Providing Evidence-based Clinical Information for 23 Years

OB/GYN CLINICAL ALERT®

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 LLC

INSIDE

Financial Disclosure: *OB/GYN Clinical Alert*'s editor, Leon Speroff, MD, is a consultant for Warner-Chilcott; peer reviewer Catherine LeClair, MD, reports no financial relationship to this field of study

SSRIs and Fractures

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Daily use of SSRIs is associated with a 2-fold increase in the risk of fractures.*

Source: Richards JB, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med.* 2007;167:188-194.

Richards and colleagues representing the Canadian Multicentre Osteoporosis Study Research Group reported the effect of daily selective serotonin reuptake inhibitors (SSRIs) use in a prospective cohort study in 7 regional centers of 5008 adults over the age of 50.[1] In this large group, 137 (2.7%) were daily SSRI users, 609 (12.2%) reported clinical depression, and 114 (83.2%) of the users were female. After adjusting for age, hip bone density, fractures at baseline, and estrogen use in women, daily SSRI use was associated with an increased risk of fragility fractures; hazard ratio = 2.1 (1.3-3.4). Daily use of SSRIs was associated with about a 2-fold increased risk of falling, and these individuals had lower bone densities. Controlling for falls and lower bone density still left an increased risk of fractures in SSRI users, that began after 1 to 1.5 years of use.

COMMENTARY

SSRIs are the favored treatment for depression in older adults, a problem that affects about 10% of the older population. Several earlier studies had reported an increased risk of fractures with the daily use of SSRIs; however, these earlier studies were unable to control for the various factors that influence this risk, especially falls, depression, and bone density. The current study indicates that the increase in fractures persisted after controlling for these factors.

Does this side effect of SSRIs make sense? Is it the SSRI or the lifestyle associated with clinical depression? Unfortunately it appears that there is a direct effect of SSRIs on bone. Components of the neural system are involved in bone metabolism. Serotonin receptors and serotonin transport have been

Volume 24 • Number 5 • September 2007 • Pages 33-40

NOW AVAILABLE ONLINE
www.ahcmedia.com

identified in osteoblasts and osteocytes. The bone effects of parathyroid hormone and mechanical stimulation are modulated by the serotonin system. Mice with a mutation for the serotonin transporter develop less bone mass and strength.[2] Therefore daily SSRI use can impair bone formation, tilting the balance in favor of resorption and bone loss, and decreased bone densities have been reported in both male and female SSRI users (but not in users of tricyclic antidepressants).[3, 4]

It is not always easy to know which came first, depression or fractures leading to subsequent depression. It has been reported that depressed people and SSRI users have a greater incidence of falls,[5] and thus it is not unreasonable to consider that depression comes first in some people. However, orthostatic hypotension and syncope are more common in SSRI users, and this could also contribute to the greater prevalence of falls.

Depressed people are sedentary and eat poorly, factors that favor bone loss. Some have speculated that increased cortisol levels associated with depression might lead to bone loss, similar to that observed with the pharmacologic administration of corticoidsteroids. On the other hand, American studies, despite finding a link between depression and fractures, failed to detect an increase in depression associated with lower bone density measurements.[5, 6] However, other studies have reported increases in depression associated with lower bone densities.[7-9]

Where does that leave us? Should consideration be given first to estrogen therapy prior to using SSRIs to treat depression? In the Canadian study, an increased risk of fracture was present in those women who had a history of estrogen treatment. But would concomitant estrogen therapy both alleviate the depression and reduce the risk of falling? Should users of SSRIs be treated with an antiresorptive agent, estrogen or a bisphosphonate? Note that the increase in fractures in the Canadian study was observed even when the data were corrected for bone density. This would suggest that SSRIs affect bone quality, not just bone density, an impact that might not be prevented with either estrogen or bisphosphonate treatment. Another important issue is whether this same problem will be encountered in younger women who have had breast cancer and are being treated with SSRIs for hot flushing.

Obviously this is a muddled picture. Considerable publicity has successfully raised clinical consciousness regarding the increased risk fractures associated with the use of corticoidsteroids. The overall risk is about the same as that reported with SSRIs, although osteoporotic and hip fractures are higher.[10] It is time that we are more aware of the increased risk of fractures with the daily use of SSRIs. Interventions that reduce the odds of falling and enhance the ability to withstand the impact of a fall are important. This includes patient education regarding hazards in the home, monitoring drug use, adequate nutrition, and a good exercise program. Aggressive monitoring of bone density is warranted; adequate calcium and vitamin D supplementation are necessary, and until more studies clarify this problem, it seems reasonable to consider treatment with one of the antiresorptive agents. ■

References

1. Richards JB, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med.* 2007;167:188-194.
2. Warden SJ, et al. Inhibition of the serotonin (5-hydroxytryptamine) transporter reduces bone accrual during growth. *Endocrinology.* 2005;146:685-693.
3. Haney EM, et al. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. *Arch Intern Med.* 2007;167:1246-1251.

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MANAGING EDITOR: Iris Young.
MARKETING PRODUCT MANAGER: Shawn DeMario.
Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to **OB/GYN Clinical Alert**, P.O. Box 740059, Atlanta, GA 30374.

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.

Subscriber Information

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

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
Add $9.95 for shipping & handling
(Resident/Student rate: $125).

Multiple Copies
Discounts are available for group subscriptions.
For pricing information, please call Tria Kreutzer at (404) 262-5482.

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

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

AHC Media LLC designates this educational activity for a maximum of 25 *AMA PRA Category 1 Credits* .Physicians should only claim 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.

AHC Media LLC

Questions & Comments

Please call **Iris Young**, Managing Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

4. Diem SJ, et al. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. *Arch Intern Med.* 2007;167:1240-1245.
5. Whooley MA, et al. Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med.* 1999;159:484-490.
6. Silverman SL, et al. Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: results from the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. *J Rheumatol.* 2007;34:140-144.
7. Robbins J, et al. The association of bone mineral density and depression in an older population. *J Am Geriatr Soc.* 2001;49:732-736.
8. Milliken LA, et al. Depressive symptoms and changes in body weight exert independent and site-specific effects on bone in postmenopausal women exercising for 1 year. *J Gerontol A Biol Sci Med Sci.* 2006;61:488-494.
9. Kahl KG, et al. Bone mineral density, bone turnover, and osteoprotegerin in depressed women with and without borderline personality disorder. *Psychosom Med.* 2006;68:669-674.
10. Kanis JA, et al. A meta-analysis of prior corticosteroid use and fracture risk. *Bone Miner Res.* 2004;19:893-899.

Gemcitabine vs Pegylated Liposomal Doxorubicin in Patients with Platinum-resistant Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Professor & Director, Clinical Research Department of Gynecologic Oncology University of Texas; M.D. Anderson Cancer Center, Department of Gynecologic Oncology, Houston

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

Synopsis: *Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer.*

Source: Mutch DG, et al. *J Clin Oncol.* 2007;25:2811-2828.

Ovarian cancer patients relapsing within 6 months of their primary therapy represent among the most challenging patients to treat. Generally, in this setting, most patients have only been exposed to one or two agents, yet they are phenotypically resistant to most chemotherapeutics, making drug discovery of paramount importance. Several clinical studies have targeted this patient population to evaluate the potential efficacy of newer agents. Based on promising early clinical reports with the nucleoside analog, gemcitabine, Mutch and colleagues conducted a randomized phase III clinical trial of this agent compared with a clinical standard, pegylated liposomal doxorubicin (PLD). Patients were eligible if they had epithelial ovarian, primary peritoneal or fallopian tube cancer, which had recurred within 6 months of their most recent exposure to platinum. Primary therapy was to be "platinum-based" and patients could not have received more than 2 prior therapies. Both measurable and evaluable (biomarker CA125 greater than or equal to 100 U/mL) disease was allowed. FDA-approved dosing of PLD (50 mg/m2 every 28 days) was mandated in the control arm; standard dosing of gemcitabine (1000 mg/m^2 days 1 and 8 every 21 days) was administered in the experimental arm. The primary efficacy endpoint was progression-free survival (PFS) and the sample size was determined based on an anticipated reduction in the hazard for progression of 37.5% (HR: 0.625). All analyses were performed under the intent-to-treat policy. Overall, 195 patients were randomly allocated (1:1) to one of the two treatment regimens. Both PFS and overall survival (OS) were statistically similar between the two agents. In addition, response rates in both measurable and non-measurable cohorts were similar. The PLD group suffered significantly higher "hand-foot" syndrome and mucositis; the gemcitabine group experienced significantly more non-complicated myelosuppression, constipation, nausea/vomiting and fatigue. The authors concluded that the two agents have a comparable "therapeutic index" and that gemcitabine may be an acceptable alternative to PLD in this cohort of patients.

COMMENTARY

While this large and highly anticipated study appears to have missed its primary endpoint, it is an informative clinical trial nonetheless and further solidifies a common use of administering single agent gemcitabine to patients with recurrent ovarian cancer. At the time of this publication, no previous phase III studies had been reported with single agent gemcitabine in any setting of recurrence and this trial joins

just one other evaluating gemcitabine in combination with carboplatin in platinum-sensitive recurrent ovarian cancer.[1] A subsequent second single-agent study of PLD vs gemcitabine has been recently presented with similar findings. The impact and effort of this trial is important to gauge against the relative paucity of similar data in the literature. Surprising to many, there have been very few randomized clinical trials exclusively in this population of patients (platinum-resistant disease) and given the relatively poor anticipated performance, it is understandable that superiority was not achieved.[2]

There are a few items about the trial, which warrant some discussion. First, the study allowed for both primary and secondary platinum-resistance. These two groups were slightly imbalanced by randomization and may represent different cohorts of patients. Currently, we do not have an accurate methodology to risk stratify recurrent patients where the underlying probability of response to treatment is equal. This is best controlled by balanced randomization and adequate sampling. Second, since the two regimens have a different schedule, the assessment of efficacy was made after 3 cycles of PLD but 4 cycles of gemcitabine. This could lead to an important imbalance of primary endpoint detection (bias) if there is a relational effect of the amount of chemotherapy exposure to response. However, in the studied population, this risk is likely low. Third, the doses and schedules of both agents have been altered somewhat in day-to-day clinical practice based on observed toxicities. While the higher dose of PLD was mandated by FDA for investigation, the much more tolerable lower dose (40 mg/m2) is almost exclusively used in the USA. Efficacy at this dose is not well studied, but was the subject of the more recently unpublished phase III study mentioned previously. Similarly, gemcitabine, which is administered to patients at all phases of their recurrence, has been shown to be quite tolerable in every 14 day dosing.[3]

Finally, even if the trial had met its primary endpoint, the frequent cross-over would likely have removed any benefit to, arguably, the ultimate endpoint, overall survival. In the context of clinical investigation, this is a difficult issue with which to wrestle. While we should be striving for the recognition of agents that "really matter" to this ultimate endpoint (as opposed to the addition of "me-too" therapeutics), it is a very difficult benchmark to move and broadening the menu of "active" agents does allow for customization of therapy based on individual patient characteristics and concurrent toxicities. Fortunately, several clinical studies are nearing completion to help clarify and illuminate this menu of options. ■

References

1. Pfisterer J, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol.* 2006;24:4699-4707.
2. Herzog TJ, Pothuri B. Ovarian cancer: a focus on management of recurrent disease. *Nat Clin Pract. Oncol.* 2006;3:604-611.
3. Bozas G, et al. Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritoneal carcinoma. *Gynecol Oncol.* 2007;104:580-585.

Neonatal and Five Year Outcomes after Birth at 30-34 Weeks of Gestation

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

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

Synopsis: *Authors evaluate the rates of in-hospital death, neonatal complications, and 5-year outcomes of infants born at 30-34 weeks of gestation.*

Source: Marret S, et al. Neonatal and 5-year outcomes after birth at 30-34 weeks of gestation. *Obstet Gynecol.* 2007;110:72-81.

In the latest issue of *Obstetrics and Gynecology* there were 3 papers, loosely tied together, that should provide important guidance to clinicians dealing with preterm labor (PTL). One article will be the source for the primary review, but the others will be folded into the comments sections.

I have found myself telling patients that once their pregnancies have reached 32 weeks, the fetus/infant

represents a nursery "slam dunk" for today's neonatologists. The following article demonstrates how inaccurate that concept is.

Marret et al compiled data from infants born in nine regions in France during 1997 and added follow-up data from these infants at 5 years of age. The author concentrated on those born between 30-34 weeks of gestation.

Neonatal morbidity dropped from 8.1% to 0.4% between 30 and 34 weeks. Respiratory distress syndrome (RDS) decreased from 43.8 % to 2.6 %, perinatal infection from 7.2 % to 2.6 %, and severe "white matter injury" from 5.5 % to 1.3 %. At 5 years of age the incidence of cerebral palsy (CP) and cognitive impairment in children born between 30 and 34 weeks dropped at each week of gestation from 6.7 percent to 0.7%, and from 35.3% to 23.9%, respectively.

COMMENTARY

It is clear from these data that being born, even at 34 weeks, is not ideal for immediate health and longer term development, thereby leading to the conclusion that we should continue doing everything we can to keep these babies from delivering early. Although this is a very logical interpretation, it should be pointed out that there may be more to the story. For example, CP and impaired childhood development can be linked directly in some cases to intrauterine infection, which often was the cause of the associated preterm labor and delivery. Since it would be far worse to attempt to keep fetuses exposed to infection in utero than to have them exposed to the complications of prematurity alone in today's improved neonatal environment, it seems that we should be very selective in our attempts to stop preterm labor. That said, information from recent investigation involving cervical length, various interleukins, amniocentesis, and other clinical tip offs should allow us to identify those in whom an aggressive attempt should be made to prolong pregnancy.

In the last 5 years most studies have yielded negative results regarding our ability to stop preterm labor, but very recently there have been encouraging results from transdermal nitroglycerine (GTN) and nifedipine in stopping preterm labor. In the same issue of *Obstetrics and Gynecology*, a randomized trial was published comparing nifedipine and magnesium sulfate ($MgSO_4$) to stop contractions for 48 hours in patients with preterm contractions. They found that, although $MgSO_4$ was slightly better in achieving that one goal, there was no difference in rate of *delivery* within 48 hours (7.6% vs 8.0%) or average time of delivery (35.8 weeks vs 36 weeks). $MgSO_4$ achieved the dubious distinction of much higher adverse maternal effects and resulted in a doubling of neonatal nursery days.

Last, another study in the same journal comparing dexamethasone and betamethasone to reduce RDS, found no difference in their abilities to do this, but dexamethasone was associated with a lower rate of neonatal interventricular hemorrhage (IVH).

So, to summarize:

1. It does make sense to try to keep fetuses in utero up through 34 weeks of gestation, as long as an aggressive attempt is made to rule out intra-uterine infection.
2. There is now more evidence that we should move away from $MgSO_4$ as a tocolytic.
3. The newest study pitting dexamethasone against betamethasone shows the former medication to be at least as effective in stimulating pulmonic maturity, and may be better at preventing IVH, (*and*, it is cheaper). ■

Change in Breast Cancer Prevalence

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *U.S. data indicate a decline in breast cancer incidence that parallels decreases in screening mammography and use of postmenopausal hormone therapy.*

Source: Glass AG, et al. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst.* 2007;99:1152-1161.

Glass and colleagues from the Kaiser Permanente Northwest Center for Health Research compared breast cancer incidence rates with use of screening mammography and postmenopausal hormone therapy prescriptions between 1980 and 2006.[1] The data were derived from tumor registry statistics and from clinical, pathological, and pharmacy records. In the 1980s, age-adjusted breast cancer increased in incidence by 25%, and through 2001, another 15%. In 2003-2004, the overall inci-

dence decreased by 18%, then increased slightly in 2005-2006. These changes were concentrated in postmenopausal women with estrogen-receptor-positive tumors. Mammography screening increased up to 1992, then leveled off. Hormone therapy prescriptions decreased by about 75% after 2002 in this Kaiser health plan. The authors concluded that the changes in breast cancer prevalence paralleled changes in both mammography screening and use of postmenopausal hormone therapy.

COMMENTARY

We now have 3 reports that have consistently indicated a decline in breast cancer incidence that began in 2003. An analysis of the U.S. national SEER data concluded that there was a 7% decrease in 9 regions of the U.S. in 2003, with the sharpest decline in estrogen-receptor-positive tumors in women ages 50-69.[2] In the Northern California Kaiser program, there was a 10% decline in 2003 and 2004 in the Kaiser members and 11% in the area's population. The decline in this current report from the Portland, Oregon, area is even greater.

The authors of all three reports carefully highlighted the small, but important decrease in screening mammography that has occurred in the U.S. since the year 2000.[3] This national change has been estimated to equal about a 4% decrease.[4] This is attributed to a phenomenon called "saturation of the population," close to everyone who can get screening mammography is doing so. The critical question then is whether the decrease in breast cancer incidence reflects the change in mammography or the decline in use of hormone therapy. In my view, the answer is: both!

If postmenopausal hormone therapy is affecting pre-existing tumors, an argument I have made often in the *OB/GYN Alert*, then one would expect small undetectable tumors to stop changing (at least temporarily) when women discontinue hormone therapy, and thus be below the detection limit. This would be consistent with the effect being reported: a decrease in estrogen-receptor-positive tumors in younger postmenopausal women.

There are good reasons to suspect that a decrease in the use of hormone therapy is not the only explanation. The decrease in breast cancer incidence rates did not begin in 2003, but actually started in 1999 in all postmenopausal age groups.[5] Between 2002 and 2003 there was a sharper decrease in estrogen-receptor-positive tumors in women age 50-69. The overall decrease may reflect the change in screening mammography and the 2002-2003 decrease is the response to discontinuation of hormone therapy. Appropriately for both of these influences, the decreases were noted only in small and localized tumors.

How much of the decrease is due to mammography and how much is due to hormone therapy? This question cannot be answered with any accuracy. Two observations give mammography an important role. In the national SEER data, the decline in breast cancer incidence was not only in women age 50-69, but also in women over age 70, a population that most likely had a much lower use of hormone therapy.[2] In the United Kingdom where postmenopausal women discontinued hormone therapy at a rate similar to that of U.S. women, there has been no decrease in breast cancer incidence in any age group, most notably in women ages 50-64.[6]

The concern is that at least some results on breast cancer prevalence reflects the behavior of existing tumors, and does this mean that tumors will emerge later of greater stage and grade of disease with poorer outcomes? Only time will tell, but this may prove to be another harmful effect of the publicity associated with the Women's Health Initiative. ■

References

1. Glass AG, et al. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst.* 2007;99:1152-1161.
2. Ravdin PM, et al. The decrease in breast-cancer incidence in 2003 in the United States. *New Engl J Med.* 2007;356:1670-1674.
3. Chagpa MC, Masters KM. Trends in mammography and clinical breast examination: a population-based study. *J Surg Res.* 2007;140:214-219.
4. Breen N, et al. Reported drop in mammography: is this cause for concern. *Cancer.* 2007;109:2405-2409.
5. Jemal A, et al. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res.* 2007;9:R28.
6. Cancer Research UK. UK breast cancer incidence statistics.http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/ August 6, 2007

Dietary Intake and Prognosis after Breast Cancer

ABSTRACT & COMMENTARY

By Eileen C. West, MD

Director of Primary Care, Women's Health, Clinical Assistant Professor of Internal Medicine, University of Oklahoma School of Medicine, Oklahoma City.

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

Synopsis: *Patients with early breast cancer did not have fewer recurrences of cancer or improved mortality after eating a diet rich in vegetables and fruit and low in fat.*

Source: Pierce JP, et al. *JAMA.* 2007;298(3):289-298.

Results of the Women's Healthy Eating and Living (WHEL) study were published in a recent issue of *JAMA*. In this multicenter, randomized controlled trial a total of 3088 women diagnosed with early-stage breast cancer (stage I-IIIa) within the previous four years were randomized to a diet rich in vegetables, fruit and fiber and low in fat, vs a regular diet. The two groups had no statistically significant differences in baseline demographics, tumor characteristics, dietary habits, or cancer treatment. The intervention group attended cooking classes, received 12 newsletters, and 18 telephone calls for counseling during the first year. The targets of the intervention group were on an intake of 5 vegetable servings plus 16 oz of vegetable juice, 3 fruit servings, 30 g of fiber and 15%-20% of calorie intake from fat. The control group was given print materials describing the "5-A-Day" dietary guidelines. The main outcome measures were invasive breast cancer event (recurrence or new primary) or death from any cause. After a mean of 7.3 years of follow-up, the authors found no differences in breast cancer events or all-cause mortality between women in the two groups.

Overall, the intervention group succeeded in eating 65% more vegetables, 25% more fruit, 30% more fiber, and 13% less fat than their colleagues ate in the comparison group, based on 24-hour telephone surveys. Investigators measured plasma carotenoid levels and confirmed the sustained change in dietary intake. In 7.3 years, 16.7% of the women in the intervention group developed an invasive breast cancer event, vs 16.9% in the comparison group. Similarly 10.1% of the women in the intervention group died, vs 10.3% in the comparison group. These numbers did not reach statistical significance at any point.

COMMENTARY

Finding any lifestyle elements which can improve outcomes of breast cancer is a worthy endeavor. Intuitively, it seems that healthy eating can and should improve outcomes of cancer survivorship. There are an estimated 2.4 million breast cancer survivors in the United States alone. Several published studies focused on breast cancer show mixed results. It does appear that a previous trial, the WINS trial, had marginally positive results that were based on lower levels of total energy intake and actual weight loss. Neither of those elements were present in this study. It can be noted that there was less success in the current study at achieving significant reduction in fat calories, and less weight loss in the groups of this trial.

As the authors point out, the WHEL study results are not intended to be applied to primary cancer prevention. Additionally, women who had undergone or were scheduled to undergo chemotherapy were not included, and there were relatively few minority women enrolled in the study.

In summary, although some dietary factors may ultimately prove to be important in reducing the risk for breast cancer recurrence, relatively small changes in vegetable, fruit, and fat intake alone did not make much difference. ■

CME Questions

17. The following statements regarding SSRIs and bone are true except:

a. Bone metabolism involves the neural system.
b. Serotonin is a functional regulator in bone.
c. The impact of SSRIs can be assessed by measuring bone density.
d. It is not known whether the adverse effect of SSRIs on bone can be prevented with estrogen or bisphosphonate treatment.

18. In the cross-over phase of the trial, 130 patients were observed for toxicities when receiving the alternative treatment. Which of the following gemcitabine-related non-hematologic toxicities remained significantly higher than PLD in this phase:

a. fatigue
b. constipation
c. nausea/vomiting
d. dyspnea

19. Which of the following is true regarding outcome of pregnancies delivering between 30 -34 weeks?

a. Even at 34 weeks there is more than a 1% risk of severe white matter injury.
b. There is about a 3 fold drop in perinatal infection during time period.
c. At 30 weeks there is about 40% risk of RDS.
d. Even if infants are born at 34 weeks, there is a 24% incidence of cognitive impairment.
e. None of the above is false.

20. Which of following is correct regarding dexamethasone in the study sited in this alert?

a. It is better than betamethasone is preventing RDS.
b. It is more expensive than betamethasone
c. It is better at preventing interventricular hemorrhage in neonates
d. It should be used weekly to be effective.

21. The following statements regarding breast cancer incidence are true except:

a. A decline in breast cancer incidence predated the decrease in the use of hormone therapy.
b. An additional decline in breast cancer incidence mirrored the decrease in use of hormone therapy.
c. The parallel decreases in breast cancer incidence and use of hormone therapy is a worldwide phenomenon.
d. Parallel changes do not prove etiologic relationships.

22. What factor has NOT been shown to reduce breast cancer recurrence rates?

a. reduced exposure to sex steroid hormones
b. lumpectomy and radiation
c. high-vegetable and fruit, low fat diet
d. chemotherapy

CME Objectives

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

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

Answers: 17 (c); 18 (a); 19 (e); 20 (c); 21 (c); 22 (c)

For access to your 2006 online bonus report, visit www.ahcpub.com

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, Travel Medicine Advisor.

Oral Anticoagulant + Antiplatelet Therapy = Danger

In this issue: *Adding an anticoagulant to aspirin is of no value in patients with peripheral artery disease, older adults with coronary disease benefit from aggressive statin therapy, simvastatin may reduce the risk of dementia and Parkinson's disease by as much as 50%, MiraLAX is safe for long-term use in patients with chronic constipation, the FDA greenlights Avandia, brings back Zelnorm for limited use, and recommends approving Evista for breast cancer prevention.*

Patients with peripheral artery disease are at high risk for cardiovascular complications. Antiplatelet drugs are routinely prescribed for these patients, but is adding an oral anticoagulant of value? No, according to a new study. In fact, the combination may be dangerous. More than 2,100 patients with PAD were randomly assigned to antiplatelet therapy with an oral anticoagulant or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes. The second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention or death from cardiovascular causes. After an average followup of 35 months, the first coprimary outcome occurred in 132 of 1080 patients receiving combination therapy (12.2%) and 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (RR 0.92; 95% CI, 0.73 to 1.16; $P = 0.48$). The second coprimary outcome occurred in 172 patients receiving combination therapy (15.9%) compared to 188 patients receiving antiplatelet therapy alone (17.4%) (RR 0.91; 95% CI, 0.74 to 1.12; $P = 0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared to 13 patients receiving antiplatelet therapy alone (1.2%) (RR 3.41; is 95% CI, 1.84 to 6.35; $P < 0.001$). The authors conclude that adding an oral anticoagulant to antiplatelet therapy in patients with PAD was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications, but was associated with an increase in life-threatening bleeding (*N Engl J Med* 2007; 357: 217-227). ■

High-Dose Statin Therapy, Value for Older Adults

Aggressive lipid lowering with high-dose statin therapy may be of value in older adults with stable coronary disease. The multicenter study from the United States included 3,809 patients 65 years or older with coronary artery disease and cholesterol levels less than 130 mg/dl who were randomized to receive atorvastatin 10 mg or 80 mg. Patients on low-dose atorvastatin achieved average cholesterol levels of 100 mg/dl versus 70 mg/dl for high dose therapy. The primary endpoint was occurrence of first major cardiovascular event such as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. Patients treated with high-dose atorvastatin were found have a 2.3% absolute risk reduction and a 19% relative risk reduction for the primary endpoint (hazard ratio 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Mortality rates were

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

lower for CHD, nonfatal non--procedure-related myocardial infarction, and stroke in the high-dose group. High-dose therapy was not associated with elevated creatine kinase levels. The authors conclude that treating older patients with coronary heart disease more aggressively to reduce low-density lipoprotein cholesterol levels provides additional clinical benefit (*Ann Int Med* 2007;147: 1-9). ■

Simvastatin, Best for Parkinson's Disease

Simvastatin, not atorvastatin or lovastatin, is associated with a dramatically reduced risk of dementia and Parkinson's disease (PD) according to a study from Boston University and VA database of 4.5 million individuals (95% men). In the observational study, over 700,000 subjects took simvastatin, nearly 54,000 took atorvastatin, and over 54,000 patients were prescribed lovastatin. Three models were used to evaluate the data, adjusting for covariates associated with dementia or Parkinson's disease. The first model was adjusted for age; the second model adjusted for 3 known risk factors for dementia: hypertension, cardiovascular disease, or diabetes; and the third model adjusted using the Charlson index, an index that provides broad assessment of chronic disease. Using the third model, the hazard ratio for dementia was 0.46 for simvastatin (CI 0.44-0.48, $P < 0.0001$) and 0.91 for atorvastatin (CI 0.80-1.02, $P = 0.11$). Lovastatin was not associated with a reduction in the incidence of dementia. The hazard ratio for newly acquired Parkinson's disease was 0.51 for simvastatin (CI 0.49-0.55, $P < 0.001$). There was no reduction in PD with atorvastatin or lovastatin. The degree of risk reduction utilizing the other models was similar with simvastatin. The authors conclude that simvastatin is associated with a strong reduction in the incidence of dementia and PD, while atorvastatin is associated with a modest reduction in incidence of dementia and Parkinson's disease that shows a trend toward significance (*BMC Med* published online July 19, 2007). The surprising finding suggests a difference between simvastatin and atorvastatin out of proportion to their cholesterol lowering effects, which the authors suggest may be due to the ability of simvastatin to cross the blood brain barrier more readily than other statins. ■

Polyethylene Glycol for Chronic Constipation

Long-term use of polyethylene glycol is safe and effective for chronic constipation according to the results of a new study from Alabama. More than 300 patients were randomized to receive polyethylene glycol 3350 (MiraLAX) in a single 17 g dose per day or placebo for 6 months. The primary endpoint of improvement of constipation on an objective scale was reached in 52% of the PEG patients and 11% placebo patients ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly patients. There were no significant adverse events other than diarrhea, flatulence and some nausea associated with PEG. The authors conclude that PEG laxative is safe and effective for use in patients with chronic constipation for up to 6 months (*Am J Gastroenterol* 2007;102:1436-1441). The study is particularly important because MiraLAX is now available over-the-counter and long-term use by patients with chronic constipation is likely. ■

FDA Actions

The FDA's Oncologic Drugs Advisory Committee, on a narrow vote, recommended approval of raloxifene (Evista) for the indication of breast cancer prevention in high risk women. The approval was based on data from the Study of Tamoxifen and Raloxifene (STAR) trial, which showed a reduction of 4 cases of breast cancer per 1,000 women (50% relative risk reduction), although it was not as effective as tamoxifen in preventing noninvasive breast cancers. Similar findings were seen in the Raloxifene for Use for The Heart (RUTH) trial although this trial revealed a higher risk of fatal stroke and blood clots with raloxifene. The FDA generally follows its advisory committee recommendations. Raloxifene is already approved for the prevention of osteoporosis.

The FDA has approved restricted use of tegaserod (Zelnorm) for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in women under the age of 55 who meet certain criteria. The drug was taken off the market earlier this year when it was linked with a higher risk of cardiovascular events including heart attack, stroke, and unstable angina. Patients must have no history of heart disease and must be in critical need of the drug. Prescribing will be under an investigational new drug protocol program that has been set up by the FDA.

Rosiglitazone (Avandia-GlaxoSmithKline) is associated with an increase risk of heart failure and myocardial infarction. Despite this, the FDA's Endocrinologic and Metabolic Drugs Advisory committee along with the Drug Safety and Risk Management Advisory Committee has advised that the drug stay on the market, albeit with increased warnings. Type 2 diabetes patients who are on insulin for those with heart disease are not the candidates for the drug. The FDA will render a final decision on the drug this fall. ■