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INSIDE

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The Impact of BRCA Mutation on Ovarian Cancer Treatment Outcomes

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: *BRCA mutation carriers demonstrate improved survival characteristics relative to age- and stage-matched population controls. The performance gains are likely due to higher than expected platinum-based cytotoxicity and have implications for future therapeutic investigation.*

Source: Tan DS, et al. "BRCAness" syndrome in ovarian cancer: A case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. *J Clin Oncol* 2008 Oct 27; Epub ahead of print.

HEREDITARY OVARIAN CANCER SYNDROMES ARE UNCOMMON, BUT are most often represented by mutation in BRCA1/2. The natural history expectations in mutation carriers who develop ovarian cancer is debated; however, the gene's function in repair of DNA double strand breaks by homologous recombination would suggest heightened sensitivity to agents, like platinum, when compromised.

To address this hypothesis, 22 women with germ-line BRCA1 or BRCA2 mutations and epithelial ovarian cancer were age-, stage-, histology- and year of diagnosis-matched (1:2) to 44 non-hereditary ovarian cancer patients. All received platinum-based primary therapy. Compared with controls, BRCA-positive women had higher overall and complete response rates to first-line treatments. They also had higher response rates to second- and third-line platinum-based therapy and a remarkable increase in both

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overall survival from time of diagnosis (8.4 years vs 2.9 years; $P < 0.002$) and overall survival from the time of first recurrence (5.0 years vs 1.6 years; $P < 0.001$). Multivariate analysis demonstrated that BRCA status, and stage and length of first response were independent prognostic factors from time of first relapse. Remarkably, the duration of secondary platinum-based therapy was no different than when administered in the primary setting; this contrasted with a decreased median treatment-free interval in the control population. The effect was limited to platinum-based treatments.

This retrospective study suggests that platinum-based therapy among BRCA mutation carriers is associated with substantially improved response rates and overall survival characteristics relative to women without BRCA-related hereditary cancer. The reason for this may lie in the inability of affected women to repair platinum-associated DNA strand breaks. Future prospective therapeutic studies will need to confirm these findings and carefully consider BRCA status in addressing inference in treatment efficacy.

■ COMMENTARY

Hereditary ovarian cancer accounts for about 10% of all ovarian epithelial cancers. Identification of at-risk women prior to the development of disease is important as interventional strategies, such as prophylactic surgery, can dramatically reduce the expression of the malignant phenotype. From the study discussed here, it is likely that identification of BRCA status in affected women is also of both prognostic and therapeutic benefit. The relationship between carrier status and outcome has been debated with some reports demonstrating improved clinical outcomes and others, adverse. However, as the function of the BRCA genes is becoming clearer, it is likely the latter associations have come from biased or incomplete analyses of population data.

The BRCA genes appear to play a dominant role in the repair of DNA strand breaks through homologous recombination. When impaired, increased pressure is placed on other DNA repair mechanisms, such as poly(ADP-ribose)-polymerase (PARP) promoting the likelihood that catastrophic cellular insults will go unrepaired. In tumors of BRCA patients, this deficit may be leveraged, therapeutically, by inducing strand breaks with agents such as platinum or by inhibiting PARP. Inhibitors of PARP are now in active clinical investigation in women selected based on their BRCA status. Preliminary results have been quite promising and appear relevant in both platinum-sensitive and platinum-resistant patients, even when administered as a single agent. Findings such as those in this report suggest attention should also be placed on DNA-damaging agents. The demonstration of improved survival from the time of first progression suggests a real treatment effect, as this reference point is less likely to be influenced by primary treatment factors such as postoperative tumor residuum and chemotherapy.

BRCA mutation status in unselected ovarian cancer patients has been added to a few ongoing and recently completed randomized ovarian cancer treatment trials, which should elucidate its prognostic and, potentially, predictive role. It is possible that a future direction in applied therapy could be the co-administration of agents, which may target BRCA function; successful modulation could broaden the therapeutic options in both selected and unselected patients with ovarian cancer. ■

Suggested Reading

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2. Chiang JW, et al. BRCA1 promoter methylation predicts adverse ovarian cancer prognosis. *Gynecol Oncol* 2006;101:403-410.
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Editorial E-Mail: paula.cousins@ahcmedia.com
Customer Service E-Mail:customerservice@ahcmedia.com

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Testosterone for Low Libido

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A randomized, controlled trial concludes that transdermal testosterone at 300 μg per day modestly increases sexuality, but side effects are a concern.*

Source: Davis SR, et al; Aphrodite Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008;359:2005-2017.

DAVIS AND COLLEAGUES REPORT THE RESULTS OF A one-year, randomized, controlled clinical trial of 814 women not on estrogen therapy from 65 centers in the United States, Canada, Australia, the United Kingdom, and Sweden with hypoactive sexual desire disorder treated with transdermal testosterone, 150 or 300 μg per day, or placebo. A subgroup was followed for an additional year. This Phase III trial was supported by Proctor & Gamble Pharmaceuticals, maker of the Intrinsa patch, which was applied twice a week. In the 71% of participants who completed 24 weeks, the higher dose of testosterone increased sexuality (including desire, arousal, orgasm, and pleasure) by 1.4 episodes per month compared with placebo. This increase appeared as early as the second month of treatment. The lower dose did not differ from placebo, although both doses significantly increased desire per day. In the higher dose group, 30% reported unwanted androgenic effects (essentially an increase in facial hair). The frequency of acne, alopecia, and voice deepening was the same in all groups. There were 4 cases of breast cancer in the treatment groups and none in the placebo group.

■ COMMENTARY

Hypoactive sexual desire disorder is defined as a decrease in sexual activity sufficient to cause distress. Previous clinical trials that concluded that the 300 μg transdermal dose of testosterone was effective for low libido consisted of women with either surgical (1172 women) or natural (549 women) menopause who also were being treated with estrogen.[1,2] The magnitude of the impact on sexuality in this study was similar to the previous clinical trials with transdermal testosterone.

Pharmacologic levels of testosterone can stimulate sexuality; there is no debate over this. The concern is that this level of testosterone can produce unwanted consequences. There was a 30% incidence of increased facial hair in this trial with the effective dose. In addition, 1 woman in the low-dose group and 3 women in the high-dose group developed clitoral enlargement (the enlargement resolved in the woman receiving the low dose, but not in the high dose women). Remember that the trials with transdermal testosterone have been relatively short in duration. We have no idea what the long-term rate of side effects would be. It is certainly plausible that with longer exposure to the high dose, more and more women would develop androgenic side effects.

In this trial, there was a 10.6% incidence of vaginal bleeding in the women receiving the higher dose who had not undergone hysterectomy, compared with 2.6% in the placebo group and 2.7% in the low-dose group. Was this due to aromatization of testosterone in the endometrium? Furthermore, we already know that in the presence of a uterus, women receiving estrogen therapy plus testosterone still need progestational protection of the endometrium. The numbers and duration of the transdermal testosterone trials have not been sufficient to provide reliable data on this potential risk. There were no cases of endometrial hyperplasia or cancer in this trial, but again, a longer duration of exposure might have unwanted consequences. Two of the treated women had proliferative endometrium, but the authors chose to interpret the bleeding as an atrophying effect of the testosterone on the endometrium. This issue cannot be resolved without long-term data.

Breast cancer also is a concern because of the possibility of local breast tissue aromatization of the testosterone to estrogen. The potential for long-term exposure to unopposed and elevated local concentrations of estrogen continues to be worrisome despite studies that indicate inhibition of breast tissue proliferation by locally applied testosterone. In the 4 treated women who had breast cancer diagnosed in this trial, 1 was diagnosed after only 4 months of treatment and 1 had a bloody nipple discharge before the trial started.

A total of 132 women completed an additional year of follow-up. This left a small number of women in each treatment group, and the report provides no information regarding side effects in these women. The authors acknowledge that numbers and duration were not sufficient to provide long-term data on safety. The long-term effects on the cardiovascular system are unknown.

Response did not correlate with testosterone levels at baseline, and higher levels during treatment did not predict androgenic side effects. This is not surprising because measurement of free and bioavailable testosterone are subject to considerable inaccuracy and variability. For this reason, testosterone levels cannot be used to diagnose hypoactive sexual desire disorder.[3] The

current trial reports that all testosterone levels remained within the premenopausal ranges. However, the mean level of free testosterone was relatively high at 6.8 pg/mL, although within the reference range. According to the data in the supplemental appendix, available only on-line, the levels were at or above the upper end of the reference age. These are not physiological levels! Isn't the fact that 30% of the women receiving the high dose reported an increase in androgenic effects evidence of a pharmacologic effect? We don't know if it is possible to avoid unwanted consequences by careful monitoring of blood levels.

There is little doubt that the administration of pharmacologic amounts of testosterone can produce favorable effects on sexuality, but it remains doubtful that maintaining testosterone levels within the normal physiologic range can have a beneficial impact on health. Some women receiving pharmacologic amounts of testosterone develop very high circulating levels. The fundamental problem is that the long-term consequences of pharmacologic amounts of testosterone are totally unknown.

I am reluctant to support the pharmacologic use of testosterone given the difficulties in monitoring dosage and the lack of knowledge regarding the long-term effects on health. 17α-methyltestosterone is available in a commercial product, administered orally in combination with estrogen. The available doses are definitely pharmacologic. The problem is that this androgen is not demethylated in the body and cannot be measured by testosterone assays; therefore, it is impossible to monitor dosage. If a clinician and a patient choose to use supplemental androgens, my advice is to select a treatment that can be monitored with measurements of total testosterone in serum. The choices include the testosterone transdermal patch (not yet on the market), a testosterone skin gel (on the market for use in men), and testosterone compounded for individual use by a pharmacist.

We are left with this question: Is a modest increase of 1.4 episodes per month sufficient to offset the unanswered question of long-term safety? Some women would say yes, but the clinician has an obligation to avoid excessive doses and to educate the patient regarding the unanswered questions. ■

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3. Davis SR, et al. Circulating androgen levels and self-reported sexual function in women. *JAMA* 2005;294:91-96.

Role of Hysteroscopy in Evaluating Chronic Pelvic Pain

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

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

Synopsis: *A review article whose objective is to "… provide a survey of various gynecological conditions …" that might be amenable to diagnosis by hysteroscopy.*

Source: di Spezio Sardo AD, et al. Role of hysteroscopy in evaluating chronic pelvic pain. *Fertil Steril* 2008;90: 1191-1196.

THE AUTHORS PRESENT A SERIES OF GYNECOLOGICAL conditions that are effectively diagnosed by hysteroscopy, including adenomyosis, chronic endometritis, Mullerian anomalies, retained fetal bones, endocervical ossification, and intrauterine abnormalities. In addition, they note that hysteroscopy can be a major part of the treatment for these conditions. They conclude that, because it can be safely performed in an office setting, hysteroscopy may be indicated as a first-level tool in diagnosing and treating chronic pelvic pain.

■ COMMENTARY

"This is a GREAT article! It really gave me some good insights." "This is a terrible paper. I can't believe it got published … in *Fertility and Sterility* no less!" Like so many articles in our peer-reviewed literature, the clinician has to wade through this one with one eye on what

is being written, and the other on common-sense clinical practice. This group of Italian authors has accomplished what it set out to do: review the literature on several conditions that can possibly be diagnosed with hysteroscopy. Unfortunately, even though they do put things in perspective with the disclaimer, "Although some clinicians already use hysteroscopy in the evaluation of chronic pelvic pain, other investigators refute its usefulness," I walked away from the paper with the impression that the unstated goal of writing the paper was getting more people to perform hysteroscopy on more patients. Why would I take such a clinical view of the article? It's because they later bemoan the fact that "… unfortunately most gynecologists still are unable to take advantage of the many potentialities of this technique or do not perform hysteroscopic procedures in the office setting." Thus, I interpret the authors' intent may be a bit less than totally objective.

Do I believe hysteroscopy is an appropriate part of the evaluation of chronic pelvic pain? The answer is an emphatic "absolutely," but in selected cases. The concern I have when reading articles such as this one is that folks will now do hysteroscopy on every patient with chronic pelvic pain. The physical examination is almost left out of the article entirely because each of the articles that is cited focused more on the technique of hysteroscopy and its applicability than on the individual patient. As clinicians, you and I are just the opposite: We are and should be more concerned about the patient and her pain than on whether a particular procedure can be used. In fact, the article appropriately points out the potential role of other procedures such as ultrasound, MRI, and the "gold standard" for pelvic pain evaluation, laparoscopy. So much for technology. It's almost like the authors have an operation looking for some indications. In reality, they have a very good diagnostic tool that can be effectively used appropriately, but in selected cases. What about the physical examination and how does that fit into the picture?

To be honest, I believe that the role of hysteroscopy in the evaluation of chronic pelvic pain should be driven more by the physical examination than by anything else. More than history or imaging, the pelvic examination is the one modality that can actually locate the source of pain. Just as importantly, the physical examination can rule out a source of pain. The bimanual examination can potentially recreate the location as well as the nature of the pain. Even if the abdominal wall is too thick to truly palpate the uterus between the two hands, at least manipulation of the cervix with the vaginal fingers can provide a suggestion that the uterus is the source of the pain. If the uterus is nontender and there is no cervical motion tenderness, I would submit that the likelihood of hysteroscopy being a useful procedure is minute. Do I have data to that effect? Unfortunately, only my experience says this. There are no published papers that I am aware of that focus on the pelvic examination exclusively. This makes sense clinically and intuitively. A comparable clinical example is in considering the diagnosis of interstitial cystitis. If the bladder is nontender, it is unlikely that interstitial cystitis is the cause of pain and cystoscopy is unlikely to be helpful.

The authors are accurate in assessing the role of hysteroscopy in diagnosing the various conditions. They tell us that there is no consensus of its role in the diagnosis of adenomyosis. The same is true regarding chronic endometritis. The other conditions may be associated with pain, but ultrasound rather than hysteroscopy would be a logical first test in the evaluation. The bibliography is also telling. Of the 62 cited articles, only one links the terms "hysteroscopy" and "chronic pelvic pain," and its conclusions actually address the role of hysteroscopy when used in combination with laparoscopy.

So did I waste the readers' time reviewing this topic? I hope not. I hope I stimulated the clinician to do what makes sense logically: See if the uterus seems to be a potential source of pain. If so, then hysteroscopy will be used appropriately to assess the endometrial cavity as a source of pain. If the uterus is nontender, then other sites can be investigated. We and our patients should remain masters of the various technological advances available to us, not slaves to them. It's time to get off my soapbox now. ■

Special Feature

The Bioidentical Hormone Conflict

By Leon Speroff, MD, Editor

THE ADVERSE PUBLICITY FOLLOWING PUBLICATIONS from the Women's Health Initiative was a multibillion dollar bonanza for compounding pharmacies providing postmenopausal hormones. Bioidentical hormones are now the focus of a political, financial, and legal conflict. Bruce Patsner, MD, JD, MBA, research professor in the Health Law & Policy Institute at the University of Houston Law Center, has written what is in my view a masterful analysis of the problem, with suggestions for its resolution.[1]

The History of the Conflict

The operations of a pharmacy are regulated in the individual states by state boards of pharmacy, in a system similar to the regulation of medical practice. The first federal law regulating drugs, the Federal Food, Drug & Cosmetic Act, was passed in 1938, at a time when most drugs were compounded according to a doctor's prescription. The American Pharmaceutical Association defines pharmacy compounding as the preparation of a prescription drug that is "individualized" to the needs of the patient. This changed after World War II with the development and growth of the pharmaceutical industry. The Kefauver-Harris Amendment in 1964 extended the FDA role to include safety and efficacy.

In the 1990s, the FDA began to regard the drugs coming from compounding pharmacies as falling under the "new drug" regulations, and, therefore, the FDA had jurisdiction over the marketing and promotion of those drugs. The pharmacy world was immediately challenged; there was no way that an individual pharmacy could carry out the kind of clinical studies required for the approval of new drugs. Thus, the pharmacists immediately realized that all compounded drugs would be illegal. At the same time, the FDA was a bit ambivalent, acknowledging that there were examples where the individual needs of a patient required the compounding of a drug, e.g., the creation of a liquid preparation when none was available. This was before compounding took to the Internet for marketing and promotion.

In 1992, the FDA issued its Compliance Policy Guide on Compounding, reserving a right for "selective enforcement," as a compromise between believing it was correct in assuming that compounded drugs represented new drugs and admitting that some patients required compounding. The pharmacy profession immediately rejected the idea that the FDA had any regulatory jurisdiction over pharmacies. The 1997 Food and Drug Modernization Act attempted to clarify the situation. An amendment was added to the existing laws stating that compounded drugs were not "new drugs," but at the same time the act prohibited the marketing of compounded drugs.

The pharmacy profession sued the FDA, arguing that a restriction on advertising and promotion of compounded drugs was unconstitutional, a restriction of free speech. The District Court ruled against the FDA in 1999. The FDA appealed and lost again in the 9th Circuit Court of Appeals, which further invalidated the entire 1997 Act. In 2002, the U.S. Supreme Court upheld the Circuit Court decision.

The FDA issued a new Compliance Policy Guide in 2002, stating that selective enforcement would hinge on 3 major factors: 1) a potential adverse effect of a drug; 2) whether drugs were compounded from non-FDA-approved components; and 3) whether compounded drugs were similar to drugs already removed from the market for safety reasons. At this point, the FDA affirmed that it did not want to infringe on the traditional practice of compounding, the preparation of a drug according to a doctor's prescription to fit an individual patient's requirements.

Wyeth Pharmaceuticals filed a Citizen Petition with the FDA in October 2005 requesting that the FDA take action against several compounding pharmacies that are primarily Internet-based. The petition's major allegation was that these pharmacies were essentially manufacturing new drugs and should be subject to new drug regulations. On Jan. 9, 2008, the FDA announced it would take action against 7 pharmacies providing prescription bioidentical hormones, and issued warning letters that potentially could be followed by seizures of drugs and injunctions against production.

The Current Landscape

Now, where are we? Currently, the FDA is caught between a rock and a hard place. The FDA would like to regard compounded drugs as "new drugs," but the legal precedent has now been set by the courts: Compounded drugs are not "new drugs." This was reaffirmed in a 2006 decision in the U.S. District Court for Texas. The FDA would further like to regard the giant compounding pharmacies, especially those operating over the Internet, as manufacturers, like pharmaceutical companies, but again, the court decisions have prevented the FDA from requiring compounding pharmacies to meet "new drug" standards. The "new drug" argument just isn't working.

"Bioidentical" and "natural" are often used in concert. Strictly defined, the hormones must be precisely the same as normal endogenous estradiol or progesterone. To argue that products are not "artificial," begs the issue because even if the source is a steroid molecule derived from plants, chemical and manufacturing processing is still required. These terms obviously have marketing value, and no one can deny that the terms are used to imply greater safety, even greater efficacy. The situation is further compounded (pun intended) because it is likely that most patients assume that the marketed bioidentical and natural hormones have been demonstrated by appropriate studies to be effective and safe. Of course this is not the case, although it seems like an obvious

conclusion to view Product A and Product B to be the same if they are the same molecule. The problem is that compounding pharmacies are not required to compare the formulation with the performance of an approved product, nor is there any way for a patient to be assured that the dosage is correct (that the drug contains what it is supposed to contain).

The large compounding pharmacies meet the "individualization" requirement that usually comes from a clinician-patient interaction by promoting salivary measurements of hormones, as interpreted by one of their employed clinicians to produce tailored hormone choices and doses. Assessment of this approach by researchers, as well as organizations such as the American College of Obstetricians and Gynecologists and the Endocrine Society, have concluded that the variations in salivary sex steroid levels from individual to individual and from specimen to specimen preclude clinical interpretation. For most patients, laboratory testing is not necessary in hormone decision making. As Patsner says, this is "pseudo-individualization." Individualization is a process that requires a clinician-patient interaction.

The politicization of this issue is well underway. See the Project F.A.N.S. (Freedom of Access to Natural Solutions) web site at www.projectfans.org. This organization and web site are headed by a physician who has his own Hotze Health & Wellness Center in Houston, TX, that promotes the "safer, natural bioidentical hormones."

A New Approach

The American Pharmacists Association and the National Association of Boards of Pharmacies define compounding as the steps required to provide a drug in response to a clinician's prescription according to an individual patient's needs, and the preparation of drugs in anticipation of a demand. Therefore, there are 3 people involved: the patient, the clinician, and the pharmacist. This is in contrast to the production of large amounts of a drug for a national market of unknown users. The American Pharmacists Association further says that if an FDA-approved product is commercially available that meets a patient's needs, it should be the drug provided.

The key to the position of the pharmacists is the contention that there are circumstances, decided by the patient, that makes the use of commercial products not a good choice. This seems reasonable, but it is also reasonable that this decision requires the involvement of the clinician because ultimately a prescription is still required. The traditional view of compounding, therefore, is one of personal relationships with patient, clinician, and pharmacists. This becomes a totally different story when a large Internet pharmacy responds to thousands of prescriptions with no knowledge of the patients. What happened to the "individualization" aspect of compounding? Is it practicing medicine by the pharmacy to have a registered clinician employed by the pharmacy to interpret hormone levels and adjust doses?

Clinicians are appropriately frustrated by the claims made that bioidentical compounded drugs have greater efficacy and safety. Signature Compounding Pharmacy (www.signaturepharmacy.com) says that natural hormone replacement therapy is safe, sensible, effective, and free from side effects caused by synthetic hormones. Of course, to claim that these products are free from side effects, to say that they protect against cancer, is a position unencumbered by data. This is a profit-driven, nonregulated market—doesn't that sound familiar?

The Wyeth petition will not meet its objective because the requests in the petition mirror the arguments already struck down by the courts, basically that compounded drugs should be regarded as new drugs and regulated in the same manner as commercial products. A new approach is needed. Bruce Patsner argues that it should be accepted that bioidentical drugs from the big compounding pharmacies do not meet the definition of compounding supported by the pharmacist's own organization, the American Pharmacists Association—a personal relationship of patient, clinician, and pharmacist addressing an individual's needs. The FDA can argue that the big operations are not legitimate compounding, but big commercial operations directed to unknown consumers.

Patsner also argues that the most vulnerable point is the false safety and efficacy claims. The contention should not be that the safety and efficacy claims are inaccurate, because the pharmacies can always compose their words to avoid legal assaults. The point of attack should go back to the pharmacist's published credo: If a commercial, approved product is available to meet the patient's needs, a compounded product is not indicated. Replacing a commercial product with a "natural," untested, unregulated product is not the same thing as prescribing a compounded product when no commercial product will meet the individual's needs.

Patsner summarizes his argument by saying that the large compounding pharmacies are not true compounders because they advertise and promote their products as replacements for commercially available, approved, and tested drugs, and that the attempt at

"individualization" uses an unsubstantiated method that marginalizes clinicians.

It is worth pointing out that this whole issue wouldn't be a problem of such a large magnitude without the involvement of physicians. There are clinicians who put the dollar ahead of good sense, and there are clinicians who don't want to take the time to counter the Internet advertisements. For this reason, it is necessary for the FDA to find a way to exert appropriate regulation. ■

Reference

1. Patsner B. Pharmacy compounding of bioidentical hormone replacement therapy (BHRT): A proposed new approach to justify FDA regulation of these prescription drugs. *Food Drug Law J* 2008;63:459-491.

CME Questions

39. Multivariate analysis for factors independently associated with overall survival from the time of first recurrence included all of the following *except*:
a. age.
b. stage.
c. BRCA status.
d. progression-free survival until first recurrence.

40. The following statements are true regarding the use of testosterone to treat libido *except*:
a. There are no laboratory tests to help diagnose hypoactive sexual desire disorder.
b. Women with a uterus who are on long-term testosterone therapy also need to take a progestational agent.
c. Long-term testosterone therapy may have adverse effects on the uterus, the breasts, and the cardiovascular system.
d. Only women with low blood levels of testosterone are candidates for testosterone treatment.

41. Which of the following is the gold standard for assessing pelvic pain?
a. Ultrasound
b. MRI
c. Laparoscopy
d. Hysteroscopy

42. The definition of compounding espoused by the American Pharmacists Association and the National Association of Boards of Pharmacies requires which of the following?
a. A physician's prescription
b. An individual patient's need
c. Lack of a comparable commercially available product
d. All of the above

Answers: 39. (a), 40. (d), 41. (c), 42. (d).

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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JUPITER: C-reactive Protein a Marker for CV Events?

In this issue: The JUPITER trial causes a stir; ACP practice guideline for antidepressant use; testosterone for low libido; continued shortage of Hib vaccine; FDA Actions.

The JUPITER trial causes a stir

Elevated high-sensitivity C-reactive protein (CRP) may help identify otherwise healthy patients with normal cholesterol levels who will benefit from statin therapy, according to the JUPITER trial published in November. Researchers randomized nearly 18,000 healthy men and women with normal cholesterol levels (LDL < 130 mg/dL) with CRP levels of 2.0 mg/L or greater to rosuvastatin (Crestor) 20 mg daily or placebo. The combined primary endpoint was myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular cause. The trial was stopped early at 1.9 years when the rate of the primary endpoint was found to be 0.77 per 100 person-years in the treatment group vs 1.36 per 100 person-years in the placebo (HR 0.56; 95% CI, 0.46-0.69; $P < 0.00001$). Overall, the rate of events was low in both groups: 142 of 8901 in the treatment group vs 251 of 8901 in the placebo group. The individual endpoints of myocardial infarction, stroke, and revascularization or unstable angina were all reduced by approximately 50% in the rosuvastatin group, LDL cholesterol levels were decreased by 50%, and CRP levels were decreased 37%. There was not a significant increase in myopathy or cancer in the treatment group, but there was a higher incidence of physician-reported diabetes. The authors conclude that in apparently healthy persons without hyperlipidemia but with elevated CRPs, rosuvastatin significantly reduced the incidence of major cardiovascular events (*N Engl J Med* 2008;359:2195-2207).

In an accompanying editorial, Mark Hlatky, MD, Stanford University School of Medicine, points out that although the relative risk reductions in the JUPITER trial were clearly significant, the absolute difference in risk was less impressive with 120 participants treated for 1.9 years to prevent one event. It is also difficult to know the role of CRP in risk stratification since patients with normal CRP levels were not treated and it is possible that lowering cholesterol with statins may benefit even those with low CRP levels. CRP may have a role in deciding whether to treat patients with intermediate risk, but it may be too early to use it to recommend treatment for those at low risk. Hlatky writes that "guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and long-term safety and cost" (*N Engl J Med* 2008;359:2280-2282). It is safe to say that JUPITER has been the subject of many lively discussions in hospital lunchrooms

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

across the country. Whether the benefit of rosuvastatin can be generalized to all statins, whether CRP should be a standard part of yearly blood panels for adults patients, and whether everyone with an elevated CRP should be offered treatment with a statin are all questions that are being hotly debated and will need further evaluation.

ACP treatment guideline for antidepressants

The American College of Physicians has issued a practice guideline for the use of antidepressants to treat depressive disorders. The guideline encompasses the use of newer "second-generation antidepressants," including the SSRIs: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox). Also included were the SNRIs venlafaxine (Effexor), and duloxetine (Cymbalta), as well as other drugs such as mirtazapine (Remeron), bupropion (Wellbutrin), nefazodone, and trazadone. After reviewing 203 clinical trials, the guideline group concluded that there were no significant differences between the drugs with regard to efficacy. The guideline group recommends that second-generation antidepressants should be selected on the basis of adverse effect profiles, cost, and patient preference. They further recommend that clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1-2 weeks of initiation of therapy and that treatment should be modified if the patient does not have an adequate response to pharmacotherapy within 6-8 weeks. Finally, they recommend that clinicians continue treatment for 4-9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients with history of depression, a longer duration of therapy may be beneficial (*Ann Intern Med* 2008;149:725-733).

Testosterone for low libido: Questions remain

Low sexual desire is commonly reported by postmenopausal women. A new study suggests that testosterone replacement may be of benefit. Researchers randomized 814 postmenopausal women with hypoactive sexual desire or disorder to testosterone patches delivering 150 or 300 mg of testosterone per day or placebo. The primary endpoint was change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes. Safety outcomes were followed out to one year. At 24 weeks the primary endpoint was significantly greater in the group receiving 300 mg of testosterone per day than placebo (increase in sexually satisfied episodes of 2.1 vs 0.7, $P < 0.001$) but not in the group receiving 150 mg per day. Both doses of testosterone were associated with significant increases in desire and decreases in distress. The rate of androgenic side effects including unwanted hair growth was higher in the group receiving 300 mg per day. Breast cancer was diagnosed in 4 women who received testosterone vs none in the placebo group. The authors conclude that a testosterone patch delivering 300 mg per day results in modest but meaningful improvement in sexual function although the long-term effects of testosterone including effects on the breasts remain uncertain (*N Engl J Med* 2008;359:2005-2017). This study confirms previous reports that testosterone has a positive effect on sexuality in women. The rate of breast cancer, although not reaching statistical significance in this study, raises concern.

Continued shortage for Hib vaccine

The continued shortage of the *Haemophilus influenza* type b (Hib) vaccine has not led to an increase in *Haemophilus* infections according to the *MMWR*. It has been a year since the CDC recommended deferring the fourth dose of the Hib vaccine in healthy children (at 12-15 months of age) because of a shortage due to contamination concerns in the manufacturing process. Merck & Co. now reports that mid-2009 is a realistic date for normal production. The CDC has undertaken national surveillance for Hib infections including 748 cases in children < 5 years old. Of these, only 6% were clearly identified as serotype b (the most invasive strain of *Haemophilus*), although serotyping information was missing in nearly 40% of cases. The CDC is concerned because antibody levels fall 12 months after vaccination in children. In the U.K., where the fourth booster was not initially recommended, Hib infections rebounded after 12-15 months. CDC is recommending vigilance on the part of pediatricians and also is emphasizing that state and hospital labs should perform serotyping on all *Haemophilus* infections.

FDA Actions

The FDA has approved fesoterodine fumarate for the treatment of overactive bladder. The drug relaxes smooth muscle of the bladder reducing urinary frequency, urge to urinate, and sudden urinary incontinence. Fesoterodine fumarate will be available in 4 mg and 8 mg strengths for use once daily. The drug is manufactured by Schwartz Pharma and will be marketed as Toviaz . ■