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INSIDE

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Bariatric Surgery Reduces the Risk of Type 2 Diabetes

By Jeffrey T. Jensen, MD, MPH

Synopsis: *In a prospectively followed cohort of obese, non-diabetic men and women from Sweden, individuals who underwent bariatric surgery had an 83% reduction in the risk of developing type 2 diabetes over 15 years of follow-up.*

Source: Carlsson LMS, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med* 2012;367:40-49.

Between September 1, 1987, and January 31, 2001, a total of 4047 obese persons were enrolled in the Swedish Obesity Study (SOS) intervention trial. The SOS evaluated 2010 participants who had chosen to undergo surgery (bariatric surgery group) and a non-surgical control group of 2037 subjects matched with the bariatric surgery group on the basis of 18 variables. The authors previously had reported that the matching process had unexpectedly resulted in adverse selection for the bariatric surgery group, as evidenced by a higher mean body weight and more severe risk factors than the control group. To evaluate the effect of bariatric surgery on incident type 2 diabetes, the current analysis was restricted to 1658 bariatric surgery and 1771 control subjects who did not have diabetes at baseline. Although the study groups had identical inclusion and exclusion criteria, the requirement that none of the patients have diabetes at baseline further exaggerated the adverse selection in the surgical cohort. The inclusion criteria for both the surgical and control cohorts were an age of 37-60 years and a body mass index (BMI) of ≥ 34 in men and ≥ 38 in women, and all subjects needed to have no contraindications to surgery. All subjects entered this study with the intention of losing weight; 73% of both cohorts were women. In the bariatric surgery group, 19% underwent banding, 69% vertical-banded gastroplasty, and 12% gastric bypass. Subjects in the control group received the customary treatment for obesity at their primary health care centers (e.g., lifestyle modification, including recommendations regarding eating behavior, food selection, energy intake, and physical activity). After adjustment for follow-up of < 15 years and for death, the 15-year participation rate was 53.5%. During the follow-up period,

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type 2 diabetes developed in 392 participants in the control group (28.4/1000 person-years) and in 110 (6.8/1000 person-years) in the bariatric surgery group (adjusted hazard ratio with bariatric surgery, 0.17; 95% confidence interval, 0.13-0.21). The effect of bariatric surgery was influenced by the presence or absence of impaired fasting glucose ($P = 0.002$ for the interaction) but not by BMI ($P = 0.54$). Sensitivity analyses, including endpoint imputations (done to adjust for the poor long-term follow-up), did not change the overall conclusions. Surgical complications included a postoperative mortality of 0.2%, and 2.8% of bariatric surgery subjects required reoperation within 90 days owing to complications. The authors concluded that bariatric surgery is markedly more efficient than usual care in the prevention of type 2 diabetes in obese persons.

■ COMMENTARY

As gynecologists, we are primary care providers for many women. Even in practices where primary care is not a focus, the OB/GYN frequently is the most trusted physician that a woman sees on a regular basis. The relationships that form during pregnancy and over years of care create a bond that is unique in medicine. Therefore, to be the best advocates for women's health, we have an obligation to provide counseling to our patients about nonreproductive health care.

As I write this, I am sitting outside noting the cooling temperatures of fall. For most of human history, the challenge in late summer was to consume as many calories as possible to store energy in the form of fat to survive the lean time of winter. Some groups evolved to be extremely efficient in converting energy to fat, and the economy of this trait varies widely in the population. Unfortunately, for modern humans eating a western diet, the challenge has changed. Winter and reduced activity arrives as it has for millennia, but now is unaccompanied by a reduction in the availability of food. In fact, the long nights of winter frequently bring feasts and more alcohol consumption. Women spend more time around food preparation than men, and this contributes to high rates of obesity. Much has been written about the obesity epidemic in the United States, and there is no indication that the trend is slowing.

Combating obesity will require a dedicated public health effort. Taxing high-calorie/low-nutrition foods, reducing subsidies for high fructose corn syrup, and promoting physical education in schools are interesting ideas to combat child obesity. But we all know that weight loss through diet is extremely difficult for adults, and that even when weight loss does occur, most fail to maintain a normal body weight. Among the many complications of obesity, type 2 diabetes is one of the principle drivers of high health care costs. Therefore, strategies that could reduce the chance that an obese individual will develop diabetes should not only improve the health of that individual, but also help stabilize health care spending.

Several important lessons emerge from the SOS. First, the risk of developing type 2 diabetes is substantially reduced by bariatric surgery. This finding was robust, as the surgical cohort was actually less healthy than the control group at baseline. The authors conducted a sensitivity analysis to compensate for the large study dropout (not surprising in a 15-year study) with no change to the overall conclusion that bariatric surgery reduces the chance of developing diabetes.

Next, bariatric surgery is far more effective than usual care in promoting weight loss. Subjects in the bariatric surgery group had an average maximal weight loss of 31 kg after 1 year. Although partial weight regain then occurred, the average weight loss from baseline values at 10 years and 15 years was approximately 20 kg. Compare this to the control group where mean weight changes never exceeded 3 kg in weight gain or weight loss. Even among those control subjects who sought additional professional help (54%), the mean weight change at year 2 was only a loss of 0.6 kg. Those who did not receive this help gained 1.4 kg! It is important to note that the magnitude of obesity was not associated with the reduction in risk; the incidence of type 2 diabetes and the preventive effect of bariatric surgery were similar among participants with a BMI at or below the median of 40.8 and those with a BMI above the median. In contrast, patients with an elevated fasting blood sugar at baseline appeared to benefit the most.

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Finally, in a system of socialized medicine, the Swedes feel it is cost effective to provide surgical treatment for obesity. In contrast to high-tech approaches like robotic hysterectomy, this surgical technique continues to provide lasting savings to the health care system. A recent review by Picot et al found that the incremental increased cost of bariatric surgery in the U.K. health system was negligible at 5 years and offset by savings over 20 years in patients with type 2 diabetes and class 2 obesity.[1] Although the SOS authors did not conduct a cost analysis, the new results from SOS suggest that cost savings also may occur in obese individuals with elevated fasting glucose, regardless of BMI.

So our role is to advise our patients. Find the trusted resources in your area (or a nearby city) for referral to a bariatric surgery specialist in a comprehensive weight loss practice. When your next obese patient presents (should be tomorrow since one-third to one-half of your patients are obese), consider taking a moment to discuss her past experience with weight loss programs and the long-term success and potential benefits of bariatric surgery (particularly if her fasting glucose is elevated). As a trusted health care provider, your input just might open the conversation and help save her life. ■

Reference

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Cystic Hygroma

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, Colorado

Dr. Hobbins reports no financial relationships relevant to this field of study.

Synopsis: *Even with emerging maternal DNA testing, first trimester fetal ultrasound continues to offer benefit in the detection of cystic hygroma, which was found to be associated with an adverse fetal outcome in 86% of pregnancies identified.*

Source: Scholl J, et al. First-trimester cystic hygroma: Relationship of nuchal translucency thickness and outcomes. *Obstet Gynecol* 2012;120:551-559.

The emergence of maternal DNA testing for fetal aneuploidies has necessitated a rethinking of our standard screening protocols. With reasonable accuracy, a single blood test can now rule out fetal trisomy 21, 18, and 13, in addition to sex chromosome abnormalities such as Turner syndrome. However, nuchal translucency (NT) testing, the staple of current screening protocols, will remain an essential adjunctive tool because, as noted below, it will continue to identify pregnancies at risk for chromosomal or non-chromosomal abnormalities not detected by current maternal serum DNA tests.

A group of investigators focused on one particularly ominous first trimester finding — cystic hygroma (CH). They culled data over a 10-year period from five centers in the Northeast. Their ultrasound definition of CH was "a large hypoechoic space on the back of the neck extending along the length of the back, containing septations." A total of 944 fetuses were labeled as having CH. Of the 729 cases where fetal diagnostic data were available, 400 (54.9%) had abnormal karyotypes. A major structural anomaly emerged in 61 of 212 with normal karyotypes (29%) and perinatal loss occurred in 115 of the 229 pregnancies not terminated (39%). Lumped together, 86.6% of pregnancies ended in adverse outcome.

After adjusting for confounding variables, for every millimeter of increase in NT diameter there was a rise in abnormal karyotype of 44%, a congenital anomaly increase of 26%, and an increase in perinatal loss of 47%. Interestingly, in those with normal karyotypes, only 2.5% had fetal anomalies that were not detected by ultrasound.

■ COMMENTARY

For every 280 pregnancies, one will be complicated by fetal CH. Since NT screening is being performed more frequently in the offices of OB/GYN generalists, some preliminary point-of-entry counseling may be required when CHs are first encountered. Formal genetic counseling and diagnostic invasive procedures (i.e., chorionic villus sampling or amniocentesis) will likely continue to be offered in referral centers. However, in many settings, waiting for a more definitive answer might leave the patient in emotional limbo for days. Couples with a fetus diagnosed with a CH will be pressing for at least a ballpark estimate of their risks of the above adverse outcomes. This study now has some of the best data available regarding the chances of having a fetus with a chromosome abnormality (55%), a fetal structural abnormality (29%), or perinatal death (39%). However, despite these gloomy statistics, the study has shown that after pregnancy terminations were excluded, almost 60% of the 180 continuing pregnancies had normal appearing fetuses at the time of birth.

I chose this CH paper to review because the diagnosis should not be difficult for someone trained in NT

exams (and those offering this test should not be doing these exams if they are not capable of interpreting the ultrasound results). Yes, the nuances involved in first trimester screening often can be difficult to deal with, but CH should represent a category where a provider should be able to counsel patients initially regarding its implications. ■

The Postmenopausal Ovary and Sexual Function

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *A history of bilateral oophorectomy was not associated with a decrease in self-reported sexual ideation or function among postmenopausal women.*

Source: Erekson EA, et al. Sexual function in older women after oophorectomy. *Obstet Gynecol* 2012;120:833-842.

ALTHOUGH THE INCIDENCE OF HYSTERECTOMY HAS DECLINED in recent years, it remains the most common major gynecologic procedure, and many women are offered or consider elective bilateral oophorectomy (BSO) at the time of hysterectomy to reduce ovarian cancer risk. Since postmenopausal ovaries continue to produce testosterone, and oophorectomy is associated with a decline in circulating androgen levels, many clinicians and patients question whether oophorectomy is associated with a reduction in libido and waning of sexual function. To address the hypothesis that BSO results in a decline in sexual function, the authors analyzed data from the 2005-2006 National Social Life, Health, and Aging Project, a cross-sectional and nationally representative probability sample of community-dwelling older adults in the United States aged 57-85 years old. The overall survey response rate was 75.5%, and this subanalysis of sexual function involved 1352 women. Women self-reporting no previous oophorectomy or a unilateral procedure were considered as having retained their ovaries. The primary outcome of interest was self-report of sexual ideation at least once monthly; this outcome was selected because having thoughts about sexual experiences should not be affected by either the woman's own physical limitations or the partner's issues. Secondary outcomes included sexual behaviors and frequency. Because sexual function is known to change with age, responses were stratified into three age categories (57-64 years, 65-74 years, and 75-85 years), and comparisons were adjusted for known confounders such as current hormone therapy, age, education, and race. The sample size provided 90% power to detect a difference of 10% in sexual ideation.

A total of 356 (25.8%) women reported previous BSO. Overall, there was no significant difference in the report of sexual ideation found between women who retained their ovaries (54.5%, 95% confidence interval [CI] 48.1-61.0) compared with women with previous BSO (49.9%, 95% CI 45.3-54.5, adjusted odds ratio 1.32, 95% CI 0.96-1.80). There also were no differences observed in the percentage of women reporting sexual activity in the past 12 months (42.2% BSO, 44.5% retained, $P = 0.61$) or in sexual frequency. Among all women with current sexual partners, women who reported previous BSO were more likely to report vaginal intercourse (90% compared with 82%). These data support a conclusion that BSO does not play a pivotal role in sexual ideation and function among older women.

■ COMMENTARY

Although alternatives to hysterectomy have reduced the number of operations performed for benign indications, recent estimates from hospital discharge data support that more than 600,000 hysterectomies are performed each year. The decision to perform a BSO at the time of benign surgery is common among women who have completed childbearing. A recent study from Belgium found that the physician's recommendation to perform an elective BSO at the time of a hysterectomy for a benign condition is strongly influenced by the patients' age and that 83% of women over age 51 underwent the procedure at the time of hysterectomy.[1] The primary concern for most of these clinicians and patients is that the non-reproductive ovary might later develop into ovarian cancer, and that oophorectomy can prevent this. A strong argument to avoid oophorectomy in premenopausal women is that compliance with estrogen replacement therapy is low, and that the premature "surgical" onset of menopause has adverse long-term health effects.[2]

But what about the postmenopausal ovary? These ovaries no longer produce estradiol, but are a major source of androgens (testosterone and androstenedione). Although these steroids are capable of aromatization to estrogens in peripheral tissue, the amount is insignificant in most women. This leaves us to consider whether ovarian androgens themselves have a central role in the maintenance of health, including normal sexual function in postmenopausal women. The issue is clouded by the high baseline prevalence of sexual problems in mature women (and men), the complexity of diagnoses (e.g., arousal, desire, or combination), and inconclusive clinical data linking testosterone replacement with benefit.[3]

The study by Erekson and colleagues uses a population approach to address the question of oophorectomy. The

authors selected the correct outcome of sexual ideation as a close proxy to sexual desire, one sexual domain that may be influenced by androgens. They found that BSO was not associated with a difference in sexual ideation or in reported sexual activity. This finding contributes to past research showing that serum androgen levels are not correlated with more favorable sexual outcomes in women. Their data are robust in that the sample was nationally representative. The absence of any effect of oophorectomy across any of the three age strata support that declining ovarian androgen production with age did not account for this lack of difference. In other words, ovarian androgen production alone does not explain differences in sexual behavior in this large group.

This study provides valuable information to clinicians counseling women regarding the pros and cons of elective oophorectomy during benign gynecologic surgery at or after menopause. It also provides guidance when we see women presenting with sexual complaints years after surgery. Since sexual concerns are common among women of all ages, this history should be solicited during routine wellness visits. But one needs to be prepared when a concern about sexual function emerges. In general, a referral to a competent sexual therapist will provide more benefit than testosterone replacement. ■

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Special Feature

Stress and Poor Cancer Outcomes: It's More Than Psychological

By Robert L. Coleman, MD

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

Synopsis: *Chronic stress has been associated with development of several diseases and the release of several cytokines and growth factors known to support cancer growth and metastases. Pharmacological agents targeting the stress response, such as beta-blockers and prostaglandin inhibitors, have been associated with improved survivorship in patients with several solid tumors, including ovarian cancer. The relationship supports prospective clinical investigation, already underway.*

Source: Diaz ES, et al. Impact of beta-blockers on epithelial ovarian cancer survival. *Gynecol Oncol* 2012; doi;10.1016/j.ygyno.2012.07.102.

Mediators of the autonomic response to stress, such as the catecholamines norepinephrine and epinephrine, promote cancer growth, metastasis, and progression in preclinical models. Pharmacological intervention with beta-blockers can abrogate this effect leading to improved patient outcomes. Further, retrospective data from studies of patients with non-ovarian tumors support this hypothesis. The authors of the current study set out to evaluate the effect in patients with ovarian cancer. Patients were collected retrospectively from an institutional database of primary ovarian cancer patients treated over a 10-year period with a minimum of 5 years of follow-up. Patients were considered beta-blocker users if there was documentation of agent use over two visits a minimum of 6 months apart. Standard intravenous paclitaxel and carboplatin was used in all recruited patients to minimize the impact of therapy on the primary endpoints of overall survival (OS) and progression-free survival (PFS). In all, 248 patients were identified; 68 (27%) were patients in whom antihypertensive agents were used. Of these, 23 (9%) of the total sample were taking beta-blockers, both selective beta and nonselective beta (and or alpha) agents. The cohorts were defined as beta-blocker users and other. The two cohorts were well matched for age, proportion of stage IV disease, grade 3 histology, percentage of non-serous histology, and optimal cytoreduction rates (which were near 90% for tumor residual < 1 cm). When compared to the non-beta-blocker group, those taking any form of a beta-blocker had a prolonged PFS (27 months vs 17 months, $P = 0.05$) and prolonged OS (56 months vs 48 months, $P = 0.02$, hazard ratio 0.56). This effect held true even when the beta-blocker users were compared to the other hypertensive non-beta blocker users and those whom were not hypertensive. In a multivariate analysis including known prognostic factors, beta-blocker use was the only independently associated factor to PFS and OS. The authors conclude beta blockade for the management of hypertension is associated with improved survivorship and supports the prospective investigation of beta-blocker therapy in ovarian cancer patients.

■ **COMMENTARY**

The study presented appears to support the hypothesis that stress response mediation in ovarian cancer patients can have an impact on long-term outcomes, such as PFS and OS. The study also supports others done under similar pretenses demonstrating remarkably consistent results despite including diseases that arise from complex and divergent pathways.[1,2] These observations suggest that central mechanisms for tumor invasion, spread, and progression exist and are mediated, in part, by effector factors from the autonomic nervous system. While the relationship of stress to cancer prognosis has been known for years, the mechanism through which this occurs and thus, the potential opportunities to interact with these response elements, is largely unknown. However, clues recently have come to light.

Perioperative Events Impact Long-term Outcomes

Four decades ago, an observation in preclinical cancer models suggested that removal of the primary tumor led to rapid growth of subclinical and known distant metastatic disease.[3] In this body of work, an antiangiogenesis growth factor secreted by the primary tumor was discovered (endostatin), which led to the development of the field of biologically targeted antiangiogenesis therapeutic agents. Indeed, surgery is known to not only shift the angiogenic balance toward proangiogenesis, but also increase tumor cell shedding and increase the production of stimulatory growth factors. The latter, which includes catecholamines, prostaglandins, glucocorticoids, and opioids, have been extensively interrogated in preclinical models documenting their critical role in tumor cell proliferation, adhesion, locomotion, extracellular matrix invasion capacity, resistance to apoptosis with loss of cell-cell contact (a process termed anoikis), and secretion of pro-angiogenic factors.[4,5] These factors also have significant impact on suppression of anti-metastatic cell-mediated immunity (CMI). Of particular relevance in the context of surgery is that these processes occur simultaneously and may leverage their effect on long-term outcomes by promoting initiation of the angiogenic switch, which could recruit dormant metastatic lesions to initial growth. In the clinic, should this hypothesis be true, it would suggest that brief interaction of the perioperative cascade could lead to long-term beneficial effects.

The Players and How they Work

Catecholamine and prostaglandin release are a common response to stress and tissue injury, both induced in operative/perioperative settings. Catecholamines act on beta-adrenoceptors, which have been identified to be present on tumor cells, inducing the release of several pro-angiogenic and pro-metastatic factors like VEGF, matrix metallopreteinases (MMP-2, MMP-9), and interleukins (IL-6, IL-8). Relatively recently it was discovered that this cascade appears to be driven through the beta-2 adrenergic receptor, which stimulates the cyclic AMP-protein kinase A pathway and leads to src-mediated focal adhesion kinase phosphorylation — all important (and targetable) processes driving the malignant phenotype. What was striking in these experiments was the efficacy of beta-2 blockade by commonly available antihypertensive agents in orthotopic ovarian cancer models.[6,7] In the latter murine model, stress was induced not by surgery or tissue injury but by chronic stress induced by a claustrophobia-inducing, non-restraint enclosure device. In these experiments, tumor growth, enhanced under a constrained environment, was associated with massive release of catecholamines, whose effect was abrogated by treatment of beta-2 blockade.

Similarly, prostaglandins, particularly prostaglandin-E2, facilitate macrophage differentiation in the tumor microenvironment toward the M2 phenotype. This differentiation promotes tumor cell survival by modulating CMI and enhancing angiogenesis. In colon cancer for instance, COX-2 expression is associated with tumor size, stage, vascular density, depth of invasion, lymph node metastasis, recurrence, and overall survival. Both classes of compounds appear to work in concert to promote tumorigenesis; fortunately, both axes can be easily targeted clinically.

The Evidence

Currently, there are no prospective randomized, clinical trials addressing the effects of beta blockade perioperatively in cancer patients, but the retrospective evidence for its efficacy is interesting. The largest study reported on the effects of beta-blocker use and cancer survival was in breast cancer. In this registry study of women with stage I-IV invasive breast cancer diagnosed between 2001 and 2006 who were taking propranolol (n = 70) or atenolol (n = 525), patients were matched 1:2 to women not taking a beta-blocker (n = 4738).[8] The primary outcome variables were of tumor invasion at diagnosis (T4), nodal/metastatic spread at diagnosis, and time to breast cancer-specific mortality. Propranolol users were significantly less likely to present with T4 lesions at diagnosis (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.07-0.85) or nodal/metastatic spread (OR, 0.2; 95% CI, 0.04-0.88) compared to matched nonusers. The cumulative probability of breast cancer-specific mortality was significantly lower for propranolol users compared with matched nonusers (HR, 0.2-0.6; 95% CI, 0.06-0.6). Interestingly, there was no difference in T4 or nodal/metastatic disease or mortality between atenolol users and matched nonusers. This trial supports the beta-adrenergic pathway's importance in tumorigenesis as well as the differential effect of beta-2 blockade.

The experience with anti-prostaglandin therapy is more diverse and has been the subject of randomized clinical trials in several tumor types. A trial of low-dose aspirin for 1 year postoperatively in patients with gastric or esophageal cancer demonstrated a significantly improved 5-year survival rate (51% vs 41%) in low-stage, non-disseminated cases. In addition, three randomized trials of celecoxib (a COX-2 inhibitor) demonstrated significant tumor-specific effects in early breast cancer, transitional cell cancer of the bladder, and prostate cancer. In the former two sites, there was significant increase in tumor cell apoptosis, and in the latter, there was reduced tumor cell proliferation, vessel density, angiogenesis, and hypoxia inducing factor 1-alpha expression with a short (2-4 week) presurgical exposure.[9,10] This further supports the hypothesis that specific tumor effects can be enabled by brief exposures of these compounds around the time of greatest expression of these pathways.

Where Do We Go from Here?

The study featured at the introduction identified that use of beta-blockers in women with newly diagnosed ovarian cancer was associated with prolonged survival. There are many questions not addressed in that report such as: Were these patients stressed? Did they take their antihypertensive agent around the time of surgery? Was a COX-2 inhibitor given in the perioperative period? Were epidurals used (reduces opioid and glucocorticoid secretion)? Would there be a difference in beta-2 blockade vs beta-1 blockade with a larger sample? Evidence presented would suggest that both beta-2 and prostaglandin blockade would have the greatest benefit to long-term outcomes if it could be safely administered. One significant question to address is safety of normotensive patients taking therapeutic beta-blockade in the perioperative setting. For ovarian cancer patients, the potential impact on long-term survival is not trivial. Fortunately, such a trial is already underway and should help to answer the feasibility of a larger randomized trial in women with ovarian cancer, the deadliest of all gynecologic cancers. ■

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16. Publication of Statement of Ownership
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17. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date: 09/26/12

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

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PS Form **3526,** October 1999 *(Reverse)*

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Instructions

To earn credit for this activity, follow these instructions:

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4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. **The main result of the SOS study was a reduction in the incidence of type 2 diabetes over 15 years in:**
   a. only men with a body mass index (BMI) > 40.
   b. both men and women with a BMI > 40.
   c. only women with a BMI > 36.
   d. both men and women independent of BMI.

2. **In a first trimester fetus with cystic hygroma, the chance of having:**
   a. aneuploidy is about 25%.
   b. a structural anomaly is less than 10%.
   c. a live normal infant at birth is more than 90%.
   d. a perinatal demise in unterminated pregnancies is about 40%.

3. **The size of the nuchal translucency in cystic hygroma does not necessarily correlate with the chance of adverse outcome.**
   a. True
   b. False

4. **In cystic hygroma, the chance of the fetus being born with a structural anomaly that was not picked up by ultrasound along the way is:**
   a. < 3%.
   b. about 10%.
   c. about 20%.
   d. > 50%.

5. **Results from the National Social Life, Health, and Aging Project survey showed that, compared to no oophorectomy, bilateral oophorectomy was associated with:**
   a. an increase in sexual desire but not orgasm.
   b. an increase in both in sexual desire and orgasm.
   c. no difference in sexual ideation or function.
   d. a decrease in sexual desire but not orgasm.
   e. an decrease in orgasm but not sexual desire.

6. **What is the principal effect of beta-blockade on tumor cells that express the beta-2 adrenergic receptor?**
   a. M2 macrophage differentiation
   b. Alteration in cell-mediated immunity
   c. Increased focal adhesion kinase expression
   d. Anti-angiogenesis

In Future Issues:

Contemporary Vaginal Surgery to Improve Sexual Function

PHARMACOLOGY WATCH

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

Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■