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## Cervical Cytology Screening

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

*The incidence of cervical cancer has decreased more than 50% in the past 30 years because of widespread screening with cervical cytology. In 1975, the rate was 14.8 per 100,000 women in the United States; by 2006, it had been reduced to 6.5 per 100,000 women. Mortality from the disease has undergone a similar decrease (1). The American Cancer Society estimates 11,270 new cases of cervical cancer in the United States in 2009, with 4,070 deaths from the disease (2). Recent estimates worldwide, however, are of almost 500,000 new cases and 240,000 deaths from the disease per year (3). When cervical cytology screening programs have been introduced into communities, marked reductions in cervical cancer incidence have followed (4–6).*

*New technology for performing cervical cancer screening 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 not discussed.*

### Background

Despite the demonstrated success of cervical cancer screening, it is estimated that 50% of the women in whom cervical cancer is diagnosed each year have never had cervical cytology testing. Another 10% had not been screened within the 5 years before diagnosis (7). 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 who are screened infrequently. Although rates of cervical cancer are on the decline in women born in the United States, women who are immigrants to the United States from countries where cervical cytology screening is not the norm are an especially high-risk group (8).

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## **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 (7, 9).

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 (10). Most revised results were downgraded to lesser diagnoses. Of those reported as atypical squamous cells of undetermined significance (ASC-US), 39% were downgraded to negative on further review. Of those originally interpreted as high-grade squamous intraepithelial lesions (HSIL), 53% were reinterpreted as LSIL, ASC-US, or negative (11).

## **Natural History of Cervical Neoplasia**

Infection with human papillomavirus (HPV) is a necessary factor in the development of squamous cervical neoplasia; however, most HPV-infected women will not develop significant cervical abnormalities (10, 12–15). 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 (12, 16–22). Factors that determine which HPV infections will develop into squamous intraepithelial lesions have been poorly identified. The HPV type and the persistence of an HPV infection are perhaps the most important determinants of progression (12). Cigarette smoking may be a cofactor, and a compromised immune system appears to play a role in some women (12).

Despite decades of study, the natural history of cervical intraepithelial lesions is still not completely understood. The oncogenic agent is well established to be one of 15–18 “high-risk” types of HPV (23). The once widely held concept that low-grade lesions are necessary precursors to the high-grade lesions and subsequent invasive cancer has been questioned (10, 12, 15, 24).

Human papillomavirus infections are most common in teenagers and women in their early 20s, with prevalence decreasing as women age (25–28). In adolescents and young women, HPV infections and dysplasia are likely to resolve spontaneously (16, 17, 19, 29–31). This suggests that HPV infections found in older women are

more likely to reflect persistent infections acquired in the past, and correlates well with increasing rates of HSIL with increasing age.

The recent introduction of a vaccine targeting HPV-16 and HPV-18, the two most common cancer causing HPV types, has advanced the promise of primary prevention of cervical cancer. The vaccine does not protect women against approximately 30% of cervical cancer caused by HPV types other than HPV-16 and HPV-18. Furthermore, women already exposed to HPV-16 and HPV-18 can expect a lower level of protection from the vaccine than the nearly 100% protection demonstrated in clinical trials involving women not exposed to the virus (32, 33). If immunization is widely implemented, it has been proposed that the impact in terms of reduction in cervical cancer will not begin to be realized for another 15–20 years (34). In the meantime, secondary prevention, through a screening regimen of cervical cytology with or without concomitant HPV DNA testing remains the best approach to protecting women from cervical cancer. Women who have been immunized against HPV-16 and HPV-18 should be screened by the same regimen as non-immunized women. Understanding the natural history of HPV infection is important to establishing a balance between sufficient testing to prevent cancer, while avoiding overtesting with its increased cost and morbidity.

## **Techniques of Cervical Cytology**

Both liquid-based and conventional methods of cervical cytology screening are acceptable for screening. The majority of cervical cytology screening performed in the United States uses a liquid-based process. According to a 2003 survey, nearly 90% of obstetrician—gynecologists use liquid-based cytology (35). Exfoliated cells are collected from the transformation zone of the cervix and may be transferred to a vial of liquid preservative that is processed in the laboratory to produce a slide for interpretation—the liquid-based technique—or may be transferred directly to the slide and fixed using the conventional technique. Performance of conventional cervical cytology requires avoidance of contaminating blood, discharge, and lubricant. The liquid-based technology will filter out most contaminating blood and inflammatory cells and debris. A small amount of lubricant may be used on the speculum and will remain on the vaginal walls prior to reaching the cervix. Lubricant on the cervix itself will interfere with the transfer of cells. Even with the liquid-based technique, heavy menstrual blood may limit the number of squamous cells available for interpretation. Prompt suspension of the cells in the liquid eliminates the problem of air drying artifact, which may limit the interpretation of conventional cervical cytology.

The use of liquid-based cytology has advantages and disadvantages compared with conventional cervical cytology screening. The principal disadvantages are the higher cost and a decreased specificity. The advantages are in the convenience of being able to test for HPV, gonorrhea, and chlamydial infection directly from the residual sample after the cells have been extracted for cytology. In addition, cytotechnologists find liquid-based tests easier to read. Some studies have found fewer “unsatisfactory” results, although this claim has not been consistent (36). Whether the liquid-based cytology tests are more sensitive or specific is unclear. A meta-analysis of eight studies identified by the authors to be methodologically sound found no significant difference in sensitivity or specificity between the two technologies in their ability to diagnose cervical intraepithelial neoplasia 2 (CIN 2) or higher using a cytology threshold of LSIL or HSIL. If the threshold for colposcopy was lowered to ASC-US, however, the liquid-based cytology had a significantly lower specificity (37).

### **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. First proposed in 1988, it was revised in 1991 and again in 2001 (38–40). Highlights of the 2001 Bethesda System classification are summarized as follows (40):

- Specimen adequacy—Slides are to be reported as “satisfactory” or “unsatisfactory” for interpretation. 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. 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. A finding of endometrial cells on cytology in asymptomatic premenopausal women is rarely associated with significant pathology (41).

- Atypical squamous cells (ASC)—The epithelial abnormality ASC is diagnosed when the degree of nuclear atypia is not sufficient to warrant a diagnosis of squamous intraepithelial lesion. It is subcategorized into “atypical squamous cells of undetermined significance” (ASC-US) and “atypical squamous cells cannot exclude HSIL” (ASC-H). The category ASC-H includes 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 CIN 2 or CIN 3 than ASC-US (42, 43).
- 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 (44, 45).
- The 2001 terminology subdivides atypical glandular cells by cell type, ie, atypical endocervical cells, atypical endometrial cells, or atypical glandular cells not otherwise specified. The subdivision of “favor neoplastic” is maintained in the 2001 reporting system. 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 HPV infections into the category LSIL.
- High-grade squamous intraepithelial lesions—The category of HSIL combines CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia, and carcinoma in situ).
- Squamous cell carcinoma
- The absence of endocervical cells or a transformation zone component may reflect that the transfor-

mation 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 (45, 46).

## Clinical Considerations and Recommendations

### ► *When should screening begin?*

Cervical cancer screening should begin at age 21 years. Cervical neoplasia develops in susceptible individuals in response to a sexually transmitted infection with a high-risk type of HPV (12–14, 20, 21). Human papillomavirus causes carcinogenesis in the transformation zone of the cervix, where the process of squamous metaplasia replaces columnar with squamous epithelium (12). Squamous metaplasia is active in the cervix during adolescence and early adulthood. Human papillomavirus infections are commonly acquired by young women shortly after the initiation of vaginal intercourse (16–20) but, in most, they are cleared by the immune system within 1–2 years without producing neoplastic changes (12, 16, 17, 22). The risk of neoplastic transformation increases in those women whose infections persist (12, 47, 48).

Further evidence for this model comes from studies of age-specific prevalence of HPV infections, which consistently show a high prevalence of infection in teenagers, peaking in the third decade of life with a subsequent decrease (25–28). In a report of 10,090 Pap tests in females aged 12–18 years, 422 (5.7%) were reported as LSIL and only 55 (0.7%) were HSIL (49). Moreover, most dysplasia in adolescents regresses spontaneously. A prospective study of 187 women aged 18–22 years with LSIL found that 61% and 91% had reverted to negative after 1 and 3 years of follow-up respectively. Only 3% progressed to CIN 3 (29). Two smaller studies of adolescents with biopsy confirmed CIN 2 showed 65% and

75% regression to negative after 18 months and 3 years respectively (30, 31).

In contrast to the high rate of infection with HPV in sexually active adolescents, invasive cervical cancer is very rare in women younger than age 21 years. Only 0.1% of cases of cervical cancer occur before age 21 years (50). In a recent analysis of national data from 1998 through 2003, researchers from the Centers for Disease Control and Prevention identified an average of only 14 cases of invasive cancer each year in females aged 15–19 years. Cancer cases in adolescents younger than 15 years were too few to report. Based on this report and Surveillance Epidemiology and End Results (SEER) data from 2002–2006, this translates to an incidence rate of 1–2 cases of cervical cancer per 1,000,000 females aged 15–19 years (1, 50).

The recommendation to start screening at age 21 years regardless of the age of onset of sexual intercourse is based in part on the very low incidence of cancer in younger women. It is also based on the potential for adverse effects associated with follow-up of young women with abnormal cytology screening results.

The American College of Obstetricians and Gynecologists endorsed the 2006 recommendations of the American Society for Colposcopy and Cervical Pathology regarding management of adolescents with abnormal cytology and cervical biopsy results (51). These guidelines stress a conservative approach to women younger than 21 years found to have ASC-US or LSIL on cytology and most with histology findings less than CIN 3. Delaying the onset of screening until age 21 years is a logical incremental step in practice guidelines, consistent with this conservative approach to management of adolescents with cervical test result abnormalities.

Earlier onset of screening may increase anxiety, morbidity, and expense from the test itself and overuse of follow-up procedures. The emotional impact of labeling an adolescent with both a sexually transmitted infection and a potential precancer must be considered because adolescence is a time of heightened concern for self-image and emerging sexuality.

Although cancer is rare in adolescents, dysplasia is not uncommon. An abnormal cervical cytology screening test leads to a sequence of additional tests designed to identify those with CIN 2 or worse. However, recent studies have documented a significant increase in premature births in women previously treated with excisional procedures for dysplasia (52). Because adolescents have most or all of their childbearing years ahead of them, it is important to avoid unnecessary excision or ablation of the cervix.

Sexually active adolescents, ie, females younger than 21 years, should be counseled and tested for sexually transmitted infections, and should be counseled regard-

ing safe sex and contraception. These measures may be carried out without cervical cytology screening and, in the asymptomatic patient, without the use of a speculum.

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

Cervical cytology screening is recommended every 2 years for women aged 21–29 years, with either conventional or liquid-based cytology. 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 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 previously treated for CIN 2, CIN 3, or cancer

Women infected with HIV should have cervical cytology screening twice in the first year after diagnosis and annually thereafter (53). Women treated in the past for CIN 2, CIN 3, or cancer remain at risk for persistent or recurrent disease for at least 20 years after treatment and after initial posttreatment surveillance and should continue to have annual screening for at least 20 years (54–58).

The optimal number of negative cervical cytology test results needed to reduce the false-negative rate to a minimum has not been determined (59, 60). It has been demonstrated, however, that the rate of dysplasia decreases as the number of sequential negative Pap test results increases (61). Studies over the past several decades 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 (62–65). One study that did show an increase in relative risk of cancer with screening at a 3- versus 1-year intervals, found no significant difference between screening at 2- versus 3-years. The absolute risk in this well-screened population, however, was very low (66).

An evaluation of 31,728 women aged 30–64 years screened in the National Breast and Cervical Cancer Early Detection Program, found a prevalence of CIN 2 and CIN 3 of 0.028% and 0.019%, respectively among those who had three or more negative Pap test results in

a row. There were no cases of invasive cancer in this group. Using a computer model, they calculated the risk of these women developing invasive cancer and estimated 4 women with cancer per 100,000 women over the next 3 years with annual Pap screening and 8 women with cancer per 100,000 women with triennial screening. Although this represents a doubling of cases with prolonging the interval to 3 years, the absolute number of cases, 4 women with cancer per 100,000 women, is very small, and the estimated cost of finding each additional case of cancer was large (61).

Formal cost-effective analysis of data from this national program showed that the most cost-effective strategy for cervical cancer screening is cytology testing no more often than every 3 years in women with prior normal screening test results (67). Moreover, regardless of age, annual Pap testing was never found to be cost-effective (67).

In several studies, age was shown to play a role in the sensitivity of screening. A negative cervical cytology screening result confers less protection on women younger than 30 years than in older women (61, 65, 68). A recent British study of 4,012 women aged 20–69 years with invasive cancer showed that whereas cytology screening in 3 years prior to diagnosis offered a 60% and 80% reduction in the incidence of cervical cancer at ages 40 years and 64 years respectively, screening between age 20 years and 24 years provided no significant reduction in invasive cancer in women younger than 30 years (69).

In a woman aged 30 years or older who is known to have multiple recent consecutive negative cervical cytology test results, the risk of developing CIN 3 or cancer is low, and screening at 3-year intervals is a safe, cost-effective approach, with either conventional or liquid-based cytology (37, 70).

Published studies have assumed a program of cervical cancer screening and follow-up. Most women in the United States get opportunistic screening as their insurance carriers and providers change. 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 (71–74). Therefore, it is important for the physician to assess a new patient's screening history—ie, the date of her most recent cervical cytology test, frequency and results of her prior tests, or prior abnormal test results and management.

It is important to educate patients about the nature of cervical cytology, its limitations, and the rationale for prolonging the screening interval beyond every year. In addition, regardless of the frequency of cervical cytology screening, physicians also should inform their patients

that annual gynecologic examinations may still be appropriate even if cervical cytology is not performed at each visit.

► ***At what age is it appropriate to recommend discontinuing screening?***

Most new cases of cervical cancer across the age spectrum are seen in unscreened or infrequently screened women (7). This has been shown to be the case in postmenopausal women as well (68). Women aged 65 years and older represent 14.3% of the United States' population but have 19.5% of new cases of cervical cancer (1, 75). In white women in the United States, the rate of new-onset cervical cancer peaks in the middle of the fifth decade of life and then decreases. The peak incidence in Hispanics is in the early 70s; for women of Asian or Pacific Island ethnicity the incidence peaks in the late 70s. The incidence of cervical cancer continues to increase throughout life in African American women in the United States (1).

Any attempt at setting an upper age for screening must, therefore, take into consideration a woman's past screening history. Postmenopausal women with multiple prior consecutive negative cervical cytology test results are at low risk for cervical cancer. In addition, mucosal atrophy common after menopause may predispose to false-positive cytology. False-positive results are likely to be followed with additional procedures, anxiety, and expense in this population (76).

The American Cancer Society recommends that screening may be discontinued at age 70 years in low-risk women after three consecutive negative cervical cytology screening tests in the prior decade (77, 78). The U.S. Preventive Services Task Force has set age 65 years as the upper limit of screening (79). An older woman who is sexually active and has 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.

Because cervical cancer develops slowly and risk factors decrease with age, it is reasonable to discontinue cervical cancer screening at either 65 years of age or 70 years of age in women who have three or more negative cytology test results in a row and no abnormal test results in the past 10 years. If screening is discontinued, risk factors should be assessed during the annual examination to determine if reinitiating screening is appropriate.

► ***When is it appropriate to discontinue screening for women who have undergone hysterectomy?***

In women who have had a total hysterectomy for benign indications and have no prior history of high-grade CIN, routine cytology testing should be discontinued. Continued vaginal cytology examinations are not cost-effective, in particular because of the very low risk of developing vaginal cancer, and may also cause anxiety and overtreatment.

Women who had high-grade cervical intraepithelial lesions before hysterectomy can develop recurrent intraepithelial neoplasia or carcinoma at the vaginal cuff years postoperatively (80–82). Women who have had a hysterectomy with removal of the cervix and have a history of CIN 2 or CIN 3—or in whom a negative history cannot be documented—should continue to be screened even after their period of posttreatment surveillance. Whereas the screening interval may then be extended, there are no good data to support or refute discontinuing screening in this population.

Primary vaginal cancer represents a very small fraction of gynecologic malignancies (2). 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 small chance of diagnosing an abnormality, and the test has a very low positive predictive value. A recent review aggregated data on 6,543 women from 19 studies who had a hysterectomy in which the cervix was benign and 5,043 women who had hysterectomies with CIN 3 (80). On follow-up, among the women with hysterectomy for benign indications, 1.8% had an abnormal cytology result and 0.12% had vaginal intraepithelial neoplasia (VAIN) on biopsy. There were no cases of cancer. In the group with prior CIN 3, however, abnormal cytology was reported in 14.1%, with VAIN on biopsy in 1.7%, and there was one case of cancer diagnosed 3 years after hysterectomy (80). The authors note that all of the studies reporting on follow-up of women with CIN 3 had reporting flaws or methodological problems. They note that there are too little data available to assess sensitivity or specificity of cytology after hysterectomy. Their results are compatible with a very low background rate of primary vaginal cancer, which they cite at approximately 7 per 1 million women per year (80).

Before considering whether a woman who has had a hysterectomy should continue regular cytology screening, the health care provider should assess the accuracy of the woman's cervical cytology history. 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.

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

Testing for HPV DNA currently is used in cervical cancer screening as a triage test to stratify risk to women aged 21 years and older with a cytology diagnosis of ASC-US and postmenopausal women with a cytology diagnosis of LSIL. It may be used as an adjunct to cytology for primary screening in women older than 30 years. It also may be used as a follow-up test after CIN 1 or negative findings on colposcopy in women whose prior cytology diagnosis is ASC-US, ASC-H, LSIL, or atypical glandular cells, and in follow-up after treatment for CIN 2 and CIN 3 (41, 55). Human papillomavirus testing should not be used in females younger than 21 years and if inadvertently performed, a positive result should not influence management.

Currently, there are two U.S. Food and Drug Administration-approved products for testing for cervical HPV DNA in clinical practice. They assesses exfoliated cervical cells for the presence of 1 or more of 13 or 14 of the 15–18 potentially cancer causing HPV types (23). The utility of HPV DNA testing has been well demonstrated for the primary triage of cervical cytology test results read as ASC-US (45, 83–88). A recent review of 20 studies assessing the efficacy of HPV DNA testing to triage ASC-US determined a sensitivity of 92.5% to detect CIN 2 or worse and 95.6% to detect CIN 3 or worse with specificities of 62.5% and 59.2%, respectively (88). The use of “reflex” HPV testing has been recommended as a convenient and cost-effective approach to evaluating ASC-US (41, 45, 89). Reflex HPV testing involves collecting a sample for high-risk HPV DNA testing at the same time as the cervical cytology and evaluating it only if the cytology is read as ASC-US. Reflex HPV testing is most commonly performed on cells from residual preservative when liquid-based cytology is used. It also may be accomplished 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. High-risk HPV test results are positive in 77% of women with LSIL making the test impractical as a test to triage women with LSIL to colposcopy (88). As might be expected, this translates to a high sensitivity, but an unacceptably low specificity. An exception is made after menopause. Because of a significant decrease in the prevalence of HPV infections with age, reflex HPV DNA testing is an acceptable option for LSIL in postmenopausal women (41, 45).

The U.S. Food and Drug Administration has recently approved a DNA test specific for HPV-16 and HPV-18, which can be used as an adjunct in women with negative Pap test results, but who have tested positive for high-risk HPV by an assay testing for 13 or 14 high-risk types.

► ***When cervical cytology and HPV DNA testing are used together, can low-risk women be screened less frequently?***

The high sensitivity of HPV DNA testing for screening has been repeatedly demonstrated (90–93). Co-testing using the combination of cytology plus HPV DNA testing is an appropriate screening test for women older than 30 years. Co-testing is not recommended for women younger than 30 years because of the very high prevalence of high-risk HPV infections in sexually active women in this age group.

Women aged 30 years and older with both negative cervical cytology test results and a negative high-risk type HPV DNA test result have been shown to be at extremely low risk of developing CIN 2 or CIN 3 during the next 4–6 years. This risk was much lower than the risk for women who had only cytology and tested negative (87, 88). Therefore, any low-risk woman aged 30 years or older who receives negative test results on both cervical cytology screening and HPV DNA testing should be rescreened no sooner than 3 years. The combined use of these modalities has been shown to increase sensitivity but also decrease specificity and increase cost. The increased cost results from both the cost of the HPV DNA test itself and additional follow-up tests inherent in reduced specificity (88, 93–96).

Pooled data from seven European studies were analyzed to compare cotesting using HPV DNA plus cervical cytology with cytology alone in a total of 24,295 women. The risk of CIN 3 or cancer after 6 years of follow-up was 0.28% in women who tested negative on both cytology and HPV testing at baseline. This rate was essentially the same as found among all those negative for HPV (0.27%) and considerably lower than all women with negative cytology results (0.97%). The rate of CIN 3 or cancer 3 years after a negative cytology result was 0.51%. In this large multinational study, cotesting at 6-year intervals offered better protection than cytology alone at 3 years (93). Studies from Sweden and the Netherlands, respectively, compared cytology screening with co-testing using conventional cytology and a polymerase chain reaction-based HPV DNA test not clinically available in the United States. The authors compared the diagnosis of CIN 3 on initial screen with findings at a second round of screening 4–5 years later. Although the overall number of cases of CIN 3 diagnosed was comparable between the groups undergoing co-testing and those having cytology alone,

most were diagnosed in the first round of screening with co-testing. Most of the cases were diagnosed in the second round in the cytology group. These authors suggest that the earlier diagnosis of high-grade lesions with co-testing may justify prolonging the interval of screening when this modality is used (95, 96).

## Summary of Recommendations and Conclusions

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

- ▶ Cervical cancer screening should begin at age 21 years. Screening before age 21 should be avoided because it may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.
- ▶ Cervical cytology screening is recommended every 2 years for women between the ages of 21 years and 29 years.
- ▶ 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 HIV infected, are not immunocompromised, and were not exposed to diethylstilbestrol in utero may extend the interval between cervical cytology examinations to every 3 years.
- ▶ Both liquid-based and conventional methods of cervical cytology are acceptable for screening.
- ▶ In women who have had a total hysterectomy for benign indications and have no prior history of high-grade CIN, routine cytology testing should be discontinued.
- ▶ Co-testing using the combination of cytology plus HPV DNA testing is an appropriate screening test for women older than 30 years. Any low-risk woman aged 30 years or older who receives negative test results on both cervical cytology screening and HPV DNA testing should be rescreened no sooner than 3 years subsequently.

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

- ▶ Sexually active adolescents (ie, females younger than age 21 years) should be counseled and tested for sexually transmitted infections, and should be counseled regarding safe sex and contraception. These measures may be carried out without cervical cytology

and, in the asymptomatic patient without the introduction of a speculum.

- ▶ Because cervical cancer develops slowly and risk factors decrease with age, it is reasonable to discontinue cervical cancer screening between 65 years and 70 years of age in women who have three or more negative cytology test results in a row and no abnormal test results in the past 10 years.
- ▶ Women treated in the past for CIN 2, CIN 3, or cancer remain at risk for persistent or recurrent disease for at least 20 years after treatment and after initial posttreatment surveillance, and should continue to have annual screening for at least 20 years.
- ▶ Women who have had a hysterectomy with removal of the cervix and have a history of CIN 2 or CIN 3—or in whom a negative history cannot be documented—should continue to be screened even after their period of posttreatment surveillance. Whereas the screening interval may then be extended, there are no good data to support or refute discontinuing screening in this population.

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

- ▶ Regardless of the frequency of cervical cytology screening, physicians also should inform their patients that annual gynecologic examinations may still be appropriate even if cervical cytology is not performed at each visit.
- ▶ Women who have been immunized against HPV-16 and HPV-18 should be screened by the same regimen as nonimmunized women.

## Proposed Performance Measure

Percentage of women between the ages 21 years and 29 years who have received a Pap test within the past 2 years

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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 July 2009. 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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