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INSIDE

More from the Women's Health Initiative

SPECIAL REPORT

In this feature, Leon Speroff, MD, discusses the most recent findings from the Women's Health Initiative study.

THE LATEST NEWS FROM THE WOMEN'S HEALTH INITIATIVE (WHI) includes 3 noteworthy reports: the news release announcing the cancellation of the estrogen-only arm of the clinical trial,[1] a comparison of the participants in the 2 clinical trial arms (estrogen-progestin and estrogen-only),[2] and the updated, adjudicated colorectal cancer results from the estrogen-progestin arm.[3]

The Estrogen-only Arm of the Clinical Trial

On March 2, 2004, the National Heart, Lung, and Blood Institute of the US National Institutes of Health (NIH) canceled the estrogen-only (0.625 mg conjugated estrogens daily) arm of the WHI multicenter, randomized, clinical trial. This arm of the WHI included almost 11,000 hysterectomized, postmenopausal women who had completed an average of nearly 7 years of follow-up. The WHI Data and Safety Monitoring Board (DSMB) made its last periodic review of the study data in December 2003. The DSMB was not unanimous in its decision; some wanted to stop the study and others wanted the study to continue after sending a letter to the participants describing the findings. The NIH made the decision to stop the study on February 2, 2004.

Why was the study stopped? The decision was based on the following results according to the NIH:

- An increased risk of stroke similar to that reported in the canceled estrogen-progestin arm of the WHI;
- No increase or decrease in coronary heart disease;
- A trend toward an increased risk of probable dementia and/or mild cognitive impairment;
- A reduction in hip fractures;
- No increase in breast cancer.

The academic grapevine has indicated that a major consideration in making the decision to cancel the estrogen-only arm of the study

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was the high drop-out rate in response to the publicity of the last 2 years, severely eroding the statistical power and leaving nothing to be gained by continuing until the scheduled termination in 2005.

With the exception of breast cancer, the results are essentially identical to those in the estrogen-progestin arm of the study. Indeed, according to the grapevine, the results with breast cancer in the estrogen-only arm were actually indicating a statistically significant decrease in risk. But keep in mind, that the increase in breast cancer in the estrogen-progestin arm was a small one, that the statistical power of the estrogen-only arm is not as great (6000 fewer participants), and the populations of the 2 arms may not be comparable (especially different ages of menopause). Indeed, the populations in the 2 clinical, randomized trial arms of the WHI were not identical.[2] Considering risk factors for cardiovascular disease, the women in the estrogen-only arm were more obese, less active, and had more preexisting cardiovascular disease. The estrogen-only arm also differed in regard to risk factors for breast cancer: more early births, bilateral oophorectomy, and more and longer duration of previous hormone therapy. In the coming months, it will be tempting to compare the 2 canceled arms of the WHI; however, these were 2 different trials with 2 different populations and treatments, making direct comparisons inappropriate.

Clinicians and patients should regard the cancellation of the estrogen-only arm of the clinical trial as good news. Clinicians and patients should accept this new report as another indicator that postmenopausal hormone therapy does not have a major effect on the risk of breast cancer. When the published results become available, it will be important to carefully analyze the statistics. The estrogen-only arm may lack the power to make a confident statement regarding breast cancer for 2 reasons: the estrogen-only arm is about 62% of the size of the estrogen-progestin arm, and a high drop-out rate may have eroded its statistical strength. In addition, as noted earlier, important risk factors that favor a reduced risk for breast cancer were predominant in the estrogen-only arm.

Like the estrogen-progestin arm, it is reasonable to expect the stroke and dementia/cognition results to reflect the effect of this dose of estrogen given to an older group of women, many years distant from menopause. According to the NIH news release, the average age of the participants in the estrogen-only arm is now nearly 70, indicating that the ages in the 2 arms of the WHI clinical trial were comparable. Most importantly, the published comparison of the 2 clinical arms indicated that preexisting cardiovascular disease was even more prevalent in the estrogen-only arm.[2] In the canceled estrogen-progestin arm, the only detrimental effect was an increase in dementia in the group of women who were 75 years and older when they started treatment, and the dementia was probably vascular in origin, not Alzheimer's. Because the ages in the 2 arms are comparable and there was more preexisting cardiovascular disease in the estrogen-only arm, it is likely that the dementia results are the same, an effect only in very old women who already have significant atherosclerosis.

The report of neither a beneficial effect nor an adverse effect on coronary heart disease gives the impression that the estrogen-only arm represents an improvement over the estrogen-progestin arm. The updated results on the risk of coronary heart disease from the canceled estrogen-progestin arm of the WHI reflect central adjudication of the cardiac diagnoses in contrast to the initial report that relied on local diagnoses.[4] Local and central reviews disagreed with 10% of

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the diagnoses for myocardial infarction and 3% for death due to coronary heart disease. This small degree of disagreement changed the strength of the conclusions comparing the initial report[5] with the updated report. Indeed, the overall results by definition did not achieve statistical significance in the follow-up report, and only the first-year results were statistically significant in the year-by-year analysis, a conclusion based on a difference of only 19 cases. In the subgroup analyses, only the women who were 20 or more years distant from menopause had a statistically significant increased risk of coronary heart disease (1.71; CI = 1.20-2.50). Subtracting this group from the rest of the participants, coronary heart disease now was observed in an identical prevalence comparing the treated and placebo groups. It is not appropriate to conclude, based on the WHI, that hormone therapy increases the risk of coronary clinical events in all postmenopausal women; this conclusion can only be applied to a specific older group of women. The WHI did not study a young postmenopausal, healthy population in order to establish that hormone therapy does not exert a primary preventive effect on the risk of coronary heart disease. That is not to say that the case for primary prevention of coronary heart disease by postmenopausal hormone therapy does not merit controversy. However, at the same time, the issue is not settled, and perhaps there never will be a large trial of the appropriate population. We cannot quarrel with the conclusion that postmenopausal hormone therapy does not reduce or slow the progression of established coronary heart disease. However, the WHI did not study the appropriate population in the appropriate time period to establish that hormone therapy does not exert a primary preventive effect on the risk of coronary heart disease.

Colorectal Cancer

Most, but not all, cohort and case-control studies have reported a significantly reduced risk of colorectal cancer incidence and mortality in users of postmenopausal estrogen.[6-12] The effect is greatest in current users and most studies have not indicated an increased effect with increasing duration of use; for example, the Nurses' Health Study (which found a 34% reduced risk in current users) could not demonstrate an added benefit with longer duration of current use.[13] A reduction in fatal colon cancer has been documented in current users.[8] There also appears to be a reduced risk of polyps, especially large polyps, among current and recent hormone users.

The canceled estrogen-progestin arm of the WHI reported a statistically significant reduced risk of colon cancer achieved with only a few years of estrogen-progestin therapy.[3] There were too few cases of rectal cancer to allow separate analysis (*see Table*).

Table

Colon Cancer and Estrogen-Progestin Therapy

	Estrogen-Progestin	Placebo	Hazard Ratio
Colorectal cancer	43 cases	72 cases	0.56 (0.38-0.91)
Invasive colon cancer	35 cases	61 cases	0.54 (0.36-0.82)

This result was not without concern, however, in that the treated group had more advanced disease. Indeed, the conclusion was largely because of a difference in localized disease, 10 cases in the treated group and 36 in the placebo group. The results suggest that already present cancers were influenced by hormone therapy to reach a more advanced stage, but that estrogen-progestin treatment reduced the risk of new colonic cancers.

One can only speculate regarding the mechanism of this benefit. The estrogen-induced change in the bile (a decrease in bile acids with an increase in cholesterol saturation) favors gallstone formation but may reduce promotion (by bile acids) of colonic cancer. Other possible mechanisms include a direct suppressive effect on mucosal cell growth and an effect on beneficial mucosal secretions. The colon contains only estrogen receptor-beta, and the reduction in the risk of colonic cancer associated with postmenopausal estrogen therapy may reflect an antiproliferative activity of the beta receptor. This potential benefit deserves greater attention; colorectal cancer ranks third in women, both in incidence and mortality, and is more prevalent than cancers of the uterus or ovary.[14]

Conclusion

So the clinical arms of the WHI are over. But, of course, we will continue to hear from the WHI for many months as the reports periodically appear. I am confident that academicians and clinicians are now better prepared to apply a critical analysis to all of the WHI data. This is a process that takes time for the consideration and appraisal of the published data. For this reason, it doesn't pay to give serious attention to those quoted experts that appear in the media during the day and week that research reports appear. I believed that, over time, the results of the WHI will be placed in their appropriate role in clinical decision making. Overall, the WHI results are not as negative (adverse effects) as many, especially the media, have portrayed. ■

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Restaging Surgery for Women with Borderline Ovarian Tumors: Results of a French Mulitcenter Study

ABSTRACT & COMMENTARY

Synopsis: *Women who initially were diagnosed with Stage IA disease and who had serous borderline tumors or underwent cystectomy appeared to derive the most benefit from restaging surgery. Nonetheless, the indications for restaging surgery remain controversial, as no difference in recurrence rate was observed between women who underwent restaging and those who did not.*

Source: Fauvet R, et al. *Cancer*. 2004;100:1145-1151.

Borderline ovarian tumors account for about 10-20% of all ovarian epithelial tumors and are characterized by occurrence in younger women, earlier stage at diagnosis and better prognosis compared to invasive ovarian cancer. In some cases, the diagnosis is made after surgery, where neither complete ovarian resection (conservative operation) nor complete surgical staging information has been obtained, leaving the clinician in a quandary as to the appropriate next step. Fauvet and colleagues attempt to address this clinical situation through a review of all ovarian borderline or low malignant potential (LMP) tumors of the ovary diagnosed in their hospital system over a 12-month period. The principal aims of this retrospective review were to determine if conservative surgery was detrimental, if incomplete staging warrants a restaging operation, and what risk factors are associated with upstaging. Although no centralized pathological review of the individual cases was made, adherence to the current FIGO recommended classification scheme was followed. Three-hundred-sixty women with an ultimate final diagnosis of LMP tumor were accessioned. Of these, 150 or 42% underwent intraoperative histologic examination from which 97 (65%) were correctly identified as having LMP tumors. The remainder were classified as either benign (23%), carcinoma (2%) or not definitive (11%). Using Fauvet et al's definition of staging (to include peritoneal cytology and biopsies, omentectomy and in the case of mucinous tumors, appendectomy), 37 women (38%) underwent complete evaluation. In this cohort, just 5 were treated conservatively defined as leaving the uterus and at least part of an ovary behind. Among the "staged" group, an additional 25 "high-risk" patients were added, as they underwent the formal staging procedure despite having inconclusive intraoperative histology.

In this cohort, one additional patient was treated conservatively, leaving 6 of 62 patients treated conservatively. Of the 298 incompletely staged or unstaged patients, 54 (18%) underwent a re-staging procedure. Although *a priori* criteria for re-staging was not discussed or presented, patients undergoing the procedure were significantly younger and more likely to have had an initial conservative procedure. Interestingly, only half of those women undergoing a second procedure actually met Fauvet et al's criteria of staging. However, the majority of those undergoing a second operation were done so with conservation of fertility as a goal (n = 48, 89%). Of these 54 secondary operations, more advanced disease was identified in 8 patients (15%), with 3 upstaged to stage IB, 1 to stage IIA, 1 to stage IIB, 2 to stage IIIA and 1 to stage IIIC. With the exception of the latter, they were all initially stage IA.

No significant characteristics were associated with upstaging although these tumors were more often serous and in women who had a cystectomy as a primary operation. At a median follow-up of 37 months, overall survival was nearly identical between those undergoing staging operations compared to those who did not. Overall, 34 patients (10%) recurred, the majority of which were those who had undergone conservative operations (25 of 160 total or 16%). This was the only factor determining recurrence risk including whether or not they underwent a re-staging procedure. Fauvet et al's con-

clude that little benefit is gained by reoperating on a patient for the purposes of staging unless a patient has a stage IA serous tumor and has undergone cystectomy as a primary operation. However, even in this scenario, no survival benefit is gained by the maneuver and its conduct remains controversial.

COMMENT BY ROBERT L. COLEMAN, MD

The results of this retrospective study of tumors fits nicely into the growing body of literature outlining the natural history of LMP ovarian tumors. Fortunately, long-term survival for women diagnosed with this disease is the rule rather than the exception and outside of those uncommon tumors demonstrating metastatic disease at diagnosis and those with invasive implants, these patients remain predominately relapse-free. As confirmed in this review, those undergoing conservative procedures, that is, in whom ovarian tissue is left behind, are the ones most at risk for relapse. However, the majority of these recurrences are of similar histology and are reliably salvaged with additional surgery to remove the adnexa. Fertility sparing should be considered in those who are interested in childbearing. These findings should be of some comfort to practitioners and patients alike.

However, it is important not to equate these survival characteristics with benignity. For instance, it is remarkable that in the current series more than 58% of the 360 LMP tumors accessioned did not have an intraoperative histological assessment (frozen section). One must remember that patients may not only recur with invasive disease but also can succumb to its "benign" natural history through indolent and progressive growth. In addition, since re-staging, as defined in this report, is not associated with variable survival dynamics, the procedure may errantly be omitted under the guise that it won't make a difference. While little appears to be gained in those patients with no macroscopic disease by a secondary staging procedure, it shouldn't preclude staging when the diagnosis is suspected intraoperatively.

As has been reported elsewhere as well as in this study, the final and intraoperative histological diagnoses are non-correlative in a significant fraction (> 20%).[1-3] Absence of important intraoperative information makes subsequent treatment decisions more problematic and may lead to both under- and overtreatment. This was highlighted in a recent review of 2 hospital systems where surgical staging for suspected early ovarian cancer was dichotomized by the presence of a gynecological oncologist. Where staging was not done routinely and treatment decisions were made on the basis of postoperative ovarian histology, approximately 20% more patients were treated than when operative information correctly identified the patients' stage. In addition recurrence rate was reduced from 28% to 10% by correctly identifying true "at-risk" patients. It is unlikely a similar policy for LMP tumors will have such a dramatic effect but we are nonetheless, left to make the decision to stage or not intraoperatively, and until we can be confident that our final histology will be represented by frozen section we must address the situation conservatively. It is likely we will increase our diagnostic precision for LMP, allowing us to be more selective in whom we stage. Once the diagnosis is confirmed, limited stage patients appear to gain very little from addition surgical evaluation. ■

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Special Feature

Non-Invasive Approach to Prenatal Diagnosis

By John C. Hobbins, MD

THE AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGY issued a statement many years ago that has been ingrained into the thinking of providers caring for patients of "advanced maternal age." The recommendation was that all pregnant women 35 years or older be offered an amniocentesis. What evolved almost immediately was that the phrase became "recommended that these individuals have amniocentesis." Many patients today are referred to us for an amniocentesis without mention by their providers of the availability of any other type of prenatal diagnostic testing. Often they expect that we will cover this prior to the procedure, but in some cases the message is "you are 38 years old. You need an amniocentesis." The reasons for the slow movement towards a more noninvasive approach are diverse, but often represent reluctance by a provider to settle for a diagnostic regimen that does not have a 100% accuracy. However, the ultimate decision about diagnostic testing should be in the hands of the patient.

In this special feature, up-to-date information will be provided regarding the risks and benefits of various diagnostic methods available today for patients of advanced maternal age (AMA).

Biochemical Testing

Maternal serum alpha-fetoprotein (MSAFP) testing was begun in the 1970s to screen for neural tube defects. Merkatz first noticed that MSAFP levels were low in many pregnancies complicated by Down syndrome (DS). Later, it was realized that when one used a 2-variable formula [maternal age and MSAFP in multiples of the median (MoM)], 30% of fetuses with DS would be screened in.

When it became clear that the addition of 2 other analytes, human chorionic gonadotropin (hCG) and estriol (E3) enhanced the predictive value of the test, these were added to bring the method up to a "triple screen." In an overall pregnant population this has a sensitivity for DS of about 60% at around a 5% screen positive rate. This sensitivity rose to about 80% in a population older than 35 years of age, using a higher preset screen positive rate of about 15%.

Now we have the quad screen. Interestingly, there is no uniformity among laboratories regarding what this fourth analyte should be. Some labs break down hCG into "total hCG" and the alpha or beta subunits, while most now add the analyte with the most available data regarding efficacy, inhibin-A. The incorporation of inhibin-A adds at least another 5% to the sensitivity without an increase in the screen positive rate.

The weakest performer is estriol, and in Europe many colleagues have found it to be cost-effective to drop this from the diagnostic package.

The beauty of the triple or quad screen is that it will often drop the risk for an AMA patient far below the risk of amniocentesis. The drawback is that the test will miss 15% of pregnancies complicated by DS. Another inherent downside is that many individuals will be unnecessarily concerned when notified that they have a "positive test." However, with proper counseling, this can be effectively neutralized. To many patients, a positive screen means that their fetus has DS, when, in fact, their risk may be, let's say, 1:200, giving her a 99.5% chance that the fetus is normal. Also, when describing the test, the fact that providers use the word "false positive" is misleading, since this would mean the test indicated that the fetus actually had a problem for which it was being screened, and the test was wrong. The term "screen positive" has a "softer" connotation.

First-Trimester Biochemistry

The 2 best performers are beta subunit of HCG (beta HCG), which tends to be elevated in DS, and pregnancy-associated plasma protein-A (PAPP-A), which is depressed. The average beta HCG in DS is 1.9 MoM and the PAPP-A is 0.44 MoM.

The sensitivity when used together is about 62% for DS at a screen positive rate of 5%.

Ultrasound

First trimester: In a beautifully designed study, Nicolaides and his team were the first to demonstrate how careful assessment of fetal nuchal translucency in the first trimester could be used to screen for DS and other aneuploidies. At first, they began using a measurement made from the inner portion of the nuchal membrane to the inner aspect of the fetal neck (NT), and, by establishing an arbitrary cutoff of 2.5 mm, they grossly adjusted the risk for a given patient. The London group then prospectively assessed the efficacy of an algorithm taking into account the patient's age, the crown-rump length of the fetus, and the NT thickness. Their findings in more than 100,000 patients were suggestive of a 77% sensitivity for DS at a 5% screen-positive rate and 82% when a cutoff of 1:300 was used.

Unfortunately, the first American study using this same concept, yielded only a 33% sensitivity and about the same time it was postulated that the performance of the London group was not quite as good as was initially reported since the authors did not account for the nearly 40% spontaneous loss rate in DS fetuses. In other words, there was complete ascertainment in the screen-positive fetuses who had second trimester invasive testing and in those who delivered toward the end of pregnancy, but chromosomal analysis was not necessarily done on all those who had spontaneous abortions. Using this principle, Haddow pointed out that the sensitivity would be more towards 60%.

Now it is clear from well constructed studies in the literature, including 2 American studies with very large numbers (BUN and FASTER trials), that Nicolaides' sensitivity figures stand up to the newer figures when quality control for NT assessment is adhered to.

For example, a collection of pooled data from 30 studies indicated a sensitivity for DS of 80% with a screen positive rate of 6%.

After the inception of the NT theme, another marker for DS also has come along. The fetal nasal bone, which, in a seminal study from London, was found to be absent in 73% of first trimester fetuses with DS. Recently, there has been a suggestion that assessment of the nasal bone is not as useful in the first trimester as in the second trimester, when the size of the nasal bone can be better quantified.

It is clear that the combination of NT testing and first trimester biochemistry is better than either alone, but, although the sensitivity is increased by only a few percentage points, from a public health standpoint this may

well be worth the extra cost of the 2 since the screen-positive rate is not increased.

The data available from the combined test (biochemistry and NT) are limited, but from BUN study results, published in the *New England Journal of Medicine* in 2003, with a cut off of 1:270 and a screen positive rate of 9%, 85% of DS fetuses would be screened in with NT, PAPP-A, and beta HCG. The FASTER trial data, published in abstract forum in the *American Journal of Obstetrics and Gynecology*, shows a 90% sensitivity at a 14% screen positive rate with the NT, PAPP-A and free beta hCG combination.

The Genetic Sonogram

There are 3 major components of a genetic sonogram. The first one involves measurements of the humerus and femur, which tend to be shorter in DS. Interestingly, only about 20% of DS fetuses will have measurements that are > 2 standard deviations below the mean for gestation, but a much larger percentage will be about a week less than dates.

The second part involves an attempt to rule out fetal anomalies such as cardiac defects, CNS or renal abnormalities. About 20% of fetuses with DS will have a "major abnormality," which includes ventriculomegaly.

The third part, varying from center to center, consists of a search for markers for DS. The best performers, and therefore the most commonly evaluated, are the nuchal skin fold thickness (NSFT), the size of the nasal bone, the presence of echogenic bowel, and iliac angle assessment. Less commonly evaluated are the middle bone of the fifth digit, ear length, frontal lobe length, and sandal gap.

The echogenic intracardiac focus (EIF) has been the source of controversy and an angst producer for diagnosticians. It is more commonly found in DS but, as with most of the other markers, it has been noted in up to 5% of normal second trimester fetuses. There is a growing feeling that if it is isolated, it should not raise the risk for a given fetus, and if found in a low-risk patient (younger than 35 years of age and/or with normal biochemical testing), it could be classified as a normal variant.

Many individual studies and pooled data show the sensitivity of a genetic sonogram to be about 75%. Once the sensitivity and specificity of a given test are known, then a likelihood ratio (LR) can be calculated. If a test has a negative LR of 0.3, which a genetic sonogram has in some hands, one can drop the risk for a given patient from her pretest value by 70%.

We have taken the approach of adjusting DS risk downward following a careful genetic sonogram by 50% (adding a cushion). This would take a 35-year-old with a risk of 1:280 to a posttest risk of 1:560. If an isolated marker (with the exception of an NSFT) is found, then we will not change her risk, and if the fetus has a major anomaly or more than one marker, we will raise her risk.

Some patients will start with a quad or triple screen risk that is higher than her age-related risk. In these patients we have been cautious with our counseling even though there is growing evidence that the same principle can be applied to those with nonreassuring biochemistry.

Invasive Testing

CVS: We quote a risk of between 1 and 1.5% procedure related risk to CVS. These data are hard to come by because of the non-randomized nature of the experience in literature. An older Canadian randomized trial, comparing CVS and amniocentesis, suggests the risk of CVS to be about 0.7% higher than that of amniocentesis. Certainly, there is evidence that the risk is lowest in experienced hands.

Amniocentesis

Although individuals and centers have reported loss rates that are at great variance with each other, the only RCT in the literature shows a procedure related risk of 1% with a spontaneous loss rate in the nonamnio group of 0.7%. This leaves one to question any individual operator citing an amniocentesis loss rate of less than 7/1000.

Unpublished data from the FASTER trial suggest the difference in loss rate between screen positive patients having amniocentesis and those not having this procedure was surprisingly low and might have to do with our inherently high spontaneous loss rate in any screen positive patient.

The "ball park" loss rate that we quote is 1:200. This was the figure used long ago when 35 was arbitrarily chosen as an age at which the risk of DS was roughly equivalent to the risk of amniocentesis.

The Integrated Screen

This puts into play first trimester ultrasound, first trimester biochemistry, and second trimester biochemistry. The method has the ability to screen in more than 90% of DS fetuses with a false positive rate of 5.4%, as stated in the FASTER abstract.

Some AMA patients want 100% assurance that their fetus does not have DS, and these individuals will always choose to have an amniocentesis. However, there is a growing number of patients who want the best non-invasive information available with

which to weigh their risk of fetal DS against the risk of amniocentesis. In our experience the majority of patients today will decline amniocentesis if there is a mis-match in these risks. Whatever the patient's choice, it is the job of their provider to give them the most up to date information with which to base their decision. ■

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CME Questions

8. With which of the following is it possible to drop the risk for Down syndrome for a given patient below the risk of amniocentesis?

a. Triple screen
b. Quad screen
c. Integrated test
d. Genetic sonogram
e. All of the above

9. The sensitivity of the genetic sonogram to detect aneuploidy is about:

a. 30%.
b. 50%.
c. 75%.
d. 100%.

10. The following statements are true regarding the recent WHI publications *except*:

a. The participants in the 2 clinical arms of the WHI randomized trial were very similar in their baseline characteristics.
b. The cardiovascular results of the WHI indicate that a dose of 0.625 mg conjugated estrogens may produce thrombogenic arterial events in elderly women long distant from their menopause.
c. It appears that hormone therapy can reduce the risk of colonic cancer by nearly 50%.
d. Close analysis of the data from the estrogen-only arm is required before concluding that estrogen-only treatment is not associated with an increase in breast cancer.

Answers: 8 (e); 9 (c); 10 (a)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *OB/GYN Clinical Alert*. Send your questions to: Robert Kimball, *OB/GYN Clinical Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *OB/GYN Clinical Alert* via the internet by sending e-mail to robert.kimball@thomson.com. ■

AMERICAN HEALTH CONSULTANTS®

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Migraine and Subclinical Brain Lesions

Source: Kruit MC, et al. *JAMA*. 2004;291:427-434.

The data on the relationship between migraine and other vascular events such as stroke have been conflicting, although in some populations (such as young women smokers who suffer migraine with aura) the adverse association is more clear-cut. Because such a high proportion of women, and a not-insubstantial population of men suffer migraine, any important association with other major morbidities becomes epidemiologically compelling.

Using MRI scans in a population of migraine sufferers without history of prior stroke or TIA, infarcts and white matter lesions were defined, all by the same neuroradiologist who was blinded to the clinical data about the patients (n = 435, inclusive of 140 controls). Most patients (71%) were female, the mean age was 48 years, and patients were equally divided between migraine with and without aura.

Although the absolute number of infarcts demonstrated only a trend towards being more frequent in migraneurs, it was the posterior circulation infarcts which were markedly more common (7-fold increase in migraine population vs controls), an effect which was even more exaggerated in the migraine with aura category (odds ratio = 13.7). In the total unselected population, no difference in white matter lesions between migraine sufferers and controls was discerned; however women migraneurs had an increased odds ratio (OR = 2.1) for white matter lesions compared to controls.

None of these patients had any prior evidence of cerebral ischemic events. The relationship between migraine and increased risk of cerebral ischemia prompts consideration of whether more vigorous prevention of migraine might reduce risk of subsequent tissue damage. ■

Memantine Treatment in Alzheimer Disease

Source: Tariot PN, et al. *JAMA*. 2004;291:317-324.

Memantine (MEM) is the first clinically available NMDA receptor antagonist with demonstrated clinical efficacy and an acceptable adverse event profile for persons with Alzheimer disease (ALZ). Cholinesterase inhibitors like donepezil (DON) might work in a complementary fashion, hence this MEM + DON trial.

Subjects with ALZ (n = 404) who had been on a stable dose of DON for at least 6 months, and were free of known secondary etiologies for dementia, were randomized in a double-blind fashion to MEM titrated from 5 mg/d up to 20 mg/d (administered as 10 mg b.i.d.) for 6 months, vs placebo. DON was continued in both the placebo and the MEM treatment arm.

Changes in cognitive function, functional capacity, and global outcome were measured throughout the trial, the primary outcome being based upon scores on the Severe Impairment Battery and Activities of Daily Living Inventory.

There was a statistically significant positive effect of MEM when added to DON, complemented with a very favorable adverse effect profile: more patients in the placebo group withdrew due to adverse events than in the MEM group. Only headache and confusion were more common in the MEM group, both of which occurred in less than 10% of recipients. In addition to being useful as ALZ monotherapy, there may be additional clinical benefits from combining MEM with DON in ALZ therapy. ■

Casual Postprandial Glucose Levels in Type 2 Diabetes Management

Source: El-Kebbi IM, et al. *Diabetes Care*. 2004;27:335-339.

Tight control of type 2 diabetes (DM2) has been proven to reduce microvascular complications. Use of the hemoglobin A1c to assess long-term control is standard, but for modulation of treatment, timed specimens (eg, fasting, 1-2 hours postprandial) obtained by patient self-monitoring of blood glucose are often the information clinicians use to make choices about therapy modification.

Unless instructed otherwise, most DM2 patients are 1-4 hours postprandial at the time of an office visit. El-Kebbi, et al, investigated whether casual glucose levels obtained at the office visit might function as an adequate barometer of glucose control to

help modify treatment.

Established DM2 patients (n = 1827) at the Grady Diabetes Clinic (Atlanta) underwent simultaneous A1c and casual glucose measurement during their regular visit. The correlation between casual glucose measurement and A1c was strong (correlation coefficient = 0.63). The presence of a casual glucose > 150 predicted an A1c > 7.0 with a sensitivity of 78% (positive predictive value = 80%).

El-Kebbi and colleagues suggest that a casual plasma glucose greater than 150 mg/dL may serve as a surrogate for A1c; results above this level should prompt an intensification of therapy. ■

Exemestane after Tamoxifen Therapy in Breast Cancer

Source: Coombes RC, et al. *N Engl J Med*. 2004;350(11):1081-1092.

Tamoxifen (TAM) is well established to reduce, over 5 years, both risk of breast cancer (BCA) recurrence (47%) and mortality (26%) among women who have undergone surgery for BCA and who have estrogen-receptor positive tumors. Exemestane (EXE) is classified as an irreversible steroidal inactivator, and works by blocking the enzyme (aromatase) which is responsible for converting androgens to estrogens, ultimately inhibiting aromatization by about 98%. Although TAM is of remarkable positive benefit, it is not without risks, including increased likelihood of endometrial cancer attributed to endometrial stimulation. EXE is not known to induce endometrial proliferation, or increase proclivity for endometrial cancer.

The Intergroup Exemestane Study (IES) investigated whether substituting EXE for TAM after 2-3 years would provide better outcomes than simply treating with TAM continuously for 5 years. Study subjects were postmenopausal women (n = 4742) who remained free of recurrence during sustained TAM treatment. EXE (25 mg p.o. q.d.) was substituted for TAM in one half of the subjects.

After a median followup of 30.6 months, the risk of recurrence, contralateral BCA, or death was reduced by 32% in the EXE group compared with TAM. The adverse effects seen more frequently with EXE than TAM included diarrhea and arthralgia, but thromboembolisms was almost twice as common in the TAM group. Coombes and colleagues suggest that switching women from TAM to EXE at the 2-3 year point in treatment may provide more favorable outcomes. ■

An Analysis of How Long Patients Remain on Various Antihypertensive Therapies

Source: Esposti LD, et al. *J Clin Hypertens*. 2004;6:76-84.

The term 'drug efficacy' is technically intended to reflect impact of an agent on a designated end point in a study population participating in a clinical trial. 'Drug effectiveness,' on the other hand, refers to the 'real life' effects drug treatment produces as seen separately from a clinical trial; ie, what impact might be seen when 'typical patients' use a medication in, for instance, the community setting.

As many as half of patients who begin antihypertensive drug therapy (HTN-Rx) discontinue treatment within a few months of initiation. Study subjects from the area in and around Ravenna, Italy comprised this hypertensive patient population (n = 14,062). All were first time recipients of a new HTN-Rx. 'Persistent patients' were defined as either maintaining, combining with, or switching from their initial HTN-Rx to another HTN-Rx, for a duration of > 273 days from the day of enrollment.

Discouragingly, 48% of patients discontinued treatment after a single prescription! Medication choices were similar to those commonly used in the United States (ACE/ARB/HCTZ/CCB/Beta Blocker). Angiotensin Receptor Blockers demonstrated the highest continuation rate, followed by ACE inhibitors, CCBs, and Diuretics.

Cost of treatment decreased as age increased, and increased for persons who switched or combined agents. Angiotensin receptor blockers were the most expensive single agents. Overall, specific individual drug cost and pattern of drug persistence correlated best with total cost for hypertension treatment. These data suggest that although drug cost is important, aspects of the drug treatment which affect persistence patterns ultimately have a substantial effect on overall cost. ■

Association of Endothelial Dysfunction with Insulin Resistance and Carotid Wall Thickening in Hypertension

Source: Suzuki M, et al. *Am J Hypertens*. 2004;17:228-232.

Endothelial dysfunction (END) is a fundamental defect in essential hypertension (HTN) and is closely associated with carotid wall thickening (CWT), a consistent marker for early atherosclerotic change. Insulin resistance (IR) is also associated with both HTN and CWT, suggesting a potential relationship between IR and END.

HTN subjects (n = 41) were studied if they met inclusion criteria including HTN, no diabetes, no suggestion of secondary HTN, no major cardiovascular, renal, hepatic, or other endocrine disease, no smoking, and no medications which modulate carbohydrate or lipid metabolism (eg, statin, steroids) for at least 12 months. All subjects underwent measurement of endothelial function, carotid interomedial thickness by ultrasound, and insulin sensitivity as defined by insulin/glucose infusion.

END was found to be associated both with IR and CWT. The changes in CWT and END were strongly associated, suggesting a close correlation between functional (END) and structural (CWT) atherosclerotic changes. The confirmed association between END, CWT, and IR may prompt consideration of investigation to seek causality between, eg, IR and CWT ■

PHARMACOLOGY WATCH

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

Atherosclerosis Reversed With Lipid-Lowering Drugs

When it comes to treating lipids in patients with heart disease, the mantra may be, "The lower the LDL, the better." Data from the multicenter Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial indicate that aggressive reduction of atherogenic lipoproteins prevents progression of disease. The study randomized 654 patients with coronary disease to pravastatin 40 mg/d (moderate lipid-lowering regimen) or atorvastatin 80 mg/d (intensive lipid-lowering regimen). After 18 months of therapy, 502 patients were evaluable with baseline and post-treatment intravascular ultrasounds. The primary outcome was percentage change in atheroma volume. Intensive lipid-lowering therapy with atorvastatin resulted in a decrease of LDL cholesterol from an average of 150 mg/dL to 79 mg/dL, while pravastatin therapy resulted in a decrease to 110 mg/dL. C-reactive protein decreased 36.4% with atorvastatin and 5.2% with pravastatin ($P < .001$). Progression of coronary atherosclerosis did not occur in the atorvastatin group, while coronary atherosclerosis progression did occur in the pravastatin group compared with baseline. The authors suggest that the data support aggressive lipid lowering, below the current national guidelines for secondary prevention in patients with coronary atherosclerosis (*JAMA*. 2004;291:1071-1080). It is of note that this study employed the relatively new technology of coronary ultrasound, which more effectively measures plaque volume as opposed to coronary angiography, which merely quantifies the lumen. Still, this technology is relatively new, as pointed out in an accompanying editorial, but the results appear to be valid. The editorial also points out that the moderate lipid-lowering regimen in the study did not achieve levels of LDL lowering recommended by national guidelines, which suggest lowering LDL below 100 mg/dL for secondary prevention. The authors recommend focus on all risk factors in patients with coronary disease, including LDL lowering at least to levels recommended in national guidelines (*JAMA*. 2004;291:1132-1134).

Positive Alendronate Data in Osteoporosis

Does alendronate prevent fractures after 10 years of therapy? According to a new multicenter placebo-controlled trial, the drug is effective and safe over 10 years in women with osteoporosis. Data from the study are from a follow-up of 2 identical 3-year trials of alendronate therapy followed for an additional 7 years. In this follow-up study, women were randomized to 3 daily doses of alendronate or placebo. The 3 active treatment groups included women who took alendronate 5 mg or 10 mg daily for the entire 10-year study. A third group took 20 mg of

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alendronate daily for 2 years and 5 mg daily in years 3, 4, and 5 followed by 5 years of placebo. This last group was called the "discontinuation group." Women in the original placebo group ended up receiving alendronate in years 4 and 5 and then were discharged. There were 247 women who participated in all 4 phases of the study. Treatment with 10 mg of alendronate daily for 10 years resulted in statistically significant increases in bone mineral density at the following sites: 13.7% increase, lumbar spine; 10.3%, trochanter; 5.4%, femoral neck; and 6.7%, proximal femur as compared with baseline values ($P < .001$; 95% CI for all groups). The percentage increases for the 5 mg group were 9.3%, lumbar spine; 4.8%, trochanter; 2.8%, femoral neck; and 2.9%, proximal femur. Alendronate also resulted in fewer fractures and lower rates of loss of stature over the 10-year period. Discontinuation of alendronate resulted in a gradual loss of bone density. The authors conclude that continued treatment with 10 mg of alendronate daily for 10 years was associated with a sustained therapeutic effect on bone density and bone remodeling. Concern over increase fracture rates with bisphosphonates over time was not validated by the study (*N Engl J Med*. 2004;350:1189-1199).

NSAIDs For Myocardial Infarction

Nonaspirin NSAIDs, especially ibuprofen and naproxen, may protect against myocardial infarction in patients who are not taking aspirin. Researchers from Pennsylvania conducted a case-control study with cases of first, nonfatal MI identified prospectively with random controls from the community. The use of a nonaspirin NSAID was associated with a significant reduction in MI compared to those not using aspirin (OR 0.53; 95% CI). The adjusted odds ratio for ibuprofen was 0.52 and for naproxen was 0.48. The odds ratio for aspirin alone in this study was 0.79. The combination of aspirin with a nonaspirin NSAID trended toward increased risk of MI and worsened as the frequency of nonaspirin NSAIDs use increased; however, the confidence intervals for this determination were very wide. The authors conclude that in patients who are not taking aspirin, a nonaspirin NSAID is associated with a reduced risk of MI. The concomitant use of aspirin for cardioprotection along with a nonaspirin NSAID needs further study (*J Am Coll Card*. 2004;43:985-993).

Four-Hour Window for CAP Patients

Medicare patients with community-acquired pneumonia (CAP) fare better if they receive their first dose of antibiotics within 4 hours of hospitalization, according to new study. The records of nearly 14,000 Medicare patients admitted for CAP, who had not received antibiotics as outpatients, were reviewed. The administration of an antibiotic within 4 hours of arrival to the hospital was associated with reduced in-hospital mortality (6.8% vs 7.4%; adjusted odds ratio [AOR] 0.85; 95% CI, 0.74-0.98), reduced mortality within 30 days of admission (11.6% vs 12.7%; AOR 0.85; 95% CI, 0.76-0.95), and reduced length of stay as measured by hospitalization exceeding the 5-day median (42.1% vs 45.1%; AOR 0.90; 95% CI, 0.83-0.96). Early administration of antibiotics also resulted in a 0.4-day shorter length of stay. The study did show that the majority of patients (60.9%) received antibiotics within 4 hours of arrival (*Arch Int Med*. 2004;164:637-644). Current CAP guidelines generally recommend initiation of an antibiotic within 8 hours of arrival, but this study suggests that those guidelines may not be aggressive enough.

FDA Actions

Rofecoxib (Vioxx) has been approved for the treatment of migraine attacks with or without aura in adults. The approval was based on a large study that showed that the single dose of rofecoxib, either 25 or 50 mg, effectively reduced migraine pain at 2 hours and reduced the use of rescue medications.

The FDA has issued a Public Health Advisory about the need for physicians, patients, and families to closely monitor adults and children with depression when beginning treatment certain antidepressants and has asked the manufacturers of these drugs to include new warnings in their labeling about the potential for increased suicidality. The antidepressant drugs are the serotonin reuptake inhibitors fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro); and the non-SSRI antidepressants bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). ■