OB/GYN CLINICAL ALERT®

Providing Evidence-based Clinical Information for 28 Years

A monthly update of developments in female reproductive medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure: *OB/GYN Clinical Alert's* editor, Jeffrey T. Jensen, MD, MPH, receives research support from, is a consultant to, and serves on the speakers bureau of Bayer Healthcare/Bayer Schering; he also receives research support from Merck Abbott Laboratories, Wyeth and Warner-Chilcott and is a consultant to Schering Plough. Peer reviewer Catherine Leclair, MD, reports no financial relationship to this field of study.

Safety of Ultrasound

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, Colorado

Dr. Hobbins reports no financial relationships relevant to this field of study.

Synopsis: *Two recent studies show that pulsed Doppler delivered at diagnostic levels can adversely affect liver cells in a fetal animal model, but standard 2-D ultrasound exposure in utero did not seem to have a significant effect on handedness in children — as suggested by other studies.*

Sources: Pellicer P, et al. Ultrasound bioeffects in rats: Quantification of cellular damage in the fetal liver after pulsed Doppler imaging. *Ultrasound Obstet Gynecol* 2011;37:643-648. Heikkila K, et al. Handedness in the Helsinki ultrasound trial. *Ultrasound Obstet Gynecol* 2011;37:638-642.

TWO RECENT STUDIES HAVE RE-ENERGIZED DISCUSSION REGARDING THE safety of ultrasound — a subject that pops up periodically and then disappears until a new study surfaces. These new studies — one with provocative findings and the other with reassuring results — were published back-to-back in the June issue of *Ultrasound in Obstetrics and Gynecology*.[1,2]

Pellicer et al used a pregnant rat model to test whether pulsed Doppler ultrasound examination of the fetal ductus venosus will have a deleterious effect on fetal liver cells.[1] Rat fetuses at 18 days gestation (analogous in size to first trimester human fetuses) were exposed to pulsed Doppler ultrasound at diagnostic levels (temperature index [TI] and mechanical index [MI] < 1.0 — more on this later) for varying lengths of time (600, 300, 60, 20, 15, 10, and 3 seconds). The animals were sacrificed at different intervals after exposure, and liver cell damage/death was assessed by the degree of apoptosis in the tissue.

They found that exposure to pulsed Doppler for 20 seconds or more resulted in significant fetal liver cell damage, and that there was a linear relationship between the apoptotic index and the exposure time.

VOLUME 28 • NUMBER 5 • SEPTEMBER 2011 • PAGES 33-40

OB/GYN CLINICAL ALERT IS AVAILABLE ONLINE
www.ahcmedia.com

Interestingly, after 12 hours post-exposure there appeared to be a full recovery of the liver cells.

The second study (the famous Helsinki Study) involved patients enrolled in a randomized clinical trial in Finland between 1985 and 1987.[2] The thrust of the initial trial was to determine the efficacy of screening all patients with ultrasound compared with using ultrasound only if there was a clinical indication (the analogous study in the USA was the RADIUS trial).[3] Since data from a Norwegian trial[4] with similar design suggested a small increase in left-handedness in boys exposed to ultrasound, the Finnish investigators decided to explore this interesting possibility in exposed children vs those completely unexposed in the Helsinki trial.

They sent questionnaires to 7773 mothers regarding the "handedness" of their, now, teenage children. Since many individuals have varying degrees of ambidexterity, the authors boiled their results down into only two categories: (completely) right-handed and non-right-handed (NRH).

The authors found that boys were 1.26 times more likely to be NRH than girls. However, there were no statistically significant differences between exposed and non-exposed children (odds ratio = 1.16; 95% confidence interval 0.98-1.37). When analyzed separately, neither boys nor girls had significant differences in NRH after ultrasound exposure.

■ COMMENTARY

To paraphrase the American Institute of Ultrasound in Medicine (AIUM) safety statement, which has been updated periodically over the last 20 years, "there is no independently confirmed evidence of harm from ultrasound when used at diagnostic dosage." However, as the authors of an excellent accompanying editorial in the same issue say, "an absence of evidence of harm is not equal to the absence of harm."[5] Because of difficulties in extrapolating the findings of the above Doppler study in the rat to the human fetus, the findings in this animal study should not necessarily trigger alarm, but they should make us take stock of how we examine patients with ultrasound, especially in the first trimester.

Scores of studies have been conducted over the years in water baths, in animal models, and in humans that have shown no evidence of bioeffect when ultrasound is used at diagnostic dosage. Until now, there has been only one other credible animal study[6] showing a possible effect from ultrasound exposure (on brain cell migration in rat fetuses). However, the experimental setting in that study certainly was not analogous to an exam in a human fetus. Regarding human investigation, other than an Australian study[7] showing newborns to be on average 26 g lighter (with later catch-up) when exposed to repetitive Doppler investigations, the only unusual finding that has emerged in humans is a slightly increased chance of boys being left-handed.[8] Although this finding has not been matched by data in the above study,[2] a very recent meta-analysis[9] that included the Finnish data showed a slight, but statistically significant, tendency for exposed boys to be NRH. Who knows whether this small difference is, in any way, meaningful? Some might point out that NRH has been linked with other brain migrational disorders, while others will counter that the difference between groups is so small that one has to accumulate huge patient numbers to find it, and some of our most creative individuals in history have been left handed.

Prior to 1992, the FDA rode herd over the intensity levels emanating from ultrasound machines. This caused clinicians to complain that, on occasion, one needed higher intensities than were previously allowed. So, in a rare capitulation (or, perhaps, in exasperation), the FDA decided to leave output levels to the discretion of the user. In order for clinicians to adjust the level to fit the clinical situation, the "output display standard" (ODS) was born.

There are two known mechanisms by which bioeffects can be produced by ultrasound at high intensities: through cavitation created by pulses of very high strength (like those used to desiccate renal stones) or through a mechanism involving a rise in temperature. Pulsed Doppler is particularly capable of increasing tissue temperatures because the pulses need to be longer in length in order to show a change in frequency. This results in higher average intensities. The peak pulse intensities are monitored by an ODS feature called the mechanical index (MI). The calculation to assess temperature rise is based on average in-

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Editorial E-Mail: leslie.coplin@ahcmedia.com
Customer Service E-Mail: customerservice@ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the OB/GYN. It is in effect for 36 months from the date of the publication.

Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

tensities over time and is displayed as a temperature index (TI). Theoretically, a TI of 1.0 would mean that the ultrasound energy being used during an exam has the ability to raise the temperature of tissue at the target site by 1°C.

It has been mandated that both MI and TI be displayed simultaneously on the screen of every machine manufactured after 1992. Probably the most important index is the TI in bone (TIb) because it is affected most by Doppler intensities.

In any case, the modulation of power, with a default set only at very high intensities, has been left to us — the users — and the admonition by the AIUM is that we adjust the power levels to fit the clinical situation by using levels that are "as low as is readily achievable" (the ALARA principle). Simply put, TIs should not exceed 1.0 and MIs should not be above 1.4 in all but a few unusual circumstances where more penetration is needed (such as obesity).

Unfortunately, most users have a limited knowledge of these indices, and those who are informed tend to be complacent about monitoring intensities. For example, a U.S. survey of "end users" (60% physicians and 40% sonographers) showed that although 32% knew the term TI, only 18% knew what it represented.[10] Only 4% knew what the MI was and 80% did not know where to find either displayed index on their machines. Results from European surveys[5,11] were similar.

The above animal study[1] should be a catalyst for an effort to keep ultrasound exposure times, especially pulsed Doppler, as short as possible. Also, this study might make us re-tool our protocols for first trimester screening for aneuploidy. Doppler examination of the ductus venosus and tricuspid valves do improve the sensitivity of the screening process. But if used only in those who are at highest risk (after standard NT, nasal bone, and biochemistry have been accomplished), the detection rate for trisomy 21 with this selective approach is essentially the same (94-96%) as if all patients had a Doppler examination as part of their first-line screening protocol.[12] This would save 85% from having unnecessary pulsed Doppler exposure. ■

References

1. Pellicer P, et al. Ultrasound bioeffects in rats: Quantification of cellular damage in the fetal liver after pulsed Doppler imaging. *Ultrasound Obstet Gynecol* 2011;37:643-648.
2. Heikkila K, et al. Handedness in the Helsinki ultrasound trial. *Ultrasound Obstet Gynecol* 2011;37:638-642.
3. Crane JP, et al for the RADIUS Study Group. A randomized trial of prenatal ultrasonographic screening: Impact on the detection, management, and outcome of anomalous fetuses. *Am J Obstet Gynecol* 1994;171:392-399.
4. Bakketeig LS, et al. Randomised controlled trial of ultrasonographic screening pregnancy. *Lancet* 1984;2:207-211.
5. Salvesen KA, et al. Safe use of Doppler ultrasound during the 11 to 13 + 6 week scan: Is it possible? *Ultrasound Obstet Gynecol* 2011;37:625-628.
6. Ang ES Jr, et al. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *Proc Natl Acad Sci U S A* 2006;103:12903-12910.
7. Newnham JP, et al. Effects of frequent ultrasound during pregnancy: A randomised controlled trial. *Lancet* 1993;342:887-891.
8. Torloni MR, et al. Safety of ultrasound in pregnancy: WHO systematic review of the literature and meta-analysis. *Ultrasound Obstet Gynecol* 2009;33:599-608.
9. Salvesen KA. Ultrasound in pregnancy and non-right handedness: Meta-analysis of randomized trials. *Ultrasound Obstet Gynecol* 2011;DOI:10.1002/uog.9055. [Epub ahead of print].
10. Scheiner E, et al. What do clinical users know regarding safety of ultrasound during pregnancy? *J Ultrasound Med* 2007;26:319-325.
11. Marsal K. The output display standard: Has it missed its target? *Ultrasound Obstet Gynecol* 2005;25:211-214.
12. Kagan KO, et al. Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing. *Ultrasound Obstet Gynecol* 2010;36:542-547.

Oral Contraceptive Suppression of Ovarian Function in Obese Patients

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Synopsis: *Ovarian suppression with oral contraceptives is similar for normal-weight and obese patients.*

Source: Westhoff CL, et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use: A randomized controlled trial. *Obstet Gynecol* 2010;116:275-283.

In this double-blind protocol, normal-weight (body mass index [BMI] 19.0-24.9 kg/m^2) and obese (BMI 30.0-39.9 kg/m^2) women with regular periods and normal ovarian ultrasound took one of two types of oral contraceptives (OCPs): either 21-day monophasic pills with 20 mcg ethinyl estradiol/100 mcg levonorgestrel or 30 mcg ethinyl estradiol/150 mcg levonorgestrel. Compliance was assessed with serial serum levels of levonorgestrel. One hundred eighty-one subjects of 226 completed the study.

Among patients who were consistent users of the pills, suppression of follicular development was similar for both doses of pills. Ovulation rates were similar among consistent users of either normal or obese weights.

■ **COMMENTARY**

Admit it. You've already answered the questions asked by this study many times with various patients. I know I have. The fact is, though, good data from good Level I evidence has been lacking and we've all responded to our patients with the best information available to us. Now we can tell our patients with confidence that OCP failures in obese patients are not due to a lack of efficacy of the pills in obese women, but, instead, a result of non-compliance. There is always that potential lingering concern for an obese woman starting on OCPs that the pill won't be strong enough, but that issue can now be addressed directly. Both doses of pills were similarly effective.

The authors were extremely diligent in designing a study that we clinicians could look to with confidence. By drawing twice weekly bloodwork and performing regular ultrasounds, better conclusions were drawn about compliance with pills and follicular development. We can be even more confident in the results because, as expected, there was more spotting in the 20 mcg pill compared with the 30 mcg pill.

What we can tell our patients is very real, i.e., the inconsistent users of the pills had substantial rates of ovulation (38.5%) whether they were obese or not. Consistent OCP users experienced ovulation only 2.7% per cycle. By enrolling only ovulatory patients, the authors were able to minimize the potential impact of anovulation among the general population of obese patients. Of interest, obese patients were less compliant in taking their OCPs. Because the authors were able to document who was compliant or not (by looking at ovarian ultrasound and progestin levels as a marker of ovulation), this aspect of the study was also useful to all of us: Patients sometimes report that they are compliant when they actually are not. (Surprise, surprise! Patients don't always report events to us accurately?!)

I really liked the study from its simplicity standpoint and also its real-life application. As often as we give out OCPs, being able to predict outcomes and warn patients of limitations of their use is critical. Of particular interest is the recent declaration from the federal government that all forms of contraception are to be covered by all insurance plans. This will bring many more patients into the contraceptive arena, some of whom are new or less-informed. We would each be wise to make sure that we ascertain the level of each patient's understanding of the contraceptive of choice in this new era. It doesn't help much to have contraception covered by insurance if the contraception isn't being used correctly. ■

(Editor's note: Compliance is critical for all users of hormonal contraception. The interactions of obesity and OCP efficacy are complex and will be analyzed in an upcoming Special Feature by Dr. Edelman.)

Screening for Ovarian Cancer: Could it Cause More Harm than Good?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Source: Buys SS, et al. Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011;305:2295-2303.

Synopsis: *Annual screening with CA125 and transvaginal ultrasound among U.S. women aged 55-74 did not improve disease-specific ovarian cancer mortality or alter stage at diagnosis among detected cases compared with usual care. Further, diagnostic evaluation in response to false-positive screens was associated with adverse complications.*

Due to the frequent identification of metastatic disease at diagnosis and its high associated mortality, ovarian cancer has been the persistent focus of many screening efforts. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer screening trial is a randomized controlled trial of 78,216 women aged 55 to 74 years assigned to undergo either annual screening (n = 39,105) or usual care (n = 39,111) at 10 screening centers across the United States.[1] Annual screening consisted of CA125 for 6 consecutive years and transvaginal ultrasound (TVU) for 4 consecutive years. Women randomized to "usual care" were not offered annual screening with CA-125 or TVU, but instead received well-woman care. Participants were enrolled between November 1993 and July 2001 and followed for a maximum of 13 years (median [range], 12.4 years [10.9-13.0 years]) for cancer diagnoses and death. The primary objective was to evaluate the impact of this screening algorithm on disease-specific mortality. Secondary objectives were: ovarian cancer incidence, stage at diagnosis, overall mortality, and complications associated

with screening examinations and diagnostic procedures. The diagnosis of ovarian cancer was made in 212 women (5.7 per 10,000 person-years) in the screened cohort and 176 (4.7 per 10,000 person-years) in the usual care group (rate ratio [RR], 1.21; 95% confidence interval [CI] 0.99-1.48). There were 118 deaths caused by ovarian cancer (3.1 per 10,000 person-years) in the intervention group and 100 deaths (2.6 per 10,000 person-years) in the usual care group (mortality RR, 1.18; 95% CI 0.82-1.71). Of 3285 women with false-positive results, 1080 underwent surgical follow-up; of whom, 163 women experienced at least 1 serious complication (15%). There was no difference in deaths due to other causes (excluding ovarian, colorectal, and lung cancer) between the two groups (RR, 1.01; 95% CI 0.96-1.06). The authors conclude that among this cohort of women undergoing annual CA125 and TVU, screening did not result in a reduction in ovarian cancer mortality, and diagnostic evaluation following a false-positive screening test result was associated with complications.

■ COMMENTARY

Just over 2 years ago, I discussed in *OB/GYN Clinical Alert* the recently published data of the PLCO study, but the data included only four rounds of screening. At that time, compliance with the planned intervention had stabilized and there appeared to be a serial reduction in the ratio of false-positive screens for each ovarian cancer identified. However, this ratio (20 to 1) was considered unacceptable for general implementation of the strategy because the primary endpoint (reduction in disease-specific mortality) was not met. The current and final outcomes from this large screening effort have essentially discounted screening with annual CA125 and TVU in the general population. In fact, it appears indiscriminant use of annual screening with these tools may cause harm. However, there are several interesting and informative observations, which bear some discussion. First, one of the principle tenets of screening is that an abnormal test should (preferably) identify pre-invasive disease, where intervention could positively affect outcome. In this case, the screening tests (CA125 and TVU) detected a higher rate of ovarian cancer in the screened women compared to the usual care group. An important consideration is there were no differences in the stage of cancer at diagnosis or overall mortality rates between the two groups, therefore suggesting that these additional cases were of no clinical significance. This potential concern that screening for ovarian cancer would not show reduced mortality was raised recently, since mathematical models show evidence of the diseases' heterogeneity.[2] These analyses suggested that "screenable" cancers may have a different biologic behavior (e.g., low-grade serous cancer), and as such, may not measurably impact overall survival, since these cancers are rare in the screened population and have a favorable prognosis.

A second important observation is that screening did not alter the detection of early- and late-stage cases. It is well appreciated that screening cannot reliably detect a pre-invasive state. However, mortality could still be reduced in a screening program if the "positive" screens, on the whole, were associated with an earlier stage than that seen in the general population. The condition for this "stage migration" could be met if the outcome of early-stage cancer is better than late-stage cancer. For instance, stage I disease is associated with an 85% or higher 5-year survival, and is significantly better than stage III/IV (about 40% 5-year survival); in addition, there are more "cures" among early-stage patients. Unfortunately, the PLCO trial clearly demonstrates that annual screening with CA125 and TVU is neither sufficiently sensitive nor specific to impact stage at diagnosis. However, this hypothesis is a potential promise for other algorithms, such as the risk of ovarian cancer analysis (ROCA), which is being explored in the yet to be reported U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[3] In their prevalence report, authors appeared to identify a higher proportion of early-stage cases when serial measures of CA125 were evaluated using a mathematical prediction model and TVU triage. Mortality data from this trial is expected in 2014.

Finally, this trial serves to remind us that responding to a patient's concern, such as ovarian cancer, by utilizing unproven testing can in fact backfire and cause harm. The overall false-positive rate per round of screening was about 5%. This led to operative complications — about one for every five operations performed. The majority of operations were indicated by abnormalities on TVU. It is not known whether different criteria for morphological aberration of the ovaries could improve the positive-predictive value. However, similar results have been reported in the initial reports from the UKCTOCS trial and from a randomized controlled trial in Japanese women.[4] Ultimately, serial blood-based biomarkers will need to be developed to identify high-risk women (higher prevalence) or women with early changes associated with disease onset. ■

References

1. Buys SS, et al. Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011;305:2295-2303.
2. Havrilesky LJ, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: Implications for potential mortality reduction. *Cancer* 2011;117:545-553.
3. Menon U, et al. Sensitivity and specificity of multimodal

and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: Results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;10:327-340.
4. Kobayashi H, et al. A randomized study of screening for ovarian cancer: A multicenter study in Japan. *Int J Gynecol Cancer* 2008;18:414-420.

Special Feature

Postmenopausal HRT: Where Do We Stand in 2011?

By Jeffrey T. Jensen, MD, MPH, Editor

A QUICK SEARCH ON PUBMED FINDS 122 MANUSCRIPTS PUBlished in the first half of 2011 that reference the Women's Health Initiative (WHI) study in the title, abstract, or as a keyword. Clearly, much continues to be learned about hormonal therapy, and this remains an important health decision for women. Therefore, I thought I would use this opportunity to provide a short review of key clinical points.

The principle risk of hormone replacement therapy (HRT) is thrombosis not breast cancer.[1] Thrombosis is related to estrogen-induced changes in hepatic globulins. Throughout evolution, the selection pressure for mammals has favored a shift toward a pro-coagulant environment during pregnancy. The benefit of avoiding hemorrhage during vaginal delivery far outweighed the risk of venous thrombosis for our ancestors. Since the liver produces and regulates the proteins involved in the coagulation cascade, it became the arbitrator of the net estrogen balance in the body. During pregnancy, the liver recognizes the sustained rise in placental estrogens and this causes a shift to a slightly prothrombotic environment. Evolution did not prepare the liver to differentiate between high circulating levels of exogenous or endogenous estrogens. Work in the rodent suggests that the effect is mediated through the estrogen receptor alpha.[2] Several important principles emerge from this knowledge:

1. Once significant atherosclerotic changes are present, the risks of hormone therapy exceed potential benefits. Therefore, therapy must be started shortly after the onset of menopause.
2. The effect of estrogen on coagulation is dose-dependent. This means that using the lowest dose of estrogen to achieve the therapeutic goal makes sense.
3. Oral dosing of estrogens provides the biggest challenge to the liver as very high concentrations are presented to hepatic metabolism during first pass absorption.
4. Progestogens affect estrogen effects in a complicated and tissue dependent fashion.
5. Cardiovascular disease develops over time and is influenced by several important factors. Age, hypercholesterolemia, and obesity are important factors that influence the risk of thrombosis.

Let's illustrate these points with some of the key findings from the WHI and beyond. The WHI documented that combined estrogen/progesterone (E/P) therapy (Prempro®) increased the risk of cardiovascular complications like coronary heart disease (CHD), venous thrombosis (VTE), and stroke.[3] Since these results conflicted with those from observational studies, subsequent analyses have revealed several key clinical points.

Timing of initiation of therapy matters. Most women evaluated in observational studies of CHD risk were younger than age 55 at the time HRT was initiated and within 2 to 3 years of menopause, while women in the WHI were almost a decade older. Mitch Harmon of the Kronos Longevity Research Institute has advanced this timing hypothesis, and provides a detailed review of the data in a recent publication in the *American Journal of Medicine*.[4] Some of the best data refuting the main WHI findings come from the WHI itself. Follow-up reanalysis of the E/P treatment group documented a nonsignificant trend toward protection (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.5-1.5) in women less than 10 years postmenopausal in contrast with the elevated risk (HR 1.71; 95% CI 1.1-2.5) observed in women starting therapy more than 20 years after menopause.[5] Harmon's group has enrolled women in the Kronos Early Estrogen Prevention Study (KEEPS). Healthy women between the ages of 42 and 58 years of age at least 6 months and no more than 36 months postmenopausal were randomized to daily placebo, oral conjugated equine estrogen (CEE), or transdermal 17β-estradiol (E_2) with placebo or pulsed progesterone for 12 days/month. The primary endpoint is to evaluate effects of hormone therapy on progression of atherosclerosis as defined by carotid intima–media thickness and coronary arterial calcification. Enrollment was completed in 2008, and initial results from this study are expected by the end of this year.

Route of administration of estrogen matters. The WHI looked only at oral dosing of CEE. As mentioned above, oral estrogens exert a potent first pass effect on the liver that influences homeostasis of the coagulation system. Bypassing the liver with transdermal or vaginal administration of estrogen can avoid this first pass metabolism. Estradiol is rapidly isomerized to estrone and estriol,

and circulates at physiologic levels. However, if a potent synthetic estrogen like ethinyl estradiol (EE) is administered transdermally the metabolites are highly active, and the liver continues to interpret the overall estrogen milieu as elevated (i.e., pregnant), shifting the balance toward coagulation. An important multicenter case-control study in France (ESTHER study) documented that oral estrogen increases the risk of VTE, but that transdermal estrogen does not.[6]

Dose and type of estrogen matters. Since WHI studied only one dose and type of oral estrogen (0.625 CEE) with or without oral medroxyprogesterone acetate, the study provides no information about dose effects. However, other epidemiologic studies and clinical investigations evaluating surrogate markers have demonstrated that increasing the dose of estrogen increases the risk of thrombosis in users of HRT and in users of combined hormonal contraception.[7] This makes biologic sense as we expect to see a dose response. In the past, we adjusted dose based on symptoms. However, to reduce the potential for harm, it makes more sense to obtain blood levels. This leads us to type of estrogen. Unlike conjugated estrogens and EE, one can order a serum assay for E_2 to ensure that a therapeutic range is maintained (40-100 pg/mL). The absence of hepatic activiation of prothrombotic globulins and ease of monitoring should make non-oral E_2 the estrogen of choice.

Progestogens affect estrogen effects in a complicated and tissue dependent fashion. The results of the combined E/P and estrogen only WHI studies differ in several clinically important outcomes. First, there was no overall impact on coronary heart disease with estrogen only treatment. Of even greater interest was the trend toward a reduction in risk of invasive breast cancer in the estrogen-only arm. The decreased risk of invasive breast cancer persists in the most recent analysis (2011) of results from this study.[8] The evidence suggesting that MPA may attenuate the favorable effects of oral estrogens on lipids emerged in the 1995 PEPI study.[9] The ESTHER study found no significant association of VTE with micronized progesterone but an increased risk with norethindrone. A recently published experiment by Zerr-Fouineau and colleagues showed that MPA attenuates estradiol-induced inhibition of platelet aggregation by endothelial cells.[10] Taken together, these data suggest that the safest choice for systemic progestogen therapy is oral micronized progesterone.

General health and duration of therapy matters. Observational studies suggest that longer duration of HRT use are associated with reduced risk of CHD and related mortality. The contradictory findings of WHI led many providers and professional organizations to recommend against the use of HRT except for short-term management of menopausal symptoms. A more selective approach makes better sense. The current literature strongly suggests that healthy menopausal women should initiate hormone therapy shortly after the onset of menopause (within 3-5 years). The Kronos study will provide important prospective information to learn whether this strategy reduces progression of atherosclerotic changes. Women with existing cardiovascular disease, such as hypertension or abnormal lipid profiles, represent a high-risk group for complications of hormonal therapy. A more detailed risk/benefit discussion is needed in this group. The central factor in all of these high-risk patients is pre-existing cardiovascular disease. Creating a prothrombotic environment with estrogen will increase the risk of an adverse event. Obesity represents a growing problem in all of our practices. The independent and additive effect with estrogen therapy of obesity on thrombosis risk is well documented. It is encouraging to note that transdermal estrogen did not elevate the risk of VTE in a case-control study of HRT in obese women by Canonico and colleagues.[11] While the overall risk for VTE was increased in overweight (OR 2.5; 95% CI 1.7-3.7) and obese (OR 3.9; 95% CI 2.2-6.9) women, a significant increase was noted with oral (OR 4.5; 95% CI 2.6-7.7) but not transdermal (OR 1.1; 95% CI 0.7-1.7) estrogen therapy. Compared with non-users with normal weight, the combination of oral estrogen use increased the risk of VTE 10-fold for overweight and 20-fold for obese women. In contrast, transdermal users with increased BMI had similar risk as non-users with increased BMI. More information regarding the safety of transdermal estrogen in high-risk individuals is needed.

In my practice, I continue to recommend hormone replacement therapy to healthy menopausal women. I discuss symptoms, bone effects, cognitive effects, sexual function, and cardiovascular effects. Breast cancer is put into perspective (and another reason to avoid MPA?), and I recommend annual mammograms. I look at blood pressure, lipid profiles, glucose tolerance, family history, and BMI as predictors of cardiovascular risk. Women with well-controlled diabetes, hypertension, or hyperlipidemia may benefit from hormone therapy, but need a more detailed discussion of potential risks and benefits. I recommend transdermal estradiol, and try to target a blood level around 80 pg/mL. Oral micronized progesterone is recommended for women with a uterus, although I also discuss the off-label use of the LNG IUS for endometrial protection. More information is available every year. We can count on hundreds of new publications; some may even prove useful! ■

References

1. Harman SM. Estrogen replacement in menopausal women: Recent and current prospective studies, the WHI and the KEEPS. *Gend Med* 2006;3:254-269.

2. Cleuren AC, et al. 17alpha-Ethinylestradiol rapidly alters transcript levels of murine coagulation genes via estrogen receptor alpha. *J Thromb Haemost* 2010;8: 1838-1846.
3. Rossouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
4. Harman SM, et al. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. *Am J Med* 2011;124:199-205.
5. Manson JE, et al. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007;356:2591-2602.
6. Sandset PM, et al. Mechanisms of thrombosis related to hormone therapy. *Thromb Res* 2009;123(Suppl 2): S70-S73.
7. Canonico M, et al. Hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840-845.
8. LaCroix AZ, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. *JAMA* 2011;305:1305-1314.
9. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199-208.
10. Zerr-Fouineau M, et al. Certain progestins prevent the enhancing effect of 17beta-estradiol on NO-mediated inhibition of platelet aggregation by endothelial cells. *Arterioscler Thromb Vasc Biol* 2009;29:586-593.
11. Canonico M, et al. Obesity and risk of venous thromboembolism among postmenopausal women: Differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;4:1259-1265.

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 Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

22. Which of the following is NOT appropriate regarding the data on ultrasound bioeffects?
a. The Norwegian study showed a statistically significant increase in non-right handedness (NRH) in boys exposed to ultrasound.
b. The Helsinki data did not show a relationship between ultrasound exposure and NRH.
c. In the randomized clinical trials, boys were more prone to be NRH than girls, irrespective of ultrasound exposure.
d. NRH boys are more prone to autism.
e. None of the above is correct.

23. It is mandatory that current ultrasound machines have a TI and MI displayed during an obstetrical examination.
a. True
b. False

24. Which of the following BEST reflects the ultrasound intensities used in obstetrical scanning?
a. Very high peak pulse intensities, well above diagnostic levels, cannot cause tissue damage.
b. A temperature index of 1.0 means that the average intensity being used can raise the temperature in target tissue by 1° C.
c. In the rat model, liver cell damage only occurred at intensities above diagnostic levels.
d. Pulse Doppler examination of the ductus venosus does not result in higher average intensities than standard 2-D ultrasound.

25. Which of the following statements regarding the conduct of the PLCO trial is TRUE?
a. There was a difference in all-cause mortality between the two arms.
b. Patients undergoing usual care underwent significantly more operations as a result of their surveillance.
c. Early-stage disease was identified in more patients undergoing screening but it did not translate into better survival.
d. TVU was performed a maximum of four times.

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.*

ACEIs and ARBs Help Patients with Aortic Stenosis

In this issue: ACEI/ARB therapy for AS; safety alert issued for dronedarone; statins and cancer risk; nesiritide and heart failure; and FDA actions.

ACEI/ARB therapy for aortic stenosis

Drugs that block the renin-angiotensin system are not only safe, they are beneficial in patients with aortic stenosis (AS) according to a new study. This runs counter to current recommendations that suggest that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are relatively contraindicated in patients with AS. The study looked at more than 2000 patients with AS in Scotland, of which the majority had mild-to-moderate stenosis, while about one-quarter had severe AS. Of the total number, nearly 700 were on ACEI or ARB therapy. Over a mean follow-up of 4.2 years, just over half the patients died, of which 48% died from cardiovascular (CV) deaths. Those treated with ACEIs or ARBs had a significantly lower mortality rate (adjusted hazard ratio [HR] 0.76; confidence interval [CI] 0.67-0.92; $P < 0.0001$) and fewer CV events (adjusted HR 0.77; 95% CI: 0.65-0.92; $P < 0.0001$) compared to those not on ACEIs/ARBs. The authors conclude that ACEI/ARB therapy is associated with improved survival and lower risk of CV events in patients with AS. These findings were consistent in patients with nonsevere and severe AS. The rate of valve replacement also was lower in patients treated with ACEIs/ARBs (*J Am Coll Cardiol* 2011;58:570-576). This study was a retrospective observational study and prospective, randomized, controlled trials are warranted to confirm these findings. ■

Drug safety alert issued for dronedarone

The antiarrhythmic dronedarone (Multaq) is again coming under scrutiny from the FDA after review of the company-sponsored PALLAS study of more than 3000 patients, which showed that the drug is associated with an increased mortality rate in patients with atrial fibrillation (AF). Dronedarone currently is approved for treatment of paroxysmal AF and atrial flutter. The new study investigated its use in patients with permanent AF. The study was halted early when the mortality rate in the treatment group was found to be double the rate in the placebo group (32 deaths [2%] in the dronedarone arm vs 14 [0.9%] in the placebo arm). The rate of unplanned hospitalization and stroke also was double in the dronedarone group vs the placebo group. All findings were statistically significant. These findings led the FDA to issue a drug safety alert on July 21, 2011. This follows a January 2011 drug safety alert regarding rare but severe liver injury associated with use of dronedarone. Currently, the FDA is recommending that physicians should not prescribe dronedarone to patients with permanent AF while they further evaluate the data (FDA Drug Safety Communication at www.FDA.gov/drugs/drug safety). ■

Statins do not increase risk of cancer

A new retrospective cohort analysis suggests that statins are not associated with an increased risk of cancer. Researchers used the General

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) 262-5404. E-mail: neill.kimball@ahcmedia.com.

Electric Centricity electronic medical record database of more than 11 million adult Americans to match nearly 46,000 patient pairs by propensity scores receiving and not receiving statin therapy. With an average time in the database of 8 years, the incidence of cancer in patients taking a statin was 11.37% compared with 11.11% in matched patients not taking a statin (HR 1.04; 95% CI: 0.99-1.09). The authors conclude that this analysis demonstrates no statistically significant increase in cancer risk associated with statins, although they do suggest that more research is needed (*J Am Coll Cardiol* 2011;58:530-537). Lingering fears about cancer risk associated with statins was strengthened by the SEAS trial published in 2008, which showed the combination drug simvastatin/ezetimibe (Vytorin) was associated with a two-fold increase in the rate of cancer in a small group of patients. The FDA has continued to study these data along with data from other studies, but this new analysis adds significant evidence of a lack of association between statins and cancer. ■

Nesiritide and heart failure

Nesiritide can no longer be recommended for use in congestive heart failure based on the findings of a new study. The drug is a recombinant B-type naturetic peptide (BNP) that was approved in 2001 for use in patients with acute heart failure. The approval was based on small studies showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea 3 hours after administration. However, subsequent data raised questions about the drug's safety, especially with regard to worsening renal function and even increased mortality. Based on the recommendations of an independent panel, the manufacturer performed a placebo-controlled randomized trial of more than 7000 patients hospitalized with acute heart failure to assess the drug's safety and efficacy. Patients with heart failure were randomized to receive nesiritide or placebo for 24-168 hours in addition to standard care. The drug was modestly effective at reducing symptoms of dyspnea at 6 and 24 hours. More significantly, however, the rate of rehospitalization for heart failure or death from any cause within 30 days was no different. Nesiritide was not associated with a worsening of renal function but was associated with worsening hypotension. The authors conclude that on the basis of these results, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure" (*N Engl J Med* 2011;365:32-43). ■

FDA actions

The highly anticipated oral factor Xa inhibitor rivaroxaban has been approved by the FDA to reduce the risk of deep venous thrombosis, blood clots, and pulmonary embolism in patients undergoing knee or hip replacement. The once-a-day medication should be taken for 12 days by patients undergoing knee replacement and 35 days for patients undergoing hip replacement. The approval was based on three studies (RECORD 1, 2, and 3) which showed that rivaroxaban is superior to subcutaneous enoxaparin in this role. Bleeding, the primary side effect of the drug, was no more common with rivaroxaban than enoxaparin. Rivaroxaban also has been looked at in phase III trials for stroke prevention in patients with nonvalvular atrial fibrillation, and treatment and secondary prevention of venous thromboembolism, although the FDA has yet to act on approval for these indications. Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals as Xarelto.

The FDA has approved ticagrelor, a new antiplatelet drug for patients with acute coronary syndrome, including unstable angina and myocardial infarction (MI). The approval was based on studies that coupled ticagrelor with low-dose aspirin. The approval recommends use with aspirin although it carries a warning that aspirin doses above 100 mg per day may decrease the effectiveness of the drug. Ticagrelor requires twice a day dosing in contrast to the other drugs in this class, clopidogrel and prasugrel, which can be dosed once daily. The approval was based on the PLATO trial, a head-to-head study with clopidogrel which showed that in combination with aspirin, ticagrelor resulted in the lower composite endpoint of cardiovascular death, stroke, or MI (9.8% vs 11.7% with clopidogrel, $P < 0.001$).

The FDA has approved six manufacturers for the 2011-2012 flu vaccine. The strains included this year are A/California7/09 (H1N10), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 — the exact same components as last year's vaccine. One of the manufacturers, Sanofi Pasteur, has received permission to market Fluzone Intradermal, the first flu vaccine administered via a novel intradermal microinjection that is touted as being more comfortable than intramuscular injections. The new intradermal system in approved for adults ages 18-64 years. ■