2003 Contraception Survey Enclosed

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INSIDE

Trends in Incidence Rates of Invasive Lobular and Ductal Breast Carcinoma

ABSTRACT & COMMENTARY

THE RATIONALE FOR THE PRESENT INVESTIGATION WAS THAT A growing number of studies have reported that the risk of breast cancer associated with use of combined hormone replacement therapy (CHRT) differs by histological type. Specifically, 5 separate studies have shown that ever use and current use of CHRT are associated with 2.0-fold to 3.9-fold increased risks of invasive lobular breast carcinoma, the second most common histological type of breast cancer. These same studies show little effect on risk of the most common histological type, invasive ductal breast cancer. Li and colleagues note that these 5 studies also found that use of unopposed estrogen replacemnet therapy (ERT) was not strongly associated with risk of either type. The 2 studies that had sufficient power to examine the relationship between duration of CHRT use and invasive lobular breast cancer found a positive correlation. Li et al also note that invasive ductal breast cancer is more likely to be hormone receptor-positive and to have a better prognosis than invasive ductal breast carcinoma. However, invasive lobular breast cancer is less likely to be detected by mammography and clinical breast examination (Li CI, et al. *JAMA*. 2003;289:1421-1424).

Given the above considerations, Li et al examined 9 cancer registries that participate in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute to ask about incidence trends in types of breast cancers. These registries cover the regions of Atlanta, Detroit, San Francisco-Oakland, Seattle, Connecticut, Hawaii, New Mexico, and Utah. A total of 190,458 women were included who were 30 years or older and who had had breast cancer. There was no increase in breast cancer rate from 1987 to 1999 (about 210 cases per 100,000). Rates of lobular carcinoma increased 1.52-fold and those of ductal-lobular 1.96-fold, for a combined increase of 1.65-fold (19.8/100,000 to 33.4/100,000). Rates of invasive ductal breast cancer remained at 154/100,000. Thus, the percentage of invasive breast cancers that was lobular increased from 9.5% to 15.6% for the 12-year interval.

VOLUME 20 • NUMBER 2 • JUNE 2003 • PAGES 9-16

The registry does not allow for ascertainment of hormone use, but Li et al note that the data are consistent with the hypothesis that CHRT is associated with an increased risk of invasive lobular breast cancer.

COMMENT BY SARAH L. BERGA, MD

I chose to review this study because it illustrates a number of important concepts and because the results suggest ways to refine our prescription of postmenopausal hormone therapy. A methodological strength of the study is that the analysis is based on a very large number of cases of known invasive breast cancer. There were more than 190,000 cases of breast cancer in which the histological type was known! In contrast, the conclusions of the Women's Health Initiative were based on only 290 cases of invasive breast cancer, and the histological type was not considered in that analysis. The conceptual strength is that the present study is based on the premises that not all breast cancers are the same and that not all hormone regimens are the same. While these caveats might seem intuitively obvious, most studies ask if "hormone use causes breast cancer," and the underlying assumptions are that hormone use is homogeneous and that all breast cancers are the same with regard to causality (and that all women have the same host characteristics). These assumptions have always struck me as unjustified simplifications, but it is nice to have data that reveal the error of this reductionistic question and analytic approach.

The current study design would have been immeasurably strengthened if actual hormone use could have been ascertained, but there are other data in which hormone use has been determined, and these studies also suggest that it is the progestin rather than estrogen component that increases the risk of breast cancer. As Li et al point out in the introduction, in the Women's Health Initiative, a strength of which is that hormone use is known, combined hormone use was associated with "a statistically nonsignificant 26% increase in risk of breast cancer after 5.2 years." If one assumes that the interpretation suggested by the present study results is valid, namely, that it is combined estrogen-progestin use that increases the risk of lobular breast cancer, then this might well change prescribing practices. One prescribing response would be to give very low doses of unopposed estrogen to women with intact uteri while monitoring the endometrium. Another strategy would be to minimize circulating progestin levels by prescribing the most minimal dose of progestin possible or by confining the progestin exposure to the uterus by inserting a progestin-containing intrauterine device (which gives trivial circulating levels of progestin). Based on extant data, it is reasonable to hope that strategies that minimize or eliminate progestin exposure also might confer better brain (mood and cognition) and cardiovascular outcomes as well.

Questions that are raised by the study include whether the type of progestin matters (Does medroxyprogesterone acetate confer greater risk than norethindrone or progesterone?) and whether there is a difference in risk between cyclic and continuous progestin regimens. The study by Marchbanks et al (*New Engl J Med.* 2002;346:2025-2032 and reviewed in the August 2002 issue of *OB/GYN Clinical Alert*) regarding risk of breast cancer among oral contraceptive users found no increase in risk from combined estrogen-progestin exposure, but both the estrogen and the progestin component in oral contraceptives differs from the most commonly used estrogen and progestin preparations used for postmenopausal hormone use during the study period. The present study

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

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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: $40.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
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(Resident/Student rate: $145).
Multiple Copies
1-9 additional copies: $213 each; 10 or more copies: $190 each
Canada
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This CME activity was planned and produced in accordance with the ACCME Essentials.

Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2003. 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.

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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. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Noller and Dr. Hobbins report no relationships related to this field of study.

provides the rationale for additional studies that address these points. Given the paucity of data that address these questions, however, it is too soon to draw conclusions or become dogmatic.

The current study illustrates another key point, which is that the best conclusions are those that reconcile competing data and conclusions by refining both the questions and the answers. In this case, the question "Does hormone use cause breast cancer?" now becomes "Does a particular regimen of postmenopausal hormone use increase the risk of any given type of breast cancer?" This would not be the end of the refinements, however, because one still wants to know about the "host characteristics" that also modify risk. It is a statement of the obvious that not all women are the same, but most epidemiological studies have done little to help us delineate which women might be at higher risk of getting lobular breast cancer from extended combined hormone use.

My final parting shot is to ask where was the news coverage about this article? It was in *JAMA*, and most of the time articles in *JAMA* about breast cancer are widely reported. There might be a number of explanations, but I wonder if the conclusions are not simple enough for the newspaper audience. In other words, the findings are too "gray" and we all know that the best news is "black and white." ■

Hormonal Contraception and Cervical Cancer

ABSTRACT & COMMENTARY

Synopsis: *An increased risk of cervical cancer is associated with long durations of use of hormonal contraceptives.*

Source: Smith JS, et al. *Lancet*. 2003;361:1159-1167.

A team of epidemiologists performed a meta-analysis of 28 studies examining the relationship between invasive and in situ cervical cancer and hormonal contraception. The analysis included 12,531 women with cervical cancer in 4 cohort and 24 case-control studies. Hormonal contraceptive use was grouped into categories: short-duration (less than 5 years), medium-duration (5-9 years), and long-duration (10 or more years). Overall, the relative risk of cervical cancer increased with increasing duration of use, from 1.1 (CI, 1.1-1.2) with short-duration use to 2.2 (1.9-2.4) with long-duration use. The risk declined gradually after discontinuation. When the analysis was confined to the 3000 cases who tested positively for HPV, the relative risks for short, medium, and long duration of use were: 0.9 (0.7-1.2), 1.3 (1.0-1.9), and 2.5 (1.6-3.9), respectively. The results were less marked in HPV negative women; indeed, a slight increase did reach statistical significance. The relationship was observed for in situ and invasive cancer and both squamous cancer and adenocarcinoma.[1]

COMMENT BY LEON SPEROFF, MD

Cancer of the uterine cervix is now believed to be significantly caused by persistent infection with certain types of the sexually transmitted human papillomavirus (HPV). The medical literature suggests that the use of hormonal contraceptives can influence whether HPV leads to cervical cancer. This meta-analysis supports this conclusion, finding an increasing risk with increasing duration of hormonal contraceptive use, persisting after adjustments for sexual partners, smoking, and use of barrier methods of contraception. The data largely reflect the use of combined estrogen-progestin oral contraceptives.

Although the data with injectable contraceptives (largely progestin only) were limited, Smith and associates report a slight increase with this method as well. All methods of hormonal contraception were lumped together; therefore, results according to specific types and doses are unavailable.

I have a slide that I have frequently used for more than 5 years. It reads: "Meta-Analysis is to Analysis like Meta-Physics is to Physics." The technique of meta-analysis dates back to the late 1970s when it was initiated as a method to bring together small, randomized trials in order to increase statistical power. In the 1980s and 1990s, meta-analysis was rapidly extended to case-control and cohort studies. Clinicians soon came to give great weight to conclusions from meta-analyses, believing that the sophistication of the method provided reliable conclusions.

The technique of meta-analysis contains an important element of subjectivity. A group of individuals makes judgments regarding published studies, decisions about how good or bad each study is, and whether the conclusions should be incorporated into their own decision-making. Meta-analysis cannot correct confounding problems and biases in the original studies, and the conclusion of a meta-analysis can be misleading. An excellent example is the 1996 meta-analysis concluding that induced abortion increased the risk of breast cancer.[1] Subsequently it was discov-

ered that case-control studies of this subject contained a major problem of recall bias (the healthy women in the control groups were reluctant to tell the truth about induced abortions). Appropriately designed studies (avoiding personal interviews) do not find an association between induced abortions and the risk of breast cancer.[2,3]

Cancer of the cervix is affected by many risk factors. Is it possible to lump 28 studies together and adequately control for confounding influences? Even the authors of this meta-analysis point out in their discussion that not a single one of the original studies adjusted for all confounding factors, and it would require uniform definitions and adjustments in each individual study to improve the reliability of the data. An excellent study from the Centers for Disease Control and Prevention (CDC) concluded that there is no increased risk of invasive cervical cancer in users of oral contraception, and an apparent increase in situ cancer is due to enhanced detection because of more frequent Pap smears.[4] However, the World Health Organization Study found an increased risk of in situ cancer even when Pap smear frequency was adjusted.[5] Very concerning is the rising incidence of adenocarcinoma of the cervix in young women over the last 20 years and impressive agreement among case-control studies that the risk of cervical adenocarcinoma increases with increasing duration of oral contraceptive use.

Fortunately, Pap smear surveillance is very effective for cervical cancer. The new methods incorporating HPV identification will be even better. This is another good argument against making hormonal contraception available over the counter. This meta-analysis of hormonal contraception and cervical cancer shouldn't change clinical practice because evaluation for cervical cancer is already part of the routine care for these women. It makes sense to me to perform cervical cancer screening every 6 months in women using hormonal contraception for longer than 5 years, especially if they are at higher risk because of their sexual behavior. ■

References

1. Brind J, et al. *J Epidemiol Community Health*. 1996; 50:481-496.
2. Mahue-Giangreco M, et al. *Cancer Epidemiol Biomarkers Prev*. 2003;12:209-214.
3. Erlandsson G, et al. *Int J Cancer*. 2003;103:676-679.
4. Irwin KL, et al. *JAMA*. 1988;259:59-64.
5. Ye Z, et al. *Int J Epidemiol*. 1995;24:19-26.

Does Cesarean Delivery Prevent Anal Incontinence?

ABSTRACT & COMMENTARY

Synopsis: *Severe anal incontinence occurs after elective cesarean delivery as well as vaginal delivery, suggesting that pregnancy itself may lead to pelvic floor disorders.*

Source: Lal M, et al. *Obstet Gynecol*. 2003;101: 305-312.

RESEARCHERS FROM THE UNITED KINGDOM COMPARED the incidence and severity of anal incontinence after cesarean and vaginal delivery among primiparous patients. Nine months after delivery, primiparas received letters inviting them to participate, followed by telephone interviews and ultimately a validated questionnaire, the "Birmingham Bowel and Bladder Questionnaire." Ultimately 184 patients were interviewed (100 vaginal deliveries, 104 emergency cesareans, and 80 elective cesareans). Anal incontinence first occurred in 8% after vaginal delivery and 5% after cesarean delivery (RR, 0.611; 95% CI, 0.25-1.53). Severe cases, requiring use of a pad, affected 2 patients after vaginal delivery and 1 after cesarean delivery. Among 22 patients with a second-degree tear, 23% had new anal incontinence compared with 3% among mothers with an intact perineum. Because anal incontinence appeared after both cesarean and vaginal delivery and because severe anal incontinence followed both elective and pre-labor emergency cesarean delivery, the role of pregnancy itself should also be considered when searching for a cause of new anal incontinence. Lal and colleagues recommend that postpartum anal incontinence should be a consideration in all women who have delivered, including those who had cesarean delivery.

■ COMMENT BY FRANK W. LING, MD

The title of the article is right on target. This is a question that all of us who deliver babies and see the mothers postpartum have struggled with. How many times have we tried to explain to a patient what effect the vaginal delivery had on their postpartum anal incontinence? What about the use of operative intervention, whether vaginal or abdominal? Couldn't a cesarean have prevented this outcome? Vaginal delivery may lead to anal incontinence by way of pudendal neuropathy or direct trauma to the anal sphincter, but the role of cesarean delivery is unclear. Two studies question whether emergency cesarean delivery is protective against anal incontinence.[1,2]

This study population comes from a single institution, is 95% white, and all the episiotomies were mediolateral. The incidence of anal incontinence following vaginal delivery is comparable to the literature, but the finding that elective cesarean and prelabor emergency cesarean are not always protective against anal incontinence is significant. Although this study is somewhat limited by recall bias, focusing on primiparous patients minimizes this concern. An additional finding that should not be lost is the relationship between second-degree tears and subsequent anal incontinence. Anal ultrasound was not used to document the degree of damage, thereby reducing the reliability of these findings.

So what's the point? I believe that the "take home message" is we should not counsel our patients that cesarean delivery will invariably protect the pelvic floor. Pregnancy itself may, in some cases, be the culprit in subsequent anal incontinence. Decisions regarding mode of delivery should not be inappropriately optimistic relative to future problems. Patients complaining of incontinence after cesarean delivery should be evaluated as completely as after a vaginal delivery. This article does add a few brushstrokes to an increasingly complex painting. ■

References

1. MacArthur C, et al. *Br J Obstet Gynaecol*. 1997;104: 46-50.
2. Fynes M, et al. *Obstet Gynecol*. 1998;92:496-500.

Prospective Study of Alcohol Consumption and Risk of Dementia in Older Adults

ABSTRACT & COMMENTARY

Synopsis: *Compared with abstention, consumption of 1-6 drinks weekly of alcoholic beverages was associated with a lower risk of dementia among adults older than 65 years.*

Source: Mukamal KJ, et al. *JAMA*. 2003;289: 1405-1413.

Alcohol consumption is a common practice, but the notion that drinking alcoholic beverages has health benefits remains controversial. Like drinking, dementia is common among adults older than 65 years and thus, is an important public health concern. Given that there are more than 360,000 new cases of Alzheimer dementia diagnosed annually in the United States, there is a pressing need to identify modifiable factors that may cause or prevent dementia. The present study was undertaken to see if there was a link between alcohol consumption and the risk of dementia. Pre-existing data were conflicting, with some data indicating that alcohol promoted cortical atrophy or cerebral hemorrhage, which would promote dementia. Other data indicated a beneficial effect, possibly because of a reduced risk of cardiovascular disease or increased cerebral circulation. Prior studies also suggested sex-linked differences in the health effects of alcohol consumption.

This was a meticulously conducted, prospective, nested case-control study of 373 persons with incident dementia and 373 controls who were among 5888 adults older than 65 participating in the Cardiovascular Health Study, a prospective, population-based cohort study in 4 US communities. Participants underwent magnetic resonance imaging of the brain and cognitive testing between 1992 and 1994 and were followed until 1999. The ascertainment of dementia was thorough, involving extensive testing done in 4 stages. Alcohol consumption was estimated by questionnaire at 6-month intervals for the course of the study. A number of factors that might modify the association between alcohol consumption and dementia were assessed, including sex, race, age, educational attainment, body mass index, diabetes, income level, physical activity, smoking, depression, use of hormone replacement therapy, cardiovascular disease, stroke, lipoprotein profiles, and apolipoprotein E genotype (ε4 allele).

Of the 373 cases, 258 had Alzheimer disease, 44 had vascular dementia, 54 had combined AD and vascular dementia, and 17 had other kinds of dementia. Age-adjusted rates of dementia were 56 per 1000 among black participants and 36 per 1000 among white subjects. Using the entire cohort, logistic regression models that adjusted for potentially confounding variables indicated that the lowest odds ratio for dementia occurred among those consuming 1-6 drinks per week. The highest odds ratio occurred among those consuming 14 or more alcoholic drinks weekly. Participants who consumed 1-6 drinks weekly had a 54% lower odds of experiencing dementia that those who abstained [OR 0.46; CI, 0.27-0.77]. This same reduction held when AD risk was analyzed separately from all causes of dementia. With increasing alcohol intake, women seemed to fare better than men. For women, the odds ratio fell to 0.23 [CI, 0.09-0.61] for those who drank 7-13 alcohol beverages weekly. For men, the OR increased to 1.42 for those consuming 7-13 drinks weekly. When considering the risk in those who drank

more than 14 drinks weekly, for women, the OR remained low at 0.39 while for men it was 2.40. Although Mukamal and colleagues state that the type of alcoholic beverage (wine, beer, liquor) did not change the association, Table 4 in the manuscript showed that among those drinking more than 14 drinks weekly, the OR for wine was 0.62, while it was 1.96 for beer and 1.08 for liquor. Having APOE ε4 further increased the risk of dementia in those drinking more than 14 drinks weekly. These associations were similar in those who met criteria for depression.

COMMENT BY SARAH L. BERGA, MD

Alcohol consumption is often considered a taboo subject of discussion, even in physician's offices. But patients need to know which lifestyle factors make a difference. Counseling patients about alcohol consumption is not as straightforward as counseling patients about smoking cessation, because there is less room for dogmatism when it comes to alcohol. As far as I know, there are no known health benefits associated with smoking or using tobacco. In contrast, studies have indicated that light-to-moderate drinking may confer a range of health benefits when compared to abstention. The present study, which has many strengths, suggested that there is a relatively narrow dose range in which alcohol may provide neuroprotection from dementia. Because the dose range for benefit was wider for women than for men and for those who drank wine rather than beer or liquor, one wonders if the different results in men and women are explained by alcohol preferences. Did women drink more wine than men? Did men drink more beer and liquor than women? Mukamal et al did not provide these data nor discuss this aspect. They do caution that the study results should not be interpreted as suggesting an increased intake of alcohol is recommended for women. As I have pointed out in previous reviews on this subject, women are more at risk than men for alcohol-induced myopathy and cardiomyopathy. Also, some have suggested a link between alcohol consumption and breast cancer in women. Women may absorb alcohol more quickly than men and achieve higher blood levels, placing them at increased risk for motor vehicle and other accidents after drinking. Thus, it would be premature on the basis of this study to counsel women that it was safe to drink more than 6 drinks weekly. We want to screen for those who are alcoholics, while reassuring the rest of our patients that "light" drinking might provide health benefits. ■

Special Feature

Should Every Patient Have Second-Trimester Biochemical Testing Regardless of Amniocentesis?

By John C. Hobbins, MD

We have had many patients decline triple or quad screen testing because "it would not be useful since I am having an amniocentesis" or "the test has too many false positives." Often these statements represent paraphrased comments made by their providers.

The "false positive" concept is one we deal with on a day-to-day basis and represents a misconception about screening tests in general. A false-positive result means that a diagnostic test indicates a problem to be present when it is not. A positive screening test indicates that a given patient is at higher or lower risk for a problem, and often the test can quantify that risk. It would be inappropriate to apply the false-positive concept to a patient with a risk of Down syndrome of 1 in 200 (designated by the lab as a "positive"). This would give her a false-positive rate of 99.5%. Also, by applying triple screening to a population at risk, the test justifiably reassures far more commonly that it raises concerns unnecessarily. That said, the point of this special feature is to demonstrate that there is more to biochemical testing in the second trimester than screening for aneuploidy or neural tube defects. Each analyte contributes selective information about a complex physiological situation involving mother, placenta, and fetus.

MSAFP

Virtually all of the AFP found in the maternal circulation comes from the fetus. The concentration of AFP in the fetal circulation, all emanating from the fetal liver in the second trimester, is in mg percentage. In the amniotic fluid it registers in microgram amounts and in the maternal circulation it is measured in nanograms. Therefore, when the placenta fails on its gate-keeping activity, even the small amounts of transferred AFP will have a major effect on maternal concentrations of the analyte.

Many studies have shown a higher rate of IUGR, maternal hypertension, and intrauterine demise when MSAFP is elevated in the second trimester. A study from Oregon has indicated that in an at-risk group of 113 patients with elevated MSAFP, 35 had an adverse pregnancy outcome. Of these, 12 had heightened surveillance testing and 22 had

routine care. The heightened surveillance did not achieve earlier or improved detection of adverse outcome.

A review of the literature has indicated that the dreaded intrauterine demise, although increased above baseline rates in elevated MSAFP, is still very uncommon and very rare in the absence of IUGR.

Human Chorionic Gonadotropin (HCG)

Most second-trimester assays only quantify total HCG, which is an exclusive product of the placenta. In vitro studies show that when placental tissue is hypoxic, HCG is released. This could suggest that a somewhat poorly perfused placenta (perhaps due to inadequate spiral artery invasion) could be responsible for the HCG elevation seen in patients developing higher rates of preeclampsia and IUGR. Also, very low HCG (< 0.20 MoM) has been associated with pregnancy loss.

Estriol

This is a product of a complex interaction involving mother, placenta, and fetus. Interestingly, it adds little diagnostic clout to the triple screen, accounting at most for a few additional percentage points to the sensitivity of the test (regarding aneuploidy). It also has very little value in prediction of later adverse outcome, perhaps because it only indirectly reflects placental function.

Inhibin-A

This is a product of the placenta and is the newest analyte now comprising the "quad screen." Individually, it may be the most sensitive screener of Down syndrome and several studies have shown it to be correlated with later IUGR and preeclampsia. When 2 or more analytes are elevated (above 2.0 MoM), the rate of adverse outcome increases appreciably, as do the chances of preterm delivery.

One study from Providence indicated that a combination of maternal age, HCG, and inhibin-A had a sensitivity of 23% and specificity of 95% in the prediction of preeclampsia. Inhibin-A was a better performer individually than HCG.

Role of Doppler Uterine Artery Assessment

Very few studies are available combining biochemical screening in the second trimester with uterine artery Dopplers, but it makes sense to evaluate the uterine arteries in patients with elevations of MSAFP, HCG, or Inhibin-A since this will provide information about trophoblastic invasion of the spiral arteries.

Role of 'Echogenic Bowel'

The presence of Echogenic fetal bowel, diagnosed through ultrasound, is strongly associated with intrauterine demise in the presence of elevated AFP. However, again this is virtually always in growth-restricted fetuses.

What to do when MSAFP, HCG, or Inhibin-A are elevated? The 2 most common problems in these patients are hypertension (generally preeclampsia) and IUGR. Clinicians should have a high level of sensitivity for early signs of preeclampsia (Proteinuria and increase in blood pressure from baseline values) in these patients. Every patient with any of these elevations should also have a careful clinical assessment of uterine size assessment at each visit and an ultrasound examination at 30-32 weeks to see if fetal growth is lagging. If so, then Doppler assessment of the fetal circulation, and non-stress testing and biophysical profiles should be initiated, along with serial biometry every 2 weeks.

Since intrauterine demise is rare in an appropriately grown fetus with normal amniotic fluid, NSTs and BPPs need not be undertaken in these patients.

Can adverse outcome be prevented in patients with elevations of components of the quad screen? In 2 large NIH-supported studies, low-dose aspirin did not diminish the incidence of preeclampsia in historically "low-risk" and "high-risk" patients. However, in a recent meta-analysis involving patients with abnormal uterine arteries at 18-24 weeks (covered in a previous *OB/GYN Clinical Alert*), there was an increase in fetal weight and a significant decrease in the development of severe preeclampsia when low-dose aspirin therapy was initiated. This type of information is not yet available regarding aspirin in patients with elevated analytes, but the data from the above meta-analysis make a case for performing uterine artery Dopplers in these patients and treating if abnormalities are found. ■

Suggested Reading

1. Hueta-Enochian G, et al. *Am J Obstet Gynecol*. 2001; 184(7):1549-1553.
2. Heikkila A, et al. *Hypertens Pregnancy*. 2001;20(1): 99-106.
3. Lambert-Messerlian GM, et al. *J Soc Gynecol Investig*. 2000;73(3):170-174.
4. Zeeman GG, et al. *Obstet Gynecol*. 2003;101(2): 232-236.
5. Silver HM, et al. *J Soc Gynecol Investig*. 2002;9(5): 308-312.
6. Vaughan JE, Walsh SW. *Hypertens Pregnancy*. 2002; 21(3):205-223.
7. Al-Kouatly HB, et al. *Am J Obstet Gynecol*. 2001; 185(5):1039-1043.

CME Questions

15. Alcohol may reduce the risk of dementia by which mechanism?

a. Decreasing cortical atrophy
b. Reducing the risk of cerebral hemorrhage
c. Increasing the likelihood of motor vehicle accidents
d. Improving cerebral circulation
e. Reducing depression

16. Which of the following statements best summarizes the results of the study by Li et al about incidence rates of breast cancer from 1987 to 1999?

a. Combined postmenopausal hormone replacement therapy causes breast cancer but unopposed estrogen therapy does not.
b. The risk of invasive lobular breast cancer might be increased by combined hormone use, but the risk of invasive ductal breast cancer does not appear to be.
c. Women who use combined estrogen-progestin therapy postmenopausally are at increased risk for breast cancer, especially invasive lobular breast cancer.
d. The primary risk factor for invasive ductal breast cancer is age, while the primary risk factor for invasive lobular breast cancer is postmenopausal hormone use.
e. Combined estrogen-progestin use of any type at any age appears to increase the risk of breast cancer.

Answers: 15 (d); 16 (b)

Note: *A full question and answer insert is included for CME subscribers.*

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Clinicians are familiar with the writings of Leon Speroff, MD, especially as the senior author of *Clinical Gynecologic Endocrinology and Infertility* currently in its 6th edition. Now Dr. Speroff's writing has taken a new direction, a biography entitled *Carlos Montezuma, M.D., A Yavapai American Hero, The Life and Times of an American Indian, 1866-1923*. The book is the culmination of four years of research and work, a product of the same enthusiasm and dedication as his medical writing. Look for this historical narrative about a remarkable man, one of the first Native-American physicians, available this summer from Arnica Publishing, Inc. A special pre-publication purchase price is available for readers of *OB/GYN Clinical Alert* at www.arnicapublishing.com.

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PHARMACOLOGY WATCH

Pneumococcal Vaccine Ineffective at CAP Prevention

Pneumococcal vaccine protects older adults from developing pneumococcal bacteremia but does not prevent community-acquired pneumonia (CAP), according to a new study from Group Health Cooperative in Seattle. The study reviewed records of more than 47,000 adults aged 65 and older who were followed for more than 3 years. During that period 1428 were hospitalized with CAP, 3061 were diagnosed with outpatient pneumonia, and 61 had pneumococcal bacteremia. Prior receipt of the pneumococcal vaccine was associated with a reduction in the risk of pneumococcal bacteremia (HR 0.56; 95% CI, 0.33-0.93), but an increased risk of hospitalization with CAP (HR, 1.14; 95% CI, 1.02-1.28). The pneumococcal vaccination did not change the risk of outpatient CAP (HR, 1.04; 95% CI, 0.96-1.13), or the combined outcome of inpatient and outpatient CAP (HR, 1.7; 95% CI, 0.99-1.14). The authors point out that these results are consistent with those of 4 meta-analyses, which also showed no reduction of CAP with the pneumococcal vaccine. They state, however, that the reduction in pneumococcal bacteremia, which is also consistent with results of other studies, is reason enough to administer the vaccine (*N Engl J Med*. 2003;348:1747-1755). A separate study in the same issue suggests that vaccinating children with pneumococcal vaccine may also benefit adults. Using CDC surveillance statistics, a dramatic reduction in invasive pneumococcal disease was found between the years 1998 and 1999 and the year 2001, one year after the licensing of the protein-polysaccharide conjugate vaccine with the largest decline in children younger than the age of 2, when a 69% reduction was seen. A reduction in disease rates for adults and, especially young adults, was also noted over this time period. Interestingly, the 35% reduction in penicillin-resistant pneumococcus was also noted over the same timeframe (*N Engl J Med*. 2003; 348:1737-1746).

Flu Vaccine Limits Hospitalization

The influenza vaccine is highly effective at preventing hospitalization and death during the influenza season. A recent study reviewed the records of more than 140,000 adults aged 65 and older during the 1998-1999 and 1999-2000 influenza seasons, during which 55.5% and 59.7%, respectively, were immunized. The flu vaccine was associated with a reduction in the risk of hospitalization for cardiac disease (reduction of 19% during both seasons [$P < 0.001$]), cerebrovascular disease (reduction of 16% during the 1998-1999 season [$P < 0.018$] and 23% during the 1999-2000 season [$P < 0.001$]), and pneumonia or influenza (reduction of 32% during the 1998-1999 season [$P < 0.001$] and 29% during the 1999-2000 season [$P < 0.001$]) and a reduction in the risk of death from all causes (reduction of 48% during the 1998-1999 season [$P < 0.001$] and 50% during the 1999-2000 season [$P < 0.001$]). The subgroups were well matched for major medical illnesses. The authors point out the extraordinary effectiveness of the influenza vaccine, which has also been seen in other studies, but they also point out that the national rate of vaccination against influenza was only 63% of adults older than the age of 65 in 2001 (*N Engl J Med*. 2003;348:1322-1332).

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Verapamil Not Up To Competition

Controlled-onset extended-release (COER) verapamil "is not equivalent to atenolol or hydrochlorothiazide in preventing cardiovascular disease-related events" is the conclusion of the CONVINCE trial (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints). The study was terminated early by the sponsor for "commercial reasons." CONVINCE was initially designed to test the hypothesis that control of early morning blood pressure might reduce cardiovascular mortality given that acute myocardial infarction (MI), cardiovascular event-related death, and stroke all have their highest incidence during the early morning hours (6 AM to noon). More than 16,000 patients were randomized to receive COER verapamil or either of atenolol 50 mg or hydrochlorothiazide 12.5 mg. Other antihypertensives were added if needed. The main outcome was stroke, MI, or cardiovascular related death. Blood pressure control was virtually identical between the 2 groups. There were fewer myocardial infarctions in the COER verapamil group, but more strokes, and cardiovascular deaths were similar (hazard ratios: MI 0.82, CVA 1.15, CV death 1.09, all-cause mortality 1.08). Both groups had more cardiovascular deaths between 6 AM and noon (COER verapamil 99/277, atenolol or HCTZ 88/274). The authors state that low-dose thiazide diuretics and/or beta blockers remain first-line therapy for hypertension, a recommendation that is in line with the recent Sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (*JAMA*. 2003;289:2073-2082).

International Companies Unite Against SARS

As researchers move closer to identifying the etiologic agent of SARS, several international drug companies are collaborating to develop a vaccine. GlaxoSmithKline has announced it is working with France's Institut Pasteur along with several other pharmaceutical companies to develop a vaccine. The SARS vaccine would have a massive worldwide market, and traditionally companies would compete to bring a product to market. But partially under urging from US government officials, companies such as Merck, Wyeth, Chiron, Baxter, J&J, and others have committed to collaborating in this important effort. Scientists involved in this process warn, however, that this process will likely take years.

New FDA Comissioner Brings Controversy

The pharmaceutical industry is still analyzing whether Mark McClellan, the FDA's new Commissioner, is friend or foe. The 38-year-old Commissioner has hit the floor running but has generated controversy in the process. Harvard trained as a physician and economist, McClellan was teaching medicine and economics at Stanford, and advising the Bush administration on health-care economics when he was tapped to head the FDA. The new Commissioner has pleased the pharmaceutical industry by pledging to speed the new drug evaluation process. But a new proposal to force drugmakers to switch some prescription drugs to over-the-counter (OTC) status is strongly opposed by the industry. Dr. McClellan confirmed to the *Washington Post* in late April that forced switches are being "actively considered." The controversy centers on nonsedating antihistamines. Schering-Plough recently took loratadine (Claritin) OTC with urging from the FDA. Now 2 competitor drugs, Aventis's fexofenadine (Allegra) and Schering-Plough's cetirizine (Zyrtec) are under consideration for forced switches to OTC status. Both these drugs have several years of lucrative patent protection during which time they are unlikely to pursue OTC status on their own. All 3 drugs are sold OTC in many other countries and are considered safer than current OTC antihistamines. The price of most drugs drop significantly when they are available OTC, a fact that is not lost on pharmaceutical companies or consumer groups. Opposing the powerful pharmaceutical lobby has never been politically savvy, but Dr. McClellan may choose to court an even more powerful lobby—the American health care consumer.

Janssen: 'Dear Doctor' Letter for Risperidone

Janssen pharmaceuticals has issued a "Dear Doctor" letter concerning its antipsychotic medication risperidone (Risperdal). The letter warns health-care providers about a possible increased risk of stroke among elderly patients taking the drug. "Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients (mean age, 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo." Risperidone is approved for treatment of schizophrenia, but it is commonly used off label to treat delusional or aggressive behavior in elderly patients with dementia. ■

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VOLUME 8, NUMBER 6 PAGES 11-12 JUNE 2003

Detection of Alzheimer's Disease and Dementia in the Preclinical Phase

Source: Palmer K, et al. *BMJ*. 2003; 326:245-247.

Alzheimer's disease (AD) is the most common form of dementia in America, but often escapes clinical attention until symptoms compromise quality of life, activities of daily living, or safety. Interventions might be enhanced by early detection of AD, but little investigation of early detection techniques has been done.

Palmer and colleagues evaluated 1435 persons aged 75-95 years who were without dementia at baseline. All persons underwent evaluation at baseline, 3 years, and 6 years with 3 different tools; subjects were asked, "Do you currently have any problems with your memory?" Additionally, each subject underwent mini-mental status examination, and neuropsychological testing assessed cognitive function.

At follow-up, almost 20% of survivors had dementia. All 3 screening tools, if positive, increased relative risk of AD. Having a memory complaint at baseline doubled the relative risk of subsequent dementia, and cognitive impairments increased relative risk of dementia by 2- to 5-fold.

Although using all 3 tools had a high predictive value if positive, the tools are too insensitive for routine employment, since only 18% of persons who ultimately developed dementia were identified using this 3-step process. That we can identify, with some reliability, a subgroup of persons likely to progress to dementia is promising. For broader applicability, more sensitive screening tools will be required. ■

Shoe Design and Plantar Pressures in Neuropathic Feet

Source: Praet S, et al. *Diabetes Care*. 2003;26:441-445.

Clinicians have tried a variety of maneuvers to reduce the incidence and effect of neuropathic foot ulcers in an attempt to reduce their subsequent morbidity. Since a substantial proportion of diabetics will ultimately develop distal sensory neuropathy and be at risk of foot ulcers, learning which type of footwear might help minimize the consequences of this neuropathy is of great importance. The most commonly used orthopedic shoe for diabetic neuropathy is the "rocker bar" variety (RB shoe), others suggest that a simple extra depth shoe, which is typically less expensive, more cosmetically pleasing, and more readily accessible, may be equally effective.

Praet and colleagues studied 10 diabetic women suffering from peripheral sensory neuropathy, but without evidence of foot deformity or ulceration. Women were tested in 3 categories of shoes: Category A were simple popularly styled traditional shoes, category B were extra depth shoes, and category C were specially crafted (based upon plaster casts of feet) shoes with rocker bottoms.

Overall, only the RB shoes effectively reduced forefoot pressure more than traditional "over the counter" footwear. Praet et al acknowledge that choosing footwear for any one individual diabetic remains a difficult choice and that shoe-specific pressure measurements in different types of footwear may be the best alternative for some patients, especially for those who balk at use of the less cosmetically acceptable RB shoes. ■

TSH in Assessment of Hypothyroidism

Source: Meier C, et al. *BMJ*. 2003; 326:311-312.

Although there is good agreement that thyroid stimulating hormone (TSH) is the most appropriate indicator of hypothyroidism, it is little understood whether absolute levels of TSH correlate either with degree of tissue effect of hypothyroidism, or levels of thyroid hormone. Meier and colleagues used a composite of clinical score, ankle reflex time, CK, and total cholesterol as markers of what they term "thyroid hormone action at the tissue level." They then correlated TSH with thyroid hormone levels and tissue parameters.

The correlation of tissue parameters and TSH was weak. This review suggests that there is a poor correlation between levels of TSH and clinical or metabolic severity of hypothyroidism. Meier et al have no quarrel with the sensitivity and diagnostic accuracy of TSH to discern the presence or absence of hypothyroidism. Rather, they hypothesize that once TSH is maximally stimulated, no further increase will occur, despite progressively greater degrees of hypothyroidism. Meier et al suggest that thyroxine treatment should be guided by clinical signs and thyroid hormone concentrations, rather than solely by TSH concentration. ■

Oral Vitamin D3 Supplementation on Fractures and Mortality

Source: Trivedi DP, et al. *BMJ*. 2003;326:469-472.

Despite recent enhanced clinician and public awareness, prevention and treatment goals for osteoporosis (OSPS) remain inadequately fulfilled. A variety of lifestyle and pharmacologic tools have been applied to OSPS management, including Vitamin D (VitD) supplementation, with some, albeit inconclusive, success.

This trial was a pilot study using VitD (cholecalciferol) supplementation in a British senior citizen population (age range, 65-85) solicited by mail (n = 2686) to participate in a placebo-controlled trial lasting 5 years. Unusual in this trial was the dosing methodology, which administered a single 100,000 IU VitD capsule once every 4 months for 5 years—not once daily, but once (total capsules administered in 5 years = 15). Participants were instructed to take the capsule they received in the mail immediately upon receipt, and respond by mail on a form indicating that they had indeed taken the medication.

Compared to placebo, the treatment group had a 22% lower rate for first fracture (any site) and a 33% lower hip, wrist, forearm, or vertebrae fracture rate. The parathyroid hormone concentrations did not differ significantly between active VitD and placebo, despite a 40% higher VitD level in the former.

Ultimately, the 100,000 IU dose of VitD is approximately equivalent to 800 IU per day, which has been used in other trials. However, the convenience, lack of toxicity, and monetary savings (in the United Kingdom, 3 capsules of 100,000 IU vitD costs less than 1 pound) provide intriguing stimuli for a larger trial. ■

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Oral Opioid Therapy for Chronic Peripheral and Central Neuropathic Pain

Source: Rowbotham M, et al. *N Engl J Med*. 2003;348:1223-1232.

Neuropathic pain (NPP) is often described as "opioid resistant," based upon some limited human and animal studies. On the other hand, parenteral opioid analgesia has produced success in NPP. Although data on postherpetic neuralgia indicate a degree of efficacy with opioid analgesia, other NPP syndromes are not well studied in prospective, blinded studies.

Because of the ethical boundary of administering placebo to patients suffering chronic pain, a study was performed comparing 2 different dosing levels of levorphanol, a potent mu-opioid agonist, for patients (n = 100) suffering chronic NPP, in a double-blind fashion. Patients were administered either 0.15 mg or 0.75 mg capsules, and allowed to titrate up to as many as 7 capsules 3 times daily (levorphanol has a 6-8 hour duration of analgesia). The primary outcome of the study was degree of pain reduction; secondary outcome was time to pain relief. The study period was 8 weeks duration.

As perhaps might be intuitive, high-strength levorphanol reduced pain to a significantly greater degree than in the lower-strength group, despite the option available to patients of up-titrating their medication dose. Encouragingly, both groups did report levorphanol efficacy (pain reductions, 21% and 36%). Contrary to popular wisdom, tolerance to opioid analgesia was not evidenced. Additionally, the magnitude of pain reduction in the high-strength group was similar to that achieved with other more traditionally used NPP tools like tricyclic antidepressants and gabapentin.

Clinicians who have excluded opioid analgesia as an effective tool in NPP may need to consider these data in their decision process. ■

Tacrolimus Ointment vs. Topical Corticosteroids in Atopic Dermatitis

Source: Ellis C, et al. *J Am Acad Dermatol*. 2003;48:553-563.

For several decades the mainstay of management of atopic dermatitis (AD) has been corticosteroids (CSD), usually administered topically. When AD is mild-moderate, low, and mid-potency, CSD often suffices, but more severe disease may require high-potency agents, or even systemic therapy. Since CSD can produce both local effects like skin atrophy and systemic effects such as hypothalamic-pituitary suppression, chronic administration requires a degree of caution. Recently, a class of topical immunomodulator agents (IMA), exemplified by tacrolimus (Protopic) and pimecrolimus (Elidel), has been offered for clinical use as an alternative to CSD and appears to be equally efficacious. There are no serious side effects of IMA, and they have been demonstrated to be both safe and effective in children as young as 2 years, with minimal side effects.

For patients with moderate-to-severe AD, the cost of treatment was similar for either high-potency CSD and IMA for a 4-week treatment regimen. For short-term treatment (2 weeks), IMA is more cost effective than CSD because there is less requirement for secondary interventions. If lower potency and less costly CSD are used efficaciously, the cost efficacy of IMA becomes less favorable. The combination of safety, efficacy, and cost has important therapeutic implications for the role of IMA in AD. ■