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INSIDE

Obstetrical Prognosis after Placental Abruption

ABSTRACT & COMMENTARY

In a recent study from Japan, Toivonen and colleagues set out to determine how much more susceptible women experiencing placental abruption were to having a recurrence of this problem in a subsequent pregnancy. They scanned a database which encompassed 14,326 deliveries during a one-year period at a busy university hospital. Fifty-nine patients who had a history of abruption in a previous pregnancy were identified, and the outcomes of these pregnancies were then compared with those from pregnancies without a recurrent abruption, and against those of the overall study population. Toivonen et al only included diagnoses made after 20 weeks.

The incidence of abruption in those having had this condition in a previous pregnancy was 11.9%, compared with a rate in the rest of the population of 0.7%. The recurrent abruptors had a very high rate of prematurity (100%), low birth weight (85.7%), low 5-minute Apgar scores (28.6%), and perinatal mortality (14%). Interestingly, those with a history of abruption who did not repeat had a rate of adverse outcome that was no different in any category from that of the overall population (Toivonen S, et al. *Fetal Diagn Ther.* 2004;19:336-341).

COMMENT BY JOHN C. HOBBINS, MD

We are often asked by our patients what the chances are of having a repeat of what, at worst, was a disaster for them or, at the least, a vexing lifestyle altering experience. Since there has been little in the literature on this, I have waffled on the answer. Now I can say that there is a 90% chance it will not recur and, if it does not, the individual's chances of having perinatal problems are no different than anyone not having had this experience in a previous pregnancy. Unfortunately, that cannot be said of those who do have a recurrence.

The incidence in the overall population of 7 per 1000 is an underestimation of the prevalence of abruption, since vaginal bleeding prior to 20 weeks is far more common, and often the bleeding is due to abruption, in spite of lack of ultrasound evi-

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dence to back up the diagnosis. The ultrasound diagnosis of abruption involves the identification of an extra membranous clot. Rarely does one actually visualize a separation of the placenta from the underlying uterine wall. In about 50% of cases, when no ultrasound clues are present, the blood from the placenta tracks extra membranously to the cervix without stopping to form a clot.

This study, like others, once again shows a higher incidence of abruption among smokers. Also, there was a greater predisposition to abruption among pre-eclamptics. Other studies show a higher rate of abruption in patients with thrombophilia (Factor V Leiden, protein S deficiency, and Methylenetetrahydrofolate reductase [MTHFR] mutations). The common denominator in all of these relationships would be an interference with normal trophoblastic invasion of the spiral arteries in the second trimester.

Fortunately, this study should better allow us to counsel patients with abruption regarding future pregnancies. ■

Suggested Reading

- Rasmussen S, et al. *Acta Obstet Gynecol Scand*. 2000; 79:496-501.
- Wiener-Megnagi Z, et al. *Am J Obstet Gynecol*. 1998; 179:1565-1567.
- Kolas T, et al. *Acta Obstet Gynecol Scand*. 2000;79: 644-648.

Venous Thrombosis and Type of Treatment

ABSTRACT & COMMENTARY

Synopsis: *A case-control study suggests that the risk of venous thrombosis differs according to the type of estrogen used.*

Source: Smith NL, et al. *JAMA*. 2004;292:1581-1587.

SMITH AND COLLEAGUES PERFORMED A CASE-CONtrol study of venous thrombosis and hormone users in postmenopausal women registered in a large health maintenance organization (the Group Health Cooperative) in the state of Washington. In October 1999 this organization switched hormone users from esterified estrogens to conjugated equine estrogens. This allowed the investigators to compare the risk of venous thrombosis associated with these 2 types of estrogen treatment. An increased risk of venous thrombosis was associated with the use of conjugated equine estrogens (OR = 1.65, 1.24-2.19), but not found with the use of esterified estrogens (OR = 0.92, 0.69-1.22). Surprisingly, the use of conjugated equine estrogens without a progestin was not associated with an increased risk.

■ COMMENT BY LEON SPEROFF, MD

Esterified estrogens contain approximately 80% estrone sulfate and 11% equilin sulfate. These are the 2 predominant estrogens in conjugated equine estrogens, but of course there is a large collection of steroids in this product, including not only estrogens, but very small amounts of progestins and androgens. There is potential, therefore, for different biologic behavior when comparing these two agents.

Smith et al performed a dose-response analysis, finding a statistically significant increase only with the stan-

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dard dose of conjugated equine estrogens and an even higher risk with higher doses of conjugated equine estrogens. However, the number of cases with low doses of conjugated equine estrogens totalled only 8, and the number of cases with high doses of esterified estrogens included only 3. I think it is difficult to make dose-response conclusions with these small numbers, even though I believe that higher doses of estrogen carry a higher risk of venous thrombosis.

Contrary to almost all of the previous literature, this study did not find a higher risk of venous thrombosis associated with use in the first year of exposure. The numbers of cases in this subgroup analysis were not provided, and it is possible that the statistical power of the study was insufficient for detection of an effect in recent exposure.

It is very unlikely that the use of conjugated equine estrogens without a progestin would not have an increased risk of venous thrombosis. This finding more likely again reflects the power to detect increases in this relatively infrequent event.

In my view, the fundamental question is whether equivalent doses of these 2 estrogens produce bioequivalent biologic responses. Is it possible that the blood levels of estrogens differ significantly comparing the 2 products because of differences in metabolism and clearance? This case-control study raises a question, but does not provide sufficient evidence to influence prescribing choices. The proper study would require comparing women with similar blood concentrations of the estrogens. ■

Usefulness of History, Physical, and Laboratory in Evaluating Vaginal Complaints

ABSTRACT & COMMENTARY

Synopsis: *In working up vaginitis symptoms, useful signs are inflammation and odor, information concerning odor and itching are useful symptoms, and office microscopy is the most accurate laboratory test.*

Source: Anderson MR, et al. *JAMA*. 2004;291: 1368-1379.

THIS EXHAUSTIVE LITERATURE SUMMARY included a MEDLINE search as well as a survey of the bibliographies of recent reviews. In addition, the primary authors of various studies were contacted for articles which evaluated the usefulness of the history, physical, and laboratory evaluations in the diagnosis of vaginitis. Criteria for inclusion were: original research, symptomatic premenopausal patients, primary care setting, comparison of a diagnostic symptom or sign with a standard, and ability to calculate sensitivity and specificity. Among symptoms, the most useful findings were a *lack* of itching (negative likelihood ratio, 0.18-0.79) and a *lack* of perceived odor (negative likelihood ratio, 0.07). The former finding made candidiasis less likely and the latter made bacterial vaginosis less likely. Physical findings predictive of candidiasis were inflammation (LR+, 2.1-8.4) and a *lack* of odor (LR+ = 2.9). Because the whiff test is a part of the reference standard for bacterial vaginosis, it was considered for purposes of this endeavor. Among laboratory tests, it is most useful to find a lack of leukocytes in candidiasis and bacterial vaginosis.

■ COMMENT BY FRANK W. LING, MD

This study takes us back to our earliest clinical experiences in obstetrics and gynecology. It also gives us something that few articles do: a way to make our office practice more efficient. How many patients have presented to us over the years with complaints of vaginitis? How many questions have we asked about the nature of the discharge? How many examinations have we done and how many times have we gone to the microscope with slides and coverslips in hand? How many cultures have we performed? I'm sure the answer to all the above is, "A bunch." How much of this effort was useful? This literature review helps us focus the questions we ask, the examinations that we do, and the laboratory tests that we perform.

I feel as though my day in the office has now been given some relief! What says "love" better than the gift of time? The questions that I need to ask can now focus on itching and odor. On examination, I can mainly look for erythema/edema/excoriations. My wet prep can remain my primary lab evaluation. Of course, we need to remain vigilant for gonorrhea and/or chlamydia when a wet prep doesn't show trichomonads. In a previous issue of *OB/GYN Clinical Alert*, we wrote about alternative treatment for resistant yeast infections, so we shouldn't forget the those outliers.[1] Remember, however, that common things occur commonly; ie, when you hear hoofbeats, think horses, not zebras.

Another implication for this paper is how you choose to manage your phone calls concerning vaginitis. Whether it's to benefit you or your office staff, if a patient is not to be seen in the office for her vaginal complaints, the questions and answers implicit in the findings here could increase the effectiveness of trying to diagnose and treat without being able to see the patient. Of course, many of our patients already self-diagnose and treat, so even these women can be better served when they call about treatment failures. ■

Reference

1. Ling F. *OB/GYN Clinical Alert*. 2004;20(10):79.

Aromatase Inhibitor for Severe Endometriosis

ABSTRACT & COMMENTARY

Synopsis: *Successful treatment of severe endometriosis in 2 premenopausal patients is reported.*

Source: Shippen ER, West WJ. *Fertil Steril*. 2004;81: 1395-1398.

TWO PREMENOPAUSAL PATIENTS WITH RESISTANT endometriosis were successfully treated with a combination of the aromatase inhibitor anastrozole, Prometrium, calcitrol, and rofecoxib. Both patients had been diagnosed with endometriosis via laparoscopy, and had undergone GnRH suppression. Although both desired to get pregnant in the future, the pain was bad enough for both patients to request hysterectomy for pain relief. Both had rejected danazol due to its side effect profile as well as the potential temporary nature of its benefits. This regimen achieved rapid success over 3 months, with relief over 24 months after therapy. Confirmatory laparoscopy at 15 revealed no endometriosis. Pregnancy was achieved in both cases after 24 months.

■ **COMMENT BY FRANK W. LING, MD**

Although just a case report, I believe that this article has an important message for all of us clinicians. There is potentially incredibly good news here, but also possibly some disturbing news. First the good news: another effective option for the treatment of endometriosis may well be available. Aromatase inhibitors have been approved by the FDA for the treatment of breast cancer, but that is all. Of course, when did the lack of FDA approval prevent insightful clinicians from seeking innovative applications of new drugs? We need to look no further than another aromatase inhibitor, letrozole, to see that its use to enhance folliculogenesis can be effective. As always, the patient must be fully informed as to potential risks as well as the potential benefits of any off-label use of medication. Interestingly, in these 2 cases, the patients chose to try the aromatase inhibitor over approved an approved medication, danazol.

That leads me to the potentially bad news. As we continue to focus on endometriosis for our patients, we sometimes lose sight of the forest for the trees. When we suspect endometriosis (or even when we have proven endometriosis), we must make sure that we have not only ruled out other etiologies for the symptoms. In the case of endometriosis, of course, pain is the primary concern of most patients and their physicians. I have seen many patients, as young as 15 years old, who have been subjected to multiple surgical interventions for pain thought to be related to endometriosis, when, in fact, it was due to another cause. In the case of the 2 patients in this case report, we are not told whether other etiologies were aggressively ruled out. As good consumers of the medical literature, we should remain aware of such issues. So we can easily get tunnel vision, focusing too much on endometriosis, even with new modalities available such as aromatase inhibitors. By the same token, our informed consent must reflect reality, ie, what are the side effects of proven medications such as danazol? Why are patients willing to take anastrozole, but not danazol? Why not other progestins? Is it possible that these patients might have gotten better on the Prometrium alone? I am not a cynic and have been in the same dilemma that these clinicians found themselves in. We have to address unusual circumstances, ie, desperate times require desperate measures. Patients have idiosyncratic biases, preconceptions, fears, etc. We need to address each. We also need to guide and provide the best information for her and her particular situation.

What do you do with this information? Is this case report useful in your practice? Maybe, maybe not. Another weapon in our war against endometriosis is a good thing. We need to use it wisely and only when it is really needed. ■

Timing Isn't Everything, Right?

ABSTRACT & COMMENTARY

Synopsis: *Nearly 70% of patients achieving a CR after primary therapy eventually recurred. Most recurrences occurred more than 6 months from completion of primary chemotherapy, and the use of second line agents at the time of recurrence was effective. In this study, the median time from CR to start of third line agent at 43 months compares favorably with the median PFS of 28 months following 12 months of Taxol reported in GOG 178 and challenges the concept of consolidation chemotherapy in ovarian cancer. A randomized trial to evaluate when to institute second line agents should be performed.*

Source: McMeekin DS, et al. *Gynecol Oncol.* 2004; 95(1):157-164.

Results from a recently published randomized clinical trial addressing the use of consolidation chemotherapy strongly suggested that the strategy improved progression-free survival in selected ovarian cancer patients. Early trial termination and recommended cross-over from the control arm limited any conclusion of an overall survival benefit, concerning some clinicians who contend the added toxicity from prolonged therapy must be accompanied with an overall survival advantage to change the standard of care. McMeekin and colleagues attempted to address this latter issue by evaluating the survival outcomes of patients in complete remission and approached by their wait and see clinical standard. In this approach patients completing primary therapy were observed until clinical progression was documented.

At that point treatment was recommended and administered. From 217 reviewed patients, 59 met a strictly-defined parallel enrollment criteria—that is, they met eligibility criteria for the published randomized trial. However, all of these patients were given their second chemotherapy at the time of a documented recurrence. Times to second- and third-line chemotherapy as well as overall survival were generated. With a median follow-up of 51 months, nearly two-thirds of the patient cohort recurred. The median time to progression for this group overall was 20 months. All but 2 patients received second-line chemotherapy at that time and from this cohort, all but 7 patients received a third-line treatment. The time from complete remission to the start of this therapy was 43 months. Relative to the randomized consolidation trial, this treatment time point would be similar to the progression-free survival time point a patient given consolidation chemotherapy and followed to recurrence (the start of their third-line treatment). By way of reference, the experimental cohort (12 months of paclitaxel) in that study had a median progression-free survival of 28 months or 40 months from complete remission. McMeekin et al concluded that while it would be improper to compare the outcomes of the two studies directly, observations from their wait and see policy suggest that overall survival may rival that achieved by consolidation.

COMMENT BY ROBERT L. COLEMAN, MD

Additional therapy after successful completion of a planned first-line regimen (consolidation) has become a popular strategy to address the 70%-plus recurrence risk ovarian cancer patients experience after achieving a primary complete remission.[1] Many different modalities have been evaluated including radiation therapy, immunotherapy, high-dose chemotherapy, intraperitoneal therapy and standard chemotherapy. Given the wide variance in patient cohorts and likely benefactors of these modalities, the most proper methodology to evaluate these treatments is a randomized clinical trial. Although many such trials have been conducted, to date, the only published clinical trial demonstrating any survival benefit, albeit progression-free survival, is the GOG/SWOG intergroup trial (GOG-178) comparing 3 cycles of paclitaxel (control) to 12 cycles of the same therapy.[2] The benefit demonstrated by the additional cycles of chemotherapy in this trial was sufficiently large to trip an early stopping rule agreed to and set ahead of the trial's initiation. Adhering to the recommendations outlined by the Data Safety Monitoring Board overseeing the trial, its principal investigators closed the trial to further entry, released interim results, and recommended that patients participating in the trial but randomized to the control group be offered extended therapy. While the recommendations were completely legitimate given the trial's design, some have argued the primary endpoint, progression-free survival, is insufficient to alter standard of care in this setting. Citing incurability and long-term toxicity, advocates of this position argue only a trial demonstrating improved longevity warrant adoption of any new such treatment paradigms.

The current trial by McMeekin et al raises another point in that in the long run whether one initiates therapy at recurrence or before recurrence (consolidation)

you may end up at the same place—equivalent survival. The trial's results are curious and speculative. If one attributes consolidation treatment as the patient's second-line, a time off therapy until recurrence was 28 months on the median—or 40 months from initiation. Waiting to treat until recurrence, in a similar cohort as presented, left one-third of patients without having to receive any therapy—they hadn't recurred.

Those that did were off treatment for 20 months and by the time they progressed again 43 months had passed; curiously closed to that seen in the randomized trial. But given the retrospective nature of its design, it can only be hypothesis generating. In fact, one could argue that the efficacy of the two trials' third-line therapy might not be equivalent. That is, the likelihood of response and survival in a patient receiving consolidation but remaining off therapy for 28 months might be superior to a patient remaining off therapy for less than 10 months. While difficult to estimate the survival difference, it is clear following the results of ICON-IV many clinicians would opt for combination chemotherapy in the former cohort, which demonstrated an overall survival benefit over non-taxane, platinum-based therapy. Patients in the McMeekin trial would likely be treated with this combination at second-line and something else, likely single agent at third-line. It is clear that this issue needs to be readdressed. A randomized controlled clinical trial involving two treatment arms vs no treatment is planned by the GOG. ■

References

1. Markman M, et al. *J Clin Oncol*. 2003;21:2460-2465.
2. Parmar MK, et al. *Lancet*. 2003;361:2099-2106.

Postmenopausal Hormone Therapy and Venous Thrombosis

ABSTRACT & COMMENTARY

Synopsis: *Postmenopausal hormone therapy increases the risk of venous thrombosis, especially in overweight, older women.*

Source: Cushman M, et al. *JAMA*. 2004;292: 1573-1580.

Results from the estrogen-progestin arm of the Women's Health Initiative confirm (after central adjudication of the diagnoses) an increase in venous thrombosis associated with a standard dose of postmenopausal hormone therapy. The important observations include:

- An overall two-fold increase in venous thrombosis, both deep vein thrombosis and pulmonary embolism
- The risk was about four-fold higher in the first year of exposure, but remained elevated throughout followup. The test for trend was significant for a decreasing risk with increasing duration of use.
- The risk was highest in overweight women and older women; thus, the highest risk was among the oldest, obese women.
- Smoking and baseline use of statins or aspirin did not alter the results.
- Among 6 genetic variants, only the presence of a mutation in factor V (the Leiden mutation) further increased the risk of venous thrombosis.

COMMENT BY LEON SPEROFF, MD

In view of the fact that the increase in coronary heart disease reported in the canceled estrogen-progestin arm of the WHI was no longer statistically significant after central adjudication of diagnosis and the relative infrequency of strokes, venous thrombosis is the most common cardiovascular complication of postmenopausal hormone therapy. But the risk varies with the individual characteristics of each patient. In the youngest age group of women, ages 50-59, those who were of normal weight had an incidence of venous thrombosis that was slightly lower than that reported in the general population. It is possible that this population does not have an increased risk with hormone therapy.

The failure to observe a protective effect of statins or aspirin is contrary to the 50% reduction in venous thrombosis observed in the HERS trial.[1] This is important because of the possibility that combined hormone therapy and statin/low-dose aspirin treatment may prevent the increased risk of venous thrombosis (although this has not been studied). In the WHI, only 16 of the 243 cases with venous thrombosis (6.6%) were statin users at baseline. This small number makes it difficult to be definitive. Furthermore, the preferred way to address this issue is a clinical trial with randomization to statins/aspirin.

Some practical recommendations:

1. It is worth considering methods to reduce the risk of venous thrombosis in overweight, older postmenopausal women. It has long been argued that the

transdermal route of administration may be safer in regard to this risk, and evidence from a French case-control study and clinical trials measuring responses in activated protein C resistance indicates that this may be so. Combining a transdermal method with either statin treatment or low-dose aspirin deserves consideration.

2. In women with a previous episode of idiopathic venous thrombosis or with a close family history of venous thrombosis, I believe that it is reasonable to screen for the presence of an inherited disorder (the most effective method is referral to a hematologist). In the presence of an inherited disorder, consideration again should be given to the combination of a transdermal method with statin or low dose aspirin treatment.

3. Appropriate prophylactic anticoagulant treatment is indicated in hormone users anticipating immobility with hospitalization (especially if overweight and older), and hormone treatment should be discontinued at least 4 weeks prior to major surgery. ■

Reference

1. Herrington DM, et al. *Circulation*. 2002;105:2962.

CME Question

10 The following statements are true regarding postmenopausal hormone therapy and the risk of venous thrombosis *except*:

a. It is possible to designate those women who are at higher risk.
b. Statins or low dose aspirin treatment prevent the risk of venous thrombosis associated with postmenopausal hormone therapy.
c. Smoking does not increase the risk of venous thrombosis in hormone users.
d. Avoiding the first-pass effect through the liver that follows oral hormone therapy may be associated with a reduced risk of venous thrombosis.

Answer: 10 (d)

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ACE Inhibitors and Receptor Blockers: Which is Inferior?

The first head-to-head comparison study of an ACE inhibitor and an angiotensin receptor blocker, to assess renoprotective effects in type 2 diabetes, has shown that the drugs are comparable in their benefit. It has been known for more than a decade that ACE inhibitors prevent progression of microalbuminuria in type 2 diabetes, out of proportion to their blood pressure lowering effects. It has also been shown that angiotensin receptor blockers are renoprotective, but it has not been shown that the drug classes are equivalent in their benefit. The Diabetics Exposed to Telmisartan and Enalapril Study Group (DETAIL study) was designed in 1996 to compare the 2 drugs in 250 patients with type 2 diabetes and early nephropathy. Patients were randomized to 80 mg of telmisartan or 20 mg enalapril daily. The primary end point was the change in Glomerular Filtration Rate (GFR) during 5 years of the study. Secondary end points included annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; the rates of end stage renal disease and cardiovascular events; and all-cause mortality. After 5 years, the change in GFR was -17.9 mL/min with telmisartan and -14.9 mL/min with enalapril (the 95% CI, -7.6- 1.6 mL/min). The data suggest that telmisartan is not inferior to enalapril in providing long-term renotection in patients with type 2 diabetes (*N Engl J Med*. 2004;351:1952-1961). In the same issue of the *Journal*, researchers in Italy compared the ACE inhibitor trandolapril plus verapamil, trandolapril alone, verapamil alone, or placebo in patients with hypertension and type 2 diabetes, and normal urinary albumin excretion. The end point was the development of persistent microalbuminuria. Over 3 years of treatment, the percentage of those patients developing microalbuminuria were: trandolapril 6%, trandolapril plus verapamil 5.7%, verapamil alone 11.9%, and placebo 10%. The authors conclude that trandolapril plus verapamil and trandolapril alone decrease the incidence of microalbuminuria to similar extent, whereas the effectiveness of verapamil alone was similar to that of placebo (*N Engl J Med*. 2004; 351:1941-1951).

The Infection Risk of Acid-Suppressing Drugs

Ever since cimetadine was first marketed in 1977, physicians have been concerned about the risk of infection associated with acid-suppressing drugs. Now researchers from the Netherlands have shown that concern is warranted, by demonstrating a link between acid-suppressing drugs and community-acquired pneumonia (CAP). Utilizing the Integrated Primary Care Information database in the Netherlands between 1995 and 2002, incidence rates for pneumonia were calculated for those exposed to acid-suppressive drugs and those who were unexposed. A case control analysis was conducted, nested in a cohort of incident users of acid-suppressive drugs, with up to 10 controls matched to each case for practice, year of birth, sex, and index date.

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The main outcome was CAP. The incidence rates for pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 in 2.45 per hundred person-years, respectively. The adjusted relative risk for pneumonia among persons currently using a proton pump inhibitor (PPI), compared with those who stopped using a PPI, was 1.89 (95% CI, 1.36-2.62). The risk for current users of H2 antagonists was 1.63 (95% CI, 1.07-2.48). The authors conclude that acid-suppressive drugs, especially proton pump inhibitors (PPIs), are associated with an increased risk of pneumonia, and suggest that these drugs should be used with caution, and at the lowest possible doses in patients who are at risk for pneumonia (*JAMA.* 2004;292:1955-1960). An accompanying editorial points out the biological plausibility of the findings and suggest that, while acid-suppressive drugs are indicated for a wide variety GI conditions, long-term, chronic use of these drugs should always be balanced with patient safety (*JAMA.* 2004;292:2012-2013).

Is Rosuvastatin As Safe As Other Statins?

Rosuvastatin (Crestor), AstraZeneca's entry into the high potency statin market, has not achieved marketshare comparable to Pfizer's atorvastatin (Lipitor) or Merck's simvastatin (Zocor). This, despite the facts that the drug is very potent and AstraZeneca has priced the drug 15-20% lower than Lipitor. Some physicians remember the cerivistatin (Baycol) withdrawal from the market, and may be concerned regarding the highest doses of rosuvastatin, especially since European regulators issued a warning earlier this year about the drug. New postmarketing data suggest, however, that rosuvastatin is as safe and well-tolerated as other statins. The records of 12,400 patients who received 5-40 mg/day were reviewed, representing 12,212 continuous patient years. In fixed dose trials with comparator statins, 5-40 mg of rosuvastatin showed an adverse event profile similar to those for 10-80 mg of atorvastatin, 10-80 mg of simvastatin, and 10-40 mg of pravastatin. Clinically significant increases in liver transaminases were uncommon (≤ 0.2%) in all groups. Myopathy with creatine kinase increases > 10 times the upper limit of normal, with muscle symptoms occurring in ≤ 0.03 % of patients who took rosuvastatin at doses of 40 mg or less. Proteinuria, at the same doses, was comparable to the rate seen with other statins as well. There were no deaths and no cases of rhabdomyolysis in patients on 40 mg or less of rosuvastatin. The authors conclude that rosuvastatin was well-tolerated, and out of safety profile similar to other commonly statins (*Am J Cardiol.* 2004;94:882-888).

Which Estrogen Preparation is the Safest?

Is esterified estrogen safer than conjugated equine estrogen? At least with regard to venous thrombosis, the answer may be yes, according to a recent study. Group Health Cooperative in Washington State, a large HMO, switched their patients from conjugated equine estrogen (CEE) to esterified estrogens (EE) in 1999. Records of perimenopausal and postmenopausal women were studied between January 1995 and the end of 2001. The primary outcome was the risk of first venous thrombosis, in relation to current use of either estrogen with or without a progestin. There were 586 cases of venous thrombosis identified. Compared with women not currently using hormones, current users of EE had no increase in venous thrombotic risk (odds ratio, 0.92; 95% CI, 0.69-1.22). Women taking CEE however, had an elevated risk (OR, 1.65; 95% CI, 1.24-2.19). Comparing users of the 2 estrogens, current users of CEE had an odds ratio of 1.78 for venous thrombosis, compared to users of EE (95% CI, 1.11-2.84), and higher doses of CEE were associated with a higher risk. Among all estrogen users, concomitant use of progestin was associated with an increased risk, compared to use with estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). The authors conclude that conjugated equine estrogen, but not esterified estrogen, is associated with an increased risk of venous thrombosis (*JAMA.* 2004; 292:1581-1587). While the authors acknowledge that these data need to be replicated, the study raises the interesting question of the differences between various estrogen preparations and the potential risks associated with them, especially when noting that conjugated equine estrogen was the only estrogen preparation used in the Women's Health Initiative.

FDA Actions

Serono has been given approval to market recombinant human luteinizing hormone (Luveris) for the treatment of infertility in women. The drug, which was granted orphan status, has been available in more than 60 countries for several years.

The FDA and Centocor have issued a warning to health care professionals about the increase risk of lymphoma associated with inflixamab (Remicade) in patients with rheumatoid arthritis and Crohn's disease. The warning applies to all tumor necrosis factor blocking agents. The drugs are associated with a 1 in 1400 risk of lymphoma, according to MedWatch, the FDA's safety information program.