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INSIDE

VBAC Revisited

ABSTRACT & COMMENTARY

In some hospitals vaginal birth after cesarean (VBAC) has been eliminated as an option for patients having had previous Cesarean sections. Although the major reason stated for this position has been risk of uterine rupture, there is more to this stance which involves potential liability and the inconvenience to providers of having to be *immediately available* for the duration of these patients' labors.

The NICHD network recently tackled the job of nailing down (again) the real risk of rupture during VBAC. In an observational multi-center trial, Landon and colleagues reviewed outcome data from 17,898 women opting to have VBAC and 15,801 women having elective repeat Cesarean sections. Landon et al were predominantly interested in the rate of symptomatic uterine rupture, which was 7/1000 in the VBAC group and the incidence of neonatal encephalopathy, which occurred in 12 cases in the VBAC group (and in none of the elective Cesarean group). Actually, only 7 of these cases of hypoxic encephalopathy were associated with uterine rupture. The remaining 5 were seemingly secondary to fetal compromise before and during in labor. Landon et al lumped together the 12 cases which resulted in a rate of neonatal encephalopathy of 0.46 per 1000 at term in those electing to have a trial of labor, but actually was only 0.27 per 1000 when associated with uterine rupture.

The need for transfusion and the complications of postpartum endometritis was higher in the VBAC group, but the need for hysterectomy was no different between groups (Landon MB, et al. *N Engl J Med*. 2004;351(25):2581-2589).

COMMENT BY JOHN C. HOBBINS, MD

From this study (and others), it is clear that there is a risk of symptomatic uterine rupture and neonatal encephalopathy in patients with VBAC but it very small (< 1:1000). The incidence of neonatal encephalopathy in the VBAC group without rupture was identical to the overall rate of this condition reported in all laboring patients (1.6 per 10,000).

What was somewhat under-played was the association between

VOLUME 21 • NUMBER 10 • FEBRUARY 2005 • PAGES 73-80

rupture and the use of oxytocics either to induce (1%) or augment labor (0.9%). Interestingly, the rate of rupture of spontaneous labor in VBAC was only 0.4% which gave a likelihood ratio of 1.0.

Landon et al were not able to detect a major effect of prostaglandins. However, a very recent investigation has shown that uterine rupture with oxytocin tended to occur more frequently away from the uterine scar in 64% of cases, while those in whom prostaglandins were used had a rupture in the old scar in 90% of cases.[1] This suggested that prostaglandins had a direct scar softening effect which is certainly not a desired tendency when attempting a VBAC.

The Cesarean rate is now 26% and climbing. To me, there is no doubt that there should be a well ensconced place for VBAC in those motivated to have it (after being presented with the above information). From the available information, the success rate is good (it was 73% in the above study), and the risk of rupture, especially if oxytocics are avoided is extremely low. If rupture is avoided the risk of neonatal encephalopathy is no greater than for any laboring patient. ■

Reference

1. Buhimschi CS, et al. *BJOG*. 2005;112:38-42.

Effects of a Low-Glycemic Load Diet on Resting Energy Expenditure and Heart Disease Risk Factors During Weight Loss

ABSTRACT & COMMENTARY

Synopsis: *The effect of caloric restriction upon metabolism was gated by whether sugars or fats were preferentially restricted. A low-glycemic load diet (glucose restriction) yielded more favorable biochemical profiles than restricting fats.*

Source: Pereira MA, et al. *JAMA*. 2004;292: 2482-2490.

GLYCEMIC LOAD REFERS TO THE EFFECT OF FOOD intake upon subsequent blood glucose levels. All else being similar, a lower glycemic load diet results in a lower postprandial blood glucose and better satiety. In contrast, a high-glycemic load diet appears to elicit hormonal changes that stimulate postprandial hunger and, therefore, increases postprandial food intake. High-glycemic load diets therefore may predispose to obesity.

Resting energy expenditure is essentially the same as what used to be termed *basal metabolic rate*. The higher the basal metabolic rate, the more calories the body burns independent of physical or mental exertion. It has been argued that individuals with a genetically endowed lower basal metabolic rate are prone to obesity and that they have difficulty losing weight because their BMR falls even lower during calorie restriction.

The present study was undertaken to determine if the kinds of calories that are restricted during weight loss matter in terms of basal metabolic rate and lipoprotein profile. Two types of energy restriction (ie, diets) were compared. One diet was low in fat but had a high glycemic index and was similar to what is currently recommended. The other diet had a low glycemic index but was higher in fat content. In the short term, both diets

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: Schandale Kornegay.
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.

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Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2005. This volume has been approved for up to 25 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

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

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Statement of Financial Disclosure

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. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol Myers Squibb, and Ortho Biotech. Dr. Hobbins reports no relationships related to this field of study.
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led to equivalent amounts of weight loss in overweight individuals with a body mass index > 27.

The study found that a lower fat, higher glycemic diet (as compared to higher fat, lower glycemic diet) led to higher insulin and glucose levels (greater insulin resistance) and lower basal metabolic rate (lower resting energy expenditure) despite equivalent weight loss and similar changes in body composition. The lipoprotein profile was better in those who consumed a higher fat but low-glycemic load diet. Pereira and colleagues speculate that the small changes associated with a higher fat and low-glycemic load diet, when summed across a longer time frame, would make a considerable difference in health outcomes and weight change.

COMMENT BY SARAH L. BERGA, MD

A subtitle for this article might be: *Metabolism Made Simple*. Pereira et al have done an artful job of making an exceedingly complicated topic understandable. This is a topic of considerable interest to patients. Patients seem to know that how they diet matters, but they would also like to be reassured that their intuitions are on target. Indeed, with the flood of recommendations available, it is extremely confusing for physicians and patients alike to make sense of all the hype. Enter the present clinical investigation. Not only is this study expertly and cleverly designed, the results are also simply conveyed. If you have any interest in this topic, read this article. It will be worth your investment in time and cognitive energy. I have heard many patients tell me that when they are dieting they are very "sensitive" to food types. Many report a sense of malaise when they eat the "wrong" foods. The present study found that subjects who ate a lower glycemic, higher fat diet has less malaise and less hunger. It appears that they were able to sustain their dieting for longer as well.

It has been hypothesized that the reason patients do not continue to lose weight during dieting is that the body "defends against" ongoing weight loss by decreasing resting energy expenditure (basal metabolic rate). A variety of physiological mechanisms may exist to limit weight loss in the face of ongoing caloric restriction, but the present study was not designed to address the topic of metabolic mechanisms. Instead, Pereira et al sought to answer the question as to which diet is best for forestalling this otherwise important adaptive response in resting energy expenditure to self-imposed famine. Their results suggest that this compensatory physiological response to fuel restriction, ie, failure to continue to lose weight due to slowing of basal metabolic rate, is gated in part by dietary composition. Paradoxically, higher fat diets yield higher resting energy expenditure and therefore, across longer time intervals, should afford greater weight loss. Conventional wisdom dictates just the opposite, ie, lower fat diets are supposed to result in both better lipoprotein profiles as well as better metabolic outcomes. The present study challenges this dictum by showing that diets with low-glycemic load but higher fat content improve lipoprotein profiles and preserve basal metabolic rate, thereby allowing ongoing weight loss. Further, Pereira et al point out that individuals experiencing a larger decline in resting energy expenditure during weight loss may feel more fatigued, colder, and hungrier and that these symptoms make adherence with dieting more difficult. In summary, the higher fat, lower glycemic load diet is better on all counts. Dieting may also compromise mood and cognitive powers, but the present study did not examine these end points. It remains to be seen, then, which diets are best for key brain outputs, but my limited clinical and personal experience would suggest that low-glycemic, higher fat diets are better for the brain, too!

Immunotherapy for Consolidation Treatment of Ovarian Cancer—Is This the One?

ABSTRACT & COMMENTARY

Synopsis: *Consolidation therapy with oregovomab did not significantly improve TTR overall. A set of confirmatory phase III studies has been initiated to determine whether the SFLT population derives benefit from oregovomab treatment.*

Source: Berek JS, et al. *J Clin Oncol*. 2004;22: 3507-3516.

It has been well described and consistently reported that more than half of advanced ovarian cancer patients achieving complete clinical remission (CCR) following primary surgery and chemotherapy will ultimately recur—the majority within 3 years of treatment completion. This observation has prompted many clinicians and researchers to evaluate alternative treatment strategies to improve, in the short term, the duration of remission—in the long term, overall survival. Berek and colleagues evaluated a novel immunotherapeutic agent, oregovomab (Ovarex™), in this setting with the primary objective of improving time-to-treatment relapse (TTR).

The study methodology was a randomized, double-

blinded, placebo controlled trial where patients who had undergone a maximal effort at surgery and chemotherapy and who had achieved CCR were offered participation. The agent, oregovomab, is a murine-derived monoclonal antibody with high affinity for CA-125—the tumor-associated antigen present in more than 90% of non-mucinous epithelial ovarian cancers. Oregovomab, or placebo, was administered to patients at baseline, 4 weeks and 8 weeks after enrollment and then every 12 weeks to 2 years in the absence of tumor progression or toxicity. Tumor recurrence was documented by CT imagery, as the effect of CA-125 immunotherapy on endogenous CA-125 values was not known. Although collected, these values were blinded to Berek as well. Enrollment goals were powered to detect a 50% improvement in TTR with oregovomab. Stratification variables as well as quality-of-life (QOL) parameters were assessed. Overall, the therapy was well tolerated, with few severe adverse events recorded. Likewise, QOL parameters were seemingly unaffected by treatment compared to placebo. Unfortunately, the primary end points were not achieved—no improvement in TTR was detected with oregovomab therapy (13.3 mos vs 10.3 mos; $P = 0.71$).

Survival data were immature and not presented. In the evaluation of risks for relapse, performance status, CA-125 values before the third cycle of chemotherapy, and baseline CA-125 values were identified as prognostic. Subgroup analysis taking these factors into account identified a population that may benefit from oregovomab therapy, demonstrating more than twice the median TTR in treated patients vs controls. Berek et al concluded that while this consolidation strategy did not significantly improve TTR, the exploratory, hypothesis-generating subgroup analysis provided information to support planned and ongoing clinical trials in selected patients.

COMMENT BY ROBERT L. COLEMAN, MD

One of the more difficult aspects of ovarian cancer management is making a solid and convincing recommendation regarding "what to do next" following initial successful therapy. At our disposal are a smorgasbord of options including surgery, observation and additional therapy. Currently, while surgery predominately represents another diagnostic modality for treatment planning, the "second-look" or "reassessment" operation itself is generally not considered standard therapy because we have yet to clearly document that doing the procedure actually improves survival. Indeed, even among those patients deemed in complete remission by pathological assessment, approximately 40-50% will ultimately recur. This event occurs principally from growth of undocumented foci of microscopic or small-volume residual disease. In this regard, additional or consolidation therapy is aimed at addressing this (likely present) disease. Informed counseling involves explaining these clinical facts, providing some estimation of their personal recurrence risk (based on previous findings at surgery, response to therapy by direct or surrogate measures and current disease status) and reviewing the clinical data of trials that have been conducted in this arena. All of these are a challenge to do, but the latter can also be confusing and frustrating to patients who naturally want to maximize their odds of cure.

The confusion stems from the plethora of phase II and III trials that have been conducted in this setting, including hormones, vitamins, radiation, chemotherapy (standard and high dose), radioimmunoconjugates, immune therapy, vaccines, gene therapy, biologics, complementary medicines, and holistic approaches. The delivery is local, regional or systemic and may be relatively invasive and toxic. The frustration (for patients and health care providers) stems from the lack of clear benefit (survival), particularly when one of these "promising" strategies or modalities fails to achieve its anticipated effect when evaluated in formal randomized investigation. To date, the only randomized trial that has demonstrated a clear survival, albeit progression-free survival, advantage has been the GOG/SWOG 178 trial, which found significant improvement in this end point after an additional year of paclitaxel chemotherapy. Of note, 24% of patients randomized to the 12-cycle arm experienced clinical relevant neurotoxicity (grade II/III). The median gain to patients was 7 months and, as discussed in an earlier edition of *OB/GYN Clinical Alert*,[1] some authors have raised the question as to whether similar survival may be achieved by simply adopting a "wait and treat" policy.

The current trial with oregovomab seems to follow suit with most other agents evaluated in this setting.[2-4] While unique and interesting in its mechanism of action, the primary objective was not reached. However, all is not lost in that, as is often the case, good clinical design has allowed for preliminary evaluation of other exploratory hypotheses. In the current trial, two important observations were discussed: mounting of individual human anti-mouse antibody (HAMA) titers and subgroup patient selection. In both of these cases, interesting findings have ushered development of follow-up protocols, which may allow this immuno-targeted strategy to succeed in the treatment of advanced ovarian cancer. ■

References

1. Coleman R. *OB/GYN Clinical Alert*. 2004;21(8):61-62.

2. Alberts DS, et al. *Int J Gyn Can*. 2004:14:224-228.
3. De Placido S, et al. *J Clin Oncol*. 2004; 22:2635-2642.
4. Markman M, et al. *J Clin Oncol*. 2003;21:2460-2465.

Improving the Use of Prophylactic Antibiotics

ABSTRACT & COMMENTARY

Synopsis: *Instituting a policy for prophylactic antibiotics can increase their appropriate use.*

Source: DiLuigi AJ, et al. *J Reprod Med*. 2004;49:949.

DILUIGI AND COLLEAGUES IN RHODE ISLAND COMpared the outcomes of 400 patients undergoing hysterectomy with 686 hysterectomy cases performed prior to the institution of a policy for prophylactic antibiotics. Abdominal, vaginal, and laparoscopic cases were included, with the primary aspects being rates and timing of preoperative antibiotic administration as well as postoperative febrile morbidity. The rate of antibiotic administration went from 50% to 91%. Febrile morbidity was 14% prior to the policy, and 11% afterwards. Because of the well-established body of literature that supports the use of antibiotics prior to hysterectomy, the authors demonstrate that implementing a policy within an institution may be needed to improve the practice of evidence-based medicine.

COMMENT BY FRANK W. LING, MD

Take note. Each of our hospitals *can* make a difference in how medicine is practiced. Given good data, how medicine is practiced *can* be affected by good hospital policy. This study is both simple and imposing. It is simple because it shows a simple outcome: you *can* markedly increase the appropriate use of antibiotics prior to hysterectomy. The implications for each of us at each of our hospitals are imposing: we *can* improve the way that evidence-based medicine is practiced if we choose to do so.

This publication is the second part of a Quality Improvement Initiative at Women and Infants Hospital. DiLuigi et al had already determined that only half of the patients were getting antibiotics prior to hysterectomy. By policy, patients were now to get cefazolin 2 gm (clindamycin 900 mg if allergic to penicillin or cephalosporin). The attending physician had to actively cancel the order for the patient not to receive the antibiotic. Not surprisingly, the patients who did not receive the antibiotics had a higher rate of febrile morbidity. These numbers were too small, however, to be analyzed separately. Those with fever, however, were hospitalized significantly longer.

It is well-established that the goal of administering antibiotics is to achieve tissue and blood levels prior to the procedure. Additional doses have been recommended if blood loss exceeds 1500 cc or the surgical time exceeds 1-2 half-lives of the antibiotic. Despite sound scientific literature, use of prophylactic antibiotics remains spotty. These data from 2000 should make us notice what is happening in our respective hospitals.

I am certainly a proponent of quality of care, but also a proponent of a physician's ability to make clinical decisions independently. In this case, I am comfortable suggesting an application of this study that could be useful in all of our hospitals. As a simple review, the hospital can see if prophylactic antibiotics are being used prior to hysterectomy—be they abdominal, vaginal, or laparoscopic. The medical staff's active participation will make this a painless and potentially useful review. If there is room for improvement, a protocol might be considered, something as simple as routine orders for pre-operative antibiotics before any hysterectomy that the attending surgeon must actively cancel in order for the protocol not to apply. Short of a protocol, the physicians, acting as a group, might make a recommendation that prophylactic antibiotics be used. Then, only if there remains a discrepancy between appropriate use and real use, would the department consider implementing a protocol.

The goal here is quality of patient care. Something as simple as prophylactic antibiotics prior to hysterectomy would seem to be a no-brainer. In one of the hospitals where I do surgery, I don't have to worry whether a patient fulfills the criteria for sequential compression boots. There is a protocol in place and they are applied before I even pre-op the patient in the holding area. My life is simpler and I'm glad the medical staff took these steps. What about other examples? I know that antibiotics have been shown efficacious for Cesarean deliveries for sure. A protocol for that wouldn't be a bad idea. My urogynecology partner recommends that prophylactic antibiotics be used anytime a sling is used for incontinence. The data to support this are few, but this is what he does. Maybe a protocol for that is still a ways away.

I think you get the point. Look around at your practice, your hospital, your environment. Would your patients and those of the other OB/GYN physicians benefit from the collective wisdom of all the doctors and the literature? This article would provide a model by which significant changes can be made in a painless and effective fashion. ■

Special Feature

The WHI-Wayne State Fracas

By Leon Speroff, MD

Women's health initiative (WHI) investigators from Wayne State University performed an analysis using the WHI database and presented the results at the 2004 annual meeting of the American Society of Reproductive Medicine (ASRM).[1,2] An oral presentation entitled *Adverse Cardiovascular Disease Outcomes Are Reduced in Women with a History of Oral Contraceptive Use* was selected as the prize paper by the ASRM-affiliated organization, the Society of Reproductive Endocrinology and Infertility. This analysis concluded that previous users of oral contraceptives (OCs) had a reduced risk of various cardiovascular outcomes, including hypercholesterolemia, angina, myocardial infarction, transient ischemic cerebrovascular attacks, and peripheral vascular disease. Another presentation indicated that previous users of OCs had reduced cancer risks (endometrial, ovarian, and breast).

Two months later, the presentation on the effects of oral contraception on cardiovascular disease drew a critical response from the director of the WHI, Barbara Alving, MD, who is also the acting director of the National Heart, Lung, and Blood Institute. Alving issued a statement revealing that the work from Wayne State had been reviewed by the WHI and that flaws were discovered in both the design and interpretation.[3] Indeed, the WHI review indicated no evidence that OC use is linked to a lower risk of cardiovascular disease. Appropriately the WHI pointed out that the Wayne State analysis was performed post hoc, using the information provided by the WHI participants based on their recall upon entry to the study, a study that was not designed to examine a relationship between OCs and cardiovascular disease. Alving emphasized that the original presentations were not reviewed by the WHI or NIH, and that subsequent review by the WHI statisticians could not find a relationship between OC use and cardiovascular disease, and that the statisticians further doubt the validity of the presentation on cancer risks.

Unfortunately, Alving then stated that "there is a large and reputable body of higher scientific evidence linking current OC use to future increases in risk of stroke and heart attack, especially in older women and in smokers." She further stated that research indicates an increased risk of breast cancer in women who have recently used OCs. Alving acknowledged a decreased risk of ovarian cancer in OC users, but stated that the decreased risk of endometrial cancer is only a slight one.

In response to the objections of the WHI, Wayne State University issued a press release, authored by 2 of the co-authors of the original ASRM presentations.[4] The press release essentially agreed with the position of the WHI, pointing out that analysis of the WHI baseline data is "exploratory" at best. But the press release goes further, essentially retracting the original conclusions, stating that "analyses of these data don't support inferences of either cardiovascular disease benefit or risk when additional account is taken of the complex relationships between the ages of participating women and OC use patterns and cardiovascular disease."

Embarrassing Moment

This is an embarrassing moment, to be sure, but also another example of the inappropriate dissemination of information by the WHI to the public. It is not good science and it is not good for the public welfare to generate conclusions from data created for a different purpose and in a design not directed for the publicized end point. The WHI criticized its own investigators for this action, but this whole scenario is not that different from previous WHI conclusions that were applied to all postmenopausal women when they were derived from a small and special group of older women. Furthermore, the WHI compounds this unpleasant story by making statements that are flat out wrong.

There is no evidence of an increase in risk of cardiovascular disease among past users of oral contraception.[5-7] In the Nurses' Health Study, the Royal College of General Practitioners' Study, and the Oxford Family Planning Association Study, long-term past use of OCs was not associated with an increase in overall mortality.[8-10] Part of the concern for a possible lingering effect of OC use was based on a presumed adverse impact on the atherosclerotic process, which would then be added to the effect of aging and, thus, would be manifested later in life. Instead, the findings have been consistent with the contention that cardiovascular disease due to oral contraception is secondary to acute effects, specifically estrogen-induced thrombosis, a dose-related event.

Almost all myocardial infarctions and strokes in OC users occur in users of high-dose products, or users with cardiovascular risk factors older than the age of 35. In the Oxford Family Planning Association cohort, cardiac deaths occurred only in women who smoked 15 or more cigarettes per day.[10] OCs containing less than 50 µg ethinyl estradiol do not increase the risk of myocardial

infarction or stroke in healthy, nonsmoking women, regardless of age. The effect of smoking in women younger than age 35 is, as we have long recognized, not detectable in the absence of hypertension. After age 35, the subtle presence of hypertension makes analysis difficult, but studies indicate that increasing age and smoking by themselves have little impact on the risk of stroke in low-dose OC users. The studies do indicate that hypertension should be a major concern, especially in regards to the risk of stroke.

Increased Risk of VT

All low-dose OCs, regardless of progestin type, have an increased risk of venous thromboembolism, concentrated in the first 1-2 years of use. The risk increases with increasing age and body weight. The actual risk of venous thrombosis with low-dose OCs is lower in the new studies compared with previous reports. Some have argued that this is due to preferential prescribing and the healthy user effect. However, it is also logical that the lower risk reflects better screening of patients and lower estrogen doses.

Patient Screening

The importance of good patient screening cannot be overemphasized. The occurrence of arterial thrombosis is essentially limited to older women who smoke or have cardiovascular risk factors, especially hypertension. The impact of good screening is evident in the repeated failure to detect an increase in mortality due to myocardial infarction or stroke in healthy, nonsmoking women.[10-12] Although the risk of venous thromboembolism is slightly increased, the actual incidence is still relatively rare, and the mortality rate is about 1% (probably less with OCs, because most deaths from thromboembolism are associated with trauma, surgery, or a major illness). The minimal risk of venous thrombosis associated with OC use does not justify the cost of routine screening for coagulation deficiencies.

OCs and Cancer

I want to emphasize that the use of OCs for at least 12 months reduces the risk of developing endometrial cancer by 50%, with the greatest protective effect gained by use for more than 3 years (this is hardly a "slight" reduction).[13-18] This protection persists for 20 or more years after discontinuation (the actual length of duration of protection is unknown) and is greatest in women at highest risk: nulliparous and low parity women.[18,19]

How about Alving's definitive statement that there is an increased risk of breast cancer in recent users of OCs? I suspect that the statement refers to the collaborative group reanalysis of data from 54 studies in 26 countries, a total of 53,297 women with breast cancer and 100,239 without breast cancer.[20,21] The relative risk analyzed by duration of use was barely elevated and not statistically significant (even when long-term use, virtually continuous, was analyzed). Women who had begun use as teenagers had about a 20% statistically significant increased relative risk. In other words, recent users who began use before age 20 had a higher relative risk compared with recent users who began at later ages. The evidence was strong for a relationship with time since last use, an elevated risk being significant for current users and in women who had stopped use 1-4 years before (recent use). Even though the data indicated that young women who begin use before age 20 have higher relative risks of breast cancer during current use and in the 5 years after stopping, this is a time period when breast cancer is very rare; and, thus, there would be little impact on the actual number of breast cancers. It is possible that early and recent use of OCs also affects the growth of a preexisting malignancy, explaining the limitation of the finding to current and recent use and the increase in localized disease. The largest case-control study thus far included 4575 American women with breast cancer, and most importantly, the women were 35 to 64 years old.[22] The risk of breast cancer was not increased in current users or past users of oral contraception. There was no adverse effect of increasing duration of use or higher doses of estrogen, with no differences in current or recent users. Initiation at a younger age had no impact, and there was no increase in risk in women with a family history of breast cancer. This large American study had consistently negative results.

It's disappointing that the NIH and the WHI can't get things right. ■

References

1. Victory R, et al. *Fertil Steril*. 2004;82:S52-S53.
2. Victory R, et al. *Fertil Steril*. 2004;82:S104-S105.
3. Alving B. Statement on Oral Contraceptive Study: www.nhlbi.nih.gov/new/press/04-12-15.htm 2004.
4. Hendrix S, Prentice R. Cardiovascular Disease. Press Statement from Wayne State University and the Women's Health Initiative. www.whi.org/news/press_oral_contraceptives.php 2004.
5. Croft P, et al. *Br Med J*. 1989;298:165-168.
6. Rosenberg L, et al. *Am J Epidemiol*. 1990;131: 1009-1016.
7. Stampfer MJ, et al. *Am J Obstet Gynecol*. 1990;163: 285-291.
8. Colditz GA, and the Nurses' Health Study Reasearch Group. *Ann Intern Med*. 1994;120:821-826.

9. Beral V, et al. *Br Med J*. 1999;318:96-100.
10. Vessey M, et al. *Lancet*. 2003;362:185-191.
11. Jick H, et al. *Lancet*. 1995;348:1589-1593.
12. Petitti DB, et al. *Stroke*. 1997;28:280-283.
13. The Cancer and Steroid Hormone Study of the CDC and NICHD. *JAMA*. 1987;257:796.
14. Schlesselman JJ. *Contraception*. 1991;43:557.
15. Vessey MP, Painter R. *Br J Cancer*. 1995;71:1340.
16. Schlesselman JJ. *Hum Reprod*. 1997;12:1851-1863.
17. Salazar-Martinez E, et al. *Cancer Res*. 1999;59: 3658-3662.
18. Weiderpass E, et al. *Cancer Causes Control*. 1999;10: 277-284.
19. Jick SS, et al. *Obstet Gynecol*. 1993;82:931-935.
20. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1996;347:1713-1727.
21. Collaborative Group on Hormonal Factors in Breast Cancer. *Contraception*. 1996;54:1S-06S.
22. Marchbanks PA, et al. *N Engl J Med*. 2002;346: 2025-2032.

CME Questions

4. The following statements are true regarding oral contraception and cardiovascular disease *except*:

a. arterial cardiovascular events are essentially limited to low-dose oral contraceptive users who are older and smokers or who are hypertensive.
b. not one study has thus far found an increase in cardiovascular disease in past users of oral contraceptives.
c. venous thrombosis occurs only in oral contraceptive users who are heavy smokers.
d. case-control and cohort studies have not found a significant increase in breast cancer in oral contraceptive users.

5. Higher fat, low-glycemic load diets appear to:

a. worsen lipoprotein profiles.
b. improve insulin resistance.
c. raise postprandial blood sugar.
d. decrease basal metabolic rate.
e. retard weight loss.

Answers: 4 (c); 5 (b)

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.*

Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

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.

Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■