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INSIDE

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Put Down the Pap and Step Away: Updated Cervical Cytology Screening Guidelines

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman is a consultant to Schering-Plough and receives grant/research support from the Society for Family Planning.

Synopsis: *Updated cervical cytology screening guidelines by the American College of Obstetrics and Gynecologists recommend a decreased frequency of pap smears for women younger than age 30.*

Source: Cervical cytology screening. American College of Obstetrics and Gynecologists (ACOG) Practice Bulletin. No. 109, December 2009. Available at: www.acog.org/publications/educational_bulletins/pb109.cfm. Accessed Dec. 8, 2009.

AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGISTS (ACOG) recently published updated recommendations on the frequency of cervical cytology screening. The main changes were in women younger than age 30, including the first pap to occur no earlier than age 21 (no longer based on the date of sexual debut) and a pap every 2 years for women age 21-29 years. No changes were made to the frequency of pap testing in women older than age 30 (healthy, immune-intact women with three consecutive negative paps may be screened every 3 years).

COMMENTARY

November was a busy month for women's health care with big changes in screening practices. If you tend toward the paranoid, you may wonder if this is part of a conspiracy to decrease costs. Let me reassure you that the recent pap recommendations have been in the pipeline for well over a year and the changes aren't actually that drastic *(see table, page 74)*. These changes are not as controversial as the mammography recommendations and have the support of the

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American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Cancer Society.[1]

There are some general caveats to decreasing the frequency of pap smears for any age group. These recommendations are for "low-risk" women, which means not immunocompromised (i.e., HIV/AIDs, transplant patients), or those with prior exposure to diethylstilbestrol (DES). Additionally, women who have undergone previous treatment for CIN 2, CIN 3, or cervical cancer are at risk for recurrent disease and are advised to have annual screening for at least 20 years.[2-4]

How do these recommendations translate to the office? Unfortunately, you probably have some women younger than age 21 who are already being followed for dysplasia. Become familiar with the ASCCP's guidelines published in 2006 for management of abnormal cytology and histology in adolescent women.[2,5] You can download the clinical algorithms at: www.asccp.org/consensus.shtml. The recommendations vary significantly from the management of adult women with a lot more watchful waiting and a lot fewer excisional procedures.

Table

Comparison of new vs old ACOG cervical cytology screening recommendations[1]

Age Group	New Recommendations	Old Recommendations
≤ 21 years	Pap at age 21	Pap at age 21 or within 3 years of sexual debut
21-29 years	Pap every 2 years	Pap every year
≥ 30 years (with three prior consecutive negative paps)	Pap every 3 years	Pap every 3 years
65-70 years	Stop paps	Stop paps
Total hysterectomy for benign disease and no history of high-grade CIN	Stop paps	Stop paps

Educating and reassuring our patients about these new screening guidelines can be challenging and time-consuming. Interestingly, my patients younger than age 30 seem thrilled by the prospect of avoiding a pelvic exam and have been very accepting of the new recommendations, while my patients older than age 30 are still skeptical regarding the triennial pap, even though this recommendation has been around for almost 10 years. In any case, here are my "60-second" counseling points, which hopefully will keep your busy clinic running on time, too:

- There are many good reasons for delaying pap screening until women are age 21, including: HPV infection is common but resolves, most dysplasia regresses spontaneously, cervical cancer is extremely rare (1-2 cases/1,000,000), and avoiding screening prevents unnecessary invasive testing (which in turn prevents preterm birth).[6-8]
- Triennial screening in low-risk women age 30 years and older has similar benefits to annual screening. A study of 31,000 women found no cancers with spacing paps every 3 years, but *theoretic* models estimate the possibility of delayed identification of 3 additional cancer cases/100,000.[9] But it's important to remember that cervical cancer is a slow-growing cancer.
- For women age 30 and older, if risk factors change (e.g., a new partner) then screening becomes more frequent again.
- Get vaccinated: HPV vaccine for eligible patients. ■

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Questions & Comments

Call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

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Cytomegalovirus Screening Strategies

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Universal screening for primary maternal cytomegalovirus (CMV) is cost-effective. More study is needed to evaluate the efficacy of CMV-intravenous immune globulin for prevention.*

Source: Cahill AG, et al. Screening and treating primary cytomegalovirus infection in pregnancy: Where do we stand? A decision-analytic and economic analysis. *Am J Obstet Gynecol* 2009;201:466.e1-7.

CURRENTLY, THERE IS NO CONSENSUS ON HOW TO screen for CMV, a problem that affects about 1% of pregnancies in the United States. Since one study has emerged showing that treatment of CMV is about 90% effective in avoiding sequelae in neonates,[1] Cahill et al from St. Louis used various assumptions while constructing a mathematical model to assess the theoretical efficacy and cost-effectiveness of three methods of screening: 1) universal screening; 2) screening of those at historical risk (those with children < 5 years of age, or who are employed in a childcare setting); or 3) screening only those with ultrasound signs suspicious for fetal CMV infection.

The screening method involved maternal blood testing for CMV IgG and IgM antibodies. If IgM was positive without the presence of IgG antibodies, the patient was considered to be screen-positive. If both IgM and IgG were present, but with the latter having < 25% avidity, these patients were also considered screen-positive. The method also assumed that every screen-positive patient's amniotic fluid would be tested for the presence of CMV/DNA by PCR. Those with the diagnosis of CMV would then be treated with 200 U/kg of CMV immunoglobulin (CMV/IVIG).

Based on a yearly birth rate of about 4 million in the United States, the authors calculated that universal screening after 20 weeks would result in 66,368 false-positive tests. In this category (category 1), there would be 1979 neonatal deaths and 615 cases of severe disability. In category 2, 2.1 million women would be screened, resulting in 26,348 patients having false-positive results, and with this strategy there would be 2058 neonatal deaths and 8253 severely disabled infants. Using ultrasound findings for screening (category 3), 1.6 million patients would be screened, resulting in 2078 neonatal deaths and 8327 cases of severe disability.

The authors concluded that the most effective strategy was universal screening, but only if there was a 47% reduction in disease with the above treatment. Specifically, when comparing universal screening (category 1) with screening only for risk factors (category 2), treatment of diagnosed cases would save 7638 more children from severe CMV morbidity, and when comparing universal screening (category 1) with ultrasound findings alone (category 3), severe disability would be averted in 7712 infants.

■ COMMENTARY

Unfortunately, as the authors point out, the efficacy of universal screening after 20 weeks is based on the assumption that treatment with CMV/IVIG will be effective in at least 1 of 2 fetuses/neonates, and, although

the study cited showed a 90% effectiveness,[1] it is the only study in the literature and the numbers of patients in the study are not overly impressive. Also, at present the therapy has limited availability and is costly.

Obviously, we are not there yet, and I am simply including this paper in this month's *OB/GYN Clinical Alert* to apprise the reader of a possibly effective screening strategy that still needs major fine-tuning through rigorous prospective investigation. In the meantime, we will certainly continue testing those with suspicious ultrasound findings such as ventriculomegaly, periventricular calcifications, large cisterna magna (with or without cerebellar hypoplasia), ascites, or intra-abdominal calcifications. Whether to screen those in category 2 is not so clear. Interestingly, the above results are essentially the same between those screened for risk factors and those with ultrasound findings. However, once the ultrasound signs appear, is it already too late? ■

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The Next Iteration of the Radical Hysterectomy?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman is a consultant to GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer, and serves on the speakers bureaus for GlaxoSmithKline, Eli Lilly Co., and OrthoBiotech.

Synopsis: *Anatomical resection of the embryologically Müllerian anlage defines a new "radical hysterectomy" procedure for women with early-stage cervix cancer with superior survival rates in a single-institution prospective study.*

Source: Höckel M, et al. Resection of the embryologically defined uterovaginal (Müllerian) compartment and pelvic control in patients with cervical cancer: A prospective analysis. *Lancet Oncol* 2009;10:683-692.

Radical hysterectomy remains the primary surgical procedure of choice for women with early-stage cervix cancer because of its ability to remove the primary site and surrounding tissues, which help to classify risk for recurrence and in some cases, indicate adjuvant therapy. The procedure itself is defined by anatomical landmarks and surgical volume to produce a "margin" of tumor-free tissue. The radical resection of the uterine corpus, fallopian tubes, broad ligament and mesosalpinx or peritoneal mesometrium, the cervix, upper vagina, lateral tissue or subperitoneal mesometrium, the pelvic tissues defining the bladder mesometrium, the anterior and lateral mesorectum, and endopelvic fascia or ligamentous mesometrium has been recently described based on embryological development paths and is termed the total mesometrial resection (TMMR) procedure. The primary difference between the two radical procedures is the extent and locality of resection, which, in the case of the latter, is directed to tissues of a common developmental ancestry. The authors prospectively compiled the outcomes of 212 consecutive patients with stage IB-IIA (and selected IIB) cervix cancer treated with the approach. In no case was adjuvant radiation therapy administered; however, patients with more than two positive nodes were administered adjuvant chemotherapy. At a median follow-up of 41 months, only 10 recurrences were identified; three of these were pelvic only, two with pelvic and distant components, and five with distant-only disease. Recurrence-free and overall survival at 5 years was 94%. Treatment-related grade 2 morbidity was 9% and was most commonly vascular. Anatomical topography from two historical patient cohorts with local recurrent disease following standard radical hysterectomy demonstrated the pelvic tissues of highest probability for recurrence were in the area of mesometrium not typically approached by the standard procedure. The authors conclude that TMMR is a viable procedure developed by embryologically guided principles that produces superior survival characteristics in the absence of adjuvant pelvic radiotherapy.

■ COMMENTARY

The current standard for primary surgical extirpation of early-stage cervix cancer includes radical resection of the uterine corpus, upper vagina, parametrium, and a portion of the utero-sacral ligaments accompanied by pelvic lymphadenectomy. Despite current trends in surgical approach (e.g., endoscopic, vaginal, and robotic techniques), the surgical procedure itself, particularly in terms of resection goals, has been modified little since its inception. Indeed, the procedure was developed according to oncological principles of wide tumor-free margins

around the primary tumor. Inability to achieve these goals essentially defines patients considered poor candidates for surgery and these patients are usually referred for primary chemoradiation therapy. The current article challenges this "standard" on several important layers that are noteworthy. For instance, the TMMR procedure is designed around the embryological Müllerian anlage of development for the uterus and cervix. The hypothesis, which the authors contend drives not only metastatic spread but also the unfortunate local recurrence, is carefully supported by their outstanding survival data, despite the absence of adjuvant therapy for "high-risk" individuals (close margins and positive node) and a graphic topographical anatomical description of recurrences in two retrospective cohorts detailing incomplete resection of this "at-risk" tissue with standard radical resection. In addition, the authors contend that cases of metastatic spread to the nodal basins require only adjuvant chemotherapy. This is based on their confidence that resection of nearly all of the mesometrial tissues (except the lowest portion of the vagina) essentially removes the local recurrence risk. This appears to be supported by the remarkably low pelvic recurrence rate, despite including nearly 100 patients with "near" margins (< 5 mm) and 50 patients with stage IIB disease.

The series is large and prospective, and deserving of further validation, particularly in the multi-institutional setting. This is an important "next step," as the research team is quite expert in the target pelvic anatomy, and in the procedure itself. Replication of their results in not only the target resection volume and survival outcome, but also the safety of the procedure in less experienced hands, is a requisite for generalization and a call for a new standard. Indeed, even in the hands of this team the median operative time was more than 7 hours, with a high incidence of intraoperative transfusion and prolonged hospitalization (median 12 days). Nevertheless, there is a certain intrigue about anatomical-specific resection for this disease and the surgical finesse, which may indeed maximize survival for this group of usually young women, if exportable. ■

Combination Therapy for Neuropathic Pain?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Combined gabapentin and nortriptyline are more effective than either drug given alone for neuropathic pain.*

Source: Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-1261.

Patients with diabetic polyneuropathy or postherpetic neuralgia were randomized to receive one of three sequences of daily oral gabapentin, nortriptyline, and the combination of both drugs in a double-dummy, double-blind, crossover study. Each treatment interval was 6 weeks, and the primary outcome was mean daily pain at maximum tolerated dose. Of the 56 subjects enrolled in the study, 47 completed two treatment periods, and 45 completed all three treatment periods. Mean daily pain (recorded on a 0-10, numerical rating scale) was 5.4 (95% confidence interval [CI], 5.0-5.8) at baseline, and at maximum tolerated dose, pain was 3.2 (95% CI, 2.5-3.8) for gabapentin, 2.9 (95% CI, 2.4-3.4) for nortriptyline, and 2.3 (95% CI, 1.8-2.8) for combination treatment. Pain with combination treatment was significantly lower than with gabapentin (-0.9; 95% CI, -1.4 to -0.3; $P = 0.001$) or nortriptyline alone (-0.6; 95% CI, -1.1 to -0.1; $P = 0.02$). The most common adverse event was dry mouth seen with the nortriptyline and combination treatments.

■ COMMENTARY

Nothing causes greater anxiety among Ob/Gyn clinicians than a new patient with chronic pelvic or vulvar pain. I teach our residents that the reason for their discomfort rests in a lack of knowledge of the pathophysiology of these pain disorders and effective treatment strategies. Too often we settle comfortably into our training as surgeons and recommend operative procedures. Our current health care insurance system reinforces this behavior as we are reimbursed much better for doing surgery than we are for office visits.

In my opinion, we focus excessively on the surgical diagnosis and treatment of endometriosis as the leading cause of pelvic pain without strong evidence that this benefits our patients. In a long-term follow-up study of patients with mild-to-moderate endometriosis who had participated in a randomized, double-blind controlled study of laparoscopic laser surgery, pelvic pain had recurred in almost 75% in less than 2 years.[1] While some surgeons view this as evidence that repeat surgery is not only necessary but desirable, substantial evidence exists that medical therapy (combined oral contraceptives, GnRH agonists, injectable or implantable progestins, or even the levonorgestrel IUS) offers benefit in terms of

pain reduction (principally reduced dysmenorrhea) and disease progression. In fact, a consensus panel concluded that "chronic pelvic pain frequently occurs secondary to nongynecologic conditions that must be considered in the evaluation of affected women. For women in whom endometriosis is the suspected cause of the pain, laparoscopic confirmation of the diagnosis is unnecessary, and a trial of medical therapy, including second-line therapies such as danazol, GnRH agonists, and progestins, is justified provided that there are no other indications for surgery such as the presence of a suspicious adnexal mass."[2]

I see far too many young women referred for consultation of chronic pelvic pain with a long surgical history. Treated aggressively with surgery for minimal to mild endometriosis, these women undergo repeat surgery every 2 years and peritoneal stripping leads to adnexal adhesions, adnexectomy, and ultimately hysterectomy. Many gynecologists abandon the patient after a pelvic "clean out." Since I see the chronic pelvic pain without pelvic organs, I recognize that a different initial paradigm is needed.

The treatment of pelvic pain requires a multidisciplinary approach. In fact, randomized studies have documented that women treated in a multidisciplinary fashion with psychosocial counseling, medical management for dysmenorrhea, and physical therapy have lower pain scores and much lower rates of surgical intervention than women treated initially with laparoscopy.[3] One of the most important and frequently overlooked treatable condition associated with chronic pelvic pain is myofascial pain.[4] To treat women with chronic pelvic pain effectively, you need to partner with a physical therapist interested in this problem. Addressing psychosocial stressors and the role of past sexual abuse is also critical, and we serve our patient best when we refer her to a compassionate and well-trained specialist.

As gynecologists, we commonly use narcotics and NSAIDs to manage acute and surgical pain. Prescribing narcotics for chronic pain makes us feel uncomfortable, and represents the principle reason why most of us dislike seeing women with chronic pain. What we often fail to appreciate is the scenarios that bring these women to the emergency room or clinic requesting pain meds. Often the medications are prescribed before and after unneeded surgical procedures. Since narcotics and NSAIDs are ineffective in treating neuropathic pain, dose escalation and iatrogenic narcotic dependence occurs.

Neuropathic pain is transmitted via small nonmyelinated nerve fibers. While the exact mechanisms involved in the etiology of neuropathic pain are incompletely understood, the general features of burning, raw, poorly localized pain without any apparent somatic cause are seen in women with both chronic pelvic and vulvar pain. While there are no large randomized studies of neuromodulators for the treatment of chronic pelvic or vulvar pain, clinicians have extrapolated success from studies of agents used to manage chronic diabetic neuropathic pain or post-herpetic neuralgia. The most widely used drugs include the tricyclic antidepressants (TCAD) and gabapentin. The principle side effect of the TCAD group is dry mouth. Nortriptyline is tolerated better than amitriptyline. Many providers recommend some of the newer, better-tolerated mixed-activity antidepressants like venlafaxine and duloxetine. The SSRIs (fluoxetine, sertraline) don't seem to work as well. Since none of these agents are approved for the treatment of chronic pain, the use is off-label and must be discussed in detail.

I suspect that many of you already are familiar and comfortable with the prescription of SSRIs for depression, and may use lower doses of TCADs for sleep or urge incontinence. While the SSRIs are not effective for pain, I personally have found that venlafaxine or duloxetine are well tolerated in young women and work well in depression and for pain. Gabapentin is an easy drug to prescribe with extremely low systemic toxicity. The principle side effect is dizziness, and this can be avoided by a slow escalation in dose. Limited evidence for the approach of combination therapy with gabapentin and amitriptyline in women with chronic pelvic pain comes from a small randomized study from Germany.[5] While we await additional randomized studies of these agents in women with chronic pelvic or vulvar pain, the current report suggests that combination therapy with a TCAD or atypical antidepressant and gabapentin is an important strategy to reduce suffering and narcotic use in women with chronic pelvic pain. ■

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Special Feature

Applying Risk/benefit Analysis Consistently in Entertainment Ultrasound

By John C. Hobbins, MD

APPEARING IN THE DECEMBER ISSUE OF *ULTRASOUND IN Obstetrics and Gynecology*, an editorial by De Crespigny et al[1] may rekindle the controversy surrounding keepsake videos and non-medical ultrasound, in general. At present, while some keepsake video businesses have continued to thrive, and providers are offering ultrasound for entertainment as part of, or in addition to, indicated scans, virtually all appropriate official medical organizations have continued to bolster their stance against these activities. The authors have separated entertainment scans into two types: those done during a medically indicated scan (MEU) and those performed separately for entertainment alone (non-medical entertainment ultrasound, NEU). De Crespigny and colleagues feel that to lobby against either type of non-medical ultrasound is "hypocritical" for a number of reasons.

Safety

If condemning NEU because of safety alone, one would have to take a schizophrenic approach to the issue of the bioeffects of ultrasound. In the many studies addressing this issue, either involving an in vitro cellular model, in animals, or in human investigation, there is no independently confirmed evidence to indicate harm to mother or fetus from ultrasound used at diagnostic dosage. Yes, one study did suggest a higher rate (5%) of "left-handedness" among male offspring exposed to ultrasound in utero compared with controls.[2] Another study showed slightly lower birth weights (average of 25 g) in infants exposed to repeated Doppler ultrasound vs controls.[3] However, later follow-up examinations found no difference in the size or neurodevelopment in these same children.[4] The only other study, initially attracting attention, involved the exposure of pregnant mice to ultrasound at diagnostic intensities.[5] Some of the offspring of those mice exposed to ultrasound for more than 30 minutes had 10% fewer brain cells than controls. However, the experimental method involved longer and more intense exposure to ultrasound, and in no way was similar to a typical examination in a pregnant woman. So based on all of the studies to date, we cannot completely preclude a subtle effect of ultrasound, but we can say that there certainly is no solid evidence to indicate that it does cause harm at diagnostic dosage.

Here is where the schizophrenia comes in. As De Crespigny and colleagues point out, based on the question of safety of ultrasound alone, we cannot have it both ways. Either it is safe or it is not, and whether it is done for an indication or for entertainment, it is the scan itself that is in question, and not the reason for the scan. They ask, why is it not justifiable to do a scan for entertainment, but it is acceptable to do an exam for teaching (a practice condoned by medical organizations)? They also point out that many women have multiple indicated exams and the addition of a single NEU, undertaken after organogenesis is complete, represents only a small contribution to the total exposure for that fetus.

Benefit

As in any ethical debate, the authors predictably bring up the question of beneficence vs risk, but in this case we have to deal with two individuals, the mother and the fetus. For the sake of argument, they propose that we assume that the risk is "sufficiently high, or sufficiently uncertain" (far more likely) to scan only if there is benefit. Here they get into the uncomfortable area of fetal beneficence, and wind up pitting an indicated exam against NEU. They claim that, since the fetal survey in the indicated exam is designed to identify an anomaly, how can the fetus benefit from something that may lead to termination of pregnancy? Then they point out that many (unnecessary) fetal exposures are required to identify one anomaly. Unfortunately, the authors chose to ignore the huge fetal benefit of identifying a non-lethal abnormality or condition (like IUGR) where adjustment of the management can be lifesaving, or life-altering, for the fetus.

Regarding benefit to the mother, they imply that comparison between MEU and NEU is a wash. Both will reassure the mother, but the NEU may add the benefit of bonding. Here I strongly disagree. Most patients I see are "wired" before their first fetal anatomy scan, and are visibly relieved when we tell them there are no obvious abnormalities. This represents a strong benefit. Interestingly, the authors also wonder why the teaching exam is acceptable, when neither the fetus nor the mother benefits directly from this.

Based on all these inconsistencies, they conclude that "given the current practice, there is no good reason on the basis of bioeffects for opposing entertainment ultrasound."

Comment

What seems to have galvanized the medical organizations to take a position against ultrasound for entertainment was Tom Cruise's purchase of an ultrasound machine for his own pleasure and the surfacing of many shopping mall ultrasound kiosks designed to stuff the pockets of their owners. The authors of the editorial made some good points, but glossed over some counter points. For example, I was surprised that they did not address some of the undesirable fallout from NEU, such as when a "technician" not trained in prenatal diagnosis has apprised the patient, erroneously, of a possible fetal anomaly, or, worse yet, when a patient whose fetus has an anomaly is so reassured by the NEU that she skips her indicated ultrasound. This definitely has happened, and, therefore, these false-positives and false-negatives cannot be ignored.

We tend to overlook the real reason that our patients head out to the shopping mall to shell out more than $200 for pretty pictures of their babies — because they think they are being shortchanged during their routine ultrasound examinations in their providers' offices. This desire could be satisfied with a few extra minutes of 4D (or even 2D) enjoyment at the end of each examination. Today's delivery of care system has evolved to a point where we often seem to find ourselves in an adversarial position with our patients. What better way to counter this tendency than by fostering another type of bonding — provider/patient bonding — through this simple activity. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Questions

38. All women age ≥ 30 years only need a pap every 3 years.
a. True
b. False

39. Women younger than age 21 years should initiate pap screening:
a. within 3 years of sexual debut.
b. immediately following sexual debut.
c. at age 21.
d. at age 30.

40. What aspect of the TMMR procedure is most distinct compared to a standard Wertheim radical hysterectomy?
a. Resection of the upper vagina
b. Resection of the parametrium
c. Resection of the endopelvic fascia
d. Resection of the mesosalpinx

41. Which of the following does *not* fit the data in the CMV screening study?
a. There was virtually no difference in efficacy of treatment category 2 and 3.
b. The treatment power of CMV/IB IG has not undergone rigorous testing.
c. CMV affects about 1% of pregnancies in the United States.
d. Screening for only those with ultrasound findings of CMV is clearly more efficacious than screening for risk factors.

42. Which is *not* applicable regarding benefits of an indicated scan?
a. It is substantially reassuring for patients when fetal anomalies are excluded.
b. Some fetuses can derive benefit when an anomaly is found, since management can sometimes be adjusted to improve outcome.
c. It is effective in detecting more than 90% of fetal anomalies.
d. Is possible to add an emotional lift to the mother if a few minutes of keepsake activity is added to the indicated (MEU) scan.

Answers: 38. b, 39. c, 40. c, 41. d, 42. c.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Hospital Medicine Alert, Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Dabigatran: An Oral Direct Thrombin Inhibitor

In this issue: Results from a Phase 3 study of dabigatran, intensive lipid-lowering in CVD, H1N1 vaccine dosing and efficacy, and FDA Actions.

Anticoagulation without monitoring?

Dabigatran is an oral direct thrombin inhibitor, currently being used in many countries as an alternative to warfarin. It is anxiously awaited in this country primarily because, unlike warfarin, it does not require monitoring with blood tests. The drug has been shown to be as effective as warfarin in preventing stroke in patients with atrial fibrillation (*N Engl J Med* 2009;361:1139-1151).

A new study published in December 2009 compares the two drugs in the treatment of acute venous thromboembolism. In a randomized, double-blind, non-inferiority trial, patients with acute venous thrombus embolism were given a median of 9 days of parenteral anticoagulation therapy, then were randomized to oral dabigatran (150 mg twice a day) or warfarin that was dose-adjusted to achieve an INR of 2.0-3.0. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Of the patients randomized to receive dabigatran, 2.4% had recurrent venous thromboembolism compared to 2.1% of patients on warfarin (difference in risk of 0.4%; 95% confidence interval [CI], -0.8 to 1.5; $P < 0.001$ for the prespecified non-inferiority margin). Major bleeding episodes occurred in 1.6% of patients on dabigatran vs 1.9% of patients on warfarin. Episodes of any bleeding were 16.1% with dabigatran and 21.9% with warfarin. There was no difference in the number of deaths, acute coronary syndromes, or abnormal liver function tests between the two groups. Treatment was discontinued due to adverse events in 9% of patients on dabigatran and 6.8% of patients on warfarin. The authors concluded that for treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has similar safety, but does not require laboratory monitoring (*N Engl J Med* 2009;361:2342-2352).

Physicians and patients alike in the United States have been awaiting an orally effective anticoagulant that doesn't require monitoring. Dabigatran, a direct thrombin inhibitor, may soon fill that role. The drug, which has the additional advantage of having minimal drug and food interactions, has been available in Canada and Europe for almost 2 years, and with the completion of Phase 3 trials such as this one, there is speculation the FDA may take action this year. ■

Intensive lipid-lowering and CVD

Follow-up analysis of two of the most famous lipid-lowering trials confirms that intensive lipid-lowering therapy continues to be beneficial in the longer term. The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, first published in 2004,

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compared moderate lipid-lowering using standard-dose pravastatin to intensive lipid-lowering with high-dose atorvastatin after acute coronary syndrome. The study showed high-dose therapy significantly reduced the occurrence of death, myocardial infarction, stroke, and unstable angina requiring hospitalization or revascularization occurring more than 30 days after the event. The new post-hoc analysis (*J Am Coll Cardiol* 2009; 54:2358-2362) followed patients for up to 2 years and showed continued benefit in reduction of the primary endpoint (16%; P = 0 .005) with high-dose therapy, as well as reduction of additional events (19%; P = 0.009).

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared high-dose atorvastatin with usual dose simvastatin for the prevention of events subsequent to a first event. The study was published in 2005, and while not showing reduction in mortality in the 4.8 years of study, it did show a reduction in secondary cardiovascular outcomes with high-dose therapy. The new analysis looked at not only time to first event, but also second, third, fourth, and fifth events. High-dose therapy significantly reduced subsequent events by 17%-28%. The authors concluded that continued intensive statin therapy continues to be more effective than standard statin therapy, even beyond the first vascular event (*J Am Coll Cardiol* 2009;54:2353-2357).

Both these studies suggest that staying the course with intensive lipid-lowering in patients with cardiovascular disease is an effective long-term strategy. ■

H1N1 dosing and efficacy

Three recent studies in the Dec. 17, 2009, *New England Journal of Medicine* confirm that a single dose of the H1N1 vaccine is effective for most healthy adults and children age 3 and older. In the first study, 240 patients were equally divided to receive 15 µg or 30 µg of hemagglutinin antigen by IM injection. By day 21, antibody titers of 1:40 were observed in 95.0% of patients who received the 15 µg dose and 89.1% of patients who received the 30 µg dose (*N Engl J Med* 2009;361:2405-2413).

In the second study from China, antibody titers were done at 21 days after a first injection of 15 µg with or without adjuvant. A titer of 1:40 was achieved in 75% of subjects between age 3 and 11, 97.1% of subjects between age 12 and 17, 97.1% of subjects between age 18 and 60, and 79.1% of subjects age 61 and older. Alum adjuvant did not significantly raise antibody titers. Although a second injection at 21 days raised antibody titers, the authors conclude that a single dose of 15 µg induced a typically protective antibody response in the majority of subjects between age 12 and 60 (*N Engl J Med* 2009;361:2414-2423).

In the third study, standard H1N1 vaccine was compared to a MF59-adjuvanted vaccine (derived from cell culture rather than egg-based). A number of injection schedules were tested. Local reactions and muscle aches were more frequent in the MF59-adjuvanted vaccine. Although higher antibody titers were seen with the adjuvanted vaccine, significant titers were also seen within non-adjuvanted vaccine within 2-3 weeks (*N Engl J Med* 2009;361:2424-2435).

These findings confirm data previously published in the *Lancet* in the fall of 2009 confirming that one dose of the H1N1 vaccine seems adequate, although two doses may be required for younger children. Currently, the Centers for Disease Control and Prevention (CDC) recommends two doses for children younger than age 10, but the recommendations may change based on these findings.

In related news, the CDC is reporting that safety data regarding the H1N1 vaccine is "reassuring," with a rate of serious complications such as Guillain-Barré syndrome no higher than "background rates." The rate of adverse event reporting has been higher with the H1N1 vaccine compared to seasonal flu; however, most of these reports have been for mild reactions and may be attributed to the higher rate of awareness associated with the new vaccine. ■

FDA Actions

The FDA has approved the first generic version of donepezil (Aricept®) for the treatment of Alzheimer's disease. The new generic will be marketed as 5 mg and 10 mg orally disintegrating tablets, which dissolve on the tongue and do not need to be swallowed. Generic donepezil is expected to be available later this year. ■

An FDA advisory panel is recommending expansion of the indication for rosuvastatin (Crestor®) to include patients with normal cholesterol levels and no history of cardiovascular disease. The recommendation is based on the JUPITER trial, which showed a reduction in cardiovascular risk in patients with normal LDL cholesterol but high C-reactive protein who were treated with rosuvastatin. ■