Update on Cervical Cancer Screening

Timothy V. Johnson, DO
Peter F. Schnatz, DO
Amy M. Johnson, MD
Joel I. Sorosky, MD

In 1941, George Papanicolaou revolutionized the detection and management of cervical cancer with the introduction of cytology-based screening.[1] Although it took 20 years to be fully incorporated into accepted medical protocols, the Papanicolaou or "Pap smear" test has dramatically reduced the incidence of cervical cancer in developed countries. Between 1950 and 1970, the mortality rate as well as the incidence of invasive cervical cancer decreased more than 70% in the United States.[2] Since then, the rates have continued to fall, with a 3.8% annual decrease in cervical cancer mortality in all US women between 1996 and 2003.[3] Developing countries, where routine Pap testing has not been incorporated, have not experienced such dramatic decreases. Of the approximately 273,505 deaths caused by cervical cancer worldwide each year, between 80% and 85% occur in developing countries.[4,5]

In 2006, there were an estimated 9700 new cases of cervical cancer and 3700 deaths due to cervical cancer in the United States.[6] Once the most common cancer-related cause of mortality in women, cervical cancer currently ranks 12th in cancer-related deaths in women.[7] The life-time risk of being diagnosed with cervical cancer is 0.74%.[7] While some guidelines suggest that cervical cancer screening can be discontinued in the 7th decade, in a study of women who developed cervical cancer, the median age at diagnosis was 65 years.[8]

Cervical cancer screening is efficient and effective. The vast majority of new cervical cancer cases in the United States are in women who have never undergone screening or who have had suboptimal screening (**Figure 1**).[7] It is of great importance that primary care and women's health physicians understand the significance of, and maintain the accepted standard of care for, cervical cancer screening and management. This article reviews current guideline recommendations on cervical cancer screening and highlights acceptable screening practices; however, more detailed discussions of the guidelines are available.[9–15] In addition, the 2006 National Institutes of Health consensus guidelines, which are expected to be published later this year, emphasize more conservative evaluation and management for adolescent women (aged ≤ 20 yr) and for women with low-grade squamous intraepithelial lesions (LSIL). These principles have been incorporated in this article.

TAKE HOME POINTS

- Cervical cancer incidence and mortality rates are declining due to excellent screening protocols; cytology-based screening tests should be appropriately offered and interpreted.
- Testing for human papillomavirus (HPV) infection should be reserved mainly for triage of patients with atypical squamous cells of undetermined significance, screening in otherwise healthy women over age 30 years, and posttreatment/postcolposcopic follow-up.
- There is a move toward less aggressive management of adolescent women (ie, ≤ 20 yr) and women with low-grade squamous dysplasia.
- Atypical glandular cells (AGC) are different from atypical squamous cells, and any patient with AGC on Pap testing requires a thorough evaluation.
- The HPV vaccine cannot take the place of cytologic screening (Pap testing), as vaccines are not effective against all high-risk HPV types. The vaccine that is now available brings great hope and promise but raises ethical challenges.

Dr. Timothy Johnson is a resident in obstetrics and gynecology; Dr. Schnatz is an associate professor of obstetrics and gynecology and internal medicine, and Director of Medical Student Education, Department of Obstetrics and Gynecology; Dr. Amy Johnson is an assistant professor of obstetrics and gynecology; they are at the University of Connecticut School of Medicine, Farmington, CT, and Hartford Hospital, Hartford, CT. Dr. Sorosky is a professor of obstetrics and gynecology, the University of Connecticut School of Medicine, Farmington, CT, and Chairman of obstetrics and gynecology, Hartford Hospital, Hartford, CT, and New Britain General Hospital, New Britain, CT.

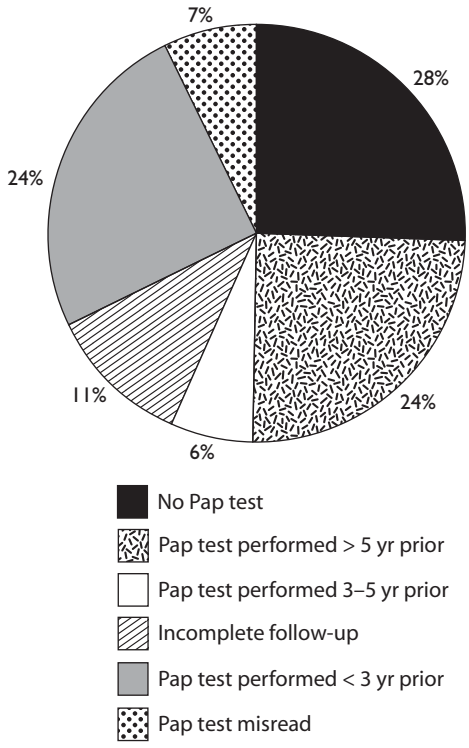

Figure 1. Screening histories of 664 cases of invasive cervical cancer diagnosed between 1 March 1985 and 23 February 1990. (Data from the Connecticut Tumor Registry, as published in Janerich DT, Hadjimichael O, Schwartz PE, et al. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health 1995;85:791–4.)

RISK FACTORS FOR CERVICAL CANCER

The main etiology of a precancerous cervical lesion is persistent infection with a high-risk human papillomavirus (HPV). Although most patients with HPV exposure do not develop dysplasia, almost all cases of dysplasia result from HPV. Fortunately, most patients clear their HPV infection in 3 months to 2 years.[16] However, certain factors can increase HPV exposure and delay clearance, thereby increasing the risk of persistence and progression to dysplasia or cancer. These factors include early age of coitarche, multiple sexual partners, history of sexually transmitted infections, multiparity, smoking, long-term oral contraceptive use, immunocompromise, and diethylstilbestrol exposure.[8,17–20] Several of these factors are based largely on high-risk behavior. In general, factors that increase the number of sexual encounters will increase the likelihood of HPV exposure.

Smoking is an important, modifiable factor that is associated strongly with squamous cell cervical cancer. The cervical mucus of smokers has been found to contain carcinogens. In a recent study of women with minimally abnormal Pap smears, the incidence of cervical intraepithelial neoplasia grade 3 or worse (CIN3, the immediate precursor of cervical cancer) was 3 times higher in HPV-positive smokers compared with HPV-positive nonsmokers.[18] Although the exact mechanism is not clear, one current hypothesis describes a smoking-mediated immune system alteration as a cause.[21] Of note, smoking is not a risk factor for adenocarcinoma of the cervix.

An expanding population of patients infected with HIV is a cause for concern as HPV DNA is approximately 2 times more common in these patients during an initial examination.[19] Not only are HIV-positive patients more susceptible to HPV infection, but the natural history of HPV is also altered in these patients.[19] Clearance of HPV from cervical cells may be impaired in HIV-positive women compared with women with normal immune function. Twenty four percent of HIV-positive women have persistent HPV infection compared with only 3% of HIV-negative women.[19] Anything that suppresses the host immune system (eg, chronic use of glucocorticoids) may cause persistent HPV infection.

In 1971, diethylstilbestrol exposure in utero was found to be a risk factor for clear cell adenocarcinoma of the vagina and cervix. While there is still some debate about the potential association between diethylstilbestrol and squamous cell cancer, a large cohort study showed that the incidence of noncervical cancers is not increased in women exposed to diethylstilbestrol.[20] Regardless, continued surveillance is still reasonable until it is determined whether these women will have an increased risk for cervical cancer during the menopausal years.

HPV AND ITS NATURAL COURSE

HPV is a sexually transmitted DNA virus that is responsible for 99.7% of cervical cancer cases.[22,23] Of the approximately 120 types of HPV viruses, more than 40 are known to infect the anogenital tract, causing genital warts and/or dysplasia. HPV types are categorized as high- and low-risk based on their predilection for causing severe dysplasia. Although there are many high-risk HPV types, approximately 70% of squamous cell cervical cancers are caused by high-risk HPV types 16 and/or 18.[22,24,25] In contrast, HPV 6 and 11 (low-risk types) are most commonly associated with the development of anogenital warts.[22] The new quadrivalent HPV vaccine (*see* The HPV Vaccine section) is efficacious for these 4 strains of HPV (6, 11, 16, and 18).

HPV is very common among sexually active women, and condoms may not provide adequate protection against this virus.[26] In a 3-year cohort study that followed

Table. Summary of Guidelines for Routine Cervical Cancer Screening

	Recommendations		
	ACOG[9]	**ACS[10]**	**USPSTF[11]**
Start	At age 21 yr or 3 yr after initiation of sexual activity	Same as ACOG	Same as ACOG
Intervals			
Conventional Pap test	Annually; every 2–3 yr at age ≥ 30 yr*†	Same as ACOG*†	At least every 3 yr*
ThinPrep test	Annually; every 2–3 yr at age ≥ 30 yr*†	Every 2 yr; every 2–3 yr at age ≥ 30 yr *†	At least every 3 yr*
HPV DNA test	Option: Reflex for ASC-US Option when age ≥ 30 yr: routine every 3 yr if Pap test and HPV DNA test are negative	Same as ACOG	No specific recommendation
Stop	No set upper limit	Age ≥ 70 yr*‡	Age ≥ 65 yr*†
History of hysterectomy with cervix removed	Discontinue if hysterectomy was for a benign indication. Continue screening if there is a recent dysplasia or a history of high-grade dysplasia. If there is no history of DES or cancer, screening can be stopped after 3 negative results.	Same as ACOG	Same as ACOG

ACOG = American College of Gynecology; ACS = American Cancer Society; ASC-US = atypical squamous cells of undetermined significance; DES = diethylstilbestrol; HPV = human papillomavirus; Pap = Papanicolaou; USPSTF = United States Preventive Services Task Force.

*After 3 normal Pap tests.

†Exceptions: Continue screening if the patient has a history of being immunocompromised or is taking an immunosuppressive medication. Additional exceptions include a history of high-grade dysplasia, cervical cancer, or in utero exposure to DES. Patients who have an exception should be followed at least annually. Patients with a history of cervical cancer should be followed, if possible, by a gynecologic oncologist.

‡If no abnormal Pap test in 10 years.

608 college women at 6-month intervals, 26% tested positive for HPV on entry to their school, whereas 60% were HPV-positive by graduation.[16] However, new data have suggested that regular condom use may lower the risk of cervical and vulvovaginal HPV infection.[27]

Despite the high incidence of HPV infection in sexually active women, the natural history of this virus favors clearance rather than progression. In fact, 70% of HPV-infected young women test negative by 12 months after a positive HPV screening test and 92% test negative by 24 months.[16] Fortunately, in the cases where HPV does progress to cytologic atypia, it is a slow process. Approximately 15% of patients with HPV will develop cervical dysplasia within 5 years.[28] Despite the rather indolent progression and tendency towards remission, HPV remains a serious health concern, especially for those without access to screening.

SCREENING GUIDELINES

There are 2 accepted techniques for Pap testing: the conventional Pap smear and the newer liquid-based technology. A conventional Pap test involves smearing the sampled endocervical and ectocervical cells on a glass slide and applying a fixative. With the liquid-based technique, on the other hand, the sample is placed in a preservative solution that is spun down to allow a more refined slide sample. Liquid-based testing is more expensive but is considered to be more sensitive. It is also possible to concurrently test for HPV and other sexually transmitted diseases with the liquid-based test.

Cervical cancer screening guidelines[9–15] address 3 major questions: when to start screening, how often screening should be performed, and when screening can be discontinued. All of these recommendations have been updated within the last several years. Previously, it was recommended that screening should begin at age 18 years or when a woman becomes sexually active. The newer recommendations take into account the natural history of HPV. The American College of Obstetrics and Gynecology (ACOG),[9] the American Cancer Society (ACS),[10] and the United States Preventive Services Task Force (USPSTF)[11] all recommend that screening should begin at age 21 years or 3 years after the initiation of sexual intercourse (**Table**).

There is no consensus, however, regarding the interval at which Pap testing should be performed. ACOG recommends performing Pap testing on a yearly basis until age 30 years. At age 30 years, if a woman has had 3 consecutively normal Pap tests and does not have a high-risk indicator, including current detection of HPV, Pap testing can be done every 2 to 3 years.[9] In addition to a positive HPV test, other high-risk indicators include

being immunocompromised (eg, a history of HIV/AIDS, chronic corticosteroids, organ transplantation, chemotherapy), in utero diethylstilbestrol exposure, or a history of high-grade dysplasia. The ACS also recommends annual Pap testing if the conventional Pap test is used; however, they recommend testing every 2 years if liquid-based Pap testing is used for women under age 30 years who are considered low risk.[10] The USPSTF recommends performing Pap tests at least every 3 years in all low-risk women.[11] A woman with HIV infection should be tested every year regardless of previous Pap test results. Any cervical dysplasia will also require heightened surveillance following appropriate colposcopy, evaluation, and potential therapy.[10]

The ACS and USPSTF suggest that Pap testing can be discontinued around age 65 to 70 years.[10,11] However, in a study that used data from the Connecticut Tumor Registry to assess why cases of cervical cancer had not been diagnosed, the average age of women with cervical cancer who had never been screened was 64.5 years.[17] The study conclusions suggest that efforts should be made to reach and screen older women. Therefore, considering older women to be low risk, especially those with high-risk indicators or an inadequate screening history, may not be appropriate. For these reasons, ACOG has not set a specific upper limit at which testing should be stopped but suggests that clinical judgment be used taking risk factors and life expectancy into consideration.

Pap testing is not necessary after a total hysterectomy if the patient has had prior screening that revealed no cervical cancer or high-grade dysplasia. Women with a history of high-grade squamous intraepithelial lesion (HSIL) or a recent dysplasia should have yearly vaginal cuff screening until 3 consecutive Pap tests are negative.[9] Women with supracervical (subtotal) hysterectomies still need standard screening.

HPV TESTING FOR SCREENING

The introduction of HPV testing has contributed greatly to our screening abilities and allows the clinician to determine if the cytologic sample contains a high-risk type of HPV. HPV testing has several important uses: the management of atypical squamous cells of undetermined significance (ASC-US), routine screening in women aged 30 years and older, and postcolposcopy or posttreatment follow-up (*see* Additional Uses of HPV Testing section). For women aged 30 years and older who have negative cytology and are negative for high-risk HPV, screening should be repeated in 3 years.[9] This technique, if not repeated sooner, provides a similar life expectancy to yearly Pap smear testing yet reduces costs dramatically. Goldie and colleagues[29] found that annual Pap testing costs approximately $2400 per patient over a lifetime and reduces the lifetime risk of cervical cancer by almost 90%. In comparison, triennial screening with HPV testing yields a similar reduction in cervical cancer risk while reducing costs by 30%.[29] Overall, combined cytologic and HPV DNA testing in women aged 30 years and older is highly sensitive and cost-effective.[30]

Routine HPV screening of women younger than 30 years is not recommended because transient HPV infection is common in this group. Likewise, immunocompromised women are not good candidates for HPV testing and should be followed with cytology alone since HPV DNA is detected in approximately 60% of HIV-infected women.[19]

THE BETHESDA CLASSIFICATION SYSTEM

It is well documented that there can be significant differences in the interobserver reproducibility of cytologic reports.[31] The Bethesda classification system, therefore, was initiated in 1988 to reduce confusion among pathologists, clinicians, and patients by providing a uniform terminology for cytology reports. Last updated in 2001, it is now a broad-based, user-friendly system from which clinical decisions can be made. The Bethesda classification system describes specimen adequacy, the presence or absence of an intraepithelial lesion, epithelial cell abnormalities, infective processes, and additional cellular changes that may be important.

To be considered satisfactory, a Pap smear slide should have 8000 to 12,000 squamous cells present if the conventional Pap test technique is used, and 5000 squamous cells if the liquid-based preparation is used. Specimens can be partially (50%–75%) or fully (> 75%) obscured by inflammatory debris or blood. Pap smears that are obscured 75% or less are considered satisfactory if the transformation zone has been adequately sampled; specimens that are more than 75% obscured are reported as unsatisfactory for evaluation. If benign endometrial cells are present, they should be reported only if the patient is aged 40 years or older. Otherwise, they have no clinical significance.[32]

After specimen adequacy, a determination of normal or abnormal cytology is made. Regardless of the finding, additional inflammatory or infectious findings should be reported if present. These may include fungal, bacterial, trichomonal, or other organisms. Normal cytology is reported as "negative for intraepithelial lesion." An abnormal result may be placed in the following categories: ASC-US, atypical squamous cells cannot exclude a high-grade dysplasia (ASC-H), LSIL,

HSIL, squamous cell carcinoma, atypical glandular cells (AGC; either endocervical, endometrial, or glandular) not otherwise specified, AGC-favor endometrial, AGC (either endocervical or glandular)-favor neoplasia (AGC-FN), adenocarcinoma in situ (AIS), and adenocarcinoma (*see* Atypical Grandular Cells section).[32]

TRIAGE OF DYSPLASIA

While there are well-defined protocols to evaluate and manage abnormal Pap smears, areas of confusion and mismanagement still exist. For those who do not perform colposcopy, the algorithm is straightforward. Any dysplasia, other than ASC-US and LSIL in adolescents (aged ≤ 20 yr), requires referral for colposcopy. It is important to keep in mind that a Pap smear is a screening test. Therefore, a final diagnosis is not assigned until further evaluation, including colposcopy, has been performed.

Atypical Squamous Cells

The clinical significance of this classification stems from the underlying risk for concurrent CIN2/3 or cancer. Atypical squamous cells (ASC) should be thought of as a gray zone in which it is difficult for the pathologist to assign a cytologic classification. In the current Bethesda system, the category of ASC is divided into ASC-US or ASC-H. The earlier nomenclature included 1 category of ASC (ie, ASC-US). Between 5% and 15% of patients with ASC-US will end up having CIN2/3. The number of women with ASC-US, however, is so large that the volume of HSIL diagnosed following an ASC-US result is greater than for all other Pap test results.[31–36] Because of the high rate of dysplasia and cancer, it was necessary to further stratify the previously defined ASC-US group into a higher- and lower-risk category. ASC-US pap smears show some, but not all, criteria for LSIL, and many will end up having LSIL. ASC-H, on the other hand, is suggestive of a more severe dysplasia. Approximately 40% of ASC-H cytology has been found to be CIN2 or greater.[37]

Management of ASC-US may follow 1 of 3 pathways (**Figure 2**). If a liquid-based cytology system is being used, then HPV DNA testing can easily be performed. The term "reflex testing" is often used to imply that the sample will automatically be sent for HPV DNA testing if ASC-US is detected during cytologic analysis. Current guidelines suggest that of the 3 pathways, reflex testing is the preferred option.[12,38] Solomon et al[33] found that HPV DNA testing has a greater sensitivity (96%) and a similar specificity (44%) compared with repeat cytology in patients with ASC-US. Reflex HPV testing, therefore, may also be more cost-effective, as it will likely eliminate several Pap tests and the associated office visits.[33,36] If infection with a high-risk HPV type is present, then colposcopy should be the next step, except in adolescents, who can be followed with a repeat Pap test in 6 months or HPV testing in 1 year.[38] If the HPV DNA test is negative, then repeat cervical cytology in 1 year is sufficient.[12]

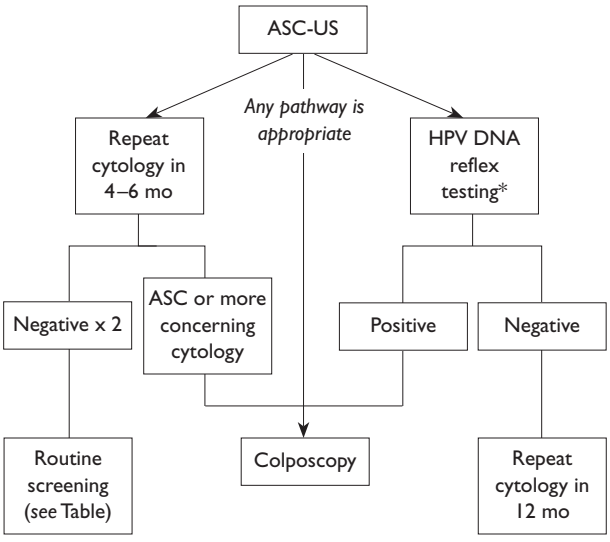

Figure 2. Screening protocol for low-risk† women with ASC-US.[9,12,15,33,38,39] ASC = atypical squamous cells; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus. *Reflex testing implies that the sample will automatically be sent for HPV DNA testing if ASC-US is detected during cytologic analysis. Current guidelines suggest that this is the preferred screening option. †Low-risk includes women without a history of high-grade dysplasia, cervical cancer, in utero exposure to diethylstilbestrol, or being immunosuppressed.

When reflex testing is not used, repeat Pap test should be done at 4- to 6-month intervals until there are 2 consecutive negative results, at which point routine screening can be resumed. If, on the other hand, one of the subsequent results returns as ASC or dysplasia, colposcopy is required.[12] When the entire transformation zone is visualized colposcopically and there is no histologic and/or visual evidence of HSIL, a repeat Pap test in 6 to 12 months is adequate. If CIN2 or CIN3 is present, an ablative or excisional procedure may be necessary. Menopausal women who have ASC-US tend to have a lower incidence of cervical dysplasia, which may be related to inflammatory changes from vaginal atrophy and can likewise be distinguished from dysplasia by HPV testing. If patients have associated atrophic symptoms, they are likely to be resolved by intravaginal estrogen, which also may restore the cytologic findings to normal.[12]

Because of the higher rate of disease associated

with ASC-H, women with this result should be treated as if they have dysplasia and undergo colposcopy with directed biopsy. If no lesion is noted on colposcopy, it does not exclude the possibility of an abnormality. Postcolposcopy HPV testing can be beneficial (*see* Additional Uses of HPV Testing section). Furthermore, there may be instances where a review of the slide with an experienced pathologist is helpful in decision making. If follow-up testing reveals either HPV or dysplasia (eg, ASC-US), repeat colposcopy is necessary.[12]

Low-Grade Squamous Intraepithelial Lesions

Up to 30% of women with a LSIL detected cytologically will actually have CIN2 or CIN3 histologically.[12] Although LSIL is a low-risk dysplasia, it requires a colposcopy and possible biopsy(ies) to make a definitive diagnosis. After confirming the presence of LSIL and absence of other more concerning dysplasia, it is generally considered an infectious process that will likely resolve.

The ACS-US/LSIL Triage Study (ALTS trial) found that HPV DNA was detected in 83% of women with LSIL, suggesting that the HPV DNA test is a poor test for guiding clinical management in patients with LSIL.[39] Therefore, most patients with LSIL should have colposcopy rather than HPV DNA testing since triage based on these results would not be appropriate. With a negative colposcopy and negative biopsy/endocervical curettage results, follow-up cytology at 6 and 12 months would be warranted. An alternative option that has been shown to have better sensitivity includes a single HPV test in 12 months instead of cytology. If the abnormality persists or worsens, colposcopy should be repeated. In adolescents and postmenopausal women, repeat cytology in 6 months or HPV testing in 1 year without colposcopy is reasonable due to the lower incidence of squamous dysplasia is these groups.[38] The use of vaginal estrogen is acceptable if the patient has atrophic changes and no contraindications.

High-Grade Squamous Intraepithelial Lesions

Patients with HSIL require colposcopy with endocervical assessment. The cytologic finding of HSIL is associated with a 75% chance of CIN2/3 and a 1% to 2% chance of invasive cancer.[40] If the histologic appearance of specimens from colposcopically directed biopsies confirms CIN2 or CIN3, management of women over the age of 20 often includes a cone biopsy (cold knife cone biopsy or loop electrocautery excision procedure) or an ablative procedure (cryotherapy or laser therapy). Up to 35% of women with CIN1 (or less severe) on biopsy after a HSIL Pap test actually have CIN2 or CIN3 after further work-up.[41] In these cases, therefore, it may help to review all histologic and cytologic specimens with a pathologist experienced in gynecology. If after review there is no change in the pathology reading, excision of the lesion is indicated.[12] The section on additional uses of HPV testing reviews the options for posttreatment follow-up of patients with HSIL.

Atypical Glandular Cells

AGCs are diagnosed at a rate of approximately 3 cases per 1000 Pap smears.[42,43] While data are needed to understand the implications of the 2001 Bethesda classification of glandular cell abnormalities, a large body of data exists to help understand the clinical significance of AGC. Although it is a relatively uncommon diagnosis, approximately 30% of patients with AGC have a dysplasia or an underlying malignancy (20% with dysplasia, 5% with malignancy, 3% with AIS, and 1.5% with endometrial hyperplasia).[43] Women with persistent AGC, AGC-FN, or an AGC with concurrent ASC (AGC-ASC) have even higher rates of disease.[42,43] In women with AGC-FN, the risk of an underlying malignancy or AIS is significantly increased. In contrast, women with AGC-ASC have higher rates of squamous dysplasia.[42]

The initial work-up for all patients with AGC includes colposcopy with directed biopsy(ies) of the ectocervix and endocervical curettage (**Figure 3**). In women over the age of 35 years or any woman who has endometrial cancer risk factors, an endometrial biopsy should also be performed. If no disease is found on this initial evaluation, a review of the pathology specimens may help further clarify the origin of the underlying glandular abnormality. During the course of the evaluation, a vaginal examination and a pelvic examination should be performed to assess for vaginal dysplasia or adnexal pathology. Because malignancy outside of the uterus can occasionally lead to a finding of AGC on Pap test, routine mammography and colon screening should also be current. An abdominal ultrasound or computed tomography scan may be considered, especially if the patient has systemic symptoms. If the patient has any of the high-risk findings of persistent AGC, an AGC-FN, or an AGC-ASC, a cone biopsy should be performed.[42,43] If testing is still negative, repeat cytology should be performed every 4 to 6 months until there are 4 consecutive normal Pap smears. If a subsequent Pap smear is abnormal, repeat colposcopy again will be necessary.[12,42,43]

A proper understanding of AGC is important, as AGC historically has not been optimally managed. It may be that providers confuse AGC with ASC or that further education is needed.[44] Additionally, patients

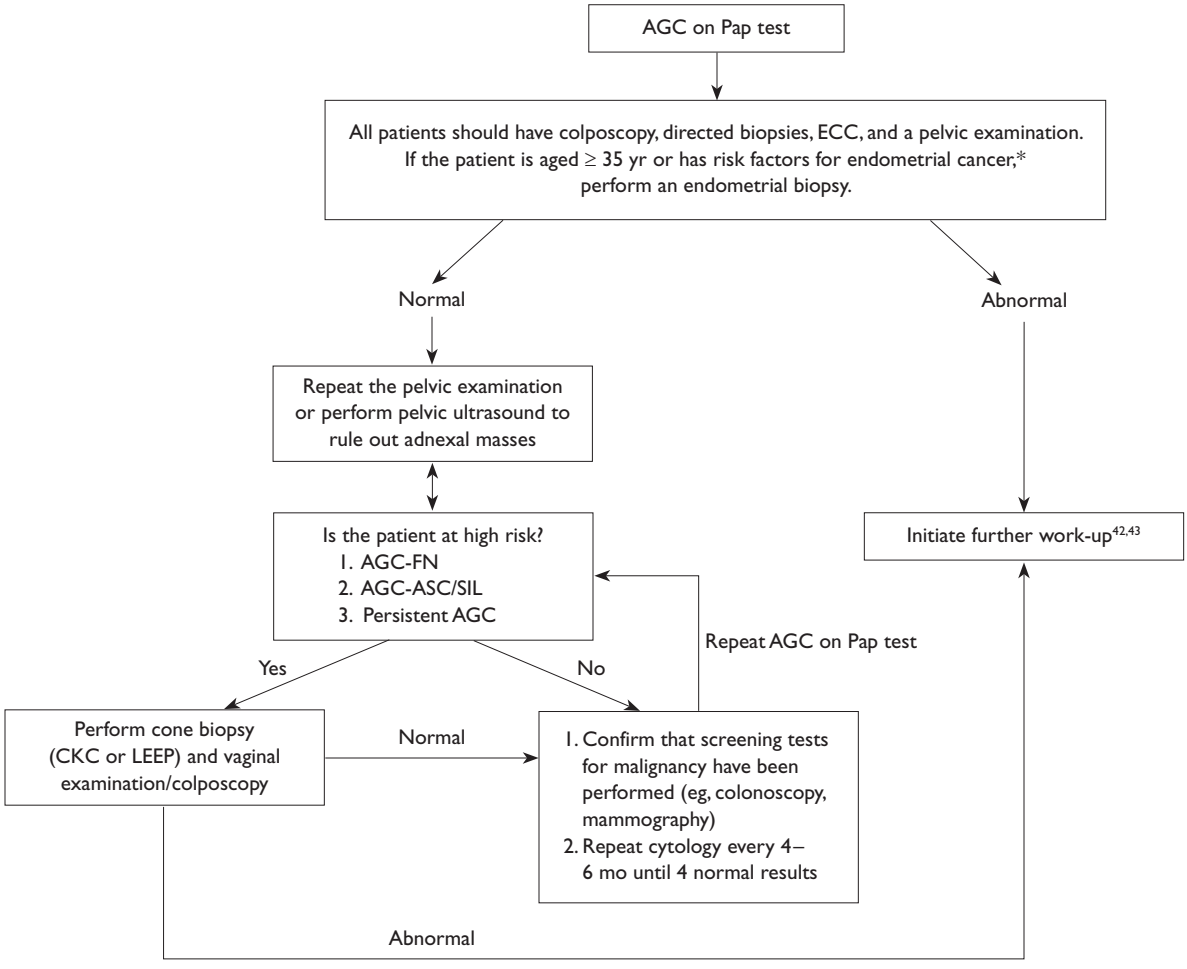

Figure 3. Screening protocol for women with atypical glandular cells (AGC).[42–44] AGC-FN = atypical glandular cells, favor neoplasia; AGC-ASC/SIL = atypical glandular cells with concurrent atypical squamous cells or dysplasia; CKC = cold knife cone biopsy; ECC = endocervical curettage; LEEP = loop electrocautery excision procedure; Pap = Papanicolaou. *Abnormal uterine bleeding, history of anovulation, or history of unopposed estrogen.

with AGC favoring a reactive process, an older term, tend to receive a less thorough work-up.[44] It is important to emphasize, therefore, that any patient with AGC on a Pap smear, regardless of the modifiers, needs to have a thorough evaluation.

PREGNANCY

Pregnant women should be evaluated in a similar manner as nonpregnant women. If colposcopy results show no evidence of malignancy, cervical biopsies can be delayed until postpartum due to the risk of hemorrhage. A biopsy of the ectocervix or gentle cytobrush sampling, however, should not be avoided if malignancy cannot be confidently excluded. If there is no evidence of malignancy by colposcopy or biopsy, repeat colposcopy each trimester until delivery is appropriate for patients with HSIL. Further work-up can then be performed 6 to 12 weeks postpartum.[12]

ADDITIONAL USES OF HPV TESTING

In addition to being used as a component of cervical cancer screening in certain patients, HPV testing also can be used for postcolposcopy and posttreatment follow-up. Patients with an ASC-US, ASC-H, or LSIL Pap test result who are diagnosed with LSIL after colposcopy or who are felt to be normal can be screened either by repeat cytology at 6 and 12 months or with a single HPV test at 12 months. The sensitivity of a single HPV test is actually greater than repeat cytology (92% versus 88%, respectively), and the likelihood of requiring subsequent colposcopy is less (55% versus 64%, respectively) with HPV testing.[38,45] Likewise, women who

are treated for HSIL can be followed by a repeat Pap test with HPV testing at 6 months.[15,38] If these are both negative, the patient can safely return to routine screening, as the sensitivity of detecting persistent CIN2 or CIN3 after 6 months is between 94% and 100%.[15,38,46–50] An abnormal HPV or Pap test result would necessitate follow-up colposcopy. An alternative follow-up regimen includes cytologic screening every 6 months until 3 or 4 consecutive negative results are obtained. Any ASC or more concerning result would likewise necessitate a follow-up colposcopy.[13,15,38]

THE HPV VACCINE

In June 2006, the US Food and Drug Administration approved a recombinant quadrivalent vaccine for prevention of cervical cancer and other diseases caused by HPV in females aged 9 to 26 years.[51] The quadrivalent vaccine is derived from virus-like particles from HPV types 6, 11, 16, and 18. The virus-like particles have no HPV DNA and no infectious potential. While future vaccines may incorporate additional HPV particle types, the 4 covered by the quadrivalent vaccine are responsible for the majority of HPV-related diseases. HPV-16 and HPV-18 cause most cases of HSIL and cancer. HPV-6 and HPV-11, while not generally associated with HSIL or cancer, are responsible for most cases of genital warts.

The HPV vaccine has been shown to prevent persistent HPV-16 infection as well as HPV-16–related HSIL.[52] Mao and colleagues[52] reported the results of a randomized controlled trial designed to evaluate the efficacy of an HPV-16 vaccine in preventing CIN. In that study, the virus-like particle for HPV-16 provided protection for at least 3.5 years. In 755 recipients of the vaccine, there were no cases of HPV-16–related CIN2 or CIN3.[52] It is important to point out that cervical cancer screening will need to continue even in those who have been vaccinated, as other HPV types may lead to disease and some patients may receive the vaccine after being exposed to the virus.

Appropriate implementation of the HPV vaccine presents a challenge. Prophylactic vaccines, by definition, should be given prior to the index exposure. While the HPV vaccine may have benefit in women previously exposed to HPV-16, this has not been proven. For this reason, the ideal time to initiate the vaccine is prior to coitarche. Even vaccines for non-sexually transmitted infections have had challenges with appropriate implementation. Strategies to overcome challenges have included efforts to reduce cost, expand access, implement in-school vaccination programs, and establish regular verification of vaccination rates, with appropriate feedback.[53] Clearly the greatest impact will be in areas of our country and the world that have the highest rates of cervical cancer as well as the poorest access to health care, health insurance, and screening in general. A widespread HPV vaccination program has the potential to change the world of cervical cancer screening but may bring new challenges in terms of vaccine delivery, ethical and moral dilemmas, and cost. Therefore, challenging decisions will need to be made over the next several years as HPV vaccination is responsibly implemented.

CONCLUSION

Cervical dysplasia remains a common source of stress for patients and a frequent challenge for clinicians. With the rapid acquisition of knowledge, the approach to cervical cancer screening has appropriately evolved, including new cervical screening guidelines and the addition of HPV DNA testing. Despite these advances, the vast majority of cervical cancer occurs in women who have had no screening or have had suboptimal screening. With a thorough understanding of screening guidelines and management rationale, along with proper implementation, we can ensure that patients will be well informed and properly treated. Time will tell whether the HPV vaccines will reduce the cervical cancer burden even further in the United States and around the world. **HP**

Acknowledgment: The authors thank John Currie, MD, J. David Schnatz, MD, and John Schorge, MD, for reviewing the manuscript, and David M. O'Sullivan, PhD, for reviewing the manuscript and providing assistance with creating the tables and figures.

Corresponding author: Peter F. Schnatz, DO, Hartford Hospital, Conklin Building 203B, 80 Seymour Street, Hartford, CT 06102; pschnat@harthosp.org

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 42.

REFERENCES

1. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. Am J Obstet Gynecol 1941;42:193–206.
2. Christopherson WM, Lundin FE, Mendez WM, Parker JE. Cevical cancer control: a study of morbidity and mortality trends over a twenty-one year period. Cancer 1976; 38:1357–66.
3. National Cancer Institute. Surveillance Epidemiology and End Results (SEER). Cancer stat fact sheets: cancer of the

cervix uteri. Available at http://seer.cancer.gov/statfacts/html/cervix.html. Accessed 31 Mar 2007.
4. Rohan TE, Burk RD, Franco EL. Toward a reduction of the global burden of cervical cancer. Am J Obstet Gynecol 2003;189(4 Suppl):S37–9.
5. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
6. American Cancer Society. Cancer facts and figures 2006. Available at www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf. Accessed 23 Jan 2007.
7. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975–2002, featuring population-based trends in cancer treatment. J Natl Cancer Inst 2005;97:1407–27.
8. Berrington de Gonzalez A, Sweetland S, Green J. Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis. Br J Cancer 2004;90:1787–91.
9. ACOG Practice Bulletin on Clinical Management Guidelines for Obstetricians-Gynecologists. Cervical cytology screening. In: ACOG Women's Health Care Physician's Compendium of Selected Publications, practice bulletin number 45, August 2003. Washington (DC): ACOG Distribution Center; 2006:398–408.
10. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. American Cancer Society. CA Cancer J Clin 2002;52:342–62.
11. U.S. Preventive Services Task Force (USPSTF). Recommendations and rationale: screening for cervical cancer. Available at www.ahrq.gov/clinic/3rduspstf/cervcan/cervcanrr.htm. Accessed 23 Jan 2007.
12. Wright TC Jr, Cox JT, Massad LS, et al. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. ASCCP-Sponsored Consensus Conference. JAMA 2002;287:2120–9.
13. Wright TC Jr, Cox JT, Massad LS, et al. 2001 consensus guidelines for management of women with cervical intraepithelial neoplasia. American Society for Colposcopy and Cervical Pathology. Am J Obstet Gynecol 2003;189:295–304.
14. Wright TC Jr, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004;103:304–9.
15. Cox JT. Human papillomavirus testing in primary cervical screening and abnormal Papanicolaou management. Obstet Gynecol Surv 2006;61(6 Suppl 1):S15–25.
16. Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338:423–8.
17. Janerich DT, Hadjimichael O, Schwartz PE, et al. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health 1995;85:791–4.
18. McIntyre-Seltman K, Castle PE, Guido R, et al. Smoking is a risk factor for cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. ALTS Group. Cancer Epidemiol Biomarkers Prev 2005;14:1165–70.
19. Sun XW, Kuhn L, Ellerbrock TV, et al. Human papillomavirus infection in women infected with the human immunodeficiency virus. N Engl J Med 1997;337:1343–9.
20. Hatch EE, Palmer JR, Titus-Ernstoff L, et al. Cancer risk in women exposed to diethylstilbestrol in utero. JAMA 1998;280:630–4.
21. Nadais Rda F, Campaner AB, Piato S, et al. Langerhans' cells and smoking in intraepithelial neoplasia of the cervix. Gynecol Oncol 2006;102:356–60.
22. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. N Engl J Med 2003;348:518–27.
23. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12–9.
24. Kurman RJ, Schiffman MH, Lancaster WD, et al. Analysis of individual human papillomavirus types in cervical neoplasia: a possible role for type 18 in rapid progression. Am J Obstet Gynecol 1988;159:293–6.
25. Arends MJ, Donaldson YK, Duvall E, et al. Human papillomavirus type 18 associates with more advanced cervical neoplasia than human papillomavirus type 16. Hum Pathol 1993;24:432–7.
26. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis 2002;29:725–35.
27. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 2006;354:2645–54.
28. Castle PE, Wacholder S, Sherman ME, et al. Absolute risk of a subsequent abnormal pap among oncogenic human papillomavirus DNA-positive, cytologically negative women. Cancer 2002;95:2145–51.
29. Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstet Gynecol 2004;103:619–31.
30. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Natl Cancer Inst 2003;95:46–52.
31. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. JAMA 2001;285:1500–5.
32. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. Forum Group Members; Bethesda 2001 Workshop. JAMA 2002;287:2114–9.
33. Solomon D, Schiffman M, Tarone R. Comparison of three

management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. ALTS Study Group. J Natl Cancer Inst 2001;93:293–9.
34. Manos MM, Kinney WK, Hurley LB, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. JAMA 1999;281:1605–10.
35. Arbyn M, Buntinx F, Van Ranst M, et al. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. J Natl Cancer Inst 2004;96:280–93.
36. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. ASCUS-LSIL Triage Study (ALTS) Group. Am J Obstet Gynecol 2003;188:1383–92.
37. Sherman ME, Solomon D, Schiffman M. Qualification of ASCUS. A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study. ASCUS LSIL Triage Study Group. Am J Clin Pathol 2001;116:386–94.
38. ACOG Practice Bulletin on Clinical Management Guidelines for Obstetricians-Gynecologists. Management of abnormal cervical cytology and histology. In: ACOG Women's Health Care Physician's Compendium of Selected Publications, practice bulletin number 66, September 2005. Washington (DC): ACOG Distribution Center; 2006: 603–22.
39. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. J Natl Cancer Inst 2000;92:397–402.
40. Jones BA, Davey DD. Quality management in gynecologic cytology using interlaboratory comparison. Arch Pathol Lab Med 2000;124:672–81.
41. Brown FM, Faquin WC, Sun D, et al. LSIL biopsies after HSIL smears. Correlation with high-risk HPV and greater risk of HSIL on follow-up. Am J Clin Pathol 1999;112: 765–8.
42. Sharpless KE, Schnatz PF, Mandavilli S, et al. Dysplasia associated with atypical glandular cells on cervical cytology [published erratum appears in Obstet Gynecol 2005;105:1495]. Obstet Gynecol 2005;105:494–500.
43. Schnatz PF, Guile M, O'Sullivan DM, Sorosky JI. Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol 2006;107:701–8.
44. Sharpless KE, Schnatz PF, Mandavilli S, et al. Lack of adherence to practice guidelines for women with atypical glandular cells on cervical cytology [published erratum appears in Obstet Gynecol 2005;105:1495]. Obstet Gynecol 2005;105:501–6.
45. Guido R, Schiffman M, Solomon D, Burke L. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. ASCUS LSIL Triage Study (ALTS) Group. Am J Obstet Gynecol 2003;188:1401–5.
46. Paraskevaidis E, Koliopoulos G, Alamanos Y, et al. Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2001; 98(5 Pt 1):833–6.
47. Jain S, Tseng CJ, Horng SG, et al. Negative predictive value of human papillomavirus test following conization of the cervix uteri. Gynecol Oncol 2001;82:177–80.
48. Lin CT, Tseng CJ, Lai CH, et al. Value of human papillomavirus deoxyribonucleic acid testing after conization in the prediction of residual disease in the subsequent hysterectomy specimen. Am J Obstet Gynecol 2001;184:940–5.
49. Kucera E, Sliutz G, Czerwenka K, et al. Is high-risk human papillomavirus infection associated with cervical intraepithelial neoplasia eliminated after conization by large-loop excision of the transformation zone? Eur J Obstet Gynecol Reprod Biol 2001;100:72–6.
50. Kjellberg L, Wadell G, Bergman F, et al. Regular disappearance of the human papillomavirus genome after conization of cervical dysplasia by carbon dioxide laser. Am J Obstet Gynecol 2000;183:1238–42.
51. U.S. Food and Drug Administration. FDA licenses quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (gardasil) for the prevention of cervical cancer and other diseases in females caused by human papillomavirus. Available at www.fda.gov/cder/Offices/OODP/whatsnew/gardasil.htm. Accessed 23 Jan 2007.
52. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial [published erratum appears in Obstet Gynecol 2006;107:1425]. Obstet Gynecol 2006;107:18–27.
53. Humiston SG, Rosenthal SL. Challenges to vaccinating adolescents: vaccine implementation issues. Pediatr Infect Dis J 2005;24(6 Suppl):S134–40.