Providing Evidence-based Clinical Information for 22 Years

OB/GYN CLINICAL ALERT®

A monthly update of developments in female reproductive medicine

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON AMERICAN HEALTH CONSULTANTS

INSIDE

Financial Disclosure: *OB/GYN Clinical Alert*'s Editor, Leon Speroff, MD, is a consultant for Barr Laboratories.

Neonatal Death and Morbidity in Vertex-Nonvertex Second Twins According to Mode of Delivery and Birth Weight

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: *The risk of neonatal death and morbidity in second-born twins is higher in the group in which both twins were delivered vaginally and the group in which the second twin was delivered by cesarean delivery after the first twin was delivered vaginally compared with the group in which both twins were delivered by cesarean delivery.*

Source: Yang Q, et al. Neonatal death and morbidity in vertex-nonvertex second twins according to mode of delivery and birth weight. *Am J Obstet Gynecol*. 2005;192:840-847.

I MISSED THIS ARTICLE WHEN IT FIRST EMERGED. HOWEVER, DURing a recent perinatal conference in California, Dr. Michael Nageotte cited it in an excellent lecture on breeches. Since the report could have an impact in current practice, I am reviewing it in this issue.

Yang and colleagues combed through birth statistics data from 15,185 births in the United States between 1995-1997 in which a second twin presented as a nonvertex. Infants with birth weights of less than 1500 grams were excluded. Thirty-seven percent were delivered by Cesarean section empirically (group 1), while 15.5% had a Cesarean section for the second twin alone (group 2), and the remaining 46.8% had a vaginal delivery for both twins (group 3).

When comparing outcomes between group 1 and group 3, the second twins in group 3 had a higher rate of total neonatal death, asphyxia-related death, low Apgar scores (less than 7 at 5 minutes), and use of neonatal ventilation. When breaking down the results according to birth weight, the 500-1500 gram second twins had more

VOLUME 22 • NUMBER 8 • DECEMBER 2005 • PAGES 57-64

NOW AVAILABLE ONLINE
www.ahcpub.com

total neonatal deaths, asphyxia-related deaths, lower Apgar scores, and ventilation use. There was no difference in neonatal injury. The heavier second twins, weighing 1500-4000 grams, had a higher rate of infant injury, low Apgar scores, ventilation use, and seizures, but no difference in neonatal death compared with those who were sectioned outright.

Yang et al concluded that their findings were "consistent with a prospective singleton term breech trial which found that planned Cesarean delivery was associated with reduced neonatal morbidity with planned vaginal birth."

COMMENTARY

While sharpening our scalpels yet again for another reason to avoid vaginal delivery, it is important to look critically at the design and results of this study. When reviewing only birth certificates and CPT codes, there is no ability to determine, who, if anyone, was attending the deliveries, whether or not the second twin was alive before delivery (where vaginal delivery would have been indicated) or whether, in the mid 1990s, all the twins were known to be twins before delivery. Also, it is unknown in many cases if an external version was attempted (since there was a trend to do this at that time).

Something in this story is clearly missing since there was a greater incidence of birth injuries in infants weighing 1500 grams than in the very delicate premature breeches that have already been shown in singleton studies to do more poorly via the vaginal route, and, intuitively should be more vulnerable to manipulation.[1-4]

The Hannah et al RCT (a subject of a previous *OB/GYN Clinical Alert*), suggesting singleton breeches faired less well by the vaginal route, was quickly endorsed formally by the ACOG, essentially putting the nail in that coffin.[1,5,6] It would be a shame if beech extraction of the second twin was completely abandoned since three randomized studies have shown no difference in outcome when the second nonvertex twin is delivered in this way, the last of which even showed a cost effective benefit in vaginal delivery.[4]

Unless new information surfaces, the available literature suggests that in experienced hands, and under the proper conditions, breech extraction should not be abandoned as an option for a second twin. The Yang study should not trump all of the other information out there. ■

References

1. ACOG committee opinion: number 265, December 2001. Mode of term single breech delivery. *Obstet Gynecol*. 2001;98:1189-1190.
2. Rabinovici J, et al. Randomized management of the second nonvertex twin: vaginal delivery or cesarean section. *Am J Obstet Gynecol*. 1987;156:52-56.
3. Chauhan SP, et al. Delivery of the nonvertex second twin: breech extraction versus external cephalic version. *Am J Obstet Gynecol*. 1995;173:1015-1020.
4. Mauldin JG, et al. Cost-effective delivery management of the vertex and nonvertex twin gestation. *Am J Obstet Gynecol*.1998;179:864-869.
5. Hannah ME, et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet*. 2000;356:1375-1383.

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Gerard Gernazian.
Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

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

Back issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421
Editorial E-Mail: robert.kimball@thomson.com
Customer Service E-Mail:customerservice@ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
(Resident/Student rate: $125).
Multiple Copies
Documents are available for multiple subscriptions.
For pricing information, please call Steve Vance at (404) 262-5511.
Canada
Add GST and $30 shipping
Elsewhere
Add $30 shipping

Accreditation

Thomson American Health Consultants (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

AHC designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This CME activity is intended for the OB/ GYN. It is in effect for 36 months from the date of the publication.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments
Please call **Robert Kimball**, Managing Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

6. Hobbins J. Is cesarean section safer for breeches than vaginal delivery? *OB/GYN Clinical Alert.* 2001;17: 81-82.

Risk of Ovarian Cancer Algorithm to Screen for Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *An OCS strategy using the ROC algorithm is feasible and can achieve high specificity and PPV in postmenopausal women. It is being used in the United Kingdom Collaborative Trial of Ovarian Cancer Screening and in the United States in both the Cancer Genetics Network and the Gynecology Oncology Group trials of high-risk women.*

Source: Menon U, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. *J Clin Oncol.* 2005;23:7919-7926.

Population-based ovarian cancer screening programs have been difficult to recommend and implement because poor sensitivity and positive predictive value characteristics accompany expensive and inefficient testing methodology and triage algorithms. Menon and colleagues approached this problem by evaluating a new prospectively based algorithm among a population-based screening program currently underway in the United Kingdom. The population cohort used to evaluate the new screening strategy comprised of 13,582 menopausal women 50 years of age or older with at least one ovary, of whom 6532 completed a first screen; the remainder served as controls. The screening strategy was a staged process by which each CA125 drawn underwent a calculation for risk of ovarian cancer. The calculation is based on the patient's age and CA125 value relative to their personal baseline. In this trial, estimated risk less than 1 in 2000 was considered normal, while a risk of greater than 1 in 500 was considered elevated; those in between were considered intermediate and required repeat testing.

Those not considered normal were referred for a second stage of screening which incorporated a transvaginal ultrasound (TVS) and a repeat CA125. TVS was considered normal, abnormal, or equivocal based on ovarian volume and morphology. Based on the combination of CA125 risk estimation and TVS, a follow-up recommendation was made which could be gynecologic oncology referral, repeat CA125 and/or TVS testing, or annual screening. Among the screened group, nearly 80% continued with annual screening; 91 (1.4%) were considered at elevated risk. Among the intermediate group, repeat testing was normal in 92%, leaving 188 (2.9% of initial population) who were to undergo second-stage evaluation. Of the 144 who stayed in the program, 95 were returned to annual screening based on CA125 and TVS findings; 6 were found with non-gynecologic malignancies, 43 were referred to a gynecologic oncologist of whom 27 were returned to annual screening and 16 women who underwent surgery. From this group, 5 ovarian cancers were identified (4 malignant epithelial and 1 borderline); 11 remaining women had benign ovarian neoplasms. Compared to Menon et al's previous algorithm based on flat CA125 values (normal ≤ 30 U/mL), the new process referred less than half to secondary screening. They concluded that the new algorithm increases screening precision. Its effect on cost and survivorship are to be determined when the trial completes its accrual of 200,000 women anticipated in 2011.

COMMENTARY

Most clinicians even remotely familiar with the story of ovarian cancer screening have at best mixed emotions for its feasibility. This has been rooted largely in the repeated lack of overwhelming success of a number of different strategies even among "high-risk" populations. While the potential for a major impact in the dismal outcome of newly diagnosed ovarian cancer patients looms, enthusiasm is tempered by the frequent observation that a large proportion (1 in 20 to 1 in 5) of patients with positive screening need to undergo surgery to identify cancer—most of which are already metastatic. The principal reason for the underwhelming success of these programs is the low prevalence of the disease in the general population. This places a high burden on individual testing characteristics. Coupled with the fact that a reproducible and detectable preinvasive state has yet to be delineated makes the prospect for perfect success improbable. In addition, population-based screening demands that the tool or tools utilized are inexpensive and acceptable to the population for widespread utilization. Even a standard test such as a CA125 or a TVS is too expensive to use routinely in all women for this purpose. However, the impact must not be understated, as therapeutic advances

over the last 20 years have not significantly altered mortality due to disease. A good example of a model and its potential impact is the Pap smear, now chiefly recognized for reducing the mortality due to cervical cancer.

Fortunately, this track record has not kept investigators from studying new and existing technologies with the intent of impacting outcome. Several recent advances in biomarkers, proteomics, genomics and risk identification have started to mature into exploratory projects with the intent of being applicable to a mass audience. These tools would help to identify patients at risk for future cancer development based on particular signals. While exciting and promising in their initial evaluation, they are undergoing validation and are currently not quite ready for "prime-time."

While prediction of disease in otherwise asymptomatic healthy patients is an ultimate goal, the differential in survival between early and advanced-stage ovarian cancer makes even identification of localized cancer a "win" scenario. This has been the focus over the last 20 years from the UK team and their collaborators. In the current report, the positive predictive value (ie, the proportion of positive screened patients in whom cancer was subsequently diagnosed) of this new algorithm is still about 1 in 5 patients taken to surgery, the number of patients referred onto secondary and tertiary evaluation is being reduced, making the overall cost for cancer detection lower. Based on this group's previous work, identified cases are in a different stage distribution than those identified by conventional means and have better long-term survival. The cohort reported in this trial is a subset of the many thousands of patients currently being screened in the ongoing prospective clinical trial so, in a sense, is only a taste of how the methodology has been improved. We can only hope that this will translate into lasting benefit for our patients. ■

Suggested Reading

1. Jacobs I, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA125 measurement and ultrasonography. *BMJ*. 1993;306:1030-1034.
2. Jacobs IJ, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet*. 1999;353: 1207-1210.
3. van Nagell JR, Jr., et al. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. *Gynecol Oncol*. 2000;77:350-356.
4. Mills GB, et al. Future for ovarian cancer screening: novel markers from emerging technologies of transcriptional profiling and proteomics. *J Natl Cancer Inst*. 2001;93:1437-1439.
5. Zhu W, et al. Detection of cancer-specific markers amid massive mass spectral data. *Proc Natl Acad Sci USA*. 2003;100:14666-14671.

Surgical Management of Adnexal Torsion

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

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

Synopsis: *Despite data supporting conservative management, oophorectomy continues to be commonly used in the management of adnexal torsion.*

Source: Ogburn T, et al. Adnexal torsion: experience at a single university center. *J Reprod Med*. 2005;50:591-594.

Ogburn and colleagues report on their experience with adnexal torsion at one university medical center from 1990 to 2001. A chart review identified 68 patients in whom laparoscopic management was accomplished 32% of the time (n = 22) and ovarian conservation in 21% (n = 14). The rate of laparoscopy (rather than laparotomy) and ovarian conservation (rather than oophorectomy) did not differ prior to 1996 when compared with the time period after 1996. The discussion by Ogburn et al questions why the findings are as reported. Given that the literature supports the use of laparoscopy for both diagnosis of and treatment of adnexal torsion, is laparotomy used merely because of the lack of a skilled surgeon? Is ovarian conservation eschewed because of the persistent fear of embolic phenomena from the ovarian pedicle, again despite the data? Ogburn et al conclude that even though their university medical center did not follow their recommendations, the literature clearly supports a management plan in all cases of torsion in reproductive-aged women to include consideration of laparoscopy, untwisting of the adnexa, and ovarian conservation.

■ COMMENTARY

Would you rather have 20 years of experience or 1 year of experience 20 times? Ogburn et al seem to be asking this very question. I can just imagine how this retrospective review came about. You can picture the discussion at

a weekly Morbidity & Mortality conference in which they are reviewing the case of a reproductive-aged woman with an acute abdomen who undergoes laparotomy and oophorectomy for adnexal torsion. An attending wants the resident to describe the work-up and the resident dutifully explains that they had ruled out appendicitis, tubo-ovarian complex, ectopic pregnancy, pyelonephritis, and diverticular disease. The ultrasound showed a cystic adnexal mass so the faculty on call that night proceeded to perform a laparotomy because of the suspicion of torsion but with the possibility that it was a malignancy. When the abdomen was opened, the torsion diagnosis was confirmed, but the attending instructed the resident to perform an oophorectomy even though she knew that the risk of embolic phenomena from the pedicle was minimal.

At the conference, there is a call for a "protocol" to manage subsequent cases. Some say that there should be a standardized fashion in which torsion is managed only via laparoscopy. Others say that the medicolegal climate is such that even though the literature says that it is acceptable to untwist the pedicle, the "safe" way to treat this patient is oophorectomy. Another attending confirms that he would also have done a laparotomy because of the chance of malignancy in the ovary. A resident states that he wondered why oophorexy wasn't done to prevent a recurrence. Eventually, one staff member offers to review all the cases that the institution has seen in the past decade and report back what had been done and what could be done in the future.

To me, that's logically how this paper could have started. In fact, Ogburn et al might be re-telling the same story that is found at most university centers. Each decision made is often independent of the ones before unless there is some continuity or "corporate memory" of cases of a certain type. As a result, it appears that the laparotomy and oophorectomy are done because "that's the way I was trained." Hopefully, however, each of us doesn't practice based on how we were trained. We use that as a base, but we build on the face using our own experiences as well as those of others, ie, the literature.

Without question, in any woman with suspected torsion, malignancy is a consideration. Ultrasound can help us determine that risk to some extent so that performing the laparotomy just because malignancy is suspected can be targeted to truly higher risk cases. Similarly, laparoscopic management can be performed in virtually all cases unless laparoscopy itself is contra-indicated. Even if cancer is found, consultation can be sought or the procedure converted to an open one. Untwisting the pedicle is clearly an appropriate treatment option. Ogburn et al cite more than 400 cases of conservative management in the literature without a case of embolus.

So what's a clinician to do? Hopefully, the right thing for his/her patient. The less morbid laparoscopy is certainly preferable to laparotomy, and ovarian conservation is preferable to oophorectomy. Should they be done in every case? Maybe not, but they should be the procedure of choice unless there are extenuating circumstances. I am hopeful that each of us problem-solves for each of our patients, be they surgical, obstetric, or ambulatory, in a fashion that reflects the most up-to-date information available, not just what we were taught in residency. ■

Antenatal Betamethasone and Incidence of Neonatal Respiratory Distress After Elective Cesarean Section

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Synopsis: *Antenatal betamethasone and delaying delivery until 39 weeks both reduce admissions to special care baby units with respiratory distress after elective caesarean section at term.*

Source: Stutchfield P, et al. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. *BMJ*. 2005;331: 662.

A SURPRISING STUDY RECENTLY SURFACED IN THE *British Medical Journal*. A randomized trial was designed to determine if giving a standard maternal dose of steroids (two injections of 12 mg of betamethasone separated by 24 hours) would decrease the incidence of respiratory distress syndrome (RDS) in infants whose mothers were to have elective Cesarean sections.

In this study, 998 women having elective sections between 36 and 39 weeks were recruited from 11 collaborating centers. Half were given betamethasone and half were not. Of the 503 women receiving steroids, 10 of their babies had transient tachypnea of the newborn (TTN), compared with 19 in the 495 controls (2.1% vs 4%). There were 5 babies with X-ray diagnosis of RDS in the control group and one in the "treated group" (1.1% vs 0.2%). There also was a decrease in admissions to the newborn special care unit in the treated group. Stutchfield and colleagues concluded that giving steroids to mothers

having elective Cesarean sections decreased the incidence of RDS and TTN enough to warrant its use.

COMMENTARY

What is going on? The latest US statistics indicate the Cesarean section rate to be 34%. An increasingly large percentage of these are elective repeat Cesareans sections, which are now sharing the spotlight with the emergence of Cesarean section by maternal choice. Our neonatologists tell me that TTN is not a big deal while, obviously, RDS can be. This study, which Stutchfield et al indicate is powered to show a statistical difference between groups, shows that giving steroids to 100 women may prevent one infant from developing RDS. It is important to note that the severity of the RDS in this study did not differ between groups. Interestingly, Stutchfield et al suggest that the reason the steroids could work in elective Cesareans is that the infants, deprived of endogenous corticosteroid release during "the stress of labor," might need some exogenous help in inducing surfactant release.

Other RCT's have failed to show a benefit of steroids in preterm delivery after 34 weeks or when membranes are ruptured after 32 weeks.[1-4] Moreover, there is now some evidence that "if some is good, more is not necessarily better," with regard to repeated dosage of steroids and its affect on the fetal brain.

Call me old fashioned, but it seems weird that the aim of today's designer births is to interrupt pregnancy before labor ensues. Then, to compound the meddling, steroids are doled out to everyone because 1 in every 100 might have needed labor to discourage the development of RDS or, perhaps, because he/she really could be a preterm baby. ■

References

1. Morrison JJ, et al. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective cesarean section. *Br J Obstet Gynaecol*. 1995;102:101-106.
2. Walters DV, Olver RE. The role of catecholamines in lung fluid absorption at birth. *Pediatr Res.* 1978;12: 239-242.
3. ACOG committee opinion. ACOG committee opinion. Antenatal corticosteroid therapy for fetal maturation. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 2002;78:95-97.
4. Guinn DA, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. *JAMA*. 2001;286: 1581-1587.

Postmenopausal Hormone Therapy and Breast Cancer: French Cohort Study

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Professor of Obstetrics and Gynecology, Oregon Health and Science University, Portland

Synopsis: *When combined with synthetic progestins, even short-term use of estrogens may increase breast cancer risk. Micronized progesterone may be preferred to synthetic progestins in short-term HRT. This finding needs further investigation.*

Source: Fournier A, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005;114:448-454.

E3N IS A FRENCH PROSPECTIVE STUDY OF CANCER RISK factors—Etude Epidémiologique de femmes de la Mutuelle Générale de l'Eduction National. The study population, after exclusions, consists of 54,548 women born between 1925 and 1950, and all belong to a health insurance program that primarily covers teachers. The data are derived from self-administered questionnaires. Hormonal treatments were identified by a booklet of photographs, but doses were not requested. The average age at the beginning of the study was 52.8, ranging from 40.0 to 66.1 years. Follow-up averaged 5.8 years, but the range was wide: 0.1 to 10.6 years. During this follow-up, 948 cases of primary invasive breast cancer were identified. The overall relative risk of breast cancer comparing users to nonusers was elevated, 1.2 (CI = 1.1-1.4).

	Cases	Adjusted Relative Risk
Estrogen alone	30	1.1 (0.8-1.6)
Estrogens and micronized progesterone	55	0.9 (0.7-1.2)
Estrogens and "synthetic progestins"	268	1.4 (1.2-1.7)
Nonoral	187	1.4 (1.2-1.7)
Oral	80	1.5 (1.1-1.9)

Conclusions: Giving estrogen by oral or nonoral routes made no difference when combined with a synthetic progestin. There was no increased risk associated with the use of estrogen alone or the use of progesterone.

Fournier and colleagues concluded that nonoral estrogen increased the risk of breast cancer only when combined with synthetic progestins.

Use less than 2 years	2-4 years	4 or more years
Any use		
185 cases 1.2 (1,0-1,5)	115 cases 1.2 (1.0-1.5)	72 cases 1.2 (0.9-1.6)
Oral E and synthetic progestins		
36 cases 1.2 (0.9-1.8)	27 cases 1.6 (1.1-2.3)	17 cases 1.9 (1.2-3.2)
Non-oral E and progesterone		
26 cases 0.9 (0.6-1.4)	13 cases 0.7 (0.4-1.2)	16 cases 1.2 (0.7-2.0)
Non-oral E and Synthetic progestins		
95 cases 1.6 (1.3-2.0)	57 cases 1.4 (1.0-1.8)	35 cases 1.2 (0.8-1.7)

COMMENTARY

In contrast to almost every other country in the world, oral hormone therapy is not popular in France—55% of the women in the study used percutaneous gels and 45% used transdermal patches. The progestational agents used were mainly micronized progesterone or progesterone derivatives (medroxyprogesterone acetate, cyproterone acetate, retroprogesterone, nomegestrol acetate, or promegestone). Hardly anyone used conjugated equine estrogens, and only 7.6% used progestins from the 19-nortestosterone family (norethindrone acetate or lynestrenol—labeled as "synthetic progestins)."

Fournier et al's main conclusion is that the association between hormone therapy and the risk of breast cancer varies according to the type of progestin used and not with the route of administration of the estrogen. More specifically, that no increase was observed with micronized progesterone.

The hormone users (29,420 women) differed considerably compared with the non-users (25,128): earlier menarche, earlier menopause, less nulliparity, more children born before age 30, more benign breast disease, less obesity, more education, and a greater previous use of oral contraceptives and progestins. Fournier et al stated that interactions with the characteristics that differed in the 2 groups of women did not change their findings—unfortunately, these manipulations are not presented, because it is surprising that a greater prevalence of recognized risk factors for breast cancer in the hormone user group would not influence the results, and it leaves a clinician uncertain that multiple mathematical adjustments can compensate for these differences.

A major problem with this study is the rapidity at which cases of breast cancer were identified. Fournier et al even calculated a relative risk associated with less than one year of exposure of nonoral estrogens combined with synthetic progestins and amazingly found an increase that was statistically significant: 1.7 (1.3-2.3). I don't think anyone, epidemiologists or clinicians, can believe that hormone therapy causes new cancers to grow in less than one year's time.

Fournier et al make the harmful statement that the "carcinogenic effect of the CEE plus MPA association in continuous administration was proved by the WHI trial and recent observational studies in the USA." The use of the word carcinogenic indicates a causal effect of hormone therapy and this is still not certain—an impact on preexisting tumors remains a very real possibility.

Do these data truly indicate a difference among various progestational agents? Perhaps, but there is an important unanswered question. To differentiate among the various agents one would have to be certain that the doses administered represented bioequivalent doses in terms of target tissue impact. Comparing micronized progesterone to progesterone and 19-nortestosterone derivatives must account for individual variability in absorption and metabolism. This would be a formidable task.

There is another possible interpretation of this report. The very rapid appearance of breast cancer cases is the most noteworthy feature of this study. Is it possible that the combination of estrogen with specific progestins leads to earlier detection of preexisting tumors, whereas lesser potent doses of progestins or qualitative differences among progestins are either lacking in this impact or it takes longer to emerge. It was surprising to me that Fournier et al didn't consider the issue of early detection in their discussion.

Fournier et al divided their hormone users into two groups: incident users who began treatment after and prevalent users who began treatment before the year preceding the beginning of the study. The risk of breast cancer was not increased in the prevalent users, and Fournier et al labeled this group as a less susceptible group of women. Is it possible that early use in the prevalent group led to detection and exclusion from the study?

A cohort study from the Kaiser health program in Southern California has reported an adjusted 31% reduction in all cause and a 48% reduction in breast cancer mortality in users of combined estrogen-progestin therapy who developed Stage I disease.[1] In women with Stage II breast cancer, the all-cause reduction was 47% and the breast cancer mortality reduction of 31%. No reduction was observed in users of estrogen only. Nonhormone users presented with larger tumors that were more likely poorly differentiated. Is it possible that this beneficial effect requires exposure to estrogen and progestin, and is it possible that the response is affected by the specific progestin used?

It seems to me that this study raises many questions, and cannot be used to support a differential impact of different progestational agents. But it does support the possibility that hormone therapy affects preexisting tumors and results in earlier detection. ■

Reference

1. Chen W, et al. Mortality following development of breast cancer while using oestrogen or oestrogen plus progestin: a computer record-linkage study. *Br J Cancer*. 2005;93:392-398.

CME Questions

12. Which is the single best preoperative imaging technique in cases of suspected adnexal torsion?

a. Ultrasound
b. MRI
c. CT scan with contrast
d. KUB
e. CT scan without contrast

13. The following statements are true regarding postmenopausal hormone therapy and breast cancer *except*:

a. A small increase in risk has been reported in current users of estrogen/progestin combinations.
b. No evidence exists indicating that the route of administration influences the risk of breast cancer.
c. The use of "natural" progesterone is safer.
d. An estrogen/progestin combination may influence preexisting tumors more than estrogen alone.

Answers: 12 (a); 13 (c)

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.

www.obgynalert.com

PHARMACOLOGY WATCH

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

Beta-Blockers Therapy for the Treatment of Hypertension

Beta-blockers should not be recommended as first-line therapy for hypertension in patients without heart disease, according to a new study. Researchers from Sweden performed a meta-analysis on 13 randomized controlled trials comparing treatment with beta-blockers with other antihypertensive drugs. Seven other studies were reviewed in which beta-blockers were compared with placebo or no treatment. The relative risk of stroke was 16% higher for patients who were treated with beta-blockers (95% CI, 4-30%) compared to other drugs. Beta-blockers reduced the relative risk of stroke by 19% compared to no treatment or placebo; however, this was about half the reduction expected from previous hypertension trials. There was no difference seen in the rates of myocardial infarction or overall mortality. A possible mechanism for these findings is that beta-blockers reduce brachial blood pressure out of proportion to central blood pressure compared with other antihypertensives.

The authors suggest that beta-blockers are less effective than other antihypertensive drugs in preventing stroke, and should not be a first choice in the treatment of primary hypertension (Lindholm LH, et al. Should Beta Blockers Remain First Choice in the Treatment of Primary Hypertension? A Meta-Analysis. *Lancet*. 2005;366:1545-1553). This same group published a study in 2004, suggesting that atenalol was a poor choice for treatment of hypertension (Carlberg B, et al. Atenolol in Hypertension: Is It Wise?*Lancet*. 2004;364:1684-1689). An accompanying editorial states "Surely, therefore, the era of beta-blockers for hypertension is over," but suggests that these drugs should not be discontinued abruptly, and should be discontinued with extreme caution in patients with coronary artery disease (Beever DG, et al. The End of Beta Blockers for Uncomplicated Hypertension? *Lancet*. 2005;366:1510-1512).

Treatments for Acute Migraine

Two studies in the September issue of the Journal of Headache find that sumatriptan alone is inferior to other treatments for acute migraine. In the first study, 972 migraine patients were randomized to treatment with sumatriptan 50 mg, naproxen sodium 500 mg, sumatriptan 50 mg plus naproxen 500 mg, or placebo at the onset of headache symptoms. The sumatriptan plus naproxen group fared the best, with 46% of subjects achieving a 24-hour pain relief response. Sumatriptan alone resulted in 29% of patients achieving the same result, while naproxen alone resulted in the 25% response, and placebo resulted in a 17% response ($P < .001$). Relief of pain at 2 hours was achieved in 65% of the combination group, 49% of the sumatriptan patients, 46% of naproxen patients, and 27% of placebo patients ($P < .001$). The incidence of recurrent headache 24 hours later was also lowest in the sumatriptan plus naproxen group. Other migraine symptoms, includ-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

ing nausea, photophobia, and phonophobia were also most effectively treated with sumatriptan plus naproxen. Adverse effects were similar in all the treatment groups (Smith TR, et al. Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine. *Headache*. 2005;45:983-991). In the second study, sumatriptan was compared with acetaminophen-aspirin-caffeine (AAC) in the early treatment of migraine. In a randomized, controlled clinical trial, 171 patients took either sumatriptan 50 mg or AAC (acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg [Excedrin Extract Strength 2 tabs], or Excedrin Migraine 2 tabs at the first sign of a migraine attack. AAC was significantly more effective ($P > .05$) than sumatriptan in the early treatment of migraine, as shown by superiority and summed pain intensity difference, pain relief, pain intensity difference, response, sustained response, relief of assisted symptoms, use of rescue medications, disability relief, and global assessments of effectiveness (Goldstein J, et al. Acetaminophen, Aspirin, and Caffeine Versus Sumatriptan Succinate in the Early Treatment of Migraine: Results From the ASSET Trial. *Headache*. 2005;45:973-982).

Statin Therapy for ACS Patients

Early aggressive statin therapy is beneficial for patients with acute coronary syndrome (ACS), according to a new study. In a continuation of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT -TIMI 22) trial, the timing of intensive statin therapy was evaluated in patients with acute coronary syndrome. A total of 4162 patients with ACS were randomized to intensive statin therapy with atorvastatin 80 mg or standard therapy with pravastatin 40 mg. The composite end points of death, MI, or rehospitalization for recurrent ACS were determined for each group at 30 days. ACS patients who were started in the hospital on intensive statin therapy fared better than those with standard therapy (composite end point at 30 days 3% intensive therapy vs 4.2% standard therapy [HR = 0 .72; 95% CI, 0.52 to 0.99; $P = .046$]). The authors conclude that ACS patients should be started on aggressive statin therapy in the hospital and continued long-term (Ray KK, et al. Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes: Results from the PROVE IT-TIMI 22 Trial. *J Am Coll Cardiol*. 2005;46:1405-1410). In another follow-up from the PROVE IT-TIMI 22 study in the same Journal, researchers looked at whether very low LDL levels from aggressive statin therapy are associated with adverse effects. Thirty-one percent of patients treated with atorvastatin achieved LDL levels between 80 and 60mg/dL, with another 34% between 60 and 40 mg/dL, and 11% less than 40 mg/dL. There were no significant differences in safety parameters, including muscle, liver, or retinal abnormalities, intracranial hemorrhage, or death in the very low LDL groups. Patients with LDL levels less than 60 had fewer major cardiac events, including death MI and stroke. The authors conclude that very low LDL levels are not associated with adverse effects, and appear to be associated with fewer adverse cardiovascular outcomes (Wiviott SD, et al. Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy: A PROVE IT-TIMI 22 Substudy. *J Am Coll Cardiol*. 2005;46:1411-1416).

The Correct Dosing for Onychomycosis

Many physicians have prescribed terbinafine in a pulse-dosing regimen of 2 pills per day for one week, one week a month, for 3 to 4 months for the treatment of onychomycosis. The regimen is thought to increase compliance, as well as reduce cost. Pulse dosing however is not an approved therapy, and now a new study suggests that it is not as effective as once daily dosing.

The study recruited 306 volunteers with onychomycosis, involving at least 25% of the toenail. Patients were randomized to terbinafine 250 mg daily for 3 months or terbinafine 500 mg daily for one week per month for 3 months. Mycological cures were higher with once-a-day dosing (71% vs 58.7%; $P = .03$). Clinical cures were also higher with once-a-day dosing (44.6% vs 29.4%; $P = .007$), as were complete cures of target toenail (40.5% vs 28.0%; $P = .02$), and complete cure of all 10 toenails (25.2% vs 14.7%; $P = .03$). Tolerability of the regimens did not differ significantly between groups.

The authors conclude that once daily dosing appears to be superior to pulse dosing, however, they also found "this expensive therapy to me much less effective than previously believed, particular for achieving complete cure of all 10 toenails" (Warshaw EM, et al. Pulse Versus Continuous Terbinafine for Onychomycosis: A Randomized, Double-Blind, Controlled Trial. *J Am Acad Dermatol*. 2005;53:578-584).

FDA Actions

The FDA has approved the once-a-day oral iron chelator for the treatment of chronic iron overload due to blood transfusions. Novartis will market deferasirox (Exjade) as an oral alternative to intravenous chelating agents. ■