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## INSIDE



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# Postmenopausal Hormone Therapy and Stroke

ABSTRACT & COMMENTARY

***By Leon Speroff, MD, Editor***

***Synopsis:*** *The Nurses' Health Study reports an increased risk of stroke associated with hormone therapy that may be related to the dose of estrogen*

**Source:** Grodstein F, et al. Postmenopausal hormone therapy and stroke. Role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med.* 2008;168:861-866.

The Nurses' Health Study reported an update of its data on the use of hormone therapy and stroke, focusing on the timing of initiation of treatment and the effect of estrogen doses.[1] In the analyses adjusted for age, BMI, cholesterol levels, diabetes, hypertension, smoking, and family history of early coronary heart disease, the following relative risks were observed for ischemic stroke (there was no significant increase in hemorrhagic stroke):

| | |
|---|---|
| Current use of estrogen alone | RR=1.43 (CI=1.17-1.74) |
| Current use of estrogen-progestin | RR=1.53 (CI=1.21-1.95) |

There was no significant increase in fatal stroke. For nonfatal stroke the relative risks were:

| | | |
|---|---|---|
| Current use of estrogen alone | 243 cases | RR=1.41 (CI=1.19-1.68) |
| Current use of estrogen-progestin | 123 cases | RR=1.31 (CI=1.05-1.62) |

The results did not change after adjustments for dietary factors, physical activity, regular aspirin use, and vitamin supplementation. Comparing initiation of hormone therapy near menopause with initiation 10 or more years after menopause, the authors concluded that there was no major difference. However a close look at the data reveals that the risks associated with estrogen alone were statistically significant for near and far initiation, but the risks with estrogen-progestin were not! Looking

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at the age of initiation, the risk of stroke for estrogen alone was significantly increased for women age 50-59, but the risk with estrogen-progestin was not statistically significant. For women 60 years of age and older, the risks with both estrogen alone and estrogen-progestin were statistically significant.

The Nurses' Health Study also reported an increasing risk of stroke with an increasing dose of estrogen:

| | | |
|---|---|---|
| 0.3 mg estrogen | 25 cases | RR=0.93 (CI=0.62-1.40) |
| 0.625 mg | 268 cases | RR=1.54 (CI=1.31-1.81) |
| 1.25 mg | 60 cases | RR=1.62 (CI=1.23-2.14) |

## ■ COMMENTARY

It is not easy to derive a take-home message from this Nurses' Health Study report. The authors provide a table of attributable risk for current hormone use based on their numbers, and the fact that the risk of stroke greatly increases with increasing age.

| | |
|---|---|
| Age less than 50 | 0.9 strokes per 10,000 women per year |
| Age 50-54 | 1.5 |
| Age 55-59 | 2.2 |
| Age 60-64 | 2.8 |
| Age 65 and older | 7.2 |

The authors state that their findings are "virtually identical to those of the WHI trials." However, in the last report from the WHI, when women with prior cardiovascular disease or those older than 60 years were excluded, the risk of stroke in women less than 10 years since their menopause was not significantly increased.[2] Therefore, there is disagreement. The authors further state that neither study found a difference in age. However, the increase with combined estrogen-progestin in the Nurses' Health Study was not statistically significant—is this because the case numbers were too small or is this real?

The authors conclude that their data suggest a small risk of stroke in younger postmenopausal women, a risk that might be further reduced with lower doses and shorter durations of treatment. The conclusions by the authors are not as clear-cut as they would seem. In my view, this risk in women who do not have risk factors for stroke (especially hypertension) may be zero. How confident can we be that the mathematical adjustment for risk factors in the Nurses' Health Study gives us a definitive answer? It makes sense that stroke risk is related to the dose of estrogen, but the Nurses' Health Study data on this issue are limited by small numbers.

So what is the take-home message? I believe the risk of stroke is minimal if not zero in young, healthy postmenopausal women. In women with risk factors for stroke, it is prudent to use low doses of estrogen and to vigorously address the risk factors, such as effective treatment of hypertension. Would the transdermal route of administration be safer? That is an important question that cannot be answered because of a lack of data, but because stroke risk is limited to ischemic events and it is possible that the transdermal route has a lower risk of thrombosis, it seems wise to promote this route of administration in older postmenopausal women and in women with risk factors for stroke. ■

## References


1. Grodstein F, et al. Postmenopausal hormone therapy and stroke. Role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med.* 2008;168:861-866.

2. Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007;297:1465-1477.



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# A New Standard for Uterine Leiomyosarcoma

ABSTRACT & COMMENTARY

***By Robert L. Coleman, MD***

*Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston*

*Dr. Coleman reports no financial relationship to this field of study.*

***Synopsis:*** *Fixed-dose rate gemcitabine and docetaxel demonstrates impressive response rates and survival characteristics in women with metastatic/recurrent previously untreated uterine leiomyosarcoma.*

**Source:** Hensley M, et al. *Gynecol Oncol.* 2008;109:329-334.

DOXORUBICIN-BASED CHEMOTHERAPY HAS remained a standard for the treatment of soft tissue sarcoma for decades. Recently, combination gemcitabine and docetaxel demonstrated significant clinical activity in a single-institution mixed population study of women with uterine leiomyosarcoma. The current report addresses the histologic diagnosis in women previously untreated for recurrent disease in a multi-institutional setting. Utilizing a two stage design, the authors designed a trial of women with measurable disease infusing gemcitabine on day 1 and both gemcitabine and docetaxel on day 8 of a 21-day cycle. The gemcitabine was administered at a fixed-dose rate of 10 mg/m2/minute. Bone marrow support was administered in all patients starting on day 9 or 10. Forty-two patients were accrued, meeting the 2-stage design requirements in 24 months of enrollment. Overall the treatment was well tolerated with infrequent grade 3 or 4 hematological toxicity. Blood transfusions were administered to 43% of the patients. No neutropenic fevers were recorded. Similarly, non-hematological toxicity, predominately fatigue, was infrequent and not dose-limiting. All patients were considered in the response despite 3 patients not completing the first cycle of protocol therapy. Nonetheless, objective response was recorded in 15 patients (36%) including 2 complete responders. The progression-free survival at 12- and 24-weeks was 60% and 40% respectively. Responders had a progression-free survival of 6 months on the median; overall PFS was 4.4 months (range 0.4 - 37.2+ months). The data are favorable to other phase II studies of alterative agents, including doxorubicin and represent a major milestone in the treatment for this disease.

## ■ COMMENTARY

Uterine leiomyosarcoma (LMS) is a tumor with some very discouraging natural history statistics. Like advanced ovarian cancer patients entering into clinical remission following primary therapy, the risk for recurrence is high, unpredictable, usually fatal when documented and is unaccompanied by an effective mechanism to prevent it. Unlike ovarian cancer, however, this disease is so uncommon that large randomized clinical trials are generally infeasible and unlikely to be nimble enough to clearly evaluate the impact of new and novel therapeutic approaches in a timely manner. However, serial evaluation of phase II studies can be instructive when the treatment population is stable. Such is the case in the current report, which is one of several conducted over the last 2 decades by the Gynecologic Oncology Group in patients with essentially the same eligibility criteria. The clinical efficacy of the regimen is remarkable and surpasses any previous single agent or combination studied to date; the oncological community has already largely embraced it. Several important issues are relevant to consider with the strategy and are highlighted in more detail in an accompanying editorial: first, the dose of docetaxel used was significant and required bone marrow support for repetitive use; could this be reduced? Second, an accompanying article in the same issue of the journal reported a 27% response rate in patients with recurrent, previously treated LMS with this same regimen. The results from that GOG study compare favorably to doxorubicin (a current front-line standard) when administered in that setting (13%); should this active combination be administered first- or second-line? Third, fixed-dose rate gemcitabine was used in this study based on preclinical (pharmacological) and clinical (PFS and OS) data supporting its use; could bolus infusion meet the same conclusion while adding convenience? And last, could this strategy be given adjuvantly to help reduce the nearly 50% recurrence rate observed at 2 years in completely resected stage I/II disease? All good questions, but unlikely to be addressed further in randomized clinical trials. However, the Group has embarked upon a randomized study evaluating the potential value-added impact of the anti-angiogenesis agent bevacizumab to this promising combination. Although the trial is expected to take more than 4 years to accrue, the results may move the benchmark further, imparting more therapeutic benefit to our patients. ■

### Suggested Reading

1. Edmonson JH, et al. Phase II study of mitomycin,

doxorubicin, and cisplatin in the treatment of advanced uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2002;85:507-510.
2. Hensley ML, et al. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol.* 2008;109:323-328.
3. Fleming G. Gemcitabine/docetaxel—welcome to a new standard. *Gynecol Oncol.* 2008;109:313-315.

# Defining Interstitial Cystitis Based on Symptoms

ABSTRACT & COMMENTARY

***By Frank W. Ling, MD***

*Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville*

*Dr. Ling reports no financial relationship to this field of study.*

***Synopsis:*** *Ninety-seven percent of women with IC/PBS described pain that worsened with certain drink or food and/or improved with urination and/or worsened with bladder filling.*

**Source:** Warren JW, et al. Evidence-Based Criteria for Pain of Interstitial Cystitis/Painful Bladder Syndrome in Women. *Urology.* 2008;71:444-448.

The authors hypothesized that certain pain symptoms characterize IC/PBS. They reviewed criteria used in two recent studies to look for commonalities. In both the 2004 "Events Preceding Interstitial Cystitis" case-control study and the Interstitial Cystitis Database, the aforementioned triad of findings was found in 97% of subjects with IC/PBS. These results may well help define the condition as differentiated from other disease states with similar symptomatology.

■ **COMMENTARY**

Finally! Maybe we're getting somewhere with interstitial cystitis, referred to here as Interstitial Cystitis/Painful Painful Bladder Syndrome (IC/PBS). As the Hall of Fame catcher Yogi Berra expressed, "If you don't know where you're going, how do you know when you get there?" Since there are no diagnostic physical signs or urologic findings or laboratory tests in IC/PBS, symptoms appear to be the best current approach to making the diagnosis.

Historically, the 4 symptoms that were felt to characterize IC/PBS were pain, urgency, frequency, and nocturia. Unfortunately, these same symptoms appear in many other conditions such as vestibulodynia, overactive bladder, endometriosis, and urinary tract infections. These 4 do accurately describe IC/PBS, but are not specific, ie, they do not exclude other conditions with similar symptoms.

With the 3 new findings, some important aspects should be explored. The dietary links to IC/PBS appear to be drinks (tea, alcohol, coffee, carbonated beverages) and food (chocolate, tomatoes, citrus fruits). Simply asking the patient whether her pain is relieved with voiding is simple enough. Increasing pain with bladder filling can easily be extrapolated from a patient's symptom pattern.

Although not in this study, those of us who see lots of patients with IC/PBS know that all 3 of the new criteria as well as the traditional quartet can be helpful in some patients. In addition, dyspareunia may well be a presenting symptom for many patients. All it takes sometimes is an index of suspicion. For many of us, our clinical problem-solving essentially boils down to seeing if a patient (the proverbial square peg) can be fit into a corresponding square hole or can forced in a proverbial round hole. We are all too often forced into the latter scenario because we don't have a sufficient number of holes to try to fit the peg into. It is critical for us, often serving as the patient's last resort, to have many different holes in which to try and fit the pegs.

To help support the diagnosis, a tender bladder base on pelvic examination might be found. Of particular help is the ability to rule out tenderness of the vestibule (using a cotton-tipped swab), the pelvic floor, and the uterus (or the vaginal cuff) as well as the adnexal regions. The thing that we absolutely don't want to do is to ascribe the pain to psychosomatic causes or phantom pain unless we have truly fully evaluated the entire spectrum within the differential diagnosis. This includes the elusive conditions related to neuropathic pain that we have written about in the past in this column.

The authors have done us a great service by saving us lots of time. If they are correct that the findings of worsening symptoms related to dietary intake and/or improvement with emptying the bladder and/or worsening with bladder filling are present in 97% of patients with IC/PBS, the time that we take to ask a multitude of questions may well be cut down considerably. Thank you! Every time saver that we can find is certainly appreciated. ■

# Sweeping Membranes—Any Drawbacks?

ABSTRACT & COMMENTARY

***By John C. Hobbins, MD***

*Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver*

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

**Synopsis:** Sweeping membranes may not accomplish its aim and could increase the chance of PROM.

**Source:** Hill MJ, et al. The effect of membranes sweeping on free labor rupture of membranes: a randomized controlled trial. *Obstet Gynecol.* 2008;111:1313-1319.

It has been common practice to "strip" or "sweep" membranes after 38 weeks to initiate spontaneous labor or, at least, to discourage patients from delivering after 42 weeks. Although the efficacy of this method has certainly not been overwhelmingly validated, studies have shown an increase in phospholipase A and prostaglandin F2 alpha, as well as an increase in uterine activity after membrane sweeping. An investigative group at Tripler Hospital in Honolulu noticed anecdotally that there appeared to be an increase in rupture of membranes prior to labor in patients having had their membranes swept. Therefore, they launched a study to see if there was such a relationship.

Hill et al[1] randomized 300 patients with normal pregnancies who had reached 38 weeks to having their membranes swept (162) or not swept (138). The technique involved a 360 degree sweep of the membranes away from the lower uterine segment—if the cervix would admit a finger. If not, the cervix was "massaged." This was repeated weekly until the patient delivered. The control group had weekly visits but no sweeping. Those managing and delivering the patients were blinded as to which patients had what done.

Although there was a trend toward higher rate of pre-labor rupture of membranes in the swept group (12% vs 7%), it did not attain statistical significance ($p$ = 0.19). However, if the cervix was dilated to more than 1 cm, there was a significant difference (9.1% vs 0%; $p$ = 0.05) in membrane rupture before labor ensued.

It is of note that there were no differences between groups regarding the incidence of post term pregnancy, going 41 weeks or longer, spontaneous labor, or average gestational age at delivery.

## ■ COMMENTARY

The authors concluded that if the patient was dilated to more than 1 cm (presumably, in those where the clinicians could "sweep" and not "massage"), there was an increase in premature rupture of the membranes. However, interestingly, the membranes sweeping maneuver did not accomplish in this small study what it was designed to do—patients in labor and/or preventing them from extending their pregnancies past 41 weeks.

A few years ago we set out to see if bacteria residing in the vagina were able to get a free ride upward through the cervix by uterine contractions occurring late in pregnancy ("in suck" theory). We recruited patients in late pregnancy to have extended transvaginal ultrasound investigations after a sterile echogenic material was inserted into their posterior fornices. The idea was that we could track the journey of the medium (and, therefore, bacteria) through the cervical canal. At the end of the observation period, one patient, who happened to be a nurse midwife, was scheduled to have her membranes stripped (our term), so we and she decided to see where the echogenic material would go after this procedure. Much to our surprise, we immediately could trace the ultrasound-opaque medium well up into the lower uterine segment—substantially further than the sweeping finger could reach.

In a few study patients we did note the presence of some contrast material in the upper cervical canal, but, obviously, if one is looking to catapult bacteria far up into the uterus, try membrane sweeping. ■

## References

1. Hill MJ, et al. The effect of membranes sweeping on free labor rupture of membranes: a randomized controlled trial. *Obstet Gynecol.* 2008;111: 1313-1319.

2. McColgin SW, et al. Parturitional factors associated with membrane stripping. *Am J Obstet Gynecol.* 1993; 169:71-77.

3. Keirse M, et al. Chronic stimulation of uterine prostaglandin synthesis during cervical ripening before the onset of labor. *Prostaglandins.* 1983;25:671-682.

# Mammography Combined with Ultrasound

ABSTRACT & COMMENTARY

***By Leon Speroff, MD, Editor***

***Synopsis:*** *Combining ultrasound with mammography in high risk women improves sensitivity, but also increases false positives.*

**Source:** Berg WA, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA.* 2008;299:2151-2163.

BERG AND COLLEAGUES FROM 21 CENTERS IN THE U.S. report the results of a prospective, multicenter, randomized trial designed to validate the performance of screening ultrasound in conjunction with mammography in women with dense breasts and at high risk for breast cancer.[1] The study is known as ACRIN, the American College of Radiology Imaging Network 6666 trial. Of the 2725 eligible women who ranged in age from 25 to 91, the average age was 55.1. Each patient underwent mammography and ultrasound in a randomized sequence. Forty cases of cancer were diagnosed, 12 on ultrasound alone, 12 on mammography alone, 8 suspicious with both techniques, and 8 with negative exams. Adding ultrasound yielded an additional 4.2 cancers per 1000 high-risk women. The false positive rate for mammography alone was 4.4%, for ultrasound alone, 8.1%, and for combined mammography plus ultrasound 10.4%. Thus adding ultrasound to mammography screening in high risk women with dense breasts improved the sensitivity of screening, but increased the rate of false positive examinations. Breast cancer mortality was not an endpoint in this trial, but the fact that the cancers detected by ultrasound are usually asymptomatic, node-negative, and not detected by mammography should yield a reduction in mortality.

## ■ COMMENTARY

The impact of screening mammography has been established by multiple randomized trials: about a 22% reduction in breast cancer mortality in women 50 years old and older, and 15% in women between ages 40 and 49. But at the same time it is recognized that it is difficult for mammography to detect noncalcified masses, especially in dense breasts. This sensitivity problem has been improved by digital mammography, but not eliminated.

Ultrasound screening can detect cancers not seen on mammography and its performance is not affected by dense breast tissue. Adding ultrasound to a screening program seems like a no-brainer, but its impact on mortality reduction has not been measured in a large trial. In the single center studies of screening ultrasound that have been published, cancers have been found only by ultrasound, and most are small, early stage tumors. During the conduct of the above trial, an Italian multicenter study reported that 29 cancers were found by ultrasound in 6449 women with dense breasts and negative mammograms.[2] Nevertheless, a majority of facilities do not offer screening ultrasound because of a lack of qualified personnel and standardized protocols.

The problem with all screening methods is a substantial rate of false positives. In this study, 91.4% of suspicious ultrasound findings were benign. The positive predictive value for ultrasound was only 8.6%, but the value for mammography was only 14.7%. Remember that ultrasound tends to find earlier tumors. The crucial question is how many false positives are worth the gain in additional cancer diagnoses. In this study, the gain was an additional 29% (the number of cancers detected only by ultrasound). In women with elevated risks, this seems worthwhile. Women at high risk probably have a greater fear of diagnosing breast cancer late than of a false positive.

Combining MRI with mammography yields a very high sensitivity, and this is now recommended for women at very high risk for breast cancer. MRI, of course, is the most sensitive technique, but it is very expensive, requires the intravenous injection of contrast, and isn't always tolerated by patients. Ultrasound has the advantage of being less expensive, easily tolerated, and widely available. Thus the combination of ultrasound and mammography seems best for women of intermediate risk. Ultrasound has a disadvantage of not detecting ductal carcinoma *in situ*, which is detected by mammography and MRI.

The final protocol for the best screening use of the three modalities—mammography, ultrasound, and MRI, will also require consideration of cost. The total cost is a complex summary of the technology, the time consumed, the increase in patient anxiety and discomfort, and the expense of additional testing because of false positives. Nevertheless, the evidence now seems sufficient to individualize decision-making and to recommend more than the single technique of mammography for high risk patients (defined as a combination of factors that produces a 3-fold increase in risk), especially in women with dense

breasts. Thus far, over 90% of cancers detected only on ultrasound have been in women with dense breasts. Ultimately the best screening method, MRI, may become cost effective. How much cost is justified for a life-saving method? ■

**References**


1. Berg WA, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA.* 2008;299:2151-2163.

2. Corsetti V, et al. Role of ultrasonography in detecting mammographically occult breast carcinoma in women with dense breasts. *Radiol Med.* 2006;111:440-448.


*Special Feature*

# Overview of The Fetal Origins of Adult Disease and The Role of The Obstetrician-Gynecologist in Predictive Health


***By Sarah Berga, MD***

*James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta*



*Dr. Berga reports no financial relationship to this field of study.*


THE TWO MAIN MODIFIERS OF PATHOGENESIS ARE age and sex. Reversible and irreversible modifications to cellular machinery through genetic and epigenetic mechanisms begin with embryogenesis. For instance, certain aspects of *in vitro* culture conditions "imprint" genetically normal embryos by altering methylation patterns and gene expression. An increase incidence of imprinting syndromes such as Beckwith-Wiederman has been described in the offspring conceived via *in vitro* fertilization and embryo transfer (assisted reproduction). Further, imprinting disorders are differentially expressed in male and female offspring due to mechanisms involving both hormone-dependent and hormone-independent gene regulation and expression. This notion is articulated in the field of reproductive endocrinology when we refer to ourselves as "gamete doctors" and in traditional obstetrics when we view ourselves as "fetal doctors." Naturally, both of these labels raise ancient ethical dilemmas regarding the balancing of maternal and paternal health interests with embryo and fetal health interests. Of note, the children of older fathers appear to have an increase in offspring with imprinting and autosomal dominant disorders, indicating that the genome not only is dynamically modified by a variety of specified and unspecified factors having to do with sex, age, and lifestyle, but that these changes may be transmitted to the next generation by either parent.

Traditional modifiers of gamete, embryo, and fetal health include a host of maternal and paternal factors, some of which are under sociocultural control, including stress, nutrition, infectious disease, and environmental exposures. For instance, maternal stress and disease alter cortisol and thyroxine rhythms and levels, which in turn modulate DNA methylation patterns in the fetus. Since the mother is the sole source of thyroxine for the developing fetal brain in the first trimester and the predominant source in the second and third trimesters, seemingly innocent alterations in thyroid function induced by disease, stress, or undernutrition may impact fetal neurodevelopment and predispose to adult neuropsychiatric disease. Some have hypothesized that subtle factors such as these underlie autism spectrum disorders, schizophrenia, and mood disorders.

In the field of obstetrics, the fetal origins of adult disease is a hot topic. There is interest in identifying modifiable factors to guide public health policy and in mechanisms of disease that might be harnessed to identify or prevent disease. For instance, we already employ pre-implantation genetic diagnosis to identify known genetic disease in embryos prior to embryo transfer. This is routinely used for carriers of cystic fibrosis. Also, there is great interest in understanding why male and female embryos appear to be differentially sensitive to certain insults. Further, somewhat unexpectedly, monozygotic twins were found to acquire epigenetic differences as they age such that they diverge in terms of gene expression and disease predilection across their lifespans. Ultimately, it is expected that these fields of inquiry and investigation will contribute to the ongoing debate about the role of medicine and government in preventing disease and promoting better societal and global health. Research in these areas will lead to better ways to harness the promise of molecular medicine for the interests of individuals and society. ■

### Suggested Reading

1. Bjornsson HT,et al. *JAMA.* 2008;299:2877-2883.
2. Fraga MF, et al. *PNAS.* 2005;102:10604-10609.
3. Gabellini D, et al. *Curr Opin Genet Dev.* 2004;3:301-307.
4. Jablonka E. *Intl J of Epidemiol.* 2004;33:929-935.
5. Makedonski K, et al. *Hum Mol Genet.* 2005;14:1049-1058.
6. Ogawa Y, et al. *Science.* 2008; 320:1336-1341.
7. Zardi G, et al. *Cell Res.* 2005;15:679-690.


## CME Questions

**15. The following statements are true regarding postmenopausal hormone therapy and the risk of stroke except:**

a. Both the WHI and the Nurses' Health Study report an increase in stroke with standard doses of estrogen.
b. The risk of stroke is greater with increasing age and with risk factors for stroke.
c. The risk of stroke may be lower with lower doses of estrogen.
d. The risk of stroke is greater with estrogen alone therapy.

**16. Which of the following is an appropriate statement?**

a. Membrane sweeping resulted in a significant decrease in rupture of membranes when the cervix was less than 1 cm dilated.
b. Membrane sweeping seemed to put patients into labor.
c. Membrane sweeping is innocuous and effective.
d. Membrane sweeping increases the appetite.

**Answers:** 15 (d); 16 (a)

## CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.



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# Bird Flu Vaccine Looks Promising

***In This Issue:*** Baxter Bioscience has developed a whole-virus, two dose vaccine against avian flu; warning label now on antipsychotics regarding an increased risk of mortality in elderly patients treated for dementia-related psychosis; vitamin D for men with heart disease on horizon? A new oral anticoagulant may soon be available for prevention of thrombotic complications of hip or knee surgery; FDA Actions

An effective two dose vaccine has been developed against the avian flu (H5N1 virus) according to a recent study in the *New England Journal of Medicine*. Researchers from Baxter Bioscience have developed a whole-virus vaccine that was tested on 275 volunteers between the ages of 18 and 45 years. Four different strengths of the vaccine were tested with and without adjuvant. The most effective regimen was a dose of either 7.5 µg or 15 µg of hemagglutinin given without adjuvant 21 days apart. The vaccine was effective at inducing neutralizing antibody response against three different viral strains. Mild pain at the injection site and headache were the most common adverse effects. The authors conclude that a two dose vaccine regimen of either 7.5 µg or 15 µg induced neutralizing antibodies against diverse H5N1 viral strains in a high percentage of subjects (*NEJM*. 2008;358:2573-2584).

## Boxed warning now required for antiphychotics for elderly with dementia

The FDA is requiring a boxed warning for conventional antipsychotics regarding an increased risk of mortality in elderly patients treated for dementia-elated psychosis. This expands the warning on the newer atypical antipsychotics which was issued in April 2005 to include the older, more conventional antipsychotics. The new warning includes medication such as haloperidol (Haldol), thioridazine (Mellaril), and chlorpromazine (Thorazine). The warning specifically states that elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are at increased risk of death. Antipsychotic drugs are not approved for the treatment of dementia-related psychosis, and physicians who prescribe antipsychotics for elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patient's families, and caregivers. It was previously thought only the newer, atypical antipsychotics were associated with increased mortality; however, multiple studies have now shown that the older antipsychotics also increase the risk. The warning can be found on the FDA web site at www.FDA.gov.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

### Vitamin D for men with heart disease?

Men may be asking about prevention of heart disease with vitamin D based on this reports of recent studies. In a follow-up from the Health Professionals Follow-up Study (HPFS) from the Harvard School of Public Health, plasma 25-hydroxyvitamin D levels were measured on over 18,000 male health-care professionals age 40 to 75 years, who were free of diagnosed cardiovascular disease at blood collection. In 10 years of follow-up, 450 men had nonfatal myocardial infarction or fatal coronary heart disease. After adjustment for matched variables, and men deficient in 25-hydroxyvitamin D (≤ 15ng/ml) were at increased risk of MI compared to those considered to be sufficient (≥ 30ng/ml) (RR 2.42; 95% CI, 1.53-3.84; *P* <.001 for trend). After adjustment for family history and multiple risk factors, the relationship remains significant. Even those with levels 22.6 to 29.9 ng/ml were at higher risk than those with levels over 30 ng/ml. The authors conclude that "low levels of 25-hydroxyvitamin D are associated with a higher risk of myocardial infarction in a graded manner even after controlling for factors noted to be associated with coronary disease." The mechanism for this relationship is unclear but may be related to vitamin D, its effect on vascular smooth muscle proliferation, inflammation, vascular calcification, and blood pressure. Whether vitamin D supplementation reverses these findings remains be seen, but it is clear that men with low vitamin D levels will require more than the current recommended daily allowance of 200-600 IU/d, perhaps even as much as 3000 IU/day (*Arch Int Med*. 2008;168:1174-1180). Another study with similar conclusions was recently published (*Arch Intern Med*. 2008;168:1340-1349).

### New oral anticoagulant tested for patients with hip or knee surgery

A new oral anticoagulant may soon be available for prevention of thrombotic complications of hip or knee surgery. Rivaroxaban is an oral direct inhibitor of factor Xa that is in phase 3 trials by Bayer and Ortho-McNeil Pharmaceutical. The drug has the advantage of being highly bioavailable when given orally and has a standard 10-mg dose given once a day. In 3 recent trials, rivaroxaban was compared to subcutaneous enoxaparin after total hip arthroplasty and total knee arthroplasty. Over 7000 patients were randomized to receive rivaroxaban 10 mg daily beginning after surgery or subcutaneous enoxaparin 40-mg once daily beginning the day before or the day of surgery. A third study compared long-term use of rivaroxaban with short-term use of enoxaparin. The primary outcomes included deep venous thrombosis, pulmonary embolism, and all cause mortality. In all 3 studies thromboprophylaxis with rivaroxaban was significantly more effective than enoxaparin, while toxicity, specifically major bleeding, was the same in both groups. The authors conclude that a once-daily 10-mg oral dose of rivaroxaban is significantly more effective than a 40 mg subcutaneous dose of enoxaparin in preventing thrombotic complications in patients undergoing total hip or total knee arthroplasty (*NEJM.* 2008;358:2765-2775, 2776-2786. *Lancet* 2008 published early online 25 June 2008). While rivaroxaban is not yet approved in this country, the prospect of an orally active direct Xa inhibitor that could take the place of parenteral heparin compounds and perhaps even warfarin is exciting to clinicians.

### FDA Actions

The FDA has approved a new pentavalent vaccine for children age 6 weeks through 4 years. The new vaccine combines diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenza type b. It is given as a 4 dose series at 2, 4, 6 and 15-18 months of age. The vaccine is marketed by Sanofi Pasteur as "Pentacel." GlaxoSmithKline has also received approval for a combination vaccine with diphtheria, tetanus, acellular pertussis, and polio for children 4 to 6 years old who require their fifth DTaP and fourth polio shot. The combination vaccine may prevent additional injections for these children. This four vaccine combination will be marketed as "Kinrix."

The FDA has issued warning letters to 23 US companies and two foreign individuals regarding the marketing of fake cancer cures on the Internet. The products which include tablets, tonics, black salves, and creams are fraudulently promoted, claiming to prevent and cure cancer. The products contained in treating such is bloodroot, shark cartilage, coral calcium, cesium, Cat's Claw, herbal tea and mushrooms. A complete list of companies and individuals concluded and the warning can be found at www.fda.gov/cder/news/fakecancercures.htm. ■