, AIS | Normal | Excisional treatment without colposcopic examination (preferred if risk of high-grade dysplasia is 60% or higher per ASCCP Risk-Based Management Consensus Guidelines*) OR Colposcopy with biopsies |
| AIS, AGC-favor neoplasia | Biopsy and endocervical sampling histology negative | Diagnostic excisional procedure recommended |
| Any of the above | Squamocolumnar junction not fully visualized (regardless of other findings) | Endocervical sampling$^a$ |

* ASCCP minimal colposcopic reporting standards: squamocolumnar junction visibility (fully visualized or not fully visualized); acetowhitening (yes or no); lesion(s) present (yes or no; acetowhite or other); colposcopic impression (normal or benign; low-grade; high-grade; cancer).

$^a$ ASCCP Risk-Based Management Guidelines: http://www.asccp.org/consensus-guidelines.
squamous intraepithelial lesion). Moreover, because these lesions originate from inside the endocervix, the abnormal cells are often missed on cytology. The ASCCP Risk-Based Management Consensus Guidelines provide individualized recommendations for evaluation of abnormal cytologic or positive HPV test results or both (http://www.asccp.org/consensus-guidelines). Although not specified by the ASCCP management guidelines, given the high rate of HPV-18–positive AIS, endocervical sampling for any patient who tests positive for HPV-18 is acceptable. An endocervical sample can be obtained using an endocervical curette, which may provide cervical stroma to aid in grading of dysplasia, or an endocervical brush, which is less prone to insufficient sampling and may have higher sensitivity.

Adenocarcinoma in situ frequently coexists with squamous dysplasia. When concomitant AIS and CIN are diagnosed, management should proceed per the recommendations for AIS. When AIS is diagnosed on cervical biopsy, approximately 15% will be associated with an invasive adenocarcinoma. Therefore, the next step in evaluation is a diagnostic excisional procedure to confirm the diagnosis, assess the extent of disease, evaluate for coexisting squamous lesions, and exclude invasive adenocarcinoma before definitive management. A diagnostic excisional procedure is also recommended when cervical biopsies and endocervical curettage are negative in the setting of cytology results of AIS, AGC-favor neoplasia, or persistent AGC-not otherwise specified. A diagnostic excisional procedure before definitive management with hysterectomy is recommended to evaluate for invasive adenocarcinoma, which may require radical hysterectomy; if negative margins are not achieved on the first excision specimen, a second excisional procedure is recommended before hysterectomy to exclude an invasive cancer unless this cannot be performed safely.

Clinical Question 2
How should diagnostic or therapeutic excisional procedures be performed?

Recommendation 2.1
Excisional procedures optimally result in removal of an intact specimen to facilitate accurate interpretation of margin status. Thus, excision by cold knife conization is preferred unless the surgeon is able to consistently remove an intact (“top hat” endocervical excision is unacceptable) specimen of adequate length and width (AII).

Recommendation 2.2
Length of the excisional specimen of at least 10 mm is preferred and can be increased to 18–20 mm in patients who have completed childbearing (BII). Endocervical sampling above the excisional bed to evaluate for residual disease is preferred (CIII).

Literature Review
Traditionally, cold knife conization has been recommended over loop electrosurgical excision procedures (LEEP) owing to concern that cautery artifact could obscure the diagnosis. However, a meta-analysis of retrospective studies showed no difference in residual disease (LEEP 9.1% vs cold knife conization 11%) or recurrence risk (LEEP 7.0% vs cold knife conization 5.6%) by excisional method despite a higher risk of positive margins with LEEP (44%) compared with cold knife conization (29%; relative risk 1.55, 95% CI 1.34–1.80). Thus, the ASCCP management guidelines allow diagnostic excision using any modality, but it is imperative that, “care must be taken to keep the specimen intact and margins interpretable, avoiding fragmentation of the specimen, including ‘top-hat’ serial endocervical excisions.” Therefore, except in the hands of a highly skilled LEEP surgeon who is able to obtain an adequate specimen without fragmentation (ie, one intact specimen removed with one pass of the loop; “top hat” excision is unacceptable), excision by cold knife conization is preferred because there is a higher likelihood of the specimen being removed in one piece with adequate depth and width. Length of the conization specimen should be at least 10 mm and can increase to 18–20 mm for patients who have completed childbearing. For surgeons who are not able to consistently obtain intact excisional specimens with adequate length, referral for the initial excisional procedure to a gynecologic oncologist or other surgeon who specializes in the management of cervical dysplasia is preferred. Data on utility of sampling above the excisional bed are conflicting, but endocervical sampling with endocervical curettage or endocervical brushing above the excisional bed to evaluate for residual disease is preferred owing to the frequent location of AIS within the endocervical canal, which makes determining the extent of the lesion more difficult, and the potential for multifocal disease.

Clinical Question 3
What are the recommendations for patients undergoing definitive surgical management with positive compared with negative excisional biopsy margins?
Recommendation 3.1
Simple hysterectomy is preferred for patients with confirmed diagnosis of AIS with negative margins on the conization specimen (BIII).

Recommendation 3.2
Either modified radical hysterectomy or simple hysterectomy is acceptable for patients with confirmed diagnosis of AIS with positive margins on the conization specimen (CIII).

Recommendation 3.3
Surgical assessment of lymph nodes is acceptable at the time of hysterectomy (CIII).

Literature Review
Margin status is a predictor for residual and recurrent disease and progression; thus, it is essential that the margin status can be assessed and that margins are negative. Recurrence risk of AIS is only 2.6% with negative margins but increases to 19% when margins are positive.7 Adenocarcinoma in situ is also associated with “skip lesions”—foci of adenocarcinoma cells that are not contiguous. Therefore, even with negative margins, the risk of residual AIS on a second excisional specimen is 20% (compared with 53% if margins are positive), and 2% of patients will be diagnosed with an invasive cancer (compared with 6% if margins are positive). Therefore, simple hysterectomy is recommended for all patients with a confirmed diagnosis of AIS with negative margins on conization. For patients with a persistent positive margin despite repeat excisional procedures, a modified radical hysterectomy or radical trachelectomy for those who desire future pregnancy is acceptable owing to an increased risk of diagnosing an occult invasive carcinoma.23,24 Although, historically, radical hysterectomy has been the treatment of choice for microinvasive adenocarcinoma of the cervix owing to concerns about skip lesions and difficulty determining depth of invasion, retrospective observational studies have not shown that radical surgery for microinvasive adenocarcinoma is associated with a survival benefit compared with simple hysterectomy.25–28; therefore, simple hysterectomy even for patients in whom a negative margin cannot be achieved with excisional procedures is acceptable. The ongoing prospective Gynecologic Oncology Group protocol 278 (NCT01649089), in which patients with stage IA1–IB1 cervical carcinomas, including adenocarcinomas, will be surgically treated with simple hysterectomy and pelvic lymphadenectomy, may help clarify whether simple hysterectomy is sufficient for all microinvasive cervical cancers.

For patients who are ultimately diagnosed with microinvasive adenocarcinoma after hysterectomy, the risk of lymph node metastases ranges from less than 1% to 3%, with observational study data limited by the fact that lymphadenectomy was not performed in all patients.27,28 Therefore, lymph node assessment at the time of surgery for AIS is acceptable but not required and should be guided by the surgeon’s risk assessment, which may include factors such as margin status of the preceding excisional specimen or postexcisional endocervical sampling results, pathologist concern for malignancy, HPV results [HPV-16 or -18–positive vs other high-risk HPV type], and patient risk factors (eg, immunosuppression).

The risk of ovarian metastases in patients with invasive adenocarcinoma is 2–5%29–34 (compared with a less than 1% risk in the setting of squamous cell carcinoma). Risk of ovarian metastases increases with increasing clinical stage of disease and deeper stromal invasion and thus is rare in the setting of microinvasive disease.29–32 Furthermore, retrospective observational studies have not shown a difference in recurrence rates or survival when ovaries are left in situ. Therefore, decisions regarding ovarian management at the time of hysterectomy should be individualized based on patient age, hormonal status, and other risk factors. Opportunistic salpingectomy at the time of hysterectomy should be discussed with patients for potential ovarian or fallopian tube cancer risk reduction per the American College of Obstetricians and Gynecologists’ Committee Opinion35 but is not required for management of AIS or adenocarcinoma of the cervix.

Clinical Question 4
Which patient and disease criteria should be used to identify patients who are eligible for fertility-sparing surgery?

Recommendation 4.1
For patients of reproductive age who desire future pregnancy, for whom negative margin status on conization has been achieved, and who are willing and able to adhere to surveillance recommendations, fertility-sparing management with a conization procedure is acceptable (AII).

Recommendation 4.2
For patients in whom negative margins cannot be achieved after multiple excisional procedures, fertility-sparing management is not recommended (DIII).
Recommendation 4.3
For patients who initially underwent fertility-sparing management of AIS and have subsequently completed childbearing, either hysterectomy or continued surveillance is acceptable for those who have had consistently negative HPV test results during surveillance (CIII). For patients who have had positive HPV test results during surveillance, hysterectomy after completion of childbearing is preferred (CIII).

Literature Review
Unfortunately, AIS is often diagnosed in patients of reproductive age who desire future pregnancy. For these individuals, conservative management with an excisional procedure achieving negative margins is acceptable. Data on long-term outcomes after conservative management of AIS are limited, with small study populations ranging from 28 to 136 patients and average follow-up period of 3–5 years. The recurrence risk for AIS among patients undergoing an excisional procedure is approximately 3%36–41 but has been reported to be as high as 12%.42 One study showed positive HPV test results during surveillance to be the only significant predictor for recurrence (odds ratio [OR] 2.72, 95% CI 1.08–6.87) and positive HPV test results (OR 3.74, 95% CI 1.85–7.62) and positive margins (OR 5.0, 95% CI 1.09–20.0) to be the only predictors for progressive disease.42 Therefore, for patients with consistently negative HPV test results during surveillance, either hysterectomy or continued observation without hysterectomy after completion of childbearing is acceptable. However, for patients who have positive HPV test results during surveillance, hysterectomy after completion of childbearing is preferred.

For patients in whom negative margins cannot be achieved after multiple excisional procedures, hysterectomy is recommended, and fertility-sparing management should be pursued only in select cases and after a frank discussion about the significantly increased risk of persistent or recurrent AIS and cancer. Data are lacking on outcomes after radical trachelectomy for treatment of persistent AIS, but it could be considered as an alternative for patients who strongly desire future fertility.

Clinical Question 5
What is the recommended surveillance after treatment of AIS?

Recommendation 5.1
For patients who undergo definitive management with hysterectomy, surveillance per the ASCCP Risk-Based Management Consensus guidelines (http://www.asccp.org/consensus-guidelines) is recommended for at least 25 years after diagnosis, even if that extends the testing period beyond the age of 65 years (CIII).

Recommendation 5.2
i) For patients who undergo fertility-sparing management, surveillance with Pap plus HPV co-testing and endocervical sampling is recommended every 6 months for the first 3 years, then annually for at least 2 years or until hysterectomy is performed (BII).

ii) For patients who have consistently negative co-testing results in the first 5 years of surveillance, extending surveillance to every 3 years indefinitely is acceptable (CIII).

Literature Review
Owing to an increased risk of developing vaginal dysplasia after a history of cervical dysplasia, it is recommended that definitive surgical management should be followed by at least 25 years of surveillance per the ASCCP Risk-Based Management Consensus Guidelines, with vaginal colposcopy performed to evaluate high-grade cytology results, persistent low-grade cytology results, or persistent positive HPV test results (two or more); although the HPV test is not currently U.S. Food and Drug Administration–approved for vaginal screening or surveillance, the high negative predictive value of the test can identify those individuals who are at low risk for developing vaginal cancer.43 Management of abnormal vaginal cytology and positive HPV test results in this setting is beyond the scope of these management guidelines and is well-defined in the review article by Khan et al.43 After fertility-sparing management, “long-term follow-up with a combination of co-testing and colposcopy with endocervical sampling” is recommended per the ASCCP guidelines.3 However, the ASCCP guidelines do not specify the frequency of follow-up. A prospective study of 119 conservatively treated patients with AIS showed a persistent, recurrent, or progressive disease rate of 13%, with 4% of recurrences occurring as late as 3 years after the initial excisional procedure.42 Notably, there were no recurrences among patients whose posttreatment surveillance HPV test results were negative, and multivariate analysis showed that HPV status was the strongest predictor for recurrent disease. Sensitivity of HPV testing for persistent, recurrent, or progressive disease is 90%, compared with 60% for cytology.44 Preliminary data
suggest the median time to HPV clearance is longer for patients with AIS compared with those with CIN, and thus prolonged surveillance is recommended.\textsuperscript{44} Given the increased risk of recurrent or progressive disease in the first 36 months after excisional procedure, we recommend co-testing (Pap plus HPV tests) with endocervical sampling (endocervical curettage or endocervical brushing) every 6 months for 3 years, then annual co-testing with or without endocervical sampling for at least 2 years or until hysterectomy at the completion of childbearing.\textsuperscript{45} For patients with a history of AIS who have at least two consecutive negative co-test results after treatment, the 5-year risk of CIN 2 or worse is 1.5\%.\textsuperscript{45} Although this risk is still substantial compared with the 5-year risk of CIN 2 or worse after negative screening test results without a history of high-grade dysplasia, lengthening the surveillance interval to every 3 years is acceptable for individuals who have consistently negative co-testing results in the first 5 years of surveillance.

**Clinical Question 6**
How should AIS be managed during pregnancy?

**Recommendation 6.1**
In the absence of a clinical or histologic suspicion of invasive cancer, excisional procedures are not recommended during pregnancy. Colposcopy omitting endocervical sampling is recommended each trimester, with an excisional procedure performed postpartum. Delaying excision to approximately 6–8 weeks postpartum is preferred, but an excisional procedure as early as 4 weeks postpartum is acceptable (BII).

**Recommendation 6.2**
If an excisional procedure is performed during pregnancy owing to suspicion for an invasive cancer, placement of a prophylactic cerclage is acceptable (CIII).

**Literature Review**
Excisional procedures during pregnancy are associated with an increased risk of hemorrhage, spontaneous abortion, and preterm delivery. Additionally, there is a higher rate of residual disease after excisional procedures performed during pregnancy compared with those performed in a nongravid state.\textsuperscript{46} Therefore, although conization is generally recommended for evaluation of AIS diagnosed on biopsy, it is not recommended during pregnancy unless there is suspicion for an invasive cancer, which would affect the timing of delivery, owing to risk of hemorrhage, infection, premature rupture of membranes, and preterm delivery. If conization is necessary during pregnancy, ideal timing of the procedure is during the second trimester. Excisional procedures should not be performed within 4 weeks of expected delivery owing to increased risk of hemorrhage or extension of the wound. If an excisional procedure is performed during pregnancy, immediate postprocedure placement of a prophylactic cerclage should be considered to decrease risk of hemorrhage and preterm delivery.\textsuperscript{47,48} If conization is delayed until after delivery, colposcopy each trimester with conization after delivery is recommended owing to a high rate of persistent high-grade dysplasia.\textsuperscript{49,50} Delaying an excisional procedure until 6–8 weeks postpartum is preferred, but, owing to concern for loss to follow-up resulting from expiration of health insurance postpartum or other factors, performing an excisional procedure as early as 4 weeks postpartum is acceptable.

**SUMMARY OF RECOMMENDATIONS**

- Incorporating age-appropriate HPV testing into cervical cancer screening is recommended, because HPV testing increases the sensitivity of screening for adenocarcinoma lesions, which often originate inside the endocervical canal and may not be detected on cytology.
- An excisional procedure to rule out an invasive adenocarcinoma before definitive surgical therapy with hysterectomy is recommended. Obtaining an intact specimen (“top hat” excision is unacceptable) with a length of at least 10 mm is preferred, with a goal of achieving negative margins. For surgeons who are unable to consistently obtain intact excisional specimens with adequate length, referral to a gynecologic oncologist or other cervical dysplasia specialist for excisional biopsy is preferred. Endocervical sampling above the excisional site is preferred to evaluate for residual disease.
- Hysterectomy is preferred for all patients who have completed childbearing. If negative margins on the excisional specimen(s) cannot be achieved, either a modified radical hysterectomy or simple hysterectomy is acceptable, recognizing the increased (6\%) risk of an occult invasive adenocarcinoma. Surgical assessment of lymph nodes is acceptable at the time of hysterectomy.
- For patients who desire future pregnancy, conservative management with close follow-up provided negative margins can be achieved is acceptable. Cotesting with endocervical sampling every 6 months for 3 years followed by annual co-testing with or
without endocervical sampling for at least 2 years or until hysterectomy at the completion of childbearing is recommended. Lengthening the surveillance interval to every 3 years is acceptable for patients who have consistently negative co-testing results in the first 5 years of surveillance.

REFERENCES

1. 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.

2. Cervical cancer screening and prevention. Practice Bulletin No. 168. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;128:e111–30.

3. Moyer VA. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;156:880–91, W312.

4. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol 2012;137:516–42.

5. Cleveland AA, Gargano JW, Park IU, Griffin MR, Niccolai LM, Powell M, et al. Cervical adenocarcinoma in situ: human papillomavirus types and incidence trends in five states, 2002-2015. Int J Cancer 2019;146:810–8.

6. Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1278 patients evaluating the predictive value of conization margin status. Am J Obstet Gynecol 2009;200:182.e1–5.

7. Plaxe SC, Saltzstein SL. Estimation of the duration of the preclinical phase of cervical adenocarcinoma suggests that there is ample opportunity for screening. 1999;75:35.

8. Monsonego J, Cox JT, Behrens C, Sandri M, Franco EL, Yap PS, et al. Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: data from the ATHENA trial. Gynecol Oncol 2015;137:47–54.

9. Hariri S, Unger ER, Powell SE, Bauer HM, Bennett NM, Bloch KC, et al. Human papillomavirus genotypes in high-grade cervical lesions in the United States. J Infect Dis 2012;206:1878–86.

10. Joste NE, Ronnett BM, Hunt WC, Pearse A, Langsfeld E, Leete T, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. Cancer Epidemiol Biomarkers Prev 2015;24:230–40.

11. Madeleine MM, Daling JR, Schwartz SM, Shera K, McKnight B, Carter JJ, et al. Human papillomavirus and long-term oral contraceptive use increase the risk of adenocarcinoma in situ of the cervix. Cancer Epidemiol Biomarkers Prev 2001;10:171–7.

12. Wentzensen N, Schiffman M, Silver MI, Khan MJ, Perkins RB, Smith KM, et al. ASCCP colposcopy standards: risk-based colposcopy practice. J Low Genit Tract Dis 2017;21:230–4.

13. Schnatz PF GM, O’Sullivan DM, Sorosky JI. Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol 2006;107:701–8.

14. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol 2013;121:829–46.

15. Mogensen ST, Bak M, Dueholm M, Frost I, 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.

16. Undurraga M, Catarino R, Navarria I, Ibrahim Y, Puget E, Royannez Drevard I, et al. User perception of endocervical sampling: a randomized comparison of endocervical evaluation with the curette vs cytobrush. PLoS One 2017;12:e0186812.

17. Wolf JK, Levenback C, Mäpica A, Morris M, Burke T, Mitchell MF. Adenocarcinoma in situ of the cervix: significance of cone biopsy margins. Obstet Gynecol 1996;88:82–6.

18. Jiang Y, Chen C, Li L. Comparison of cold-knife conization versus loop electrosurgical excision for cervical adenocarcinoma in situ (ACIS): a systematic review and meta-analysis. PLoS One 2012;7:e3170587.

19. Oz M, Cetinkaya N, Korkmaz E, Seckin KD, Meydanli MM, Gungor T. Optimal cone size to predict positive surgical margins after cold knife conization (CKC) and the risk factors for residual disease. J Turk Ger Gynecol Assoc 2016;17:159–62.

20. Bertrand M, Lickrish GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. Am J Obstet Gynecol 1987;157:21–5.

21. 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.

22. Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. Obstet Gynecol 1997;90:1–6.

23. Eisenkop SM, Spiritos NM, Lin WM, Felix J. Laparoscopic modified radical hysterectomy: a strategy for a clinical dilemma. Gynecol Oncol 2005;96:484–9.

24. Costales AB, Melbourne AM, Rhodes HE, Munsell MF, Wallbich JJ, Brown J, et al. Risk of residual disease and invasive carcinoma in women treated for adenocarcinoma in situ of the cervix. Gynecol Oncol 2013;129:513–6.

25. Baalbergen A, Smeds F, Helmerhorst TJ. Conservative therapy in microinvasive adenocarcinoma of the uterine cervix is justified: an analysis of 59 cases and a review of the literature. Int J Gynecol Cancer 2011;21:1640–50.

26. Reynolds EA, Tierney K, Keeney GL, Felix JC, Weaver AL, Roman LD, et al. Analysis of outcomes of microinvasive adenocarcinoma of the uterine cervix by treatment type. Obstet Gynecol 2010;116:1150–7.

27. Smith HO, Qualls CR, Romero AA, Webb JC, Dorin MH, Padilla LA, et al. Is there a difference in survival for IA1 and IA2 adenocarcinoma of the uterine cervix? Gynecol Oncol 2002;85:229–41.

28. Bean LM, Ward KK, Plaxe SC, McHale MT. Survival of women with microinvasive adenocarcinoma of the cervix is not improved by radical surgery. Am J Obstet Gynecol 2017;213:332.e1–6.

29. Hu J, Xiao X, Yang Z, Cui H, Guo H, Wu Y, et al. Should ovaries be removed or not in early-stage cervical adenocarcinoma: a multicenter retrospective study of 105 patients. J Obstet Gynaecol 2017;37:1065–9.

30. Lu H, Li J, Wang L, Zhou H, Liu Y, Wang D, et al. Is ovarian preservation feasible in early-stage adenocarcinoma of the cervix? Med Sci Monit 2016;22:408–14.
31. Natsume N, Aoki Y, Kase H, Kashima K, Sugaya S, Tanaka K. Ovarian metastasis in stage IB and II cervical adenocarcinoma. Gynecol Oncol 1999;74:255–8.

32. Chen J, Wang R, Zhang B, Lin X, Wei J, Jia Y, et al. Safety of ovarian preservation in women with stage I and II cervical adenocarcinoma: a retrospective study and meta-analysis. Am J Obstet Gynecol 2016;215:460.e1–13.

33. Shimada M, Kigawa J, Nishimura R, Yamaguchi S, Kuzuya K, Nakanishi T, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol 2006;101:234–7.

34. Matsuo K, Shimada M, Yamaguchi S, Kanao H, Nakanishi T, Saito T, et al. Identifying a candidate population for ovarian conservation in young women with clinical stage IB-IIB cervical cancer. Int J Cancer 2018;142:1022–32.

35. Opportunistic salpingectomy as a strategy for epithelial ovarian cancer prevention. ACOG Committee Opinion No. 774. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;133:e279–84.

36. Bull-Phelps SL, Garner EI, Walsh CS, Gehrig PA, Miller DS, Schorge JO. Fertility-sparing surgery in 101 women with adenocarcinoma in situ of the cervix. Gynecol Oncol 2007;107:316–9.

37. Kim ML, Hahn HS, Lim KT, Lee KH, Kim HS, Hong SR, et al. The safety of conization in the management of adenocarcinoma in situ of the uterine cervix. J Gynecol Oncol 2011;22:25–31.

38. Li Z, Zhao C. Long-term follow-up results from women with cervical adenocarcinoma in situ treated by conization: an experience from a large academic women’s hospital. J Low Genit Tract Dis 2013;17:452–8.

39. Munro A, Codde J, Spilsbury K, Stewart CJ, Steel N, Leung Y, et al. Risk of persistent or recurrent neoplasia in conservatively treated women with cervical adenocarcinoma in situ with negative histological margins. Acta Obstet Gynecol Scand 2017;96:432–7.

40. Bai H, Liu J, Wang Q, Feng Y, Lou T, Wang S, et al. Oncological and reproductive outcomes of adenocarcinoma in situ of the cervix managed with the loop electrosurgical excision procedure. BMC Cancer 2018;18:461.

41. Baalbergen A, Molijn AC, Quint WG, Smedts F, Helmerhorst TJ. Conservative treatment seems the best choice in adenocarcinoma in situ of the cervix Uteri. J Low Genit Tract Dis 2015;19:239–43.

42. Costa S, Venturoli S, Negri G, Sideri M, Preti M, Pesaresi M, et al. Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: an analysis of 166 cases. Gynecol Oncol 2012;124:490–5.

43. Khan MJ, Massad LS, Kinney W, Gold MA, Mayeaux EJ Jr, Darragh TM, et al. A common clinical dilemma: management of abnormal vaginal cytology and human papillomavirus test results. Gynecol Oncol 2016;141:364–70.

44. Costa S, Venturoli S, Origoni M, Preti M, Mariani L, Cristofonti P, et al. Performance of HPV DNA testing in the follow-up after treatment of high-grade cervical lesions, adenocarcinoma in situ (AIS) and microinvasive carcinoma. Ecanermedscience 2015;9:528.

45. Katki HA, Schiffman M, Castle PE, Fetterman B, Psitras NE, Lorey T, et al. Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. J Low Genit Tract Dis 2013;17:S78–84.

46. Douvier S, Filipuzzi L, Sagot P. Management of cervical intraepithelial neoplasm during pregnancy [in French]. Gynecol Obstet Fertil 2003;31:851–5.

47. Goldberg GL, Altaras MM, Block B. Cone cerclage in pregnancy. Obstet Gynecol 1991;77:315–7.

48. Dane C, Dane B, Cetin A, Erginbas M. Haemostasis after cold-knife conisation: a randomised prospective trial comparing cerclage suture versus electro-cauterization. Aust N Z J Obstet Gynaecol 2008;48:343–7.

49. Kaplan KJ, Dainty LA, Dolinsky B, Rose GS, Carlson J, McHale M, et al. Prognosis and recurrence risk for patients with cervical squamous intraepithelial lesions diagnosed during pregnancy. Cancer 2004;102:228–32.

50. Fader AN, Alward EK, Niederhauser A, Chirico C, Lesnock JL, Zwiesler DJ, et al. Cervical dysplasia in pregnancy: a multi-institutional evaluation. Am J Obstet Gynecol 2010;203:113.e1–6.

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