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Cesarean Section for all Breeches? Is the Final Answer In?

ABSTRACT & COMMENTARY

In December, a group from Austria published a report evaluating outcomes of infants presenting at term with breeches whose mothers were scheduled to have either an elective cesarean section or a planned vaginal birth. The study group included 699 pregnancies delivered in 1 hospital between January 1993 and December 1999. Patients whose fetuses were between 2500 and 4000 grams, who were in a frank breech position with maternal pelves of adequate size were offered a planned vaginal delivery. Outcomes in this group were compared with those in breech fetuses born during the same time period by planned cesarean section.

Outcome variables included serious neonatal morbidity (birth trauma, seizures, hypotonia, Apgar scores of < 4 at 5 minutes, cord blood acidosis, prolonged intubation, or simply > 4 days in the Newborn Special Care Unit). Pediatric follow-up was possible in 635 children (91%), at an average of 57 months.

Of the 699 term breeches, 218 (31%) had planned cesarean sections. Of the 481 (69%) scheduled to have a vaginal delivery, 342 (71%) did and 139 (29%) eventually had a cesarean section because of CPD, fetal heart abnormalities, or prolapse cord.

Giuliani and colleagues chose an "intention to treat" method to analyze the data. There were no perinatal deaths in either group. Serious perinatal morbidity occurred in 11 fetuses (2.3%) in the planned vaginal group and 1 (0.5%) in the cesarean group. However, the results were not statistically significant. The cord blood pH was statistically lower in the vaginal group (7.23 vs 7.26). There were slightly more cord pHs below 7 (1.5% vs 1.0%) and base deficits above 15 (1.2% vs 0%) but neither was statistically significant, and there were no cases where both pH and base deficit were low.

Developmental delay occurred in 8 of 432 (1.9%) children studied in the vaginal group and 1 of 190 (0.5%) in the cesarean section group, but also this did not obtain statistical significance. Interestingly, of the 10 children able to be studied at 33 months, deemed earlier to have had "serious neonatal morbidity" at birth, none had long-term sequelae.

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INSIDE

Giuliani et al's conclusion was that "planned vaginal delivery remains an option for selected term breech presentations." (Giuliani A, et al. Mode of delivery and outcome of 699 term singleton breech deliveries at a single center. *Am J Obstet Gynecol.* 2002;187:1694-1698.)

COMMENT BY JOHN C. HOBBINS, MD

The now famous study by Hannah and associates[1] was the cover story reviewed in a previous *OB/GYN Clinical Alert*.[2] This very large randomized trial involved 121 centers in many countries and included more than 2000 patients randomly allocated to have an elective cesarean section or a planned vaginal delivery. Their results strongly suggested the benefit from cesarean section. For all the reasons stated in the previous *OB/GYN Clinical Alert*, this represented a bombshell, and, not surprisingly, it generated responses critical of the study design and conclusions rendered. The methodological problems involved low recruitment rate, surprisingly low infant mortality rates in hospitals in the underdeveloped countries which were similar to results from countries with intrinsically low perinatal mortality rates, and the inclusion of perinatal deaths that seemed to have nothing to do with the route of delivery.

Now we have a study indicating no statistically significant difference in outcomes (with the exception of cord pH) in infants scheduled for vaginal delivery. However, the study falls short of being the "be all and end all" of studies addressing this issue.

First, it is not a randomized trial. Second, when knit-picking through the study, I came up with different numbers for cases fitting Giuliani et al's definitions for serious neonatal morbidity. Last, in every category evaluated there appears to be fewer neonatal problems in the cesarean group (although not significant), and I doubt that there are adequate numbers in the study to allow the statistical power to say that there might not be a difference.

The only significant difference in any of the variables (in cord pH) probably can be explained by the fact that 62 patients in the planned cesarean delivery group required an emergency cesarean section (53 for fetal heart rate abnormalities and 9 for prolapsed cord). Rightfully so, the intention-to-treat analysis assigned these cases to the vaginal group, since this "goes with the territory."

So where do we go from here? To me, the decision of whether or not to deliver all breeches by cesarean section should not be based on either study because of the inherent problems in design, which were beyond Giuliani et al's controls. One has to weigh the possible benefit of a very modest decrease in perinatal morbidity (and probably not mortality in US hospitals) against the potential increase in maternal morbidity and cost of a cesarean section. For example, the Austrian study showed that 71% of patients in the vaginal delivery group were spared from a cesarean section.

Today this decision is best made by the patient who must be fully informed of the facts available as well as the unknowns regarding the risks and benefits of each option.

Unfortunately, I am very pessimistic that an ideal study can be launched now to accurately answer our patients' questions. ■

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In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Pfizer, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Pfizer, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Dr. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Ling and Dr. Hobbins report no relationships related to this field of study.

Walking and Leisure-Time Activity and Risk of Hip Fracture in Postmenopausal Women

ABSTRACT & COMMENTARY

Synopsis: *Moderate levels of activity, including walking, are associated with substantially lower risks of hip fracture in postmenopausal women.*

Source: Feskanich D, et al. Walking and leisure-time activity and risk of hip fracture in postmenopausal women. *JAMA*. 2002;288:2300-2306.

The aim of this study was to determine how much protection from hip fracture exercise confers. The study population was the Nurses' Health Study, which is an ongoing cohort of 121,700 women who were nurses between the ages of 30 and 55 years at the time of enrollment in 1976. Approximately 98% of the participants are white. Data from 61,200 subjects were used in the present analysis. During the median length of follow-up of 11.6 years, there were 415 cases of hip fracture. The median age of fracture was 67 years. Physical activity was estimated by means of a questionnaire. Each activity was assigned a metabolic equivalent. One MET is the energy expenditure from sitting quietly.

The group was relatively sedentary, with a median of 7 MET h/wk (2.3 h/wk of walking at an average pace). Nineteen percent reported no activity. Active women had a lower BMI, were less likely to smoke, and were more likely to take hormones and calcium supplements. Both activity and body mass index (BMI) were inversely associated with risk of hip fracture. Women in the highest category of activity (MET > 24) had a relative risk of hip fracture of 0.45 (confidence interval, 0.32-0.63) and there was a dose-related reduction in risk. Women with a BMI < 23 had a significantly higher risk of hip fracture regardless of activity and those with a BMI > 30 had a significantly lower risk. The association between activity and hip fractures was dissimilar in hormone users and nonusers, such that hormone use protected most from hip fracture in those users who were sedentary. In those with the highest level of activity, hormone use added very little to the reduction in risk of hip fracture.

COMMENT BY SARAH L. BERGA, MD

What intrigued me most about this otherwise straightforward report was the finding that, at the highest levels of activity, hormone use offered little additional benefit over exercise alone in protecting from hip fracture. Estrogen was most effective in safeguarding the hip in sedentary women. This same relationship also held for calcium intake and activity. However, a high BMI did confer some additional protection from hip fracture even at the highest activity levels. This is important information to share with patients who are looking for nonhormonal strategies for managing menopause and aging.

The study has some important limitations, however, and patients must be cautioned about these as well. The mechanisms by which exercise or activity protect someone from hip fracture were not studied. Other studies have shown that activity correlates with bone density, but exercise also reduces falling, a major cause of hip fracture, by improving balance and muscle strength. Other types of fractures, including vertebral crush fractures, were not included in this analysis. Exercise and activity are less likely to strengthen vertebral bodies, and vertebral crush fractures are not typically attributable to falls. Given these considerations, it is premature to conclude that exercise is a good substitute for estrogen or other agents intended to reduce the risks of developing the clinical manifestations of osteoporosis. Also, it is not clear what role exercise or activity have in the treatment of established osteoporosis. Most importantly, as Feskanich and colleagues carefully point out, for exercise to safeguard against hip fracture, it must be ongoing. Women who decreased their activity levels during the follow-up period had an increased incidence of hip fracture. It is not uncommon for my patients to tell me that they are not worried about osteoporosis because they led an active life when they were younger. Apparently, this is not enough.

Another reason I chose to review this article is that doctors and patients alike are wondering what to do in the wake of the WHI. It has been suggested that alternative strategies other than HRT should be the mainstay for the prevention and treatment of osteoporosis. While there are many agents available, none of them are risk-free. For instance, the long-term effect of bisphosphonates has not been chronicled because not enough women have used them long enough to know. Some have suggested that hormones are better because they build bone of normal architecture, whereas this cannot be said for bisphosphonates. There is some concern that bisphospho-

nates may confer bone fragility after extended use or as bones age (because the bisphosphonates are incorporated into the bone matrix). Further, now that parathyroid hormone (PTH) is about to become available, we will have to figure out where it fits in the schemata for the prevention and treatment of osteoporosis. ■

Management of Invasive Carcinoma of the Uterine Cervix Associated with Pregnancy: Outcome in Intentional Delay in Treatment

ABSTRACT & COMMENTARY

Synopsis: *Delay in treatment to allow for fetal maturity is safe in patients with early stage I cervical carcinoma associated with pregnancy.*

Source: Takushi M, et al. Management of invasive carcinoma of the uterine cervix associated with pregnancy: outcome of intentional delay in treatment. *Gynecol Oncol*. 2002;87:185-189.

TAKUSHI AND COLLEAGUES RETROSPECTIVELY reviewed the medical records of 28 patients with invasive cervical cancer diagnosed during pregnancy or within 1 month after pregnancy to investigate maternal and neonatal outcomes after planned treatment delay to improve fetal maturity. Twenty-two patients (79%) had stage I disease, and 6 (21%) had stage II or III disease. All but 1 patient had squamous cell histology. Twenty cases were diagnosed before 22 weeks gestation, 4 between 22 and 36 weeks, 1 after 36 weeks, and 3 were diagnosed postpartum. In the immediate treatment group (n = 16), the stage was IA in 3 cases, IB in 7, and II or III in 6 patients. In 11 patients, hysterectomy was performed after therapeutic abortion or with fetus in situ. In 2 patients, cesarean section was followed by hysterectomy or radiotherapy. Three patients diagnosed postpartum were treated with either hysterectomy or radiotherapy. Fifteen patients were free of disease during the follow-up of 27-114 months. In the delayed treatment group (n = 12), the stage was IA1 in 8 cases, IA2 in 1, IB1 in 2, and IB2 in 1 case. In the 8 patients with stage IA1 tumor, the treatment was deferred until term with a delay of 6-25 weeks, and hysterectomy or therapeutic conization was performed after delivery. In the 4 patients with stage IA2, IB1, or IB2 tumor, the treatment was postponed until after 30 weeks' gestation with a delay of 6-15 weeks. No disease progression was documented. Cesarean delivery was followed by hysterectomy in these patients. All patients were free of disease during the follow-up of 70-156 months, and their offspring were well with no sequelae. Takushi et al concluded that delay in treatment to allow for fetal maturity is safe in patients with early stage I cervical carcinoma associated with pregnancy.

COMMENT BY DAVID M. GERSHENSON, MD

The association of cervical cancer with pregnancy is fortunately quite rare, occurring in about 1 in 2000 to 10,000 pregnancies. When it does occur, obvious important considerations include the health of the mother and the viability and health of the fetus. No study has demonstrated an adverse effect of pregnancy on the biology or disease progression of the cervical cancer. Of course, there are no large prospective studies on this topic, and there never will be. Historically, cervical cancer in pregnancy was generally treated immediately, with the pregnancy being terminated. With advances in neonatal medicine and improved outcomes for increasingly premature infants, reports of planned delay of treatment began to emerge. This study from Japan certainly confirms the experience from several other studies, most of which originate from the United States. Takushi et al cite 10 other studies in which a small number of patients, 1-8, with cervical cancer in pregnancy (stages IA2 to IB2) are managed with delays in treatment of 1-32 weeks. And, with rare exception, the outcomes have been favorable. However, one wonders whether there has been lack of reporting in cases with poor outcomes. For patients with preinvasive cervical disease, the rule of thumb would be close monitoring during the pregnancy without intervention. The same has generally been true of stage IA1 disease (usually confirmed by conization). For those with stage IA2 or more advanced disease, however, firm guidelines become obscured. While the outcomes reported in all these studies are impressive and provide some reassurance that definitive treatment can be safely delayed in some pregnant patients with cervical cancer, this approach must be individualized, and the patient and her family must make the final determination after comprehensive informed consent. One must

emphasize, as Takushi et al do, that there are no absolutes here. The precise risk of disease progression associated with treatment delay cannot be ascertained. Underestimation of the extent of disease remains a major concern. In general, for patients with stage II, III, or IV disease, immediate treatment, as practiced in this study, is recommended. The real dilemmas are in those patients with stage IA2, IB1, and IB2 disease. ■

Better Methods for Emergency Contraception

ABSTRACT & COMMENTARY

Synopsis: *A single dose of 1.5-mg levonorgestrel and a single low dose of 10-mg mifepristone are effective methods for emergency contraception.*

Source: von Hertzen H, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: A WHO multicentre randomised trial. *Lancet*. 2002;360:1803-1810.

THE WORLD HEALTH ORGANIZATION CONDUCTED A randomized, double-blind trial in 15 clinics in 10 countries comparing 3 methods of emergency contraception in 4136 women. The results were as follows when each treatment was administered up to 120 hours (5 days) after unprotected coitus:

10-mg single-dose mifepristone	1.5% pregnancy rate
1.5-mg single-dose levonorgestrel	1.5% pregnancy rate
2 doses 0.75 mg levonorgestrel given 12 hours apart	1.8% pregnancy rate

The results and side effects did not differ significantly among the 3 groups. About 1% experienced vomiting.

■ COMMENT BY LEON SPEROFF, MD

The Yuzpe regimen for emergency contraception was established 20 years ago—2 tablets of oral contraceptives followed by 2 tablets 12 hours later. The pregnancy rate (the failure rate) of this method is about 2-3% when administered within 72 hours of unprotected coitus. This method was supplanted by a 0.75-mg dose of levonorgestrel given twice, 12 hours apart, available in the United States as "Plan B." This levonorgestrel method is more successful and better tolerated than the combination oral contraceptive method. Indeed, the risk of pregnancy is 60% lower with the levonorgestrel-only method.[1] The use of mifepristone for emergency contraception has been associated with a similar reduction of dose, from 600 mg to an amazingly low dose of 10 mg.

The current, well-designed and executed large study now establishes that a single low dose of either mifepristone or levonorgestrel can provide very effective emergency contraception with few side effects. There was no evidence that treatment within 72 hours after coitus or after 72 hours had a significant effect on outcome. However, the pregnancy rate after 72 hours was 2.4% compared to 1.5% in those treated within 72 hours. In fact, those treated on day 5 had a pregnancy rate of about 5%. The clinical conclusion is apparent: Recommend emergency contraception within the 72-hour window after coitus.

The disadvantage associated with mifepristone is a delay in ovulation with a longer cycle and later return of menses in about 10% of treated women. In women who continue to have unprotected coitus, this produces a 22% higher pregnancy rate compared to women who use a contraceptive method. For practical purposes, therefore, the single-dose levonorgestrel method is preferred, providing an easier method that offers better compliance without an increase in side effects.

Emergency contraception has received the attention it deserves in the last few years. This is an important method to reduce the number of unintended pregnancies and induced abortions. The Office of Population Research at Princeton University maintains a web site (http://opr.princeton.edu/ec/) and a hot line (1-888-668-2528) for patients and clinicians. In many areas, local Planned Parenthood Clinics offer emergency contraception without physician prescriptions, and in some states, emergency contraception is available directly from pharmacists. ■

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Suspected Pulmonary Embolism in Pregnancy

ABSTRACT & COMMENTARY

Synopsis: *Ventilation/perfusion scanning appears to be safe and effective, at least in ruling out significant clinical pulmonary embolism in pregnant patients. However, prospective studies over longer time periods should be undertaken to validate these conclusions.*

Source: Chan WS, et al. Suspected pulmonary embolism in pregnancy: Clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes. *Arch Intern Med*. 2002;162:1170-1175.

PULMONARY EMBOLISM (PE) IS A PREVENTABLE CAUSE of maternal mortality during pregnancy and the postpartum period. Once PE is suspected, many clinicians begin their evaluation with a ventilation/perfusion scan. Although scanning is assumed to be safe during pregnancy based on low fetal radiation exposure,[1] no clinical data exist to support the notion that there are no adverse outcomes in pregnancy. In addition, little is known about ventilation/perfusion scan interpretation in pregnant women and the safety of withholding anticoagulation in those with normal or nondiagnostic scans.

The purpose of this multicenter, retrospective, observational study was to examine the distribution and safety of ventilation/perfusion scanning in pregnant patients. The safety of withholding anticoagulation therapy in pregnant women with normal or nondiagnostic scans was also examined.

A total of 120 consecutive pregnant patients who presented with suspected PE and had ventilation/perfusion scans were identified through the nuclear medicine departments. Patient demographics, stage of pregnancy, symptomatology, and treatment strategy at the time of original evaluation were recorded. Two independent experts re-interpreted the original ventilation/perfusion scans and categorized them as normal, nondiagnostic, or high probability. Patients were later contacted by telephone to determine postpartum venous thromoembolic events, and pregnancy outcomes.

Scan readings were as follows 87 (72.5%) normal, 29 (24.2%) nondiagnostic, and 4 (3.3%) high probability. Seven were receiving anticoagulation prior to presentation for previously diagnosed PE or deep venous thrombosis; eight women received anticoagulation subsequent to their evaluation. Of the 104 untreated women (1 died secondary to primary pulmonary hypertension), 80 had normal scans and 20 scans were nondiagnostic. In this group, no thromboembolic event was reported after a mean follow-up of 20 months.

Of 110 obstetrical and pediatric outcomes examined over 20 months, 3 spontaneous abortions, 4 congenital, and 4 developmental abnormalities were reported. No childhood cancers or leukemias were reported.

COMMENT BY ALAN FEIN, MD, & JONATHAN EDELSON, MD

In this retrospectively examined group of pregnant patients, the prevalence of high probability scans is low (1.8%), compared to the other patients with suspected PE (10%). There were no thromboembolic events reported in those with normal or intermediate probability lung scans, suggesting that ventilation/perfusion scanning in pregant patients has a good negative pedictive value. Importantly, fetal risk was minimal in this population. The percentage of adverse fetal outcomes after ventilation/perfusion scanning was similar to that in the general population, 2.6% compared to 3.6%. These numbers are supported by previous studies that suggested no increase in fetal malformation risk for exposures less than 1 rad; radiation exposure in ventilation/perfusion scans is significantly lower.[2]

In summary ventilation/perfusion scanning appears to be safe and effective, at least in ruling out significant clinical PE in pregnant patients. However, prospective studies over longer time periods should be undertaken to validate these conclusions. ■

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Dr. Fein is Director and Dr. Edelson is Fellow, Division of Pulmonary and Critical Care Medicine, North Shore University Hospital, Manhasset, NY.

Special Feature

Total or Subtotal Hysterectomy: Which is Superior?

By Frank W. Ling, MD

AS THE "NEW KID ON THE *OB/GYN Clinical Alert* block," and as the generalist among the editors, I intend to focus on topics that come up commonly in my

own practice of obstetrics and gynecology. The beauty of having this format is that cutting edge science can be presented, but also sacred cows can be challenged.

So our topic this time around is the most common major gynecologic surgical procedure in the United States, the hysterectomy. Stimulus for this discussion was provided in the *New England Journal of Medicine* in which Thakar and colleagues looked at the outcome of 279 benign cases randomized to either subtotal or total abdominal hysterectomy.[1] Total hysterectomy was associated with longer operating time, more blood loss, longer hospitalization, more postoperative fever, and more frequent use of antibiotics. One-year follow-up revealed some complications more commonly associated with subtotal hysterectomy (cyclic vaginal bleeding, 6.8%; persistent pelvic pain, 2.3%; and cervical prolapse, 1.5%) and some with total hysterectomy (bowel obstruction, 1.4% and pelvic pain, 4.8%).

Of great interest to our patients are the following findings in both groups: 1) the incidence of bowel dysfunction did not increase over the preoperative state; 2) the incidence of lower urinary tract dysfunction decreased after surgery; 3) frequency of intercourse increased after surgery; 4) prevalence of deep dyspareunia declined after surgery; and 5) orgasms did not change from baseline.

These data should reinforce to each of us who performs hysterectomy the potential effect of how we counsel our patients regarding the surgical approach that we recommend. As gynecologic surgeons we are in a unique position to truly improve quality of life. Unlike other surgical specialties in which the doctor-patient relationship may well be limited to the procedure and the immediate postoperative period, ours is a lasting one. We will continue to see our surgical patients for both specific concerns as well as health care maintenance. It should be reassuring to both us and our patients that abdominal hysterectomy, either total or subtotal, does not appear to be associated with an increased incidence of problems related to gastrointestinal, urinary, or sexual functioning.

As an extension of these findings, each of us should also be reassessing what we recommend to our patients regarding which type of hysterectomy to have (total vs subtotal/supracervical) as well as what approach should be taken (abdominal vs vaginal vs laparoscopic-assisted vs laparoscopic). I raise these issues here because the data that can help us guide our patients must be based on sound evidence and not anecdotal information. Remember: not all publications are created equal. It is a good thing that our peer-reviewed literature provides an opportunity for a novel approach to be described or a series of satisfied patients to be reported. Neither of these examples, however, should necessarily change our pattern of care. Similarly, articles on "My favorite approach to . . ." or "How I perform . . ." in nonpeer-reviewed journals should not convince us or our patients to question established care. It is, however, a bad thing if choices of patient care on based upon inappropriate claims of superiority or inadequate data.

The discriminating consumer and the astute clinician cannot avoid being exposed to claims that supracervical hysterectomy is superior to total hysterectomy in terms of sexual functioning and organ prolapse. Is it true? It certainly has not been proven. By the same token, who has the experience to say that it isn't? Answer: Nobody. There are no definitive data to support or refute the claim. Our job as both the surgeon and patient advocate should be to make sure that the patient truly is given informed consent about the risk and benefits of both, and that her concerns and preferences are fully addressed. One hint to keep perspective: If you feel as though you're "selling" an operation, you probably are. Back up half a step and make sure that the informed consent is balanced and based on what we know. It remains a privilege to have women trust us as their surgeon and physician. These patients deserve the best that we can do, both in the operating room as well as in the office counseling session. ■

Reference

1. Thakar, R, et al. Outcomes after total versus subtotal abdominal hysterectomy. *N Engl J Med*. 2002;347: 1318-1325.

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Effective with this issue, OB/GYN Clinical Alert *is changing its testing procedure. You will no longer need to return a Scantron answer sheet to earn credit for the activity. Please review the text, answer the following questions, check your answers against the key on the following page, and then review the materials again regarding any questions answered incorrectly.* ***To receive credit for this activity, you must return a CE/CME evaluation at the end of the testing term.*** *For further information, refer to the "CE/CME Instructions" below.*

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5. **Which of the following represents a reasonable strategy for menopausal women to reduce their risk of hip fracture?**
   a. Bisphosphonate use
   b. Maintaining a BMI lower than 22
   c. Walking several hours a week
   d. Hormone use
   e. Adequate intake of vitamin D

6. **The following statements regarding emergency contraception are true *except*:**
   a. The levonorgestrel-only method is superior to the use of oral contraceptives for emergency contraception.
   b. Emergency contraception is not 100% effective.
   c. Emergency contraception loses efficacy after 3 days after coitus.
   d. Emergency contraception always requires a physician's prescription.

Answers: 5: B; 6: D

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Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **At the end of the testing period, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a certificate of completion.** When your evaluation is received, a certificate will be mailed to you.

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PHARMACOLOGY WATCH

FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. 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.

cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (*JAMA*. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (*JAMA*. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan (P = .001) in the intention to treat analysis (n = 57). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (*JAMA*. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (*Ann Intern Med*. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (*N Engl J Med*. 2002;347:2104- 2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■