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INSIDE

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Determining the Optimal Time to Deliver

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: *Neonatal mortality and morbidity are not inconsequential after late preterm birth (34-36 weeks) and, with the exception of macrosomia, infant morbidity increases with each week after 39 weeks of gestation.*

Source: McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with birth at term. *Obstet Gynecol* 2008;111:35-41.

THE STARS WERE ALIGNED WHEN FOUR PAPERS APPEARED IN TWO obstetrical journals within a month of each other dealing with the optimal time in gestation to deliver. Although I will initially be focusing on the index article by McIntire and Leveno, the others will be touched upon later.

McIntire and Leveno reviewed singleton records from Parkland Hospital in Dallas from 1988 through 2005. Since they were particularly interested in neonatal morbidity and mortality in the late preterm infant (34-36 weeks), they compared outcomes in this group with those born later in gestation. During this time the overall preterm birth rate was 9% at this hospital, but 75% of these were contributed by births between 34-36 weeks (representing 133,022 infants).

Looking at neonatal mortality per 1000, the authors found this to be 0.2 in those born at 39 weeks, compared with 1.1 at 34 weeks, 1.5 at 35 weeks, and 0.5 at 36 weeks. Morbidity was described as: respiratory distress syndrome (RDS) requiring mechanical ventilation, transient tachypnea of the newborn, grade 1 or 2 intraventricular

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hemorrhage, need for sepsis workup and/or positive cultures, intubation, or use of phototherapy for hyperbilirubinemia. One or more of these were present in 34% at 34 weeks, 24% at 35 weeks, and 17% at 36 weeks.

The authors concluded that being born at 34-36 weeks is not great for one's health and obviously can be expensive, but when one looks for nuggets in the data to help with prevention, one comes up empty. For example, 80% of the late preterm births resulted from "idiopathic" preterm labor. The remaining 20% were delivered because of "obstetrical complications."

This article, and another in the October issue of the *American Journal of Obstetrics and Gynecology* by Bastek et al,[1] points out that one should not be cavalier about a birth that is a week or two less than 36 weeks, but what about the risks to the neonate of birth at the very end of pregnancy? Another paper in the same issue of *American Journal of Obstetrics and Gynecology* by Cheng et al dealt with this question.[2] The authors sifted through data from the U.S. Vital Statistics Birth Certificate Registry for 2003, concentrating on deliveries occurring between 37-41 weeks. When comparing those born at 37 weeks vs 39 weeks, they found a two-fold greater need for mechanical ventilation and a 70% greater chance for low 5 minute Apgar scores at 37 weeks. Rates of macrosomia went up every week after 37 weeks and neonatal injury rose at 40 weeks. The cesarean section rate increased appreciably at 41 weeks, as well as the incidence of meconium aspiration. With the exception of macrosomia, all adverse outcomes were lowest at 39 weeks.

■ COMMENTARY

The above studies suggest that the further birth is away from 39 weeks (in either direction), the greater are the neonatal mortality and morbidity, but this information needs to be put into proper perspective. In the McIntire study, 80% of the late preterm births resulted from "idiopathic" labor or premature rupture of membranes. We now know from the comprehensive research in preterm labor in the perinatal division of the NICHD that 19% of patients in preterm labor with intact membranes and 34% of those with premature rupture of membranes have positive amniotic fluid cultures, and the earlier in pregnancy these events occur, the greater is the chance of intrauterine infection. It has also recently become clear from work by the same group that antibiotics might temporarily discourage uterine contractions in the face of intrauterine infection, but they provide no deterrent to the infection itself or to bacteria's detrimental effect on the fetal brain through cytokine elaboration. So, if we are thinking that aggressively attempting to stop all labors occurring between 34 and 36 weeks will remedy prematurity, in some cases we may be exchanging an infant with less need for mechanical ventilation for one who later develops cerebral palsy. Regarding steroids, no study has shown their efficacy in preventing the 34-36 week infant from getting RDS, but the prevalence of bona fide RDS is so low in this group of infants that one would need a huge randomized clinical trial to show any benefit.

Although recent evidence indicates that most tocolytics are ineffective or, in some cases, harmful, there is some suggestion that calcium channel blockers (nifedipine) may actually work. Then we should do everything possible to rule out infection before attempting to extend a 34-35 week pregnancy when preterm labor occurs. However, my gut feeling is that a good portion of the neonatal morbidity does not come from prematurity per se as much as from the reasons for their mothers having preterm labor.

One way to make sure that a fetus is not less mature than expected is to make every attempt to document dates early in pregnancy. The RADIUS study showed us that if we depended upon well-remembered last menstrual period (LMPs) alone, more than 1 out of 10 times we would be off by more than one week, as indicated by second trimester ultrasound examinations.[3] Since decisions regarding whether to stop labor, whether to induce labor, or even whether to do a cesarean section, can be

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Questions & Comments
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very dependent upon gestational age, unexpected prematurity should not be surprising in a pregnancy that is less than scrupulously dated.

At the end of pregnancy there has been a general trend toward earlier deliveries. A few years ago, there was an ongoing debate about empirically delivering all post-term patients (42 weeks or more) or managing them expectantly. However, recently it seems that the definition of "post-term" has evolved to include pregnancies that have extended past 40 menstrual weeks by one minute. Now, simply based on a statistical trend, the authors of the above paper showing optimal outcome at 39 weeks are suggesting greater use of "stripping membranes and induction" rather than even waiting for 40 weeks, the average time for labor to spontaneously ensue. Based on this mindset, it is no wonder that our cesarean section rate is now 30.5%, and, as Ken Leveno has pointed out in a companion commentary in *Obstetrics & Gynecology*, births at 40 weeks have declined by 29% and the average birthweight has dropped in the United States.[4]

Last, two studies from San Antonio and Canada have shown increased rates of the need for mechanical ventilation in neonates delivered by cesarean section at 36-39 weeks. One wonders how many of these infants were really as old as they were thought to be.

The point is that in every pregnancy dates should be confirmed as early as possible and, in the absence of evidence-based proof of benefit, interventions such as induction should be employed for more compelling reasons than "designer timing." On the other hand, in a patient with preterm labor, every attempt should be made to rule out an underlying cause that may have a detrimental long-term affect on the fetus if left in the uterus. ■

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Hyperinsulinemia a Risk Factor for Breast Cancer in Non-HT Users

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

Synopsis: *Higher insulin levels were associated with an increased risk of breast cancer in postmenopausal women who participated in the observational arm of the Women's Health Initiative, but the association held only for women who did not use hormone therapy.*

Source: Gunter MJ, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 2009;101:48-60.

THE ABOVE STUDY INVOLVED A DETAILED ANALYSIS OF data obtained in the observational arm of the Women's Health Initiative. As a rationale, the authors note that obesity is a well-established risk factor for breast cancer. While the customary explanation for this association has been that obesity raises estrogen levels, another candidate is insulin, which is a potent mitogen and is elevated by obesity. In this study, therefore, the investigators primarily sought to determine whether hyperinsulinemia was associated with breast cancer in postmenopausal women. To address this query, they conducted a prospective case-cohort study by drawing from a pool of 93,676 women in the observational arm of the Women's Health Initiative (WHI) and from the roughly 1800 women who developed incident breast cancer. The study group included 835 women without diabetes who developed incident breast cancer and 816 women who were randomly chosen using the same inclusion and exclusion criteria as the cases.

The investigators found that insulin levels more than estradiol levels were associated with the development of incident breast cancer, but only in women not using hormone therapy (HT) after menopause. Higher insulin levels were not associated with incident breast cancer in women using either unopposed estrogen therapy or estrogen + progestin therapy.

In non-users, fasting insulin levels were parsed into quartiles, with the highest quartile being women with fasting insulin levels ≥ 8.8 μIU/mL. A hazard ratio (HR) of 2.48 (confidence interval [CI], 1.38-4.47; $P < 0.001$) was reported for incident breast cancer when the top

quartile was compared to the bottom quartile. There was no association between fasting glucose levels and breast cancer in HT users and non-users. In non-users, a body mass index (BMI) ≥ 30 kg/m^2 (top quartile) was associated with a HR of 1.91 (CI, 1.11-3.27; $P = 0.02$). In non-users, an estradiol level in the top tertile was associated with a HR of 1.59 (CI, 1.00-2.55; $P = 0.04$). Thus, the investigators concluded that there was "a positive association between fasting insulin levels and the risk of postmenopausal breast cancer that was unaffected by adjustment for endogenous estradiol levels, supporting a mechanism that is independent of circulating estradiol." As for the lack of an association between insulin levels and breast cancer and between obesity and breast cancer in HT users, they note that insulin levels were significantly lower among HT users than non-users. Glucose and total and free IGF levels bore no consistent relationship with incident breast cancer in any group.

■ COMMENTARY

This is an important but dense study that is likely to receive a great deal of attention. The investigators state in the last line of the abstract that "hyperinsulinemia is an independent risk factor for breast cancer and may have a substantial role in explaining the obesity-breast cancer relationship." So far, none of the various media releases about this study have explained that this relationship was seen only in non-users of HT, so I wanted to be sure that this aspect of the study came to your attention.

The study raises an important question about trade-offs and about our model of carcinogenesis. If hormone use after menopause reduces the risk of hyperinsulinemia and diabetes, will it also reduce the risk of breast cancer by this mechanism? The present investigation did not directly addresses this. Another interesting report that indirectly addresses this point involved a population-based study done in Korea in which ~1.3 million men and women age 30-95 were followed for 10 years.[1] For persons with a diagnosis of diabetes or a fasting serum glucose ≥ 125 mg/dL, cancer incidence and mortality were generally elevated. However, as glucose levels rose, the impact was greater for men than for women; women did not show an elevated mortality until glucose ≥ 140 mg/dL as compared to ≥ 110 mg/dL for men. In women, age-adjusted mortality rate from breast cancer was increased only in those with diabetes but not hyperglycemia (HR = 2.23; CI, 1.49-3.33). Similarly, age-adjusted incidence of breast cancer was elevated only in women with diabetes but not for hyperglycemia (HR = 1.51; CI, 1.26-1.80). A BMI ≥ 23 kg/m^2 augmented the hazard ratio associated with increasing glucose levels.

Insulin might well be the hormone of interest for the 21st century. Obesity is on the rise, with nearly 25% of Americans currently qualifying for the label "obese" (BMI ≥ 30 kg/m^2). Obesity elicits hyperinsulinemia and a myriad of clinical sequelae, including gestational diabetes and polycystic ovary syndrome. Thus, the associations noted above are likely to have clinical significance and may serve to guide screening protocols for all, including postmenopausal women. Of course, prevention is the key and lifestyle measures are critical to prevention.

This study raises the question as to whether we should recommend postmenopausal hormone use to reduce the likelihood of hyperglycemia and hyperinsulinemia in aging women. Should we see postmenopausal hormone use as one of the strategies to maintain body composition and decrease the risk of diabetes and its clinical consequences in older women? The authors did not emphasize this point, but the WHI also showed that HT use reduced the risk of diabetes (HR = 0.79 [0.67-0.93]; $P = 0.004$ for the E+P arm; and HR = 0.88 [0.77-1.01]; $P = 0.07$ for the E alone arm).[2,3] The WHI also found that the low-fat diet intervention reduced the risk of diabetes, but only when the diet caused weight loss, leading the authors to opine that "weight loss, rather than macronutrient composition, may be the dominant predictor of reduced risk of diabetes." Only time will tell, but we may yet come full circle in our attitudes towards postmenopausal hormone therapy as our population and individual needs change and hyperinsulinemia becomes the specter that heralds accelerated aging and its concomitants such as cardiovascular disease and breast cancer. ■

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Ginkgo biloba for Dementia Prevention

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A randomized, double-blind trial found no difference comparing* Ginkgo biloba *with placebo in the incidence of dementia or Alzheimer's disease.*

Source: DeKosky ST, et al. *Ginkgo biloba* for prevention of dementia: A randomized controlled trial. *JAMA* 2008; 300:2253-2262.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED trial comparing *Ginkgo biloba* with placebo for the prevention of dementia enrolled 3069 elderly individuals (older than age 75) in 5 academic centers in the United States. The participants were randomized to bid doses of 120 mg ginkgo or placebo (45% female in the ginkgo group and 47% female in the placebo group). The ginkgo formulation and dosage were that used in many of the brands sold in the United States. The dementia rate steadily increased in both groups over a 7-year period of follow-up, accumulating 277 cases (17.9%) in the treatment group and 246 cases (16.1%) in the placebo group. The rate of dementia did not differ between the two groups, nor did the rate of Alzheimer's disease. There were no differences in adverse events or mortality rates. The authors concluded that ginkgo at a dose of 120 mg bid was ineffective for the prevention of dementia.

■ COMMENTARY

Ginkgo biloba is an extract prepared from the leaves of the *G. biloba* tree. It contains flavonoids and unique terpene lactones. *Ginkgo biloba* is a multi-million dollar herb sold in the United States for the preservation of memory. In vitro studies suggested that ginkgo had antioxidant (from the flavonoids) and anti-amyloid (from the lactones) effects. Indeed, the biologic studies provided a strong rationale for the use of ginkgo, but early clinical trials had mixed results. This American trial and one ongoing trial in Europe are the first to be adequately powered to evaluate the efficacy and safety of ginkgo.

The American trial robustly demonstrated that *Ginkgo biloba* in the tested and commonly used dose did not delay the onset of dementia. The concept of "delay" is important. A treatment that could delay the onset of dementia by 5 years would reduce the number of dementia cases by 50%. In fact, this clinical trial found a statistically significant increase in the risk for developing dementia with ginkgo treatment in the 25% of participants who had cardiovascular disease prior to enrollment (hazard ratio = 1.56; confidence interval, 1.14-2.15). However, the authors appropriately urge caution in interpreting this subgroup analysis. A Cochrane review in 2007 of 35 clinical trials with 4247 participants concluded that there was no convincing evidence that ginkgo treatment benefited individuals who already had dementia or cognitive impairment.[1]

This was a well-designed, strong study, with a high rate of follow-up and adherence to treatment (a real tribute to the motivation of this elderly population). This is mainly a true primary prevention trial in that the participants had normal cognition at baseline. Nevertheless, some of the participants must have had the early pathology of Alzheimer's, even though they were free of symptoms. But it should be noted, that there was no difference between the groups when participants with mild cognitive impairment before treatment were compared. The outcomes were adjudicated by a blinded expert committee. It is possible that some benefit might have emerged with longer treatment, but this is unlikely. Most importantly, the formulation and dose of the herb were standardized and comparable to what is being sold and used in the United States. Besides the lack of effect on dementia, the study detected no favorable effects on cardiovascular events. A warning was raised because of more hemorrhagic strokes in the treated group, but the numbers were very small (16 in the treated group and 8 in the placebo group).

Besides the negative results of this clinical trial, there are other lessons to be emphasized. First, "alternative" treatments that are not regulated must be subjected to the same rigorous studies as branded drugs. Second, it is striking that studies that are independently funded usually have negative results in contrast to alternative industry-funded studies. Third, preclinical studies that are encouraging do not always translate into true clinical efficacy.

I have often stated that "there is only one medicine." When alternative treatments yield beneficial results in well-designed clinical trials, then these treatments will be incorporated into our practices. When they fail to demonstrate efficacy and safety, as is often the case, it is appropriate to discourage their use, and ultimately, this will be the future of alternative medicine. ■

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Teenagers, Bone Loss, and Long-term Depot Medroxyprogesterone Acetate Use (24 Months)

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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

Synopsis: *Although bone loss does occur in adolescent depot medroxyprogesterone acetate (DMPA) users, this loss slows after one year and even with continued use, bone density appears to be maintained in the normal range.*

Source: Cromer BA, et al. Bone mineral density in adolescent females using injectable or oral contraceptives: A 24-month prospective study. *Fertil Steril* 2008;90: 2060-2067.

CROMER ET AL PERFORMED A 24-MONTH OBSERVATIONAL, prospective cohort study of adolescents in the Midwest using depot medroxyprogesterone acetate (DMPA), oral contraceptives (OCs), or nothing. DEXA scans were performed at baseline and 6-month intervals. Over 24 months, DMPA users lost a small percentage of bone mineral density (spine = -1.5%, femoral neck = -5.2%), whereas OC users and the control group gained (OC: spine = +4.2%, femoral neck = +3%; control: spine = +6.3%, femoral neck = +3.8%). The majority of the bone loss in the DMPA group occurred in the first 12 months of use (1.4%) and then slowed to (0.1%) with continued use over the next 12 months. Even with loss of bone mineral density in the DMPA group, values remained in the normal range and no participant met the criteria for osteopenia.

■ COMMENTARY

Depot medroxyprogesterone acetate or DMPA (150 mg intramuscularly every 12 weeks) is a highly effective, reversible, long-acting contraceptive method that requires minimal effort for the user to be compliant. In addition, its invisibility (injectable delivery system with no necessary home-based paraphernalia) offers privacy to the user — a very important quality in a contraceptive method for many teens. Other advantages of DMPA include many noncontraceptive benefits (reduction of menstrual symptoms such as excessive bleeding and dysmenorrhea, and improvement of anemia) and, as a progestin-only method, it can be used safely in women with contraindications to estrogen.[1,2]

Unfortunately, in November 2004, the FDA issued a black box warning for DMPA, which unnecessarily scared many providers and users away from this very reliable and useful method. This warning stated that prolonged use of DMPA may result in significant loss of bone mineral density, the loss is proportional to the amount of time on DMPA, and the bone mineral density decrease may not be completely reversible. The warning went on to state that women should use DMPA for more than 2 years only if other contraceptive methods are "inadequate."[3]

We fully acknowledge that DMPA affects bone mineral density, but the warning overstated many of the concerns, did not specifically address unique populations like adolescents, and did not offer any practical clinical advice on how to manage patients. In addition, the FDA did not address the limitations of DEXA scanning in premenopausal women (DEXA scanning can document changes in bone mineral density but this has no relationship to fracture risk).

In reviewing research regarding DMPA use in teens, it is reassuring to note that the recovery of bone density after DMPA use appears to be no different than bone density recovery following breastfeeding.[4,5]

I found the recent publication by Cromer et al reassuring as well.[1] The original FDA warning stated that the bone loss was proportional to the amount of time on DMPA; however, Cromer et al found that the effect on bone loss significantly slowed during a second year of use. It is still unknown if DMPA use in teens affects peak bone mass, but this needs to be offset by the risk for pregnancy and pregnancy's effect not only on bone but also a teen's overall future. Even taking a study population where contraceptive compliance is often higher, Cromer et al had a 15% pregnancy rate in their OC users and none in their DMPA users.

For a more balanced, evidence-based clinical approach to DMPA use in teens, you can go to the World Health Organization's statement on DMPA use at www.who.int/reproductive-health/family_planning/bone_health.html.[6] ■

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Bazedoxifene Prevents Fractures

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Bazedoxifene treatment reduces fractures in postmenopausal women with osteoporosis.*

Source: Silverman SL, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: Results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 2008;23:1923-1934.

A 3-YEAR RANDOMIZED, DOUBLE-BLIND CLINICAL trial in 206 sites throughout the world compared bazedoxifene (20 mg or 40 mg) and raloxifene (60 mg) with placebo. A total of 7492 postmenopausal women, age 55-85, with established osteoporosis were enrolled in the study, and about 1200 completed treatment in each group. The results are provided in the Table *(above, right)*.

Table
Incidence of new vertebral fractures after 3 years

Treatment	Rate
Bazedoxifene (20 mg/d)	2.3%
Bazedoxifene (40 mg/d)	2.5%
Raloxifene	2.3%
Placebo	4.1%

The approximately 40% reduction in new vertebral fractures compared with placebo was statistically significant. In a subgroup of women at higher risk for fractures, bazedoxifene had a reduced risk of nonvertebral fractures (50% reduction with 20 mg), compared with both raloxifene and placebo. The only adverse event that differed with treatment was an increase in venous thrombosis with treatment compared with placebo (13, 12, and 10 cases with 20 mg bazedoxifene, 40 mg bazedoxifene, and raloxifene, respectively; 5 cases with placebo).

■ COMMENTARY

Bazedoxifene belongs to the selective estrogen receptor modulator (SERM) family of drugs. It has favorable effects on bone and lipids, but does not affect the endometrium or the breast. The results of this trial indicate that the effect of bazedoxifene on bone should be comparable to that of estrogen and bisphosphonates.

The reduction of nonvertebral fractures with bazedoxifene compared with raloxifene should not be ignored. We have known for some time that even with 8 years of follow-up, raloxifene has no impact on the risk of hip fractures. This is presumably because raloxifene is less potent, and thus the hip, with a mixture of cortical and trabecular bone, is more resistant to raloxifene's effects compared with the spinal column that is composed of sensitive, trabecular bone. In this clinical trial, this difference was also observed in the bone mineral density responses at the hip; bazedoxifene was significantly better.

There were fewer cases of breast cancer and benign breast disease in the bazedoxifene groups, but the numbers were too small to give any confidence to this conclusion.

Wyeth has partnered bazedoxifene with estrogen, and called it TSEC (tissue-selective estrogen complex). The idea is to gain the benefits of estrogen (bazedoxifene has little impact on hot flushes), protect the endometrium and possibly the breast, and enhance some actions of estrogen, such as a reduction in fractures. This approach to postmenopausal hormone therapy would eliminate

the need for progestational agents. Phase III trials are complete with this combination, and FDA approval is pending. ■

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.

CME Questions

43. Which of the following does *not* fit regarding morbidity at the end of pregnancy?
a. Meconium aspiration increases after 40 weeks.
b. Neonatal injury increases at 40 weeks.
c. Macrosomia levels off at 40 weeks.
d. Cesarean section rate increases dramatically after 41 weeks.

44. According to results from the RADIUS trial, as many as 30% of patients are off on dates when using LMP as the sole source of information regarding gestational age.
a. True
b. False

45. Which of the following statements is appropriate regarding preterm labor and its causes?
a. Most patients in preterm labor have a smoldering intrauterine infection.
b. Most tocolytics are effective in preventing preterm birth.
c. About 35% of patients with preterm PROM will have a positive amniotic fluid culture.
d. There is now some information to suggest steroids may work to decrease RDS in late preterm deliveries (34-36 weeks).

46. In women who did not use hormones postmenopausally, an increase in which of the following factors was most associated with the risk of breast cancer?
a. Estradiol
b. Body mass index
c. IGF-I
d. Insulin
e. Glucose

47. The following statements regarding *Ginkgo biloba* are true *except*:
a. Ginkgo extract is available, but unregulated, in the United States.
b. Ginkgo has favorable effects on the lipid profile.
c. Ginkgo improves Alzheimer's disease.
d. Ginkgo does not prevent Alzheimer's disease.

48. The bone loss that occurs with DMPA use in teens is directly proportional to the amount of time that DMPA is being used.
a. True
b. False

49. The following statements are true regarding bazedoxifene *except*:
a. Bazedoxifene is more effective at the hip and spine compared with raloxifene.
b. A small risk of venous thrombosis appears to be associated with bazedoxifene.
c. Bazedoxifene does not stimulate the endometrium.
d. Bazedoxifene does not stimulate breast tissue.

Answers: 43. (c), 44. (b), 45. (c), 46. (d), 47. (c), 48. (b), 49. (a).

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*.

How Best to Control Hypertension?

In this issue: Drug combinations for hypertension; tenecteplase for out-of-hospital cardiac arrest; CAM most commonly used for back, neck, and arthritis pain; FDA Actions.

Combination therapy for hypertension

What's the best drug combination with an ACE inhibitor for treatment of hypertension in patients at risk for cardiovascular disease? Current guidelines recommend a diuretic, as witnessed by the number of ACE inhibitor/diuretic combination products that are currently marketed. However, a new study suggests that the calcium channel antagonist may be a better selection than a diuretic. Researchers from several medical schools in the United States and Sweden randomized 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The average patient was 68 years old at entry and the group included patients with a history of ischemic heart disease, peripheral vascular disease, stroke, LVH, and diabetes. The study was terminated early after 3 years when it was found that the benazepril/amlodipine group had a significantly lower risk of the primary endpoint: 9.6% vs 11.8% (hazard ratio 0.80; 95% confidence interval, 0.72-0.92; $P = 0.002$). This represents a 2.2% absolute risk reduction and a 19.6% relative risk reduction in the benazepril/amlodipine group vs benazepril/hydrochlorothiazide. The authors conclude that the combination of benazepril/amlodipine is superior to benazepril/hydrochlorothiazide in reducing cardiovascular events in patients with hypertension who are at risk (Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. *N Engl J Med* 2008;359:2417-2428). An accompanying editorial from the chair of the seventh report of the Joint National Committee on hypertension suggests it is time to re-examine the recommendation of initial therapy with a thiazide-type diuretic. He also states, however, that regardless of the drugs chosen for treatment of hypertension, the most important factor is reducing blood pressure to goal levels (Chobanian AV. Does it matter how hypertension is controlled? *N Engl J Med* 2008;359:2485-2488).

A survival benefit with tenecteplase?

Thrombolytic therapy during out-of-hospital cardiac arrest does not improve outcomes according to a new study. There has been considerable interest in thrombolytic therapy during cardiopulmonary resuscitation since it has been shown that 70% of these arrests are due to acute myocardial infarction or pulmonary embolism. European researchers randomized 1050 patients with witnessed out-of-hospital cardiac arrest to tenecteplase or placebo during cardiopulmonary

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resuscitation. The primary endpoint was 30-day survival and the secondary endpoints were hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, and neurologic outcomes. The trial was discontinued early when it was found that there was no survival benefit with tenecteplase. Thirty-day survival was 14.7% with tenecteplase and 17% with placebo. Secondary outcomes similarly showed no benefit from tenecteplase. The authors conclude that when tenecteplase was used during advanced life support for out-of-hospital cardiac arrest there was no improvement in outcomes in comparison to placebo (Bottiger BW, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 2008;359:2651-2662).

CDC report on CAM use

There is a 40% chance that your patients are using complementary and alternative remedies according to new report from the Centers for Disease Control & Prevention. Not including vitamins and minerals, the use of a complementary and alternatives medicine (CAM) in adults and children has increased in the last 5 years. Treatments include non-vitamin, non-mineral natural products (fish oil, flaxseed oil, echinacea), chiropractic or osteopathic manipulation, deep breathing exercises, massage, and meditation. Children are also using alternative treatments, especially if their parents use them. Despite lack of evidence of efficacy, echinacea is the most common remedy used by children. In adults, use of CAM treatments for URIs is actually down, perhaps indicating better patient education. Back pain, neck pain, and arthritis pain are the most common reasons why people turn to CAM, according to this recent survey. These results point out the need to query patients about the use of complementary and alternative medicines.

FDA Actions

The FDA is requiring a boxed warning on sodium phosphate bowel-cleansing products because of the risk of acute phosphate nephropathy associated with use of these products. Sodium phosphate cleansing products are most commonly used as bowel preparation for procedures such as colonoscopy. According to the warning, the products Visicol® and OsmoPrep® should be used with caution in people older than age 55; those suffering from dehydration, kidney disease, colitis, or delayed bowel emptying; and people taking other medications that may affect kidney function. These products should also not be used in conjunction with other oral laxatives containing sodium phosphate, and over-the-counter products, such as Fleet® Phospho-Soda®, should also be used with caution if given in a high dose to the patient population at risk.

The FDA is requiring a warning on all anti-epileptic drugs regarding the risk of suicidal thoughts and behavior. The warning is based on review of nearly 200 studies that showed that patients on anti-epileptic drugs were at almost twice the risk of suicidal behavior or thoughts compared to patients on placebo. Along with the warning, the agency is also requiring a Medication Guide for patients as part of its Risk Evaluation and Mitigation Strategy. Over 20 drugs will be required to change their labeling including the commonly used agents phenytoin, carbamazepine, divalproex, gabapentin, lamotrigine, primidone, and topiramate.

The FDA is considering a ban on the long-acting beta agonists salmeterol (Serevent®) and formoterol (Foradil®) for the treatment of asthma. An expert committee comprised of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee voted unanimously to withdraw the indication for the treatment of asthma for the two drugs based on evidence from meta-analyses showing increased risk of death associated with use of long-acting beta agonist when not paired with a steroid inhaler. The committee did not vote to ban Advair® or Symbicort®, inhalers that combine a long-acting beta agonist with a steroid. If the FDA follows the subcommittee's recommendations, the drugs would no longer be indicated for treatment of asthma but would remain on the market to treat chronic obstructive pulmonary disorders. The FDA has not indicated when it will act on the subcommittee's recommendations.

The FDA has approved fenofibric acid (Trilipix™) for use with a statin for the treatment of dyslipidemia. This is the first fibrate approved for use with statins. The approval is based on a large trial in which the drug was used in combination with rosuvastatin (Crestor®), atorvastatin (Lipitor®), and simvastatin (Zocor®). There have been safety concerns about using fibrates and statins together, particularly gemfibrozil, but the newer generation fibrates appear safer. Abbott, the manufacturer of Trilipix, is collaborating with AstraZeneca to develop a fenofibric acid/rosuvastatin fixed combination product within the next year. ■