OBG MANAGEMENT

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Pap test every year? Not for every woman

New recommendations say a Pap test every 3 years is sufficient in some women. Solid data explain why, but old habits are hard to change.

SCREENING RECOMMENDATIONS

- Begin screening approximately 3 years after coitarche, or at age 21, whichever comes first.
- Test every 1 to 2 years until age 30.
- Test every 2 to 3 years after age 30 in well-screened women whose Pap tests have been negative for CIN 2 or CIN 3.
- Consider discontinuing Pap tests after age 65 to 70 in well-screened women with no history of significant dysplasia. Evidence does not support a specific age to stop screening.
- Discontinue further Pap testing in women whose uterus and cervix have been removed and who have no history of high-grade cervical dysplasia or cancer.
- Continue annual Pap testing in women with a history of cervical cancer, in utero exposure to diethylstilbestrol (DES), or who are immunocompromised.

COMMENTARY Page 47
Putting new guidelines into practice is easier said than done
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Is the Pap test still necessary for every woman, every year? No, according to the latest guidelines, but old habits die hard, even for physicians.

And there is little doubt that yearly screening, though not scientifically based, has contributed much to the reduction of cervical cancer incidence and mortality in American women. Our patients and we as providers have long considered a Pap test the cornerstone of the annual gynecologic exam, as we've been urged to do for decades by our leading academic institutions. However, the American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society (ACS) revised their guidelines last year, and no longer support yearly screening for every woman, every year.[1,2] The US Preventive Services Task Force (USPSTF) revised its guidelines in accord, with the exception that it found the evidence insufficient to support screening low-risk women more often than every 3 years, at any age.[3]

Original rationale: "Pap smear prompt"

These organizations, as well as the National Cancer Institutes (NCI), had sup-

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INTEGRATING EVIDENCE AND EXPERIENCE

Frequent screening would detect exceedingly few additional cancers, at an exceedingly high cost

We can confidently counsel patients
A previously well-screened woman over age 30 who has no history of dysplasia has an exceedingly small risk of cervical cancer, whether her next Pap test is 1, 2, or 3 years after her last.

How many cancers will we miss?
Miller MG, Sung HY, Sawaya GF, Kearney KA, Kinney W, Hiatt RA. Screening interval and risk of invasive squamous cell cervical cancer. Obstet Gynecol. 2003;101:29–37.

This matched case-control study assessed the odds of being diagnosed with squamous cell cervical cancer when a Pap test is performed 2 or 3 years versus 1 year after a normal Pap. Data from the Kaiser Permanente Medical Care Program in Northern California was used to identify 482 women who were diagnosed with invasive squamous cell cervical cancer between 1983 and 1995, and to compare each woman with 2 control individuals matched for age, race/ethnicity, and length of program membership. An intact cervix and no prior cervical, uterine, or vaginal cancer were required. A woman who had a Pap test within 18 months of her last negative test was half as likely to have invasive cancer as a woman who waited 3 years (31 to 42 months).

The odds ratios for invasive cancer diagnosed by screening at 1, 2, or 3 years were 1.00, 1.72, and 2.06, respectively. The differences between intervals of 2 or 3 years versus 1 year were significant. The odds ratios increased to 2.15 and 3.60, respectively, in women with at least 2 consecutive negative Pap tests prior to diagnosis.

In all analyses, the odds ratios continued to increase as screening intervals were prolonged beyond 3 years.

Increased relative risk and very small absolute risk. The new ACOG and ACS guidelines recommend extending the screening interval only for women over 30 who have been well screened over

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ported annual Pap testing since the mid-1950s—long before any data suggested whether one screening interval might be better than another.

In fact, part of the original rationale for annual screening was that it would serve as a vehicle to bring women in for their annual gynecologic exam.[4]

Why change? How will patients react?

Cumulative findings suggest an age- and risk-based approach

Research over the past few decades has revealed much about the pathogenesis of cervical cancer which supports an age- and risk-based approach to screening for cervical cancer — when to start, when to stop, and how often to perform cervical cytology.

The main questions

In this article, I'll review some of the data on these concerns:

- Why wait 3 years after first intercourse for the first Pap test?
- Why is 21 the 'default' age for first Pap test?
- What are the risks and costs of screening every 2 to 3 years in well-screened women over age 30? Over age 65?
- Do most women without a cervix require screening?
- What is the role of HPV DNA testing?
- How should we deal with abnormal results?
- How should we counsel the patient?
- What's the harm in continuing Pap tests in all women?
- Will women return for annual exams as we advise, if we change their Pap test routine?

CONTINUED

The yearly Pap test was advocated long before data suggested one interval might be better than another.

INTEGRATING EVIDENCE AND EXPERIENCE

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the previous decade. This study does not break down the relative risks by age, nor does the sample size allow assessment of the risks for women with more than 2 consecutive negative Paps.

The authors note that the age-adjusted incidence of invasive cervical cancer among all Northern California Kaiser Permanente members is only 6.2 per 100,000 women. In this well-screened population, even doubling the relative risk leaves a very small absolute risk of cervical cancer.

How many fruitless interventions?

Sawaya GF, McConnell KJ, Kulasingam SL, et al. Risk of cervical cancer associated with extending the interval between cervical-cancer screenings. N Engl J Med. 2003;349:1501–1509.

If screening were done annually rather than every 3 years, how many additional tests would be needed to diagnose each additional cancer expected to be found? To find out, Sawaya et al applied data from the National Breast and Cervical Cancer Early Detection Program to a Markov model. They studied 32,230 women with 3 successive negative Pap tests, each no more than 36 months apart.

They predicted that, in a theoretical cohort of 100,000 women who had at least 3 consecutive negative Pap tests, screening at 1-year rather than 3-year intervals would uncover 3 additional cancers in women aged 30 to 44, a single additional cancer in women aged 45 to 59, and no additional cancers for women 60 to 64 years of age.

They calculated that, for this theoretical cohort of 100,000 women:

- **To find all 3 additional cancers** in the 30- to 44-year-old group would require 69,665 Pap tests and 3,861 colposcopies.
- **To find the only additional cancer** in the 45- to 59-year-old group would require 209,324 Pap tests and 11,502 colposcopies.

As with all modeling studies, Sawaya's analysis is limited by the assumptions introduced into the model.

Among them:

- perfect compliance on the part of this cohort of hypothetical patients,
- use of conventional Pap tests only, and
- uniform sensitivity and specificity.

Interventions too early may lead to destruction of the immature transformation zone.

ADOLESCENCE

Why wait 3 years after onset of intercourse for first Pap test?

Care is not compromised

Delaying screening until at least 3 years after coitarche does not compromise the diagnosis of high-grade lesions, yet does allow discovery and eradication long before they become malignant. On the other hand, screening young women sooner than 3 years after first sexual intercourse risks diagnosing numerous self-limited HPV infections and transient low-grade dysplastic lesions, which have very low premalignant potential.

Persistent high-risk HPV must precede cancer. Cervical cancer develops only after persistent HPV infection, many years from the initial HPV exposure.

We now know that at least 15 to 18 types of human papillomavirus (HPV) can cause cervical cancer, and that infection with a high- risk type of HPV is the necessary antecedent—but not by itself a sufficient antecedent— for high-grade cervical dysplasia and cervical cancer.[5,6]

We also know that HPV is most often acquired through sexual intercourse and that it is very efficiently acquired by young women.[7,8] For example, a study of young college women who were initially HPV negative acquired HPV at a rate of 14% per year.[7]

HPV infections in young women are usually transient, however. Up to 90% of young women who test positive for HPV DNA will revert to negative within 2 years.[9]

The problems of screening too early. Squamous cancer of the cervix is exceedingly rare in women under age 21.[10] Diagnosis of self-limited HPV infections and transient low-grade dysplastic lesions

would likely result in repeat Pap tests and colposcopies. In addition to being costly and anxiety-provoking, these interventions may lead to needless destruction of the immature transformation zone in young women of low parity.

Don't neglect counseling, STD testing, birth control

Delaying the first Pap test in young women until 3 years after initial intercourse, however, does not mean we should neglect gynecologic examinations in this group. They are at high risk for sexually transmitted infections and at extremely high risk for unintended pregnancies. So, while waiting 3 years to do the first Pap test makes sense, an early visit, before or soon after first intercourse is essential for gynecologic health care, including prevention of pregnancy and sexually transmitted disease.

October 2004 opinion on Gyn visits for young teens. ACOG published a committee opinion[11] to clear up confusion over when adolescent girls should have their first Pap test versus when they should have their first gynecologic visit. The opinion advises a first visit at age 13 to 15, for health guidance, screening, and preventive services, and says parents and patients need to understand that this visit does not necessarily include a pelvic exam or a Pap test. The advisory stresses that adolescents are unlikely to acknowledge sexual activity without sensitive and direct questions, and suggested a resource: "Asking the Right Questions," from the STD/HTD Prevention Training Center of New England.

AGES 21 TO 30

Why is age 21 the "default" for first Pap?

Because the incidence of high-grade squamous intraepithelial lesions (HSIL) increases with age,[12] cytology screening should start at age 21, irrespective of sexual history. Saslow et al[1] writing for the American Cancer Society, acknowledged the difficul-

COMMENTARY

Putting new guidelines into practice is easier said than done

The new recommendations on cervical cytology are evidence-based and endorsed by our scholarly and professional societies. It's difficult to disagree. Difficult, but not impossible.

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The field is still evolving, and it is evolving so rapidly that I believe the changed recommendations may be premature. As our understanding of the high-risk types of human papillomavirus evolves, the time may soon come when exfoliative cytology as we know it may not be the screening method of choice. The introduction of liquid-based Pap smears and reflex high-risk HPV testing has caused tremendous change in how we collect and interpret smears.

But the task of putting new technologies into practice can be somewhat daunting.

Application of the new guidelines depends in part on an accurate sexual history, past and present. Even in this era of awareness and "safe sex," we often cannot pinpoint at what age a patient became sexually active or whether her history includes multiple partners. Furthermore, use of Viagra among men, and the soon-to-be available testosterone patch for women mean we cannot assume that our graying population is sexually inactive, monogamous, or "safe." To apply the guidelines consistently, we may need to adjust our own thinking and recognize today's realities.

Patients need a clear message

But most important is the mixed message to patients. As Dr. Waxman acknowledges, patients have come to equate their annual visit with a Pap test—evidence of a successful public awareness effort since 1975, when an ACOG Technical Bulletin recommended the annual test. Every clinician would agree with Dr. Waxman that we must teach our patients that the value of the annual exam is not limited to cervical cytology screening.

But that is easier said than done. A massive campaign to raise awareness of the importance of annual exams is needed *before* we can expect patients to be comfortable with less frequent Pap testing.

As with most controversies, the answer probably lies somewhere in the middle.

Tell patients: Don't stop annual exams

I use a hybrid approach. For a patient who has no history of cervical disease, I suggest that we forgo the Pap test for 1 year if she is older than 65 and sexually inactive, or, if she is younger than 65 and sexually active with a single partner.

However, I carefully point out to these patients that, although their risk is low, their annual visit is still important.

ty of obtaining a reliable sexual history. This may be especially true with patients who may have suffered sexual abuse as adolescents. The default age of 21 for initial Pap test allows the provider to sidestep the question of age at first intercourse. On the other hand, a 21-year-old who has never had vaginal intercourse does not need to be screened for cervical cancer.

Aggressive screening until age 30

Women should be screened every year until age 30 if conventional Pap smears are used.[1,2] During a woman's 20s, precancerous lesions become more common and invasive cancer, while still rare, is seen with increasing frequency. Both ACOG and ACS consider this period of a woman's life to be a time for aggressive cervical cancer screening.

Frequent screening until age 30 allows us to identify and treat young women with histologic cervical intraepithelial neoplasia (CIN) 2 and 3 or worse, and to identify those who, because of persistently negative Pap tests, are at lowest risk.

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Since these women schedule more frequent visits for contraception and prenatal care, we have greater opportunities for cervical cancer screening.

Does type of Pap test determine screening interval?

Every 2 years is sufficient if the liquid Pap test is used: ACS.[1] This recommendation is based on balancing the increase in abnormal results found with liquid-based Paps against the likelihood that most of the additional abnormal findings will be only atypical squamous cells, undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL). These minimally abnormal results, while needing follow-up, have a relatively low rate of CIN 2 or 3 on biopsy.

Annual tests until age 30, irrespective of Pap technology: ACOG.[2] That decision recognizes the fact that, while the data suggest increased sensitivity of liquid-based cervical cytology, this observation is not conclusive, and both technologies fall short of 100% sensitivity.

The squamous metaplasia area–the substrate for neoplasia–is diminished in most women in their 30s.

AGES 30 TO 65

Why extend the interval between Pap tests?

High risk calls for yearly screens

Both ACOG and the ACS agree that women at high-risk should be screened annually regardless of age.

Risk factors include:

- history of cervical cancer,
- immunocompromise including HIV,
- in utero exposure to diethylstilbestrol (DES), and
- women over age 30 who were not well screened in their 20s; these women should have at least 3 negative annual exams before the screening interval is extended.

Longer interval if risk is low

Up to age 30, frequent screening can be expected to significantly reduce a woman's risk of cervical cancer. Multiple negative Paps offer a high degree of protection—the more consecutive normal tests, the higher the level of protection.[13]

Research indicates, however, that it seems reasonable to reduce the screening interval from every year to every 2 to 3 years in previously well-screened women over age 30:

- These women have the protection offered by frequent Pap tests during the previous decade.
- By the time most women reach their 30s, the area of active squamous metaplasia, which serves as the substrate for cervical neoplasia, is reduced.[14]

Studies of screening effects

National Breast and Cervical Cancer Early Detection Program. Using data from this program, Sawaya et al[13] studied 31,728 women aged 30 to 64 with 3 or more consecutive negative Pap tests spaced no more than 3 years apart. They found only 9 women (0.028%) with biopsy-proven CIN 2, only 6 (0.019%) with CIN 3, and none with invasive cancer.

International Agency for Research in Cancer[15] data showed essentially no difference in the protective effect of cytology screening at 1-, 2-, or 3-year intervals in women enrolled in screening programs in 7 Western European countries and 3 Canadian centers, among women aged 35 to 64 who had at least 2 previous negative Pap tests. The authors calculated a cumulative reduction in cervical cancer of 93.5% with annual screening, 92.5% with screening every 2 years, and 90.8% with screening every 3 years, compared to women who had no screening.

National Breast and Cervical Cancer Early Detection Program[16] data also support extending the screening interval beyond 1 year. In 128,805 women followed after at least 1 prior negative Pap, no significant difference was noted in the incidence of cytologic HSIL on a subsequent Pap performed 9 to 12 months, 13 to 24 months, or 25 to 36 months later. The rates of HSIL were 25, 29, and 33 per 100,000 women, respectively.

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Do postmenopausal women need screening?

Women over 65 do get cervical cancer. While they represent 13% of the total U.S. population, they have 25% of new cases of cervical cancer and suffer 41% cervical cancer mortality.[17] Incident cases of squamous cancer among older women, however, come from the cohort who have not previously been well screened.

An older woman in a long-term monogamous relationship who has a history of frequent negative Pap tests is at such low risk for acquiring cervical cancer that the US Preventive Services Task Force recommends discontinuing screening in this group at age 65.[3]

The American Cancer Society recommends discontinuing screening at age 70 in low-risk previously well screened women.[1]

ACOG does not set a specific upper age for cytology screening.[2] While acknowledging the recommendations of these other professional organizations, ACOG notes that there is no good evidence to establish one age over another to discontinue screening, and instead encourages individualization.

If an older woman's sexual practices change, consider restarting screening.

ACOG recommends that if an older woman's sexual practice changes after she is no longer being tested with cytology, some consideration should be given to reinitiating screening. If screening is restarted, 3-year intervals seems appropriate, as older women may have immunity to many HPV types, and their active transformation zone is generally retracted and very narrow.

Why not just continue frequent screening in this less vulnerable population? The consequences of continuing screening in the older, previously well-screened population were nicely illustrated in a study by Sawaya et al,[18] using data from the Heart and Estrogen/Progestin Replacement Study (HERS) of postmenopausal women, they evaluated the cytology results of 2,561 women followed over a 4-year period. These women had a Pap test 2 to 2 years after a normal entry cytology.

Subsequent follow-up of cases in which the Pap test was abnormal found only 1 woman with histologic dysplasia, which was a case of mild to moderate dysplasia. To make this diagnosis involved inconvenience, cost and morbidity to the group. To find this single case of mild to moderate dysplasia, 110 women were recalled for follow-ups, which required 231 interventions that included repeat Pap smears, colposcopies, endometrial biopsies, cervical and endocervical biopsies, D&Cs, and excision procedures.

Add to the additional tests, the anxiety inherent in a report of an abnormal Pap test and its follow-up, and the value of limiting screening in this very low risk population become more apparent.

Screen for cervical cancer if there is no cervix?

Since 1996, the US Preventive Services Task Force has recommended against cervical cytology screening in women whose uterus and cervix have been removed for benign indications. Despite this, a recent study showed, as many as 45.6% of such women were still having Pap tests.[19]

For any screening procedure to be cost effective, there must be a threshold prevalence of the disease in the population to be screened. While women with prior cervical cancer or high-grade dysplasia remain at increased risk for recurrences at the vaginal cuff, women with no history of such disease are at extremely low risk.

In essence, screening in these women becomes a search for primary vaginal cancer, which is one of the rarest of gynecologic malignancies— only 0.3% of cancers in women, a frequency less than that of cancer of the tongue.[9] Continued screening in the absence of a cervix implies the need to screen an unacceptably large number of women to diagnose a single lesion. Cytology screening in this group is far more likely to diagnose low-grade vaginal intraepithelial neoplasia

(VAIN). VAIN 1 reflects self-limited epithelial changes that are extremely unlikely to progress to cancer.

What is the role of HPV testing?

Last year, the US Food and Drug Administration approved the Hybrid Capture 2 test for high-risk HPV DNA (*Digene, Gaithersburg, Md*) for use in addition to cervical cytology for screening women over age 30. Both ACOG and the ACS acknowledged this combination of tests as an acceptable option as long as women who test negative on both tests are not retested for 3 years.[1,2]

Using HPV DNA screening in women under 30 makes little sense. Many studies have confirmed the high prevalence of high-risk HPV in this age group whose risk of invasive cancer is quite low.[7,12,20] Screening with HPV before age 30 would result in an unacceptably high false-positive rate, with no advantage over annual screening with cytology alone.

High negative predictive value after age 30

On the other hand, after age 30, as the prevalence of HPV declines, the specificity of this test improves markedly.[12] Why wait 3 years before retesting if both tests are negative? The answer lies in the extremely high negative predictive value of the combination. Sherman et al[21] determined that the negative predictive value of the combination of cytology plus HPV DNA testing 33 months after both tests are negative is 99.88%. At 45 months, it was still 99.84%.

Thus we can provide excellent assurance to women who test negative that their risk of CIN 3 or squamous cancer is negligible over at least the intervening 3 years.

It's worth noting that in this same study, the negative predictive value of cytology alone at 33 and 45 months was also quite high: 99.61% and 99.47%, respectively.

ABNORMAL RESULTS

Consensus guidelines for combined testing

Management is clear when both tests are negative, or when the Pap shows SIL and the HPV is positive. But what if only 1 of the tests is abnormal? A February 2003 consensus workshop held by ACS, the American Society for Colposcopy and Cervical Pathology, and the National Institutes of Health developed recommendations for managing the various combinations of results.[22]

ASC-US and positive HPV

Data clearly support triaging these patients to colposcopy. The National Cancer Institute's ASCUS/LSIL Triage study (ALTS) study showed that, in a group of 1,161 women, this combination of results had a 92% sensitivity for diagnosing CIN 3.[23] Solomon Other studies, done under perhaps less rigorous scientific conditions, also showed high sensitivity, though generally not as high as in the ALTS study.

When cytology results are more severe than ASC-US

If results are ASC-H, AGC, LSIL, or HSIL, manage with colposcopy regardless of HPV results.

Negative cytology and positive for high-risk HPV

This scenario is more difficult for both the physician and patient. High-risk HPV is a clear risk factor for subsequent dysplasia.[21] While most HPV infections are transient, the risk of dysplasia increases when they persist.[24] A reasonable course is to repeat both Pap and HPV in 6 to 12 months. This allows time for transient HPV infections to clear and for persistent infections to be identified on the repeat test.

The ultimate prognosis and management are determined by the repeat cytology plus HPV. If both repeat tests are negative, further repeat screening should be delayed for 3 years.

If the cytology is ASC-US, but HPV is negative, the patient may safely be

When cytology is negative and HPV is positive, repeat both tests in 6 to 12 months.

screened again in 1 year with Pap plus HPV. Colposcopy is indicated if the cytology is worse than ASC-US and/or if the HPV remains positive.

Counseling HPV-positive patients

Perhaps the most difficult aspect of screening with cytology plus HPV DNA is what to advise patients whose Pap test is normal but whose HPV is positive.

Many women are aware that HPV is sexually transmitted, and a positive HPV test conjures fears of spousal infidelity, concerns about spreading the infection, and fear of other sexually transmitted infections.

Long latency. I have found it useful to defuse the infidelity concern by pointing to the long latent period associated with HPV infections. A recently diagnosed HPV infection may have been acquired years in the past from a prior partner, or from her current partner early in their relationship.

Neither partner should construe a positive test for high-risk HPV as an indicator of promiscuity. It is just as likely that a temporary change in her immune status allowed a previously latent infection to become productive.

Highly prevalent. The patient may be reassured by knowing that HPV is exceedingly common; up to 75% of women will have one or more subtypes of HPV in their lower genital tract at some time in their lives. Pointing out that it can be considered a marker of ever having had vaginal intercourse may help to eliminate the stigma of a sexually transmitted disease.

Let her know her partner probably carries the same HPV type, or has cleared it in the past.

Low risk of cancer for the partner. Male partners of women who test positive for high-risk HPV DNA do not require any testing. Reassure the couple that the male's risk of cancer is very low since the penis lacks a transformation zone, the substrate for efficient neoplastic transformation.

Reassure her of low risk without neoplastic changes. The presence of HPV on the cervix is of little clinical importance unless the cervical epithelium has begun to undergo neoplastic changes. Reassure the patient that as long as she has no squamous intraepithelial lesions on Pap testing or a persistently positive HPV DNA test over time, she has a low risk developing cancer.

I find it useful to defuse the infidelity concern by pointing out the long latency of HPV infection.

What's the harm in yearly testing?

Will our patients skip annual gynecologic exams if we tell them they no longer need an annual Pap test? If Paps are performed only every 3 years, will many women wait 4 or 5 years between screenings?

These and other concerns make it difficult to change an ingrained routine, despite data that support new practice guidelines.

Besides, the Pap test is inexpensive, so what's the harm in doing it annually? While the Pap test itself remains relatively inexpensive, the wide popularity of the liquid-based Pap test has doubled or tripled the cost of the test in many markets. And annual testing in low-risk women has a high rate of false positives, which require costly follow-up testing.[13]

Though future studies must determine the optimal interval for gynecologic examinations in asymptomatic women, periodic examinations are certainly important—even if a Pap test is not done each year. As primary-care providers, gynecologists offer periodic screenings for conditions such as diabetes, cardiac disease, and colon cancer, in addition to gynecologic evaluations. And it makes good sense to encourage frequent periodic exams for patients at risk, such as young women in need of contraceptive counseling or evaluation for sexually transmitted disease, and older women in need of breast surveillance.

But if we provide periodic screening without the "Pap-smear prompt," we'll need to redouble our efforts to teach patients the value of the annual exam for other health assessments, not cervical cytology screening alone. ■

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Without a yearly 'Pap smear prompt,' we must teach our patients why they need annual exams.

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