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New Parents and Mental Disorders

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics; Emory University School of Medicine, Atlanta

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

Synopsis: *The risk of postpartum mental disorders necessitating hospital admission or outpatient treatment is increased among primiparous mothers for several months after childbirth, but an increase is not seen in fathers.*

Source: Munk-Olsen T, et al. *JAMA.* 2006;296:2582-2589.

THE AIM OF THE PRESENT STUDY WAS TO DETERMINE THE extent to which there is an excess risk of postpartum psychiatric disorders in women vs men. The authors note that postpartum depression afflicts about 10-15% of women and postpartum psychosis about 0.1%. Previous research showed that the risk is highest in primiparous women. One study found that 4% of men reported depressive symptoms postpartum but other studies have not confirmed this. The investigators estimated the risk of postpartum mental disorders requiring hospital admission or outpatient contact in fathers and mothers for one year following the birth of a first live-born child by performing a cohort study and survival analysis. The study population included all persons born in Denmark between January 1, 1955 and July 1, 1990 who survived to age 15 years (n = 2,357,942). The study population was linked with the Danish Psychiatric Central Register, which was computerized in 1969. There are no private psychiatric inpatient facilities in Denmark, which ensured that all admissions were represented. From 1995 onward, information on outpatient visits to psychiatric departments was included in the register. Potential psychiatric disorders included schizophrenia, unipolar depression, bipolar affective disorder, adjustment disorder, and puerperal disorders. Study participants were followed until July 1, 2005. The study population was limited to those parents who experienced a live-born singleton. Events following elective terminations and miscarriages were not included. From 1973 to 2005, a total of 630,373 women and 547,431 men became parents for the first time. A total of 1171 women and 658 men were admitted with a mental disorder to a psychiatric hospital during the first 12

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months after parenthood. The prevalence of severe mental disorders for the first three months after childbirth was 1.03 per thousand births for women and 0.37 for men. The highest risk was for the interval from 10 to 19 days, which showed a RR of psychiatric hospital admission of 7.31 (CI 5.44 -9.81) compared with women who had given birth 11 to 12 months prior. The increased risk of admission among mothers remained elevated for 3 months regardless of the age of the mother. Women giving birth to their second live-born child still had an increased risk of postpartum mental disorders. After the birth of a third child, no association was found between birth and mental disorders. An excess risk of unipolar depression persisted for 5 months postpartum. The risk of outpatient contact was also increased and the highest risk (RR 2.67, CI 1.99 - 3.59) was also for the interval of 10 to 19 days postpartum. The risk of outpatient contact during pregnancy was decreased compared with the postpartum period. Given that men were much less likely to experience a severe mental disorder postpartum than women, the investigators interpreted the results as suggesting the causes of postpartum depression are more strongly linked to physiological processes related to pregnancy and childbirth than to the psychosocial aspects of parenthood. They further suggest that about 40 to 50% of postpartum depression episodes go undetected and that this has public health implications.

COMMENTARY

I chose this article because it highlights an ongoing gap in the fabric of care for American families, namely the timely detection and treatment of women with postpartum depression and related mental health conditions. In an accompanying editorial (Wisner KL, et al. Postpartum Depression: A Major Public Health Problem. *JAMA.* 2006;296:2616-2618), Wisner et al note that this is the first large-scale epidemiological study of postpartum psychiatric illness since the work of Kendell in Scotland more than 20 years ago. Because the findings of the two major studies converge and the risks of untreated severe postpartum psychiatric conditions are so deleterious, the collective data argue for universal screening. Wisner et al recommended that screening begin by week 2 postpartum and continue until at least 12 weeks. They advocated using the Edinburgh Postnatal Depression Scale, which is a validated 10-item questionnaire that can be readily utilized by health professionals not specifically trained in psychiatry.

The alternative reactive approach depends on mothers or family members recognizing postpartum mental health problems and initiating timely and appropriate interventions. It is hard enough for enlightened physicians who recognize postpartum depression to find appropriate referrals, but it is a nearly impossible task for new parents. Most of us are aware of the tragic consequences of untreated postpartum psychosis, including infanticide and suicide. We may be less cognizant of the toll exacted by depression or other mental health conditions that far short of psychosis. However, innumerable studies document that postpartum depression robs the infant of a mother and sets the stage for life-long emotional difficulties. The negative effects of maternal depression include impaired mental and motor development, difficult temperament, poor self-regulation, low self-esteem, and myriad sub-syndromal behavioral problems. Of promise, however: Legislation mandating education and screening for postpartum mental disorders was recently enacted in New Jersey.

It has been suggested that the quality of a society or culture can be assessed in terms of how it cares for its poor and infirm. I would make appropriate care of parents and children one of the yardsticks too. In the United States, we still generally lack enlightened employment policies that support parents, and access to care for those with postpartum depression is difficult to find. Further, despite decades of advocacy, affordable and high-quality childcare is far from being universally available. No wonder, despite our robust economic engine and high socioeconomic status, our health falls behind that of our peer group (Banks J, et al. Disease and advantage in the United States and in England. *JAMA.* 2006;295:2037-2045).

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Endometrial Cancer Staging: Who Should Get It?

ABSTRACT & COMMENTARY

by Robert L. Coleman, MD

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

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

Synopsis: *Surgeons operating on patients with endometrial cancer frequently decide in whom systematic staging is required based on intraoperative assessment of uterine and extrauterine features.*

Source: Case AS, et al. A prospective blinded evaluation of frozen section for the surgical management of endometrial cancer. *Obstet Gynecol.* 2006;108:1375-1379.

Case and her co-authors performed a blinded and prospective evaluation of the accuracy of frozen section analysis in a cohort of 60 patients undergoing a surgical staging attempt. Their institutional policy was to formally stage all patients regardless of the uterine tumor characteristics. However, the uterine specimen was sent to the pathology lab and underwent frozen section evaluation by standard techniques. The information was blinded to the surgeons and to the pathologists (different physicians) performing the final uterine evaluation. They were also blinded to the referent histological diagnosis for which the surgery was indicated. Overall, 76% of patients were formally staged. The concordance of grade by frozen section and final pathology was 58%. Higher grade tumors had better concordance. Nearly half of the grade 1 tumors were upgraded on final diagnosis. Depth of myometrial invasion was concordant in 67% of cases. Nearly half of the patients with no suspected myometrial invasion were upstaged on the basis of identified myometrial invasion. Preoperative histology correlated to final histology in just 56% of the specimens; however, higher grade tumors were more consistently identified preoperatively. If a commonly used criteria to decline formal staging (grade 1 or 2 tumors and less than 50% invasion) was followed, the authors report they would have missed upstaging 18% of their patients in whom they would have administered adjuvant therapy, including 2 with metastatic nodal disease. They concluded that frozen section for grade and depth of myometrial invasion correlates poorly with final pathology and should not be used as criteria to determine in whom surgical staging should be performed.

COMMENTARY

In 1988, FIGO amended the staging scheme for endometrial cancer to include findings based on surgical extirpation. This was done principally to more accurately reflect the distribution of disease and address the inconsistency of clinical staging. A series of clinicopathological studies from the Gynecologic Oncology Group and others identified that extrauterine disease, particularly nodal metastases, could be related to grade, depth of myometrial invasion and histology. In this analysis, patients with low grade and superficially invasive tumors were found to have a very low probability of nodal spread and represented a cohort in whom the added morbidity of nodal staging could be safely avoided. Since that time, several retrospective studies have documented that intraoperative evaluation by frozen section could provide important "real-time" information so that the decision to stage or not to stage could be made following hysterectomy. Early reports suggested that the correlation of frozen section diagnosis and final diagnosis was more than 90%. However, pathologists were frequently aware of the determinations by referent pathology and intraoperative assessment. More recent studies, including the Case article, have questioned the accuracy of frozen section and through more careful investigation, have documented that significant variations exist, particularly in patients with lower grade and stage disease.

The clinical implication is these findings are relevant but must be considered in the context of institutional policies and attitudes toward adjuvant therapy and operative morbidity. The institution from which this report comes only treats those patients with documented extrauterine disease. In this setting, the absence of accurate staging information would proscribe adjuvant therapy based on the potential for missed disease. The authors document that this situation would have arisen in nearly one in five patients. Differing policies or attitudes to adjuvant therapy may alter the importance of accurate surgical staging information. For instance, preliminary data presented from the A Study in the Treatment of Endometrial Cancer trial, suggested there was no therapeutic impact of surgical staging in early endometrial cancer. Final scrutiny of these data when available will help to clarify the decision tree of whom to and not to stage and assess its impact on survival.

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Special Feature

A Limit to Bisphosphonate Treatment

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

BLACK AND COLLEAGUES REPORTED THE RESULTS OF an extension of the alendronate Fracture Intervention Trial (FIT) in which the participants were randomized after 5 years of treatment either to another 5 years of treatment or placebo.[1] The group that discontinued alendronate treatment (5 or 10 mg per day) experienced average losses of bone mineral density over 5 years as follows: total hip - 2.4%, spine - 3.7%. The levels, however, remained above the pretreatment levels 10 years previously. There were no differences in nonvertebral fractures between the treatment and placebo groups. There was a twofold higher rate of clinically recognizable vertebral fractures in the placebo group (5.3% vs 2.4%).

COMMENTARY

The unique tight binding of bisphosphonates to bone matrix causes this drug to remain in the body for decades. This is believed to be the explanation for why there is no rapid bone loss after discontinuing bisphosphonate treatment in contrast to the rapid loss that follows the termination of estrogen therapy. This is also the reason why concerns have been raised regarding long-term treatment: because when bone remodeling releases bound bisphosphonate, it is free to be active again, and the result is that endogenous bisphosphonate is added to the administered bisphosphonate, raising dosage exposure. At this time, we don't know the lowest effective dose and the lowest effective duration of exposure. The potential risk that has been long recognized is that prolonged exposure to bisphosphonates or excessive dosage would oversuppress bone resorption, thus oversuppressing bone turnover and affecting the biomechanical strength of bone; indeed, allowing microcracks to accumulate.

Here is the critical point: Even though continued treatment produced a slightly greater bone density compared with the placebo group, the difference was small, and not meaningful clinically. The small difference indicates a residual effect of the previously administered alendronate that probably lasts longer than 5 years. The authors concluded that most women do not need long-term treatment, and that long-term treatment should be limited to high-risk women (women with existing vertebral fractures or very low bone densities).

It seems to me that several conclusions are warranted at this time:

1. An increased susceptibility to nonspinal fractures may occur relatively early when bisphosphonate treatment is combined with another antiresorptive treatment (such as estrogen), and this should be avoided because no additional benefit or fracture risk has been demonstrated with combined treatment.
2. Bisphosphonate treatment is best reserved for older postmenopausal women. It is not a drug of choice for the prevention of osteoporosis in relatively young postmenopausal women.
3. In all except high-risk patients being treated with bisphosphonates, it would be wise to consider a 5-year time limit for duration of exposure, followed by monitoring of bone density, with a resumption of treatment in those who rapidly lose bone or in those who accumulate a loss of 5% to 10% in one year. ■

REFERENCE

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Psychological Well-being After Hysterectomy

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

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

Synopsis: *the general psychological well-being of patients after laparoscopic and abdominal hysterectomy is comparable 6 months after surgery.*

Source: Persson P, et al. *BJOG.* 2006;113:1023-1030.

THIS IS A PROSPECTIVE, RANDOMIZED, MULTICENTERED study from Sweden in which the psycholog-

ical well-being of 125 women scheduled for hysterectomy was evaluated for up to 6 months post-operative. Of those enrolled, 119 completed the study with 56 undergoing abdominal hysterectomy and 63 having a laparoscopic hysterectomy. Assessments addressing general well-being, depression, and anxiety were performed preoperatively, at 5 weeks and 6 months. There was improved psychological well-being in both groups at 5 weeks compared to preoperative assessment. Laparoscopic hysterectomy was associated with a shorter hospital stay and shorter sick-leave, but a longer operating time.

COMMENTARY

This is another piece of the puzzle in trying to determine the advantages and disadvantages of the various hysterectomy approaches that are available to us. The obvious strengths of this study include the number of patients, the prospective nature, and certainly the randomized study design. Even though the study was performed in Sweden rather than the United States, the findings should certainly be generalizeable.

Surgical procedures and postoperative care were standardized across institutions. Four different validated instruments were utilized to assess psychological well-being, anxiety, and depression. The findings were consistent with what we find in other studies, i.e., laparoscopic procedures take longer (64 vs 99 minutes), but result in shorter hospitalization (2 vs 3 days) and convalescence (26 vs 33 days). All other parameters such as complications, blood loss, and testing outcomes were not significantly different between the groups.

Even though something is statistically significant, is it necessarily clinically significant? For example, does the extra half an hour make a difference? In terms of cost, it certainly does add to the expense, but the patient is not necessarily aware, nor did the longer operating time result in more complications. Shorter hospitalization and briefer convalescence would certainly seem to logically be of clinical importance to the patient. Does this mean that laparoscopic hysterectomy is better than abdominal hysterectomy, especially in light of comparable psychological outcomes?

As with most studies like this, the answer is "it depends." It also has to be put in context of your individual practice. The study was conducted by skilled surgeons with the requisite laparoscopic and abdominal surgical abilities such that only 3 laparoscopic cases had to be converted to laparotomy.

The reassuring aspect is that the patients in the 2 groups had similar outcomes psychologically. There was no satisfaction survey done and that would certainly have helped us try to compare the 2 techniques better since our goal is deliver care in a fashion that satisfies the patients. Since all patients had to agree to randomization, we might expect that satisfaction was similar since the patients did not have a choice as to approach. That is where we must be extremely sensitive as to how we apply this to our respective practices. Often, patients will seek a specific surgical approach and it is paramount that we, as the surgeons, make sure that the surgical technique fits the clinical condition.

The sequence of decision-making should be:

1. Is a hysterectomy necessary?
2. Is the patient willing?
3. What surgical approaches are within the skills of the surgeon?
4. What are the expectations of the patient?
5. How is the patient doing post-op?

By checking the expectations of the patients, then addressing these afterwards, we maximize the opportunity to achieve a successful outcome psychologically. As long as we choose the surgical approach on sound medical grounds, both the patient and the surgeon will do well.

Osteoporosis and Depression

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Women with fractures have a greater prevalence of clinical depression.*

Source: Silverman SL, et al. Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: results from the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. *J Rheumatol.* 2007;34:140-144.

Silverman and colleagues reported the prevalence of depression in a cross-sectional subset of 3798 women in 6 English-speaking countries, who participated in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.[1] Depression was assessed by the Geriatric Depression Scale. Women with vertebral fractures recorded a greater number of depressive symptoms, accounting for a 6.6% prevalence and a 2.5% absolute increase com-

pared with women without fractures. Women with 3 or more vertebral fractures had a 12.8% prevalence of depression.

COMMENTARY

Because there are so many women with osteoporosis, a greater prevalence of depression in this population would amount to a clinical problem of considerable proportions. According to the National Osteoporosis Foundation, 44 million people (55% of the people over age 50) have either osteoporosis or low bone mass, and it is predicted that this number will increase to 52 million (35 million women) by the year 2010 (www.nof.org/advocacy/prevalence).

It is well recognized that fractures secondary to osteoporosis are accompanied by a reduction in psychological and physical well-being. As far as depression goes, it is difficult to know which came first, depression or fractures leading to subsequent depression. It has been reported that depressed people have a greater incidence of falls,[2] and thus it is not unreasonable to consider that depression comes first in some people. Furthermore, depressed people are sedentary and eat poorly, factors that favor bone loss. The authors also speculate that increased cortisol levels associated with depression might lead to bone loss, similar to that observed with the pharmacologic administration of glucocorticoids. On the other hand, the current study as well as a cohort study of American women, despite finding a link between depression and fractures, failed to detect an increase in depression associated with lower bone density measurements.[2] However, other studies have reported increases in depression associated with lower bone densities.[3-5]

Bone loss has been documented in an established rodent model for stress-induced depression, characterized by a decrease in osteoblastic bone formation that can be attenuated by an antidepressant drug.[6] In this experimental model, osteoblastic inhibition was mediated by stress-induced stimulation of the sympathetic nervous system. Although this response is associated with an increased secretion of adrenal glucocorticoids, the evidence also indicates a direct role for sympathetic fibers in bone.

There are several clinical lessons to be derived from these reports. Older, depressed women should be assessed for potential pharmacologic treatment to prevent osteoporosis-related fractures. We need to be aware that women who have experienced fractures may have depressive symptoms, and appropriate interventions can have a beneficial impact on quality of life. The important point is that depression and fractures are linked; one may precede the other and vice-versa in different patients.

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New Look on an Old Debate: Neoadjuvant Chemotherapy for Ovarian Cancer

ABSTRACT & COMMENTARY

by Robert L. Coleman, MD

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

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

Synopsis: *Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease.*

Source: Hou JY, et al. *Gynecol Oncol.* (2007), doi:10.1016/j.ygyno.2006.11.025.

NEOADJUVANT CHEMOTHERAPY (NACT) FOR ovarian cancer refers specifically to the adminis-

tration of cytotoxic therapy ahead of a planned surgical resection usually for primary therapy. Traditionally, the approach has been principally reserved for medically infirmed patients or those in whom the tumor burden precludes an adequate cytoreductive effort. However, observations of reduced operative morbidity have encouraged some investigators to use the strategy in selected patients. Hou and colleagues reviewed their experience with NACT over a seven-year period, focusing on perioperative morbidity and survival compared to women approached by conventional surgery followed by chemotherapy, and in cohorts of women treated before and after introduction of a taxane-platinum combination. Overall, 172 patients were identified; approximately 37% of these patients were given NACT (median 6 cycles) before a debulking attempt. Compared to women undergoing primary debulking surgery (PDS), women getting NACT before surgery had significantly shorter operations, less blood loss, fewer transfusions and shorter hospitalizations. In addition, they were less likely to need radical surgical procedures to make them "optimal" and achieved this milestone significantly more often. Survival between to two therapy styles was nearly identical (PFSNACT: 16 mos vs PFSPDS: 14 mos; OSNACT: 46 mos vs OSPDS: 47 mos); however, significantly better PFS and OS was observed among stage IV patients. Patients achieving "optimal" status defined as less than 1 cm residuum had similar outcomes for both survival endpoints. Taxane based combinations outperformed non-taxane combination for both cohorts. The authors concluded that NACT is associated with superior operative endpoints without diminution in survival and should be prospectively studied.

COMMENTARY

There are few more controversial topics in the discussion of primary ovarian cancer management than NACT vs primary surgical resection. A prior report by this group a few years ago (demonstrating similar general results) initiated a firestorm of letters to the editor claiming "foul-play" and cautioned that the approach could ("in fact") hurt patients by denying them appropriate care.[1,2] There was also the intimation that the approach (NACT) is being increasingly performed due to declining surgical skills in some gynecologic oncologists.

Since that time, reports of expanding radical surgical procedures to more women documented that the concept of aggressive primary surgery is important to outcome and as such would support the concept of redefining the "optimal" endpoint as no visible residual (see "Outcome of cytoreductive surgery in primary ovarian cancer: what is 'optimal'?" in *OB/GYN Clinical Alert*, January 2007). However, current reports consistently highlight the reduction in operative morbidity, and despite the obvious negative selection bias of sicker and more advanced disease patients, similar survival.

The foundation for these observations lies in the clinical aspect of chemo-sensitive tumor. Chemonaïve ovarian cancer, even large volume disease, for the most part, has a significant probability of response to taxane and platinum-based therapy. The responses can be dramatic.[3] However, critics suggest the exposure of large volume tumor to active therapy may heighten chemo-resistant clones due to the mixed and large population of such cells in a bulky tumor nodule. In this setting, NACT only perpetuates a select population of resistant cells which should reduce survivorship. Contemporary reports such as the current paper suggest otherwise and do provide some basis for randomized evaluation. Fortunately, some information will be available following the report of the EORTC 55971 trial.

Many questions remain in optimal NACT delivery. For instance, how many cycles should be given ahead of surgery? There is some evidence more (6 or more) has a detrimental effect on survival. In whom is it most appropriate? The significant selection bias has limited this approach to sick and advanced stage (extra-abdominal) disease patients. Would less sick patients also benefit to the same degree? How do you select patients unable to undergo optimal primary surgery? Imaging is of some help but clearly imperfect as are the cadre of biomarkers. Finally, patients with bulky intraperitoneal disease are probably not good candidates for intraperitoneal chemotherapy in the neoadjuvant setting. Would denying, delaying or restricting use of this modality, which has been demonstrated in Phase III clinical trials to be beneficial to survival, be detrimental in the long run? Further work will help to elucidate optimal patients for this approach as has been done for patients with colorectal and breast cancer. ■

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CME Questions

5. For how long does the risk of postpartum depression remain elevated in primiparous women?
a. 1 month
b. 12 months
c. 3 months
d. 10 to 19 days
e. 5 months

6. Factors evaluated in this study for correlation between intra-operative frozen section and final pathological diagnosis were:
a. histology
b. lymphatic space involvement
c. cervical stromal involvement
d. depth of myometrial invasion

7. The following statements are true regarding depression and fractures except:
a. It is possible that depression causes bone loss in some men and women.
b. Osteoporosis should be suspected in depressed individuals.
c. Metabolic changes secondary to depression can cause bone loss.
d. When present, one can assume that depression preceded bone loss.

8. Which of the following factors was significantly different between the cohort of patients treated with NACT compared to those treated by conventional PDS?
a. age
b. proportion of Clear Cell Carcinoma
c. proprotion of Grade 3 tumors
d. baseline CA-125 value

Answers: 5 (e); 6 (d); 7 (d); 8 (b)

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:
- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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Higher HDL Cholesterol in Statin Therapy, Key to Slowing Atherosclerosis?

Aggressive statin therapy is associated with slowed progression and even regression of atherosclerosis. A new study suggests that, when monitoring statin therapy, increases in HDL cholesterol may be as important as decreases in LDL cholesterol in preventing disease progression. Researchers from the Cleveland Clinic reviewed 4 large studies from United States, North America, Europe and Australia in which 1,455 patients with angiographic coronary disease underwent serial intravascular ultrasonography while receiving aggressive statin therapy for 18 or 24 months. During therapy, mean LDL levels dropped from 124.0 mg/dl to 87.5 mg/dl, and mean HDL levels increased from 42.5 mg/dl to 45.1 mg/dl, and LDL to HDL ratios were reduced from a mean of 3 to 2.1 ($P < 0.001$ for all). These changes were accompanied by a small, but statistically significant decrease in atheroma volume as measured by intravascular ultrasound. The largest decrease in atheroma volume was associated with patients with LDL cholesterol less than the mean of 87.5 mg/dl, and percentage increases in HDL cholesterol of greater than 7.5%. The authors conclude that when treating with statins, decreases of LDL cholesterol and increases in HDL cholesterol are independently associated with regression of atheroma volume. They also note that these changes were not associated with reductions in clinical events or improved clinical outcomes and that more research is needed (*JAMA*. 2007; 297:499-508).

Citalopram Useful for Depression in CDA Patients

Major depression affects up to one quarter of patients hospitalized with coronary artery disease and these patients have a worse prognosis than non-depressed patients. A new study from Canada compares the efficacy of citalopram vs interpersonal psychotherapy in reducing depressive symptoms among these patients. The study randomized 284 patients with CAD and major depression to 12 weeks of interpersonal psychotherapy plus clinical management vs clinical management only, and a second randomization compared 12 weeks of citalopram 20-40 mg/day vs placebo. The main outcomes were scores on objective depression scales. Citalopram was superior to placebo in reducing depression scores ($P = 0.005$), but interpersonal psychotherapy was ineffective, being no better than clinical management. The authors conclude that citalopram administered in conjunction with weekly clinical management was effective in treating depression whereas there was no evidence of value for interpersonal psychotherapy. The authors suggest that citalopram or sertraline (based on previous studies) should be considered as first-step treatment for patients with CAD and major depression (*JAMA*. 2007;297:367-379). An accompanying editorial agrees that citalopram and sertraline are safe and effective for treatment of depression in patients with coronary heart disease, and suggests physicians should actively screen for signs and symptoms of depression in these patients. However, there is not yet

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) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

any evidence that treating depression in this patient population reduces subsequent cardiac events (*JAMA*. 2007;297:411-412).

When to Stop Anticoagulation Before Surgery?

For patients on warfarin who have been bridging therapy with low molecular weight heparin (LMWH) prior to surgery, when is the best time to stop anticoagulation? A new study suggests that the evening before surgery is too late. Researchers in Ontario, Canada, looked at 80 patients who were scheduled for surgery or invasive procedures and were bridged with LMWH. All 20 patients had normal renal function and were given enoxaparin 1 mg/kg of body weight twice daily with the last dose administered the evening before surgery. Blood anti-factor Xa heparin levels were measured shortly before surgery, an average of 14 hours after the last dose. Two-thirds of patients had anti-Xa heparin levels of 0.5 U/ml or higher shortly before their invasive procedure. Patients with higher BMIs were more likely to have higher levels as were patients with lower creatinine clearances. The authors conclude that preoperative bridging with twice daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. They recommend that the last dose be given the morning on the day prior to surgery (*Ann Int Med.* 2007;146:184-187).

Drug Warnings: Ranibizumab and Bevacizumab

Both of Genentech's anti-angiogenic agents, ranibizumab (Lucentis) and bevacizumab (Avastin), have been the subject of new warnings from the company and the FDA. Ranibizumab, which is used for the treatment of neovascular (wet) macular degeneration, has been associated with increased risk of stroke in elderly patients. The drug, which is administered as an monthly intraocular injection, was found to be associated with a 1.2% risk of stroke at the recommended dose of 0.5 mg compared to a 0.3% risk associated with the lower-than-recommended 0.3 mg dose ($P = 0.02$) at an average follow-up of 230 days. Patients who had a history of stroke were at the highest risk. Bevacizumab, which is approved for treatment of non-small cell lung cancer and metastatic colorectal cancer, was recently found to be associated with increased risk of gastrointestinal perforation and potentially fatal pulmonary hemorrhage. Gastrointestinal perforation was seen as a complication of patients treated for colorectal cancer, while pulmonary hemorrhage was seen in patients receiving chemotherapy plus bevacizumab for lung cancer. Other bleeding complications seen in bevacizumab-treated patients including GI hemorrhage, subarachnoid hemorrhage and hemorrhagic stroke.

Growth Hormone Treatment, More Harm Than Good

The January 16, 2007, *Annals of Internal Medicine* includes a review of the safety and efficacy of growth hormone in the healthy elderly. The review was undertaken because growth hormone is widely recommended and sold as an anti-aging agent in this population. The authors reviewed 31 articles, which included a total of 220 participants who received growth hormone. The mean age was 69 and patients were generally overweight. Treatment duration mean was 27 weeks. Growth-hormone-treated patients compared to placebo- treated patients were noted to have decreases in overall fat mass and increases in overall lean body mass, but weight did not change significantly. Total cholesterol decreased, although not significantly, after adjustment for body composition changes. Bone density and other lipid levels did not change. Those treated with growth hormone were significantly more likely to experience soft tissue edema, and arthralgias, carpal tunnel syndrome, and gynecomastia as well as a slightly increased rate of diabetes and impaired fasting glucose. The authors conclude that growth hormone use in the elderly is associated with small changes in body composition and an increased rate of adverse events and cannot be recommended (*Ann Int Med*. 2007; 146:104-115).

FDA Actions

The FDA has warned against unsupervised use of topical anesthetic products for cosmetic procedures. The agency has received multiple reports of adverse events associated with patients applying excess amounts of topical agents containing lidocaine, tetracaine, benzocaine, and prilocaine. Two women who used topical anesthetics with lidocaine and tetracaine died after applying the creams to their legs and wrapping their legs in plastic to increase absorption. Healthcare professionals are cautioned to prescribe topical anesthetics with caution in the lowest concentration consistent with pain relief goals and to advise patients in their safe use.

The FDA has approved Roche's orlistat for over-the-counter use to facilitate weight loss. The drug, available in prescription form under the trade name "Xenical," blocks absorption of fat by inhibiting pancreatic lipase thus preventing triglyceride absorption in the small bowel. The over-the-counter version will be available as a 60 mg dose, half the prescription dosage. Orlistat over-the-counter will be marketed as "Alli." ■