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This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Alan G. Waxman, MD, MPH. 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.



Cervical Cytology Screening

Although cervical cancer was the leading cause of cancer death in American women as recently as the 1930s, both the incidence and mortality from cervical cancer have decreased by almost one half since the early 1970s, largely as a result of widespread screening with the Pap test (1–3). However, the annual incidence rate has remained at approximately 8 cases per 100,000 women over the past few years (4). New technology for performing cervical cytology is evolving rapidly, as are recommendations for classifying and interpreting the results. The purpose of this document is to provide a review of the best available evidence on screening for cervical cancer. Specific equipment and techniques for performing cervical cytology and interpretation of the results are discussed elsewhere.

Background

Value of Cervical Cytology

Although the incidence and mortality from cervical cancer have decreased substantially in the past several decades among women in the United States, cervical cancer remains the third most common gynecologic malignancy (2, 5). In countries where cytologic screening is not widely available, cervical cancer remains common. Worldwide, it is the second most common cancer among women, the third most common cause of cancer-related death, and the most common cause of mortality from gynecologic malignancy (3, 6, 7). When cervical cytology screening programs have been introduced into communities, however, marked reductions in cervical cancer incidence have followed (7–9).

Cervical cytology screening is, in many respects, the ideal screening test (8). Cervical cancer has a defined premalignant phase of many years, which allows repeated tests to significantly reduce the impact of individual false-negative test results. Cervical cytology is inexpensive and is readily accepted

among American women. In 1998, 79% of women aged 18 years and older had cervical cytology screening in the preceding 3 years (10). Treatment is effective in reducing the chance of progression to invasive disease.

Despite effective screening measures and treatment, it is estimated that 50% of the women who receive cervical cancer diagnoses each year have never had cervical cytology screening. Another 10% had not been screened within the 5 years before diagnosis (11). Thus, one approach to reducing the incidence and mortality of cervical cancer would be to increase screening rates among women who currently are not screened or undergo screening infrequently (5).

Addressing Errors in Cervical Cytology

In some cases, cervical cancer is undetected despite a recent screening test because of errors in sampling, interpretation, or follow-up. Sampling errors occur when dysplastic cells on the cervix are not transferred to the slide; errors of interpretation are attributed to lack of recognition of abnormal cells in the laboratory. These two sources of false-negative test results are associated with 30% of the new cases of cervical cancer each year (12, 13).

The problem of errors in interpretation is compounded by inconsistency among cytologists. When results of monolayer cytology specimens were reviewed by quality control pathologists, only negative and low-grade squamous intraepithelial lesion (LSIL) readings had greater than 50% consistency (14). Most revised results were downgraded to lesser diagnoses. Of those reported as atypical squamous cells of undetermined significance (ASCUS), 39% were downgraded to negative on further review. Of those originally interpreted as high-grade squamous intraepithelial lesions (HSIL), 50% were reinterpreted as LSIL, ASCUS, or negative.

The 1998 Clinical Laboratory Improvement Amendments (CLIA), passed in response to claims of poor or absent quality control practices in U.S. cytology laboratories, limited the number of cervical cytology tests a technician could read each day to a maximum of 100. In addition, CLIA mandated that each laboratory rescreen at least 10% of the cervical cytology tests that have negative results (15).

Techniques of Cervical Cytology

Sampling involves collecting exfoliated cells from the ectocervix and endocervical canal and transferring them to a glass microscope slide or into a liquid transport medium for review. Patient preparation and proper provider technique can help optimize the collection of cells:

- Cells should be collected before the bimanual examination.

- Care should be taken to avoid contaminating the sample with lubricant.
- If testing for sexually transmitted diseases is indicated, cell collection for cervical cytology should be undertaken first.
- Ideally, the entire portio of the cervix should be visible when the sample is obtained.
- Routine swabbing of the discharge from the cervix may result in cytologic samples of scant cellularity (16).
- In an effort to reduce air-drying artifact, the specimen should be transferred and fixed as quickly as possible.

When performing cervical cytology by standard preparation, a single slide, combining both the endocervical and ectocervical samples, or two separate slides can be used. The most important consideration is rapid fixation. If liquid-based preparations are used, rapid immersion in liquid media is equally important.

New Screening and Interpretation Devices

Many methods to refine and improve cervical cytology have been proposed (17). In the 1980s, new devices were developed for enhancing the collection of exfoliated cells from the cervix. These included nylon brushes for sampling the endocervix and “broom” sampling devices, which simultaneously sample both the ectocervix and endocervix. These devices have been shown to increase the amount of cells captured from the transformation zone and to increase the amount of dysplastic cells collected when compared with cotton-tipped applicators and wooden Ayre’s spatulas (18, 19). In 1996, the U.S. Food and Drug Administration (FDA) approved the first of two currently available liquid-based thin-layer cytology preparations for cervical screening. In addition, automated, computer-based technologies have been marketed that use digitally scanned images to facilitate primary screening and the CLIA-mandated rescreening of cervical cytology tests that have negative results.

Cytologic Reporting

The nomenclature for reporting cervical cytology results has undergone several changes since the publication of the original Papanicolaou system. The Bethesda System of reporting is the most widely used system in the United States (20). First proposed in 1988, it was revised in 1991 and again in 2001 (21–23). The most important changes in the 2001 revised terminology are listed as follows (23):

- Specimen adequacy—Slides are to be reported as “satisfactory” or “unsatisfactory” for interpretation.

“Satisfactory, but limited by ...” is no longer reported as a separate category under the heading “specimen adequacy.” The presence or absence of an endocervical or transformation zone component is described in the narrative portion of the laboratory report, as are other quality indicators, such as partly obscuring inflammation or blood. If a slide is categorized as unsatisfactory, the reason should be specified. If abnormalities are found on an otherwise unsatisfactory slide, it will, by definition, be considered satisfactory for interpretation.

- Negative for intraepithelial lesion or malignancy—This designation should be used for slides with no cytologic evidence of neoplasia. This category includes findings previously designated as “benign cellular changes.” When specific organisms are identified (eg, *Trichomonas vaginalis*, *Candida* species, shift in flora suggestive of bacterial vaginosis, bacteria consistent with *Actinomyces* species, and cellular changes consistent with herpes simplex virus), they are reported and categorized as “negative for intraepithelial lesion or malignancy.” Other nonneoplastic findings, including reactive cellular changes associated with inflammation, radiation, or an intrauterine device, as well as glandular cells posthysterectomy or atrophy, also may be included in this category. Endometrial cells found in a woman aged 40 years or older will be listed under this category, but the finding of endometrial cells will not be reported routinely if noted in a woman younger than 40 years.
- Atypical squamous cells—The epithelial abnormality ASCUS has been replaced by “atypical squamous cells” (ASC) with the subcategories “atypical squamous cells of undetermined significance” (ASC-US) and “atypical squamous cells cannot exclude HSIL” (ASC-H). The modifier of “favor reactive” was eliminated. The category ASC-H was introduced to include those cytologic changes suggestive of HSIL but lacking sufficient criteria for definitive interpretation. The literature suggests ASC-H should represent 5–15% of the total pool of ASC but would have a significantly higher predictive value for diagnosing cervical intraepithelial neoplasia (CIN) of grades 2 or 3 than ASC-US (24, 25).
- Atypical glandular cells—This term designates cells exhibiting atypia that are of glandular rather than squamous origin and replaces the term “atypical glandular cells of undetermined significance.” The finding of atypical glandular cells on cytology is more likely to be associated with both squamous and glandular abnormalities than is ASC-US, and the workup required of atypical glandular cells is

more aggressive (26, 27). The 2001 terminology subdivides atypical glandular cells by cell type, ie, atypical endocervical cells, atypical endometrial cells, or atypical glandular cells not otherwise specified. Although the subdivision of “favor neoplastic” is maintained in the 2001 reporting system, favor reactive is not. In addition, because sufficient cytologic criteria exist to designate endocervical adenocarcinoma and adenocarcinoma in situ, these two findings are reported when identified.

- Low-grade squamous intraepithelial lesions—As in the original terminology, the 2001 nomenclature combines cytologic findings of CIN 1 (mild dysplasia) and those consistent with human papillomavirus (HPV) infections into the category LSIL (22, 28, 29).
- High-grade squamous intraepithelial lesions—The 2001 nomenclature maintains the category of HSIL, which combines CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia, and carcinoma in situ). Although the natural history of CIN 2 lies between CIN 1 and CIN 3, the virology of CIN 2 is more like CIN 3 than CIN 1 in its likelihood of representing aneuploidy and monoclonal proliferation with a single high-risk HPV type (29).
- The absence of endocervical cells or a transformation zone component on the cervical cytology sample may reflect that the transformation zone was not well sampled. This finding is common in pregnant women and in postmenopausal women in whom the transformation zone has receded onto the canal. Data conflict as to whether the lack of these cells is associated with an increase in squamous intraepithelial lesions. Women with this finding whose recent cervical cytology test results have been normal without intervening findings of ASC-US or worse may be monitored by repeat cervical cytology screening in 1 year. Others, including those with incompletely evaluated abnormal test results, incompletely visualized cervix, immunocompromised status, and poor prior screening, should have repeat cervical cytology screening within 6 months. Pregnant women lacking endocervical cells or transformation zone component should have repeat cervical cytology screening postpartum (30).

Natural History of Cervical Neoplasia

Infection with HPV is a necessary factor in the development of cervical neoplasia; however, most HPV-infected women will not develop significant cervical abnormalities (7, 29, 31–33). The infection is easily transmitted during sexual intercourse. Most women, especially

younger women, have an effective immune response that clears the infection or reduces the viral load to undetectable levels in an average of 8–24 months (32, 34–36). Factors that determine which HPV infections will develop into squamous intraepithelial lesions have been poorly identified. Cigarette smoking may be a co-factor, and a compromised immune system appears to play a role in some women (7, 29, 32).

Despite decades of study, the natural history of cervical intraepithelial lesions is still not completely understood. The once widely held concept that low-grade lesions are necessary precursors to the high-grade lesions that, in turn, may progress to invasive cancer has been questioned as the sole pathogenesis (32, 33, 37). It has been observed, for example, that many women present with CIN 2 or CIN 3 without prior CIN 1 lesions. Foci of CIN 1 and CIN 3 with different HPV types have been reported in the same cervical lesion, which raises the possibility that concomitant development of different grades of CIN may occur (37). A few cases of invasive cancer of the cervix have been reported despite continuous and appropriate screening.

Multiple longitudinal studies have attempted to document rates of “progression” and “regression” of CIN. A review of the literature since 1950 reported that 57% of patients with CIN 1 and 32% with CIN 3 undergo spontaneous regression (38). However, the same review reported that 1.7% of all patients with CIN of any grade progress to invasive cancer, ranging from 1% for CIN 1 to more than 12% for CIN 3. Progression from CIN 3 to invasive cancer has been reported in up to 36% of cases (29). A review of 30 years of the literature calculated pooled rates of progression from LSIL and HSIL to invasive cancer to be 0.15% and 1.44%, respectively, over 24 months (39). In that analysis, 47% of LSIL and 35% of HSIL regressed to normal during the 2-year observation period. Conclusions from reviews of multiple natural history studies must be interpreted with caution. The studies included in these reviews used varying diagnostic criteria (biopsy or cytology or both), populations, and duration of follow-up. Moreover, they did not account for the poor reproducibility inherent in both cytologic and histologic diagnoses (14).

Clinical Considerations and Recommendations

► *When should screening begin?*

Cervical neoplasia develops in susceptible individuals in response to a sexually transmitted infection with a high-risk type of HPV (28, 29, 31, 40). The cervix is especial-

ly vulnerable to this infection during adolescence when squamous metaplasia is most active. Human papillomavirus infections are commonly acquired by young women (34, 35), but, in most, they are cleared by the immune system within 1–2 years without producing neoplastic changes. The risk of neoplastic transformation increases in those women whose infections persist (35, 41). Most cervical squamous intraepithelial lesions do not progress to cervical cancer (29, 38, 39). The small proportion of women who do develop invasive squamous cancer generally do so over many years, and the transition from CIN to cancer takes longer in younger women (29). Cervical cancer screening in adolescents within the first 3 years after initiation of sexual intercourse is not likely to result in the identification of HSIL or cancer. In addition, earlier onset of screening may increase anxiety, morbidity, and expense from increased follow-up procedures. Furthermore, squamous cell cervical cancer is exceedingly rare in the first two decades of life (4). Therefore, it seems reasonable to begin cervical cancer screening approximately 3 years after initiation of sexual intercourse, but no later than age 21 years. Recognizing the time course in the progression of CIN and the unpredictable nature of follow-up in younger women, cytologic screening may be initiated earlier at the discretion of the clinician.

► *What is the optimal frequency of cervical cytology screening?*

The optimal number of negative cervical cytology test results needed to reduce the false-negative rate to a minimum has not been demonstrated (3, 42). Several studies have shown that in an organized program of cervical cancer screening, annual cytology examinations offer little advantage over screening performed at 2- or 3-year intervals (43–45). These studies showed minimal difference in the acquisition of cervical cancer or HSIL at screening intervals of 1, 2, or 3 years in women who had at least one prior normal screening result and who were enrolled in health care programs that provided and monitored cervical cytology screening.

Several practical considerations must be examined before biennial or triennial screening can be adopted as a national standard. Published studies have assumed a program of cervical cancer screening and follow-up. In the current U.S. practice climate, a woman’s care provider may change frequently, as employment and insurance carriers change. Consequently, the physician may be unable to determine a woman’s screening history—ie, the date of her last cervical cytology test, frequency and results of her prior tests, or prior abnormal test results and their management. Patients are frequently inaccurate

in recalling the timing and results of recent screening, more often underestimating the time elapsed and incorrectly recalling abnormal results as normal (46–49). In addition, the high false-negative rate of cytology screening remains a concern, as does the relatively poor reproducibility inherent in cervical cytology (14). Performing multiple screening tests at regular intervals remains the best way to ensure existing premalignant cervical disease has been ruled out before extending the interval between screenings. This is especially true for young women who have a high likelihood of acquiring a high-risk type of HPV (34, 35).

There is room to individualize screening frequency in a woman who is known to have a negative history and several recent annual cervical cytology tests. The chance such a patient will develop CIN 2 or CIN 3 is extremely low, and screening at intervals of every 2–3 years is a safe, cost-effective approach. It is important to educate patients about the nature of cervical cytology, its limitations, and the rationale for prolonging the screening interval. Physicians also should inform their patients that annual gynecologic examinations are still appropriate even if cervical cytology is not performed at each visit.

Annual cytology screening should be recommended for women younger than 30 years. Women aged 30 years and older who have had three consecutive cervical cytology test results that are negative for intraepithelial lesions and malignancy may be screened every 2–3 years. Certain risk factors have been associated with CIN in observational studies; women with any of the following risk factors may require more frequent cervical cytology screening:

- Women who are infected with human immunodeficiency virus (HIV)
- Women who are immunosuppressed (such as those who have received renal transplants)
- Women who were exposed to diethylstilbestrol in utero

Women infected with HIV should have cervical cytology screening twice in the first year after diagnosis and annually thereafter (22, 50). Women treated in the past for CIN 2 or CIN 3 or cancer remain at risk for persistent or recurrent disease and should continue to be screened annually (51, 52). Women with previously normal cervical cytology results whose most recent cervical cytology sample lacked endocervical cells or transformation zone components and those with partly obscuring red or white blood cells should be rescreened in 1 year (30).

► *When is it appropriate to recommend discontinuing screening?*

Although the rate of new-onset cervical cancer plateaus at age 65 years in U.S. women in general, among certain subsets—most notably, African-American women—the incidence increases steadily across the age spectrum (2, 7). Most new cases are seen in unscreened or infrequently screened women. It is difficult to set an upper age limit for cervical cancer screening. Postmenopausal women screened within the prior 2–3 years have been shown to have a very low risk of developing abnormal cytology (53, 54).

The American Cancer Society recommends that screening may be discontinued at age 70 years in low-risk women (5). The U.S. Preventive Services Task Force has set age 65 years as the upper limit of screening (55). An older woman who is sexually active and has had multiple partners may be at lower risk for new-onset CIN than a younger woman because of her decreased rate of metaplasia and less accessible transformation zone; however, she is still at some risk for acquiring HPV and CIN. A woman with a previous history of abnormal cytology also is at risk; women in both of these categories should continue to have routine cervical cytology examinations.

Primary vaginal cancer represents a very small fraction of gynecologic malignancies (5). The vaginal mucosa lacks a transformation zone. Women who have had a hysterectomy and have no history of CIN are at very low risk of developing vaginal cancer. Cytologic screening in this group has a low rate of diagnosing an abnormality and a very low positive predictive value. In a study of 9,610 Pap tests performed among women who had a hysterectomy for benign indications an average of 19 years previously, only 1.1% had cytologic abnormalities. Biopsies of these women showed no vaginal intraepithelial neoplasia grade 3 or cancer (54). Continued routine vaginal cytology examinations in such women are not cost-effective and may cause anxiety and overtreatment. Thus, women who have had a total hysterectomy and have no prior history of high-grade CIN may discontinue screening.

Women who had high-grade cervical intraepithelial lesions before hysterectomy can develop recurrent intraepithelial neoplasia or carcinoma at the vaginal cuff several years postoperatively (56, 57). Women who have had a hysterectomy and have a history of CIN 2 or CIN 3—or in whom a negative history cannot be documented—should continue to be screened annually until three consecutive satisfactory negative cervical cytology results are obtained. Routine screening may then be discontinued. A woman who has had three consecutive satisfactory negative examinations following treatment for

CIN 2 or CIN 3 before she had a hysterectomy also may discontinue screening.

Before considering whether a woman who has had a hysterectomy should continue regular cytology screening, the provider should be sure the woman's cervical cytology history is accurate. The history should confirm that she had benign findings at the time of hysterectomy and that her cervix was removed as part of the hysterectomy. However, when a woman's past cervical cytology and surgical history are not available to the physician, screening recommendations may need to be modified.

► ***How do the various methods of cervical cytology compare in terms of effectiveness?***

Cervical cytology is the basis of the most effective and cost-effective cancer screening program ever implemented. Cervical cytology, however, is not a diagnostic test (1). The sensitivity of cervical cytology recently has been reported to be lower than the previously estimated 60–85% (29). A recent comprehensive review of the literature evaluated the accuracy of screening cervical cytology in screened populations with a low prevalence of cervical disease (42). For inclusion in this review, a study was required to have sufficient verification of both negative and positive cervical cytology to calculate sensitivity and specificity. Only three studies met the inclusion criteria to evaluate the standard preparation for cervical cytology at a threshold of ASCUS or worse and estimate its ability to diagnose CIN 1 or more severe lesions. At these thresholds, the standard preparation had a sensitivity of 51% and a specificity of 98%. The authors also calculated performance measures based on nine studies that permitted evaluation at the cytologic threshold of LSIL. The mean sensitivity was 47%, and specificity was 95% (58).

Studies comparing the accuracy of liquid-based thin-layer cervical cytology with the standard preparation have used 1 of 2 study designs. The split sample design prepares the specimen by first placing cells on a glass slide for a standard preparation, then suspending the remaining cells in liquid medium for liquid-based cytology. This design has the potential to falsely decrease the sensitivity of the liquid-based preparation. The direct-to-vial technique, however, prepares the entire specimen for liquid-based cytology but compares a screened population with historic controls. Although most studies have included confirmation of positive test results with colposcopy and biopsy, which allows an estimate of sensitivity, few have used sufficient verification of negative cervical cytology to determine specificity. With both study designs, liquid-based cytology diagnosed from 36% to more than 200% more cases of LSIL and from

26% to 103% more cases of HSIL than the conventional method (59–63). True-positive rates documented with biopsy were improved with the use of liquid-based cytology in some but not all studies (60–64).

Although liquid-based thin-layer cervical cytology appears to have increased sensitivity for detecting cancer precursor lesions over the conventional method, the degree to which sensitivity is increased is unknown. Equally important, the difference in specificity between the liquid-based and conventional tests has not been determined. Although an increase in sensitivity will permit earlier detection of cancer precursor lesions, any decrease in specificity can result in increased cost and morbidity from false-positive diagnoses. The conventional test, although disappointing in its documented sensitivity, has proved effective in reducing cervical cancer rates where screening programs exist. Liquid-based products can be effective in population screening as well. Their reported increase in sensitivity may make them especially useful in women who are screened infrequently. Providers selecting a cervical cytology method should consider the screening history of their patient, the cost of the test, and the possible effects of false-negative or false-positive results.

► ***Is the recommended frequency of screening affected by the method of screening?***

The American Cancer Society recommends that women younger than 30 years undergo cervical cancer screening annually if the conventional method is used or every 2 years if a liquid-based method is used (5). However, there are very limited data to support this approach. The recommendation of biennial cytology using the liquid-based method discounts the possibility of false-negative results, a consideration with both liquid-based and conventional methodologies. Moreover, the increased sensitivity of liquid-based methods over conventional methods is small with studies showing overlapping confidence intervals. According to FDA-required labeling, the ThinPrep technique may be marketed as better able to detect LSIL and HSIL than the conventional Pap test, and the SurePath technique may be marketed as equivalent to the conventional Pap test (17).

► ***When is HPV testing appropriate?***

Although it is estimated that up to 100% of women with histologic CIN 2 or CIN 3 will test positive for a high-risk type of HPV, many women harbor the virus in their lower genital tracts without showing cytologic or histologic changes (31, 32, 34, 40, 65). Currently, only one product, Hybrid Capture II, is FDA-approved for testing for cervical HPV DNA. It assesses exfoliated cervical cells for the presence of 1 or more of 13 high- and inter-

mediate-risk HPV types. Although the test appears to be very sensitive, rare cross-reactivity with low-risk HPV types and HPV types of undetermined significance has been reported. The clinical implications of this finding are unknown (66).

Its utility has been well demonstrated for the primary triage of cervical cytology tests read as ASC-US (23, 67–70). In this setting, high-risk HPV DNA testing has been shown to have a sensitivity ranging from 78% to 96% for the detection of CIN 2 or CIN 3, with rates of referral for colposcopy ranging from 31% to 56%. The use of “reflex” HPV testing has been recommended as a convenient and cost-effective approach to evaluating ASC-US (68, 71, 72). The technique involves collecting a sample for high-risk HPV DNA testing at the same time as cervical cytology screening and evaluating it only if the cytology is read as ASC-US. Reflex HPV testing may be done by testing from residual preservative if liquid-based cytology is used or by performing a separate HPV DNA test at the same time as cervical cytology and storing it for use if ASC-US is the result.

High-risk HPV DNA test results would be expected to be positive when cervical cytology results indicate HSIL, so the test has little utility in this setting. Likewise, up to 83% of women with LSIL diagnosed by cervical cytology have been shown to be positive for high-risk HPV types, thus limiting the usefulness of the test in this setting as well (73). Because HPV is more prevalent in younger women and the rate of CIN 2 and CIN 3 increases with age, it has been suggested that HPV DNA testing might be a more selective test in older women (68). However, stratifying results by age demonstrated only minimal differences in the sensitivity of HPV DNA testing when used as a triage test for ASCUS results (74). The rate of referral to colposcopy decreased with age, however, from 68% in women younger than 29 years to 31% for women aged 29 years and older (74).

Another clinical setting in which HPV DNA testing may be useful is in the secondary triage of women with a cytologic diagnosis of ASC-US, ASC-H, or LSIL in whom colposcopy is negative or biopsy fails to reveal CIN. A protocol of follow-up in 1 year with HPV DNA testing has been suggested as an alternative to repeat cytology in this group, with repeat colposcopy for those with positive test results (71).

▶ ***When cervical cytology and HPV DNA testing are used together, can women be screened less frequently?***

The FDA has recently approved the combination of cervical cytology and HPV DNA testing for primary screening for cervical cancer for women aged 30 years and

older. This new indication for the use of HPV DNA testing was based on information from several large studies (71, 75–78). These studies demonstrated that women aged 30 years and older who had both negative cervical cytology test results and negative high-risk type HPV-DNA test results were at extremely low risk of developing CIN 2 or CIN 3 during the next 3–5 years. This risk was much lower than the risk for women who had only cytology and tested negative. Because the FDA approval for the use of HPV DNA as a primary screening modality was based on clinical study data, whether the combination of virus screening and cytology will perform equally well when applied to population-based screening practice is unknown.

Any woman aged 30 years or older who receives negative test results on both cervical cytology screening and HPV DNA testing should be rescreened no more frequently than every 3 years. The combined use of these modalities has been shown to increase sensitivity but also decrease specificity and increase cost. However, it has been estimated that the increase in screening interval will offset the cost of this new screening regimen (79).

It is important to note that the FDA approval for use of this approach is only for the panel of high-risk HPV types. In addition, the combination of cytology and HPV DNA screening should be restricted to women aged 30 years and older because transient HPV infections are common in women younger than 30 years, and a positive test result may lead to unnecessary additional evaluation and treatment. Routine testing using cytology alone remains an acceptable screening plan.

Summary of Recommendations

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

- ▶ Annual cervical cytology screening should begin approximately 3 years after initiation of sexual intercourse, but no later than age 21 years.
- ▶ Women younger than 30 years should undergo annual cervical cytology screening.
- ▶ Women aged 30 years and older who have had three consecutive negative cervical cytology screening test results and who have no history of CIN 2 or CIN 3, are not immunocompromised and are not HIV infected, and were not exposed to diethylstilbestrol in utero may extend the interval between cervical cytology examinations to every 2–3 years.

- ▶ Evidence-based data indicate both liquid-based and conventional methods of cervical cytology are acceptable for screening.
- ▶ Women who have undergone hysterectomy with removal of the cervix for benign indications and who have no prior history of CIN 2 or CIN 3 or worse may discontinue routine cytology testing.

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

- ▶ Women previously treated for CIN 2 or CIN 3 who have completed their posttreatment follow-up should be monitored annually until at least three consecutive negative cytology screening results are documented.
- ▶ The use of a combination of cervical cytology and HPV DNA screening is appropriate for women aged 30 years and older. If this combination is used, women who receive negative results on both tests should be rescreened no more frequently than every 3 years.
- ▶ Women who have undergone hysterectomy with removal of the cervix and have a history of CIN 2 or CIN 3 should continue to be screened annually until three consecutive negative vaginal cytology test results are achieved.

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

- ▶ Physicians should consider individualization in determining the time to begin screening, the interval between cervical cytology examinations, the age at which cervical cytology testing is no longer needed, and the testing methodology to be used. In addition to considering risk factors for cervical cancer, the provider ideally should be able to determine the patient's past screening history and reliably monitor the patient in the future.
- ▶ Evidence is inconclusive to establish an upper age limit for cervical cancer screening. If screening is discontinued, risk factors should be assessed during the annual examination to determine if reinitiating screening is appropriate.
- ▶ Yearly testing using cytology alone remains an acceptable screening plan.
- ▶ Regardless of the frequency of cervical cytology screening, women should be counseled that annual examinations, including pelvic examination, are still recommended.

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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 1985 and May 2003. 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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