Volume 22 Index Enclosed

OB/GYN CLINICAL ALERT®

A monthly update of developments in female reproductive medicine

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INSIDE

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Breast Cancer Risk in the WHI Estrogen-Only Arm

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The estrogen-only arm of the WHI reports a reduction in invasive breast cancer.*

Source: Stefanick ML, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*. 2006;295:1647-1657.

THE UPDATED BREAST CANCER RESULTS IN THE CANCELED estrogen-only arm of the Women's Health Initiative (WHI) are based on 237 cases of invasive breast cancer and 55 cases of cancer in situ, diagnosed by the February 29, 2004, date of study cancellation.[1] Overall, a reduction in invasive breast cancer in the treated group did not reach statistical significance (HR = 0.80; CI = 0.62-1.04). However, when the group adherent to treatment (accounting for the 54% drop-out rate) was analyzed, there was a statistically significant 33% reduction in invasive breast cancer (HR = 0.67; CI = 0.47-0.97). No effect was observed on in situ disease. The reduction in invasive breast cancer was confined to ductal carcinomas (no significant effect was seen with lobular cancer) and in women who had no prior exposure to hormones. A protective effect of estrogen treatment was observed in women without a history of benign breast disease, and in women without first-degree relatives with breast cancer. No interaction was seen with body mass index; oophorectomy status; age at menarche, first birth, or menopause; or with prior oral contraceptive use. The invasive breast cancers in the treated group were slightly larger (but the standard deviation was very wide), and there was no significant difference in the number of positive nodes. The treated group of women had more mammograms requiring follow-up, leading to more biopsies or aspirations.

COMMENTARY

This updated report from the WHI differs from the initial report from the cancelled estrogen-only arm in that a reduction in invasive

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breast cancer achieved statistical significance in those women who adhered to their estrogen treatment. The most important and difficult-to-answer questions are the following:

1. Do the differences between the estrogen-progestin and estrogen-only arms of the WHI reflect an adverse impact of progestins on breast cancer risk?
2. Do the epidemiologic studies reflect an impact of hormones on pre-existing tumors?

The cancelled estrogen-progestin arm of the WHI reported an increase in invasive breast cancer that reached statistical significance in the 5th year of exposure.[1] Even the WHI investigators have cautioned clinicians to avoid comparing the 2 trial arms because the participants in the 2 arms were considerably different.[2] In regards to breast cancer risk, the women in the estrogen-only arm had a higher rate of previous exposure to hormones and for longer durations. In the current WHI report, the investigators performed 2 calculations that led them to conclude that differences in the patient characteristics in the 2 arms could not explain the different conclusions. First, the 5-year Gail breast cancer risk estimates of the participants in the 2 arms were similar. Second, The rate of invasive breast cancer per year was similar in the placebo arms of the 2 trials. Nevertheless, the differences in previous hormone exposure continue to be reason for caution because the estrogen-only arm found a reduction only in women who had not previously used hormones.

To this date, not a single study has reported that hormone use increases the risk of ductal in situ breast cancer. If hormone exposure was causing the growth of new tumors, one would expect a difference in in situ disease as well as invasive disease. Is it possible that the apparent differences in estrogen-progestin and estrogen-only exposure are due to a greater differentiation effect of estrogen-progestin? In a Kaiser cohort study from Southern California, a reduction in breast cancer mortality was statistically significant in users of estrogen-progestin, but not in users of estrogen-only.[3]

The breast cancer results in the WHI do not allow us to answer the above questions with any confidence. Exposure to estrogen-progestin either has a greater risk of breast cancer, or pre-existing tumors respond differently to various hormone regimens, accounting for differences in epidemiologic reports.

Many of the WHI conclusions are the result of statistical manipulations. For example, the investigators concluded that there was no interaction with oophorectomy status, despite the fact that the treated group had fewer bilateral oophorectomies. How confident can clinicians be with conclusions derived from Cox proportional hazard models? In another analysis, there was no trend with time for the risk of invasive breast cancer. What does this mean? Is an effect on pre-existing tumors seen only early during exposure? Keep in mind that all studies that have reported an increase in breast cancer with hormone therapy have found the increase very rapidly, within a few years. This contrasts with the well-recognized relatively slow growth of tumors until they reach a clinically detectable stage.

Rather than bringing clarity to this troublesome problem, the recent studies only raise more questions. Until we have more definitive data, I am comfortable telling patients that there is either a small increase in breast cancer risk with hormone therapy or the studies reflect an effect on pre-existing tumors. I also believe it is appropriate to share with patients the strong possibility that hormone users have lower grade, lower stage disease with better outcomes. ■

References

1. Chlebowski RT, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative Randomized Trial. *JAMA*. 2003;289: 3243-3253.
2. Stefanick ML, et al. The Women's Health Initiative

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postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol.* 2003;13(9 Suppl):S78-S86.
3. Chen W, et al. Mortality following development of breast cancer while using oestrogen or oestrogen plus progestin: a computer record-linkage study. *Br J Cancer*. 2005;93:392-398.

Pulmonary Embolism after Major Abdominal Surgery in Gynecologic Oncology

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *Patients with cancer undergoing major abdominal surgery and using pneumatic compression for thromboembolic prophylaxis had 14-fold greater odds of developing a pulmonary embolism compared with patients with benign disease. Randomized studies are needed to determine whether additional prophylactic measures may benefit this high-risk group of patients.*

Source: Martino M, et al. Pulmonary Embolism After Major Abdominal Surgery in Gynecologic Oncology. *Obstet Gynecol.* 2006;107:666-671.

Venous thromboembolism (VTE) is a major complication following gynecologic abdominal surgery that may be fatal in up to 1 in 4 affected patients. While several risk factors for VTE have been identified, carcinoma remains among the most significant. Incidence rates of VTE in gynecologic cancer patients are estimated to be among the highest of all primary carcinoma sites. Martino and colleagues conducted a retrospective cohort study to evaluate the incidence of VTE among gynecologic cancer patients who had undergone surgery at their center over a 3-year period. Both major (n = 839) and minor (n = 507) procedures were evaluated among patients with known or suspected malignancy. Surgical VTE prophylaxis was pneumatic compression boots alone. Cancer diagnosis, age, and type of surgery (major vs minor) were evaluated in the context of VTE which was confirmed by spiral CT, pulmonary angiography or ventilation/perfusion scans. Overall, 22 cases of VTE were diagnosed among the 839 patients undergoing major abdominal surgery. Twenty-one of 507 (4.1%) cancer patients were identified with VTE—a mean 11 days post-operatively. Only 1 of 332 (0.3%) patients with benign disease were diagnosed with VTE. The odds ratio for VTE in cancer patients relative to those with benign disease was 13.8 ($P < 0.001$). Other factors identified with increased risk were ovarian cancer and age. Survival was statistically unaffected by the occurrence of VTE. The authors concluded that patients undergoing major abdominal surgery and using pneumatic compression devices for prophylaxis had 14-fold greater odds of developing a pulmonary embolus than patients with benign disease. The incidence of VTE identified in this study provides important baseline information upon which to develop randomized clinical trials to improve prophylaxis.

COMMENTARY

The clinical evaluation of VTE prophylaxis among patients with gynecologic malignancy has spanned more than 20 years. In 1983, Clarke-Pearson and colleagues conducted 2 randomized, controlled clinical trials of heparin and pneumatic compression to controls and confirmed that the latter was effective in preventing VTE. Pneumatic compression in that study was administered before surgery and continued for 5 days post operatively. The 2 modalities were studied against each other in a follow-up trial 10 years later documenting equivalency in the prevention of VTE. However, patients receiving heparin experienced bleeding complications. With the development of low molecular weight heparin (LWMH), Maxwell and colleagues re-evaluated this therapy compared to pneumatic compression in gynecologic oncology patients. In this randomized trial, both were effective in preventing VTE and bleeding complications were similar, prompting the authors to recommend either as a reasonable option for VTE prophylaxis in this cohort. Nonetheless the current trial, consistent with others in the literature, document that nearly 1 in 20 cancer patients and nearly 1 in 15 ovarian cancer patients will suffer a VTE under one of these recommended prophylaxis strategies. Clearly, this represents an important area of clinical investigation. While a small trial combining LWMH and compression boots was unable to document an improvement over single modality prophylaxis, it remains to be seen if other combination strategies can "move the bar" in VTE prophylaxis. Given the low overall absolute risk of VTE as identified in the current study, such trials will be necessarily large and focused in the gynecologic oncology population. Fortunately, the

Gynecologic Oncology Group is currently developing such a study. ■

Suggested Reading

1. Maxwell GL, et al. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *Obstet Gynecol*. 2001;98: 989-995.
2. Geerts WH, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(Suppl):338S-400S.

Diagnosis of Polycystic Ovary Syndrome

SPECIAL REPORT

By Leon Speroff, Editor

THERE HAVE BEEN 2 ATTEMPTS TO PRODUCE A CONsensus definition of the polycystic ovary syndrome by expert conferences. The NIH-sponsored conference in 1990 was highlighted by the difficulty in achieving consensus; nevertheless the experts concluded that hyperandrogenism after the exclusion of other etiologies (such as adrenal disorders) and menstrual dysfunction were required for diagnosis, and that ultrasound diagnosis of polycystic ovaries was controversial. In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) organized an expert conference that produced the Rotterdam criteria: the diagnosis of polycystic ovary syndrome could be diagnosed if 2 of the following 3 features are present—1) oligo- or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; and 3) polycystic ovaries established by ultrasonography. Thus according to the Rotterdam criteria, the diagnosis could be made without ovulatory dysfunction or without hyperandrogenism.

Ricardo Azziz from UCLA editorially considers the Rotterdam criteria to be a problem.[1] He believes that assigning this diagnosis to ovulatory women or to anovulatory women without hyperandrogenism can have negative consequences. The use of the Rotterdam definition to establish inclusion and exclusion criteria in clinical studies may make it difficult to establish common abnormalities and future risks associated with this syndrome. Importantly, the Rotterdam criteria imply to both clinicians and patients that ovulatory women or anovulatory women without hyperandrogenism have future metabolic and cardiovascular risks, something we do not know. Azziz also raises the disturbing thought that assigning this diagnosis according to the Rotterdam criteria can impact the insurability of some women.

Stephen Franks from the Imperial College and Hammersmith Hospital in London argues that the Rotterdam criteria are important and helpful.[2] Franks believes that the presence of polycystic ovaries on ultrasound in ovulating women with hyperandrogenism confirms the diagnosis of polycystic ovary syndrome, and that ovulatory women with polycystic ovaries and hyperandrogenism should be included in the definition of the syndrome. More problematic is the woman with polycystic ovaries and anovulation without hyperandrogenism. Franks contends that such patients can be excluded by establishing the causes of anovulation. He further asserts that the broader definition and application of the Rotterdam criteria are important for the clinical management of these patients.

■ COMMENTARY

The discussions and disagreements regarding the polycystic ovary syndrome always remind me of Justice Potter Stewart , who upon hearing a case of pornography at the US Supreme Court, said he couldn't define pornography, but "I sure recognize it when I see it." For most, if not all, gynecologists, the same can be said regarding polycystic ovary syndrome. It is a clinical diagnosis easily made in nearly all patients who present with this problem.

It seems to me that there are two basic reasons for confusion and disagreement. First is the role assigned to the presence of polycystic ovaries demonstrated by ultrasonography, and second is the constant search of authors and investigators to find a single cause for this clinical syndrome.

A clear difference exists between North American and European clinicians and investigators regarding the sonographic appearance of the ovaries (the ultrasound demonstration of polycystic ovaries is commonly a diagnostic feature of the polycystic ovary syndrome in Europe). The emphasis on ovarian morphology in the Rotterdam criteria reflects this European standard.

It has been long established that polycystic ovaries can be found by ultrasound in a substantial percentage of normal (ovulating), reproductive age women. The critical question is whether these women have metabolic consequences and risks. The few studies exploring this question have found absent or small biochemical differ-

ences compared with controls. In my view, if there are no clinical disruptions of normal function and no long-term risks, then the presence of polycystic ovaries is meaningless.

Recognizing that polycystic ovaries are not etiologic but a histologic manifestation seen with many clinical states easily solves this clinical dilemma. For this reason, the presence or absence of polycystic ovaries is not an essential element in the diagnosis of polycystic ovary syndrome, and ultrasonography is not a required part of the diagnostic process. Indeed, there is no single biochemical or genetic diagnostic marker. This syndrome remains a clinical diagnosis, recognizing that women with ovulatory dysfunction and hyperandrogenism have the clinical problems of infertility and hirsutism and increased risks of diabetes mellitus and cardiovascular disease. The syndrome reflects a broad spectrum of patients with multiple causes, ranging from simple weight gain to adrenal disease, hyperprolactinemia, thyroid disease, and androgen-producing tumors. Even ovulatory dysfunction can be evasive, moving back and forth in individual patients from regular menses and ovulation to oligo-ovulation to anovulation.

Is too much fuss being made over this issue? From a clinical point of view, the manifestations of this syndrome in an individual patient reflect the position of that patient in the broad spectrum of ovulatory, endocrine, and metabolic dysfunction determined by the specific cause and how long it has been present. But this is precisely why it has been so confusing for investigators. The collection of patients is large and diverse, a situation making precise definition and study easier said than done. This debate requires future studies to determine whether women with polycystic ovaries on ultrasonography but without hyperandrogenism and anovulation, have increased risks for metabolic and cardiovascular diseases. In the meantime, for most patients, the clinical presentation of the patient is sufficient for clinicians to provide effective and appropriate counseling and therapy. ■

References

1. Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. *J Clin Endocrinol Metab*. 2006; 91:781-785.
2. Franks S. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam criteria. *J Clin Endocrinol Metab*. 2006;91: 786-789.

Does Time Affect Rupture in Appendicitis?

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: *Rupture risk in cases of appendicitis was less than 2% when symptoms went untreated for less than 36 hours, whereas the risk exceeds 5% when the duration of symptoms is more than 36 hours.*

Source: Bickell NA, et al. How time affects the risk of rupture in appendicitis. *J Am Coll Surg*. 2006;202:401-406.

A RETROSPECTIVE CHART REVIEW IN 219 OF 731 randomly selected cases of appendicitis was conducted at 2 municipal/tertiary care hospitals. Compared to the rupture rate of < 2% when the untreated symptoms were of 36 hours duration or less, patients with symptoms beyond 36 hours had a rate of rupture exceeding 5% (RR = 6.6).

Other significant factors for ruptured appendix included age 65 years and older (RR = 4.2), fever > 38.9°C (RR = 3.6), and tachycardia > 100 bpm (RR = 3.4). The time between the first physician evaluation and treatment was statistically shorter (7.1 vs 10.9 hours) if the patient presented to the Emergency Department. Also, the duration to treatment was shorter (6.3 vs 11.3 hours) if the physician's primary differential diagnosis was appendicitis. Interestingly, patients sent for CT scan had delayed time to surgery compared to those patients who did not have a CT scan (18.6 vs 7.1 hours).

COMMENTARY

I really like studies that try to answer clinical questions that make me wonder. This is one such study. Although retrospective, it tries to address the always-difficult concern of: "Gee, I wonder what will happen if surgery for the suspected appendicitis is delayed?" Data from the 2000 National Hospital Discharge Survey suggest that the overall ruptured appendix rate is approximately 13%. With the attendant peritonitis, sepsis, and even mortality, it behooves us to try to avoid appendiceal rupture if at all possible.

For the first 36 hours after the onset of symptoms, the

authors found a 0-2% risk of rupture in each 12-hour period. The risk rose and remained stable at 5% during subsequent 12-hour periods. The clinical message should not be lost on those who primarily look after the healthcare of women. Even though acute appendicitis typically is a general surgical problem, the differential diagnosis of this condition in women is primarily gynecologic. Given the classic history, physical, and laboratory findings in cases of appendicitis, the gynecologic disorders can usually be ruled out in a timely fashion.

Even if we are remote from the patient, we regularly use ultrasound reports to image ovarian cysts, the pregnancy test to rule out ectopic pregnancy, and the complete blood count to provide insight into blood loss as well as leukocytosis. By no means would I advocate making a presumptive diagnosis without a thorough history and physical, but the primary gynecologic etiologies for right lower quadrant pain can be ordered and performed by the time we arrive to see the patient. My take-home message from this article is that we need to minimize our role in any undue delay that might lead to a ruptured appendix. It is my opinion that we can greatly help our colleagues in the Emergency Department or on the General Surgery service with timely and efficient use of the skills and tests available to us. This article helps us focus on that effort. ■

Association Between Low Day 16 hCG and Miscarriage After Proven Cardiac Activity

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

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

A GROUP FROM AUSTRALIA RECENTLY PUBLISHED A study that provides some insight about miscarriage after 8 weeks of gestation. They analyzed data from 1050 patients having in vitro fertilization. Serum hCG levels were measured at 16 days post-conception (approximately for menstrual weeks). All patients had transvaginal ultrasound examinations at 6 to 7 menstrual weeks, but were followed at varying intervals thereafter. Most women in this study had nuchal translucency (NT) testing between 11 and 13 weeks.

The authors included only those embryos with documented fetal heart rate activity at the 6 to 7 week ultrasound examination because they were more interested in the ability of these hormonal levels to predict things to come, rather than events that have already happened. Spontaneous abortion was defined as an inability to document fetal life from 8 weeks until 19 menstrual weeks.

The overall miscarriage rate was 11% and the authors found that the average hCG level in those pregnancies ending in losses was 182 mIU/mL vs 233 mIU/mL in those who did not miscarry. If the hCG level was below the 25th percentile, the loss rate was 16.7%, compared with 8% if the hCG level was above the 75th percentile. The average age of those who miscarried vs those who did not was 38 and 36, respectively—and this was statistically significant.

COMMENTARY

This report strongly suggests that the writing is already on the wall for many seemingly normal pregnancies since their placentas produce lesser amounts of hCG at 4 weeks of gestation. Aneuploidy screening studies are further evidence to support the concept of showing that the beta subunit of hCG is lower in pregnancies destined for intrauterine demise.

The good news is that, even when the levels of hCG at 4 weeks are below the 25th percentile, more than 4 out of 5 pregnancies will continue at least past the 20th menstrual week.

Here are some milestones which may help the practitioner in following patients anxious about their chances of a successful pregnancy:

Seen on transvaginal ultrasound
Time of visualization
Appearance of gestational sac at 5 menstrual weeks
Appearance of a yolk sac at a mean sac diameter of 8 mm
Embryonic pole at 5 weeks or an hCG of 1000 mIU
Fetal heart activity when CRL is 5 mm

In addition, crown-rump length of the fetus should grow at a rate of 1 mm per day and, as indicated above, should increase by at least 66% in 48 hours. ■

Suggested Reading

1. Tong S, et al. Association between low day 16 hCG and miscarriage after proven cardiac activity. *Obstet Gynecol*. 2006;107:300-304.
2. Baird DD, et al. Rescue of the corpus luteum in human pregnancy. *Biol Reprod*. 2003;68:448-456.
3. Dugoff L, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a popula-

tion-based screening study (the FASTER Trial). *Am J Obstet Gynecol*. 2004;191:1446-1451.

Pretreatment CA125 and Risk of Relapse in Advance Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *The baseline CA125 level before initiation of maintenance chemotherapy strongly predicts the risk of subsequent relapse.*

Source: Markman M, et al. Pretreatment CA-125 and risk of relapse in advanced ovarian cancer. *J Clin Oncol*. 2006; 24:1454-1458

It has been recently identified that nadir values in serial CA125 values during adjuvant primary post-operative chemotherapy are prognostic even within the normal range (less than 35). Markman and colleagues set out to determine if a similar finding might be observed in evaluating the outcomes of patients entered into clinical trials evaluating the efficacy of maintenance therapy. Two trials were included in the current report: GOG-178/SWOG-9701, a phase III randomized study which evaluated paclitaxel (3 vs 12 cycles) and SWOG-9386, a single-arm open-label phase II trial that evaluated altretamine in patients with complete clinical response.

Consistent with the adjuvant study, the authors of the current study defined 3 categories of CA125 (≤ 10 u/mL, 11-20 u/mL and 21 to 35 u/mL). In addition to CA125, residual disease and age were considered in the final analysis. Similar to the previous report, patients with pre-registration CA125 values of 10 or less were associated with the best survival. This was observed in each of the 3 cohorts and in both studies. Overall, median PFS was 24 months, 17 months, and 7 months in the three CA125 groups. Of interest, in the randomized trial (GOG-178/SWOG-9701), the effect amounted to an improvement (12 cycles vs 3 cycles) of 9 months, 4 months, and 0 months in the 3 CA125 groups. The authors concluded that pre-treatment CA125 strongly predicts relapse in patients with complete clinical response following primary adjuvant chemotherapy.

COMMENTARY

Most patients and clinicians are acutely aware of the prognostic significance a normal CA125 implies following therapy. It has also been recognized that patients will typically manifest a nadir value from which serial determinations are compared in estimating recurrence. Sequentially doubling of these values even within the normal range (35 u/mL or lower) has been used as a surrogate of disease recurrence even in the absence of measurable disease. In addition, a provocative recent finding is that the value of this nadir is prognostic of recurrence.

The current trial expands this line of investigation by documenting a similar prognostic effect in pretreatment CA125 values for patients with a clinical complete response undergoing maintenance chemotherapy. No difference in effect was observed between agents or among the treatment arms. The magnitude of the observed differences by CA125 category was impressive and amounted to nearly a year and a half. Perhaps even more provocative, in the randomized trial, the observations in PFS demonstrated that no difference was observed between the 12-month and 3-month arms for patients with CA125 values of 21-35 u/mL.

While the data are retrospective and not properly powered to determine the effect, they provides some insight into a potentially important factor by which patients may be identified who could benefit most from the maintenance strategy. Prospective trials with defined CA125 stratification will help to shed light on this important prognostic variable. Since maintenance therapy is not without complication, improving the precision of therapy will be a welcomed clinical finding. ■

CME Questions

7. The following statements are true regarding polycystic ovary syndrome *except*:

a. The presence of polycystic ovaries on ultrasonography does not establish anovulation.
b. The diagnosis of hyperandrogenism requires laboratory measurement of androgens.
c. Women with anovulation and hyperandrogenism have an increased risk of diabetes mellitus.
d. Not all women with polycystic ovaries are hyperandrogenemic.

8. **The risk of rupture in cases of acute appendicitis appears to increase after how many hours?**
   a. 12
   b. 24
   c. 36
   d. 48
   e. 60

9. **The following statements are true regarding postmenopausal hormone therapy and the risk of breast cancer *except*:**
   a. It is possible that estrogen-progestin therapy is associated with a small increase in breast cancer.
   b. It is possible that estrogen-only therapy is associated with a small reduction in breast cancer.
   c. Postmenopausal hormone users have more questionable mammograms, requiring further study.
   d. It is known that the risk of breast cancer steadily increases with increasing duration of exposure to postmenopausal hormone therapy.

10. **Which of the following statements is *false*?**
   a. hCG should double every 48 hours.
   b. A gestational sac should be seen by 5 menstrual weeks.
   c. A level of 1000 units/mL at 4 days is suspicious for fetal demise.
   d. Fetal heart activity should be seen when the crown-rump length is 5 mm.

Answers: 7 (b); 8 (c); 9 (d); 10 (c)

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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Reversal of Atherosclerosis Via Intensive Statin Therapy

Aggressive LDL lowering with statins, so-called "very intensive statin therapy," leads to reversal of coronary atherosclerosis, according to a new study. The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, a perspective, open label, blinded end-points trial, utilized the potent statin rosuvastatin in evaluating whether very intensive statin therapy resulting in LDL cholesterols in the low 60s associated with increases in HDL cholesterol could reverse atherosclerosis. Five hundred and seven patients were initially evaluated with intravascular ultrasound (IVUS) to determine baseline atheroma burden. Patients were then treated with intensive statin therapy with rosuvastatin 40 mg daily for 24 months, which resulted in an average LDL cholesterol of 60.8 mg/dL (mean reduction, 53.2%) and increased HDL cholesterol by 14.7%. IVUS was performed again at 24 months. The mean change in atheroma volume in the most diseased 10 mm sub segment was -6.1 (10.1) mm^3, with a median of -5.6 mm^3 ($P < .001$ vs baseline). Change in total atheroma volume showed a 6.8% median reduction. Adverse events were infrequent. Specifically there were no cases of rhabdomyolysis.

The authors conclude that lowering LDL-C to levels below currently accepted guidelines, when accompanied by significant increases HDL-C, can regress atherosclerosis in coronary disease patients, and is indicated for high-risk patients with established coronary disease (*JAMA*. 2006;295:1556-1565). An accompanying editorial notes that the study had several limitations, including lack of a control group or a comparator drug. They also note that the modest plaque reduction noted in this study "may not be the best measure of the treatment's effect on hard cardiovascular end points", however, they do applaud the pioneering work using intravascular ultrasound to help understand the anatomy and pathophysiology of coronary atherosclerosis and the effect of medical therapy on atheroma (*JAMA*. 2006;295:1583-1584).

Alternative Therapy for Depression?

Patients who fail SSRI treatment for depression may respond to an alternative medication, or the addition of a second medication, according to 2 studies in the March 23 *New England Journal of Medicine*. In the first study, 727 adults with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram (Celexa) were randomized to receive sustained release bupropion

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(Wellbutrin) in a maximal daily dose of 400 mg, sertraline (Zoloft) at a maximum daily dose of 200 mg, or extended release venlafaxine (Effexor-XR) at a maximal daily dose of 375 mg for up to 14 weeks. The primary outcome was remission of symptoms based on the Hamilton Rating Scale of Depression (HRSD-17). Secondary outcomes included scores on the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16). Remission rates, as assessed by the 2 scales, respectively, were bupropion - 21.3% and 25.5%, sertraline - 17.6% and 26.6%, venlafaxine - 24.8% and 25.0%. Response rates based on the QIDS-SR-16 were bupropion 26.1%, sertraline 26.7%, and venlafaxine 28.2%. There was no significant difference with respect to outcomes, tolerability, or adverse effects among the 3 drugs.

The authors conclude that after unsuccessful treatment with an SSRI, 1 in 4 patients have a remission after switching to another antidepressant, and all 3 drugs in the trial were reasonable choices (*N Engl J Med*. 2006;354:1231-1242). Another option for treating patients who failed treatment with citalopram was explored in the second study in the same issue. In the study, 565 adults who had a nonpsychotic major depressive disorder without remission after 12 weeks of citalopram therapy were randomized to receive add-on therapy with sustained release bupropion up to 400 mg per day, and 286 were randomized to receive buspirone (Buspar) at a dose of up to 60 mg per day. The same depression rating scales were used in this study as in the previous study. For bupropion and buspiron, respectively, HRSD-17 remission rate was 29.7% vs 30.1%, QIDS-SR-16 remission rate was 30.9% vs 32.9%, and QIDS-SR-16 response rate was 31.8% vs 26.9%. Bupropion was associated with a greater change in QIDS-SR-16 score, as well as the overall lower QIDS-SR-16 score at the end of the study and a lower dropout rate to due to intolerance (12.5% vs 20.6%, $P < 0.009$).

The authors conclude that the addition of bupropion or buspirone to citalopram is useful; however, the addition of bupropion may have some advantages, including a greater reduction in the severity of symptoms in fewer side effects (*N Engl J Med*. 2006;354:1243-1252).

FDA Actions

The FDA has approved the first generic HIV/AIDS drug for use in the United States. Zidovudine, manufactured under the trade name Retrovir by GlaxoSmithKline, was initially approved in 1987, and the company has had exclusive manufacturing rights until the drug's patent expired in September 2005. The generic is made by Aurobindo Pharma LTD of India. This is the same company that recently received approval from the FDA to co-package 3 antiretroviral drugs for the treatment of HIV/AIDS outside the United States. The regimen consists of lamivudine/zidovudine combination tablet along with efavirenz tablets. The co-packaging of these products has met the clinical safety, efficacy, and manufacturing quality standards required by the FDA. The approval is part of the Presidents Emergency Plan for offering full HIV treatment regimens for targeted areas of the world that are at risk to prevent HIV transmission and to treat AIDS and associated conditions. Patents and exclusivity prevent marketing of this combination in United States.

The FDA has approved a transdermal patch for the treatment of children with attention-deficit hyperactivity disorder. The patch delivers methylphenidate, the same ingredient found in Ritalin, in a daily patch that is applied early in the morning and removed 9 hours later. Methylphenidate patch is manufactured by Shire Pharmaceuticals and Noven Pharmaceuticals under the trade name Daytrana.

Salix pharmaceuticals has received approval to market a new tablet bowel prep for colon cleansing prior to colonoscopy. The virtually tasteless sodium phosphate tablets are an alternative to traditional liquid PEG bowel preps. The recommended dose is 32 tablets taken orally with a total of 2 quarts of clear liquids, administered as 4 tablets with 8 ounces of liquid every 15 minutes. Twenty tablets are given on the night prior to the procedure, with the remaining 12 tablets administered 3 to 5 hours prior to colonoscopy. Sodium phosphate tablets will be manufactured under the trade name OsmoPrep. ■