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INSIDE

Trends in Surgery and Chemotherapy for Women Diagnosed with Ovarian Cancer in the United States

ABSTRACT & COMMENTARY

Synopsis: *Despite guidelines presented by several organizations, significant numbers of women with ovarian cancer are not being provided with appropriate care.*

Source: Harlan LC, et al. *J Clin Oncol*. 2003;21:3488-3494.

HARLAN AND COLLEAGUES SAMPLED PATIENT CASES FROM within the Surveillance, Epidemiology, and End Results (SEER) program to examine trends in care of women with ovarian cancer. They abstracted medical records of 601 patients with ovarian cancer diagnosed in 1991 and 566 women with ovarian cancer diagnosed in 1996 to compare findings. In addition, they verified treatment data with the attending physicians. Across these 2 time periods, the percentage of women with presumptive stage I, II, and IV disease who received lymph node dissection increased. However, a significant number still were not precisely staged. More than 65% of women with ovarian cancer were given cyclophosphamide in 1991 compared with about 14% in 1996. Paclitaxel use increased from 1% to 62% during that time. After adjusting for age, race or ethnicity, registry, income, insurance status, Charlson score, residency training program, and marital status, women with early stage disease were significantly more often given National Institutes of Health Consensus Development Conference guideline therapy in 1996 than in 1991. However, for women with stage III and IV disease, the use of guideline therapy did not significantly increase. Older women and minorities consistently received less guideline therapy, and lack of private insurance was an impediment for both Hispanic and non-Hispanic black women.

Harlan et al concluded that, despite guidelines presented by several organizations, significant numbers of women with ovarian cancer are not being provided with appropriate care. This was particularly true for older and minority women, especially those without private

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insurance. They recommended that educational strategies be devised to increase the number of women receiving guideline therapy and decrease disparities across population groups.

COMMENT BY DAVID M. GERSHENSON, MD

Ovarian cancer remains the most challenging of the gynecologic malignancies, with the highest death rate. Patients treated in a hospital with a residency program were more likely to having appropriate treatment compared with patients treated in a hospital without a residency program. For stage I and II patients, this was principally related to have lymph node sampling as part of surgical staging. Furthermore, non-Hispanic white women were more likely to receive appropriate therapy than non-Hispanic black women. In a multivariate analysis, women treated for apparent stage I and II disease received appropriate therapy significantly more often in 1996 than in 1991. For women with stage III and IV disease, approximately 40% did not receive appropriate therapy. This latter observation was essentially unchanged from 1991 to 1996. Age did, however, influence treatment. For women with advanced-stage disease, only 53% of women 65 years and older received guideline therapy compared with 73% of women younger than 65 years of age. The lack of private insurance also negatively influenced a woman's ability to receive guideline therapy. These findings are encouraging, in that some progress occurred in the period between 1991 and 1996. But it is not enough. American women in general are not receiving the level of excellence in ovarian cancer care that they deserve, and the elderly, minorities, and those without private insurance are being shortchanged the most. Oncologists and advocacy groups cannot relax their resolve to continue the fight for state-of-the-art care for all women with ovarian cancer.

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Have You Heard About Equol?

ABSTRACT & COMMENTARY

Synopsis: *People are either equol producers or non-equol producers, and the clinical benefits of soy isoflavones may be limited to equol producers.*

Source: Setchell KR, et al. *J Nutr*. 2003;133: 1027-1035.

Setchell and colleagues from the University of Cincinnati College of Medicine studied the pharmacokinetics of isoflavones in 10 healthy women; half were postmenopausal. The women were administered increasing oral doses of soy nuts in single boluses that provided known amounts of daidzein and genistein (from 16 mg to 66 mg of isoflavones—equivalent to the amounts ingested by individuals who use soy regularly). The pharmacokinetics of daidzein and genistein were similar in premenopausal and postmenopausal women. Peak blood levels were attained after 4-8 hours, indicating that absorption occurs throughout the small intestine. With increasing doses, the levels of daidzein and genistein declined, indicating the activation of metabolic pathways or reduced absorption. Because of the pharmacokinetics (for example, the half-life of the isoflavones), Setchell et al concluded that reduced absorption occurred with increasing doses. Most of the ingested isoflavone that was excreted appeared in the urine within 2 days. However, a significant portion, an average of 50% for daidzein and 84% for genistein, in amounts that

increased with increasing does, was not recovered, due to metabolic degradation in the intestine. The metabolite equol was identified in only 3 of the 10 women, being consistently present in the blood and urine in the same individuals and appearing relatively late consistent with an origin in the colon. Setchell et al concluded that optimal blood levels of isoflavones would be best obtained from modest intakes of soy found consumed throughout the day, rather than from a single intake of a high dose.

COMMENT BY LEON SPEROFF, MD

Although the number of subjects in this study was not large, the results provide some interesting clinical insights. For example, because the bioavailability of the isoflavones decreases with the ingestion of increasing doses, the practice of ingesting large doses, especially single doses, is not advisable.

"Phytoestrogens" is a descriptive term applied to nonsteroidal compounds that have estrogenic activity or are metabolized into compounds with estrogen activity. Phytoestrogens are classified into 3 groups: isoflavones, lignans, and coumestans. They are present in about 300 plants, especially legumes, and bind to the estrogen receptor. Soybeans, a rich source of phytoestrogens, contain isoflavones, the most common form of phytoestrogens, mainly genistein and daidzein, and a little glycitin.

Isoflavones exist in plants bound as glycoside conjugates called glycones. The carbohydrate component requires gut bacteria to remove the sugar moiety to produce active compounds, the aglycones. Intestinal metabolism is essential for the bioactivity of the isoflavones because the conjugated forms are not absorbed. After hydrolysis of the isoflavone glycoside conjugates, the isoflavones are further metabolized by bacterial reactions in the colon. Individual variability in gastrointestinal microflora, as well as absorption, influences the bioavailability of isoflavones. The results of this study are consistent with this very important characteristic: There are marked individual differences in intestinal absorption and metabolism.

The average Japanese intake of isoflavones is about 50 mg per day.[1] The rest of Asia has an average consumption of about 25-45 mg per day, and Western consumption is less than 5 mg per day.[2,3] Most of the studies in the literature have used relatively large intakes of soy isoflavones, much greater than the average intake in Asia.

Equol was first isolated and its structure determined in 1932. It is one of the estrogenic compounds in pregnant mare's urine, hence its name. It is now apparent that it is derived from plant intake.[4] Equol is a bacterial metabolite of daidzein (not genistein), and it is believed to be the only hormonally active metabolite. Genistein has a high binding affinity for the beta estrogen receptor and daidzein considerably less so. Equol binds to the alpha and beta estrogen receptors in a fashion similar to genistein (greater affinity for beta). At least in vitro, equol stimulated gene transcription with both estrogen receptors and greater potency than any other isoflavone.[5]

Bochanin and formononetin are methylated precursors that are metabolized to genistein and daidzein. Red clover and lentils contain significant amounts of these precursors that are converted to the isoflavones by ruminal bacteria, and then to the estrogenic equol. Because equol is estrogenic, its high intake was responsible for disruption of reproduction in sheep (but not in cattle), a problem known as "Clover disease." A similar daily intake in humans would have to amount to more than 1000 liters of soy milk, 8600 soy burgers, or 360 kilograms of tofu.[4]

Equol formation is totally dependent on intestinal microflora; therefore, strictly speaking, it is not a phytoestrogen. To be accurate, equol is a nonsteroidal estrogen, a member of the isoflavone family, and exclusively a metabolic product of intestinal bacteria. When given as a single bolus, equol reaches peak blood levels after 4-6 hours, and disappears with a half-life of about 9 hours.[4] Thus its pharmacokinetics are similar to daidzein and genistein. Antibiotics that reduce the intestinal flora will cause a decrease in equol production.

The most important observation regarding equol is that 30-50% of adults do not produce equol, even when challenged with high doses of soy.[4] This is a contrast to nonhuman primates and other animals; all that have been studied produce high levels of equol. Thus, there are 2 human populations: equol producers and nonequol producers. The equol-producing status of individuals can be determined by measuring the plasma equol concentration (equol producers have concentrations greater than 20 µg/L). Unfortunately, equol measurement requires mass spectrometry. Dietary studies have determined that equol producers consume less fat and more carbohydrates and fiber. This suggests that the nature of the dietary intake influences the characteristics of the intestinal bacterial population. However, the administration of large amounts of dietary fiber did not change urinary equol excretion.[6] Furthermore, equol producers are always equol producers, suggesting that dietary intake is not the most critical factor. The key question is whether equol producers receive greater clinical effects from phytoestrogens than nonequol producers.

Clinical Effects

Thus far the clinical effects of isoflavones on hot flushing and bone have not been impressive. The study of hot flushing requires randomization to placebo treatment because placebo treatment is associated with an average 51% reduction in hot flush frequency. An Italian study found a 45% reduction in flushing with 60 g of isolated soy protein daily (76 mg isoflavones), compared with a 30% reduction in the placebo group.[7] Two other studies, both with 50 mg/day of isoflavones, found a similar 15% reduction in the number of flushes compared with placebo.[8,9] Another placebo-controlled short-term trial found a greater reduction in flushes with 70 mg isoflavones daily.[10] In a randomized, crossover study of a high dose of isoflavones, 150 mg/day, for flushes in breast cancer survivors, the treated group and the placebo group demonstrated equal effects.[11] The dose was 150 mg isoflavones per day, similar to 3 glasses of soymilk daily.

An Australian study randomized women to 118 mg/day isoflavones or placebo and could detect no difference after 3 months in hot flushing, libido, vaginal dryness, or any of a long list of symptoms.[12] In a randomized study in Iowa, no differences were found in hot flush frequency comparing isoflavone-rich soy protein to a whey protein control.[13] And finally, another randomized trial of breast cancer survivors found no difference comparing placebo with 90 mg isoflavones daily.[14] Overall, the effects have been either similar to placebo treatment or there has been a small beneficial reduction that would have little clinical effect. Phytoestrogens are effective in preventing bone loss in rats but not in monkeys.[15] In women, studies have demonstrated at best a slight effect on spinal bone, but no effect on hip bone.[16-18]

In view of the apparent importance of equol, all previous studies assessing the effect of isoflavones must be reassessed. In a 2-year randomized trial of postmenopausal women, isoflavone-rich soy milk increased spinal bone mass in the 45% of the subjects who were equol producers, with essentially no effect in nonequol producers.[19] More profound beneficial effects on the lipid profile have been reported in equol-producing women.[4] And in a case-control study, women with a high excretion of equol had a reduced risk of breast cancer.[20]

The population destined to receive a benefit from soy intake may be limited to equol producers. Studies need to be repeated measuring the responses in individuals who are identified as equol producers or nonequol producers. If the population destined to receive a benefit from soy intake is limited to equol producers, a convenient, inexpensive method must be developed to identify equol production. In addition, methods need to be developed to convert nonproducers to producers. ■

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Reducing Blood Loss and Time in Vaginal Hysterectomy

ABSTRACT & COMMENTARY

Synopsis: *An electrosurgical bipolar vessel sealer reduces the operating time and blood loss in a series of vaginal hysterectomies.*

Source: Levy B, Emery L. *Obstet Gynecol*. 2003;102: 147-151.

In a single surgeon's practice, 60 patients scheduled for vaginal hysterectomy were randomly assigned to 1 of 2 operative techniques for hemostasis: sutures or electrosurgical bipolar vessel sealer. The vessel sealer technique resulted in statistically shorter operative time (39 vs 54 minutes) and less blood loss (69 mL

vs 127 mL). Complication rates and hospital lengths of stay were similar. Since the same surgical technique was used by a single surgeon for all cases, it appears that the use of the electrosurgical bipolar vessel sealer is an effective option to sutures, resulting in less time in the operating room and less blood loss.

COMMENT BY FRANK W. LING, MD

This certainly looks good, doesn't it? A simple, well-designed study that could change the way we do vaginal hysterectomy. We are being told about a surgical technique that reduces blood loss as well as time spent in the operating room. Sounds like a "no brainer," right? The new instrument can seal vessels and vascular bundles up to 7 mm in diameter. It delivers both mechanical and electrosurgical energy. The entire cycle of sealing and subsequent cooling takes about 5 seconds. It's basically a standard Heaney-type clamp modified with a bipolar electrode so that it clamps, seals, and cuts. It was used on the cardinal, uterine vessel, and upper pedicles. The study has many things going in its favor.

First, it's randomized. That definitely speaks in favor of the study results, since so many surgical papers do not randomize patients. They even did a power analysis. That is extremely unusual in a surgical paper. Because it was a single surgeon doing the cases, technique is as standardized as it could be. Another good aspect of study design was that blood loss was estimated by the anesthesia personnel to avoid surgeon bias. Not so fast, though! What is blunting my enthusiasm for this technology?

Even though we'd love to embrace new modalities that help the patient, we should do so cautiously. For example, one must first look at the financial disclosure statement: Dr. Emery works for the manufacturer and Dr. Levy is a member of its advisory group and gives educational talks for the company. Remember also that even though it was randomized, the surgeon had to know what technique for hemostasis was being used. As a result, one must wonder whether the surgeon performed with equal efficiency in all cases and whether the reduction of surgical time was attributable to the instrument only. In fact, Levy and Emery readily admit that the surgical time saving had no clinical significance because 78% of patients were done as outpatients anyway, and the rate of hospitalization was not greater with one technique or the other.

If the savings in the operating time wasn't clinically significant, wasn't the blood loss clinically significant? Again, one must look carefully at a couple of aspects. First, the accuracy must be evaluated. Even though it was done by anesthesia personnel, were they blinded as to the overall study design and the specific hemostatic technique in each case? Doubtful on both, so bias could have been introduced into the estimated blood loss. Even more relevant: Does the loss of an additional 60 mL of blood make a difference? You be the judge. So if the accuracy and clinical importance of blood loss are both in question, how significant is the study and its results? Why is it even being presented?

The good news related to a study such as this is that gynecologic surgery technique is not standing still. New instruments are being developed and people are trying to study them in a scientifically sound method. Are there flaws here? Sure there are, but that doesn't mean that the overall message should be lost. The technique can potentially allow vaginal surgeons who wish to find a slight advantage to do so. Maybe more vaginal cases can be done, with less morbidity. Certainly, the individual surgeon must decide for himself/herself. As practitioners, however, we should always be looking for techniques and devices that really do help us take better care of our patients.

Is this instrument one of those great leaps forward? You be the judge.

Fetal Myelomeningocele Repair: Short-Term Clinical Outcomes

ABSTRACT & COMMENTARY

Synopsis: *Early experience with fetal MMC repair suggests a decreased need for ventriculoperitoneal shunting, arrest, or slowing of progressive ventriculomegaly, and consistent resolution of hindbrain herniation. However, further long-term follow-up is needed to evaluate neurodevelopment and bladder and bowel function.*

Source: Johnson MP, et al. *Am J Obstet Gynecol*. 2003;189:482-487.

The team at Children's Hospital of Philadelphia has been involved in various in utero fetal surgical ventures. In the August issue of the *American Journal of Obstetrics and Gynecology* they have reported their experience with open repair of fetal neural tube defects. They selected for analysis 50 fetuses operated upon between 20 and 25 weeks who had defects that started at S1 or higher and had no ultrasound signs of lower limb dysfunction. These fetuses were compared with historical control fetuses with similar lesions who were not operated upon in utero.

They found that all the repaired fetuses had reversal of their hindbrain herniation, and, as an indirect result, only 48% required ventriculo-peritoneal shunts after birth, compared with 85% of historical controls. They also found that in 57% of cases the infants had better motor function than would be predicted by the anatomic level of the defect—this was not compared against historical controls.

COMMENT BY JOHN C. HOBBINS, MD

Recently I had a patient, referred for an ultrasound evaluation because of an elevated MSAFP, who said, "I want you to look for any cause for this elevation other than a spinal defect. This I am not worried about because I know it can be fixed." I recently saw an article in a popular magazine extolling the virtues of in utero spinal surgery. One mother being interviewed, after elevating the surgeons to deity-like status, indicated that her child was now "fine."

Based on all the experience to date there is no indication that this infant is "fine," but these examples show the status that these ventures have achieved in the lay press and in the public. The above paper does show some potential benefit from early repair in fetuses with lesions above S2. However, the results need to be evaluated objectively. It seems very reasonable to try to reverse or ameliorate the hindbrain herniation, but the reduction in the initial need for shunting may simply result in postponement of the shunt until later, but at some expense. For example, the average time of delivery was 34 weeks, and 3 neonatal deaths occurred as a result of preterm birth. Twenty-two percent had premature rupture of the membranes at an average of 31 weeks requiring hospitalization thereafter. The average time of delivery in those with premature rupture of the membranes was 32 weeks. Although the incidence of oligohydramnios was modest in this study (6%), other studies report a 48% incidence of this finding post-surgery, and all patients require a "hysterotomy" for delivery.[1] Cases are springing up of ruptured uteri secondary to the procedure.

Regarding neurological outcome, another group has not reported benefit in neurological function, and in 16% of the infants in the above study the neurological outcome was worse than expected from the anatomic level of the defect.

Actually, many variables get put into play when considering neurological outcome. For example, a study years ago by Luthy et al in the *New England Journal of Medicine* showed that neurological outcome in infants with neural tube defects (with regard to anatomic level) was better when cesarean sections were performed before labor ensued than when patients had their sections after labor.[2] In fact, there was little difference between infants in the latter category and those born vaginally, suggesting that uterine contractions may have had a deleterious effect on neurological outcome. Although the patients in this and other studies had cesarean sections because of the potential for rupture, it was difficult to control for preterm contractions and for early labor (remember the average delivery time was 34 weeks).

The good news is that there is definitely a theoretical advantage to surgical repair and, in fact, the earlier the better. During the procedure the spinal cord, which is stuck to the placode at the superior portion of the defect, is freed up, allowing it to move freely in the canal instead of being tethered. Also, cerebral spinal fluid loss is stopped by closing off the channel into the amniotic cavity. This is why fluid appears to find its way back into the foramen magnum and cisterna magna post-repair. For this reason, and because of the suggestion of reversal of the Arnold Chiari abnormality as noted in the above study, there has been reason enough to initiate a randomized clinical trial supported by the NIH. This is the only way to really test the concept. Historical controls simply will not "cut it," since there are so many "apple and orange" issues to deal with.

In the meantime, appealing to a very vulnerable group of patients in magazines and on the Internet without proper referral should not be condoned. ■

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Special Feature

A (Not Really So) Rare Cause of a Common Presentation

By Sarah L. Berga, MD

Menstrual irregularities are arguably the mainstay of gynecologic office practice. The differential diagnosis for this common presentation is quite extensive, but a common cause is reduced central hypothalamic GnRH drive due to "lifestyle issues." This cause is easy to recognize clinically when there is a dramatic loss of weight or the patient tells you that she has been training for a marathon. Weight loss and excess

energy expenditure represent forms of metabolic imbalance, and it is now well established that metabolic and nutritional signals modulate the hypothalamic GnRH pulse generator. Depending on the degree of metabolic imbalance and compounding psychogenic factors, the reduction in GnRH may be partial or complete and continuous or intermittent. Menstrual patterns range from luteal insufficiency with preservation of menstrual interval, to prolonged folliculogenesis with a long menstrual interval, or a short menstrual interval due to partial and unsustained folliculogenesis. Indeed, the menstrual interval and flow may vary from cycle to cycle as the extent of GnRH varies from day to day. It takes a minimum of 14 "good days" to grow a follicle and anything less than that may interfere with optimal folliculogenesis. When the lifestyle issues that initiate or maintain the suppression of GnRH are less obvious and the suppression is incomplete, this form of reproductive compromise can be exceedingly difficult to recognize in the office, as neither metabolic imbalance nor GnRH suppression is readily documented using clinical chemistries.

It is not well appreciated that metabolic imbalance can exist in the absence of weight loss. For instance, overnutrition or periodic hypoglycemia from poor control of diabetes may also engender metabolic imbalance without resulting in weight loss or gain. In general, when there is weight loss or low weight, a clinical or subclinical eating disorder needs to be considered; however, not even all weight loss is due to an eating disorder or voluntary food or nutrient restriction. Indeed, there is growing recognition of another form of metabolic compromise that can cause and present as menstrual irregularities, namely adult-onset malabsorption syndromes.

An apparently common cause of malabsorption is food allergies and conditions that masquerade as food allergies, such as lactose deficiency, gastrointestinal infections, cholestasis, metabolic disorders such as galactosemia, and irritable bowel syndromes, including Crohn's disease. The topic of food allergies was recently extensively reviewed.[1] Interestingly, food hypersensitivity reflects a malfunction of the normal immune response to dietary proteins and may range in prevalence from 4-20%. Symptoms vary widely. In children, the typical allergens are egg, milk, peanut, wheat, and soya, whereas in adults, typical allergens are peanuts, tree nuts, and seafood. Arguably, the most insidious of these syndromes is celiac disease, which is an irreversible food allergy to gluten and wheat.

It is commonplace to think of food allergies as presenting in childhood and therefore not the domain of the gynecologist. However, a common presentation of celiac disease is menstrual irregularities, miscarriage, and infertility. Thus, it seems very likely that gynecologists and reproductive endocrinologists will be the physicians who will see and care for these women. Thus, I thought a quick review of this topic might be worthwhile.[2] Celiac disease, originally thought to occur only rarely in childhood, is a food allergy to the storage proteins of wheat, which are called glutens, that results in a T-cell mediated chronic inflammatory bowel disorder with an autoimmune component. In adults, the symptoms of celiac disease might include diarrhea, bloating, or abdominal pain with meals, but many of those with celiac disease who do not have obvious gastrointestinal complaints nonetheless suffer the long-term consequences, including metabolic bone disease, osteoporosis, anemia, malaise, autoimmune disorders, folate deficiency, severe liver disease, neurological symptoms, dental disease, and excess mortality primarily due to malignancy, including an 80-fold excess risk of small bowel adenocarcinoma. Even in patients with diarrhea, there tends to be a delay in diagnosis due almost exclusively to physicians failing to test for this condition. Diarrhea represents a late finding and is due to progression of the disease into the distal small bowel. Pregnancy can serve as a trigger for the development of symptoms. Based on symptoms, the disease was previously estimated to occur in 1/3500 people worldwide, but serological screening has revealed the prevalence to be around 1/250 worldwide.

Gynecologic manifestations can include delayed menarche, premature menopause, amenorrhea, recurrent miscarriage, and sexual dysfunction. The potential obstetrical manifestations include intrauterine growth restriction, increased perinatal mortality, and inadequate lactation. Further, there is an excess risk of celiac disease among patients with infertility.[3,4]

The diagnosis of celiac disease is based on the presence of histological changes in a small bowel biopsy, although there may be false negatives because the disease is patchy. The major histological feature is villous atrophy with crypt hyperplasia and intraepithelial lymphocytosis. In adults, although histological features can improve with a gluten-free diet, they often do not completely normalize. Serological tests have an important role in the diagnosis and management of celiac disease and provide the greatest chance of establishing the diagnosis. The presence of IgA and IgG antibodies against endomysium is almost 100% specific but only 80% sensitive. The total amount of gluten consumed by a patient will alter the results of serological testing. Therefore, other antibody tests should be done, usually

anti-gliadin, both IgA and IgG. Total IgA should also be measured, because IgA deficiency is 10-fold higher in those with celiac disease and may render the tests falsely negative.

The treatment is a strict gluten-free diet. Since most commercial flavorings and colorings use gluten, this is a burdensome task. However, with increasing recognition, some commercial manufacturers have begun to accurately label their foods, and some stores even have gluten-free aisles. When a patient with celiac disease is contemplating pregnancy, the obstetrician must be certain to emphasize that it is critical to ensure appropriate folate levels, but the patients must be cautioned to acquire gluten-free vitamins.

In short, although most gynecologists and reproductive endocrinologists may not be aware of it, celiac disease and other food allergies are a relatively common cause of typical reproductive complaints, including menstrual irregularities, amenorrhea, infertility, sexual dysfunction, premature menopause, recurrent miscarriage, and poor obstetrical outcomes. The long-term sequelae of untreated celiac disease are far from benign and therefore, when there is the least suspicion, testing should be done. Certainly, the relatives of anyone with celiac disease must be tested, regardless of the absence or presence of symptoms. To optimally protect the health of women and their infants, it is clear that obstetrician-gynecologists need to become familiar with gynecological manifestations and also to be able to order the appropriate screening tests. ■

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CME Questions

15. Which of the following is *not* a common cause of food allergies?

a. milk
b. soya
c. gluten
d. seafood
e. rice

16. The following statements are true regarding equol *except*:

a. No differences in equol production have been detected comparing men and women.
b. Isoflavones are not absorbed from the G-I tract unless they are metabolized by bacteria.
c. Genistein is the most potent estrogenic isoflavone.
d. Increasing intake of isoflavones does proportionately increase blood levels and biologic effects.

17. Based on the findings of Harlan et al. in their study of trends in surgery and chemotherapy for women with ovarian cancer in the United States, the main factor responsible for an improvement in the frequency of appropriate treatment for women with early-stage disease has been:

a. Higher rate of cytologic washings
b. Higher rate of peritoneal biopsies
c. Higher rate of omentectomy
d. Higher rate of lymph node sampling.
e. None of the above

18. The vaginal hysterectomy technique using the electrosurgical sealing device is superior to that using standard suture ligatures with regard to:

a. operating time.
b. hospital length of stay.
c. rate of complications.
d. convalescent time.

Answers: 15 (e); 16 (c); 17 (d); 18 (a)

Attention Readers

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

PHARMACOLOGY WATCH

Eplerenone Cleared for CHF Patients with Sustained MI

The FDA has approved Pfizer's eplerenone (Inspra) for the treatment of congestive heart failure (CHF) in patients who have sustained a myocardial infarction. The drug is a selective aldosterone blocker, a new class of drug for the treatment of CHF. It differs from spironolactone in that it selectively blocks the mineralocorticoid receptor, but not the glucocorticoid, progesterone, or androgen receptors. The approval of eplerenone for the treatment of CHF was based primarily on the findings of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which was published in the April 2003 issue of the *New England Journal of Medicine*. In EPHESUS, nearly 7000 patients with acute myocardial infarction and left ventricular dysfunction and heart failure were randomized to eplerenone 25 mg per day titrated up to 50 mg per day or placebo. Both groups also received optimal medical therapy. Following 16 months of follow-up, there was a significant reduction in death rate (RR, 0.85; 95% CI, 0.75-0.96; P = 0.008) in the eplerenone group. The drug also resulted in significant reductions in cardiovascular deaths and sudden cardiac death (*N Engl J Med*. 2003;348:1309-1321). The drug appears to be well tolerated with the primary adverse events being hyperkalemia and increased creatinine levels. Because of the selectivity of the drug for the mineralocorticoid receptor, there is no reported increase in menstrual disorders, gynecomastia, or impotence with eplerenone, adverse reactions that are frequently associated with spironolactone usage. Pfizer will make the drug available through an early access program by December 2003. Eplerenone was previously approved for treatment of hypertension alone or in combination with other antihypertensive agents.

No Adverse Effect with Concomitant Aspirin and ACE Inhibitor Use in CHF Patients

Aspirin does not adversely affect survival in patients with stable CHF who were being treated with an ACE inhibitor, according to a French study published in October. This study contradicts earlier studies, which raised concern about the concomitant use of aspirin and ACE inhibitors in CHF patients. In a retrospective analysis, 755 stable patients with left ventricular systolic dysfunction were followed for nearly 5.5 years. Most patients were on an ACE inhibitor and 317 were on aspirin, the majority on low-dose aspirin (< 200 mg/d). End points included cardiac-related deaths, version transplants, nonurgent transplants, and noncardiac deaths. The analysis revealed no relationship between the use of aspirin and survival among patients taking ACE inhibitors. Brunner-La Rocca and colleagues conclude that aspirin is not harmful for heart failure patients who are taking ACE inhibitors (*Chest*. 2003; 124:1192-1194, editorial 1250-1258).

HIV Treatment Shows High Failure Rate

A once-daily, triple nucleoside reverse transcriptase inhibitor (NRTI) HIV treatment regimen has seen a high number of treatment failures and HIV

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resistance. The rate of virologic failure reached 91% along with a high rate of HIV resistance to NRTIs in treatment-naive patients. Gilead Sciences has taken the step of notifying health-care professionals to discontinue the regimen in a "Dear Doctor" letter. The treatment failures were seen with a regimen containing didanosine enteric-coated beadlets (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead) in HIV-infected treatment-naive patients. Tenovir DF is no longer recommended for use in combination with didanosine and lamivudine in treatment-naive or experienced patients with HIV infections. The FDA is also recommending that patients currently on this regimen should be considered for treatment modification (http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#viread [Accessed Nov. 5, 2003]).

New Psoriasis Treatment Approved

The FDA has approved the second biologic for the treatment of psoriasis. Genentech's efalizumab (Raptiva) was approved for the treatment of moderate-to-severe psoriasis in October. It joins Biogen's alefacept (Amevive), which was approved in January 2003 and will probably soon be joined by Amgen's rheumatoid arthritis drug etanercept (Enbrel), which is also seeking approval for the treatment of psoriasis. Efalizumab is a humanized therapeutic antibody that blocks the activation, reactivation, and trafficking of T-cells that lead to the development of psoriasis symptoms. The drug requires a once-a-week self-injection and will cost $14,000 a year.

THG Controversy Gains Steam

The FDA has issued a warning regarding tetrahydrogestrinone (THG), a synthetic "designer" steroid, which is derived by simple chemical modifications from another anabolic steroid. Little is known about the safety of the drug or its structure, but its relationship to better-known products suggests that it may represent a considerable health risk. THG has been marketed as a dietary supplement; however, the FDA has determined that it is an unapproved drug and as such cannot be legally marketed. Urine assays have recently been developed for THG, and testing of athletes has revealed some disturbing findings. Four US Olympic athletes, as well as Britain's leading sprinter, have tested positive in the initial assay—further tests are to follow. A San Francisco grand jury is looking into a California nutritional supplement manufacturer that may be the source of the drug. The FDA statement is available at www.fda.gov/bbs/topics/NEWS/2003/NEW00967.html (accessed Nov. 5, 2003).

New Study Examines Sulfonamide Nonantibiotics

Is it safe to use a sulfonamide-based nonantibiotic in patients who have an allergy to sulfonamide antibiotics? A large retrospective cohort study from the United Kingdom looked at this issue and suggests that penicillin allergy is as likely or more likely to be associated with nonantibiotic sulfonamide reactions as a history of sulfonamide antibiotics allergy. Nearly 10% of patients with a history of allergy to a sulfonamide antibiotic had an allergic reaction after receiving a sulfonamide nonantibiotic compared to only 1.6% of patients who have no history of allergy to sulfonamide antibiotics. Patients who had a history of hypersensitivity to penicillin were most likely to have an allergic reaction to a sulfonamide nonantibiotic (adjusted odds ratio, 0.6; 95% CI, 0.5-0.8). Strom and associates conclude that there is a relationship between hypersensitivity to sulfonamide antibiotics and subsequent allergic reaction with sulfonamide nonantibiotics such as thiazide diuretics; however, this risk seems to be due to a predisposition to allergic reactions rather than a cross reactivity between sulfonamide-based drugs (*N Engl J Med*. 2003;349:1628-1635).

FDA Actions

Novavax Inc has received FDA approval to market a new topical estrogen therapy for the treatment of hot flashes in menopausal women. The white lotion is an emulsion of estradiol topical that women apply only to their legs, thighs or calves on a daily basis. The topical preparation is absorbed through the skin allowing estradiol to bypass enterohepatic circulation. Estradiol topical emulsion will be marketed under the trade name Estrasorb.

The FDA has issued an approvable letter to Cephalon, Inc. regarding expanded indications for modafinil (Provigil). The drug is currently approved for excessive daytime sleepiness associated with narcolepsy. The letter states that modafinil is approvable for improving wakefulness in patients with excessive sleepiness associated with shiftwork and in patients with obstructive sleep apnea/hypopnea syndrome. Cephalon had also sought approval for other causes of excessive sleepiness including jet lag; however, the FDA panel could not come to agreement on that recommendation. ■