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Ulipristal Acetate for Uterine Fibroids

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *In a randomized, placebo-controlled study, daily oral treatment with ulipristal acetate for 13 weeks effectively controlled excessive menstrual bleeding due to uterine fibroids and reduced the size of the myomas. In a second companion RCT by the same group, daily oral ulipristal acetate was shown to be as effective as leuprolide acetate, and better tolerated.*

Sources: Donnez J, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med* 2012;366:421-432.
Donnez J, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med* 2012;366:409-420.

The results of the PEARL I and PEARL II studies were published recently in the same issue of the *New England Journal of Medicine*. Both were well-designed, randomized, controlled, double-blinded studies that assessed the safety and efficacy of ulipristal acetate (UPA) for the treatment of symptomatic uterine fibroids.

In the PEARL I study, women with symptomatic fibroids resulting in excessive uterine bleeding (defined as a score of > 100 on the pictorial blood-loss assessment chart [PBAC]) and anemia (hemoglobin level of ≤ 10.2 g per dL) were randomized to receive treatment with oral UPA (5 mg per day [96 women] or 10 mg per day [98 women]) or to receive placebo (48 women) for up to 13 weeks. All patients received iron supplementation. The co-primary efficacy endpoints were control of uterine bleeding (PBAC score of < 75) and reduction of fibroid volume at week 13 (after 13 weeks, the subjects could elect to undergo surgery). By 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5 mg of UPA and 92% of those receiving 10 mg, compared to only 19% of those receiving placebo ($P < 0.001$ both doses). The rates of amenorrhea were 73%, 82%, and 6%, respectively. Of note, amenorrhea occurred within 10 days in the majority

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of patients receiving UPA. The median changes in total fibroid volume were -21%, -12%, and +3% (significantly smaller with both active treatment groups, $P < 0.01$).

The PEARL II study was a double-blind non-inferiority trial that randomized 307 patients with symptomatic fibroids and excessive uterine bleeding to receive 3 months of daily therapy with oral UPA (at the same doses of either 5 mg or 10 mg) or once-monthly intramuscular injections of leuprolide acetate (LA) at a dose of 3.75 mg. The primary outcome in this study was the proportion of patients with controlled bleeding (defined as a PBAC score of < 75) at study end, with a prespecified non-inferiority margin of -20%. After 13 weeks of treatment, uterine bleeding was controlled in 90% of subjects receiving 5 mg, in 98% of those receiving 10 mg of UPA, and in 89% of those receiving leuprolide acetate. These differences compared to LA (1.2% [95% CI, -9.3 to 11.8] for 5 mg and 8.8 % [95% CI, 0.4 to 18.3] for 10 mg of UPA) were both within the non-inferiority margin. The median times to amenorrhea were 7 and 5 days for subjects receiving 5 mg and 10 mg of UPA, compared to 21 days for those receiving LA. Moderate-to-severe hot flashes were reported significantly less frequently (11% [5 mg] and 10% [10 mg] in subjects who received UPA than in those who received leuprolide acetate [40%, $P < 0.001$]).

Across both studies, headache and breast tenderness were the most commonly reported adverse events, but there was no difference between the UPA and placebo groups. Hot flushes occurred significantly more often (65% vs 26% and 24%) in women treated with leuprolide acetate than those treated with either dose of UPA.

Results of these two studies demonstrate that UPA is a well-tolerated and effective oral treatment regimen for heavy menstrual bleeding due to fibroids that is clinically equivalent to leuprolide acetate but better tolerated.

■ COMMENTARY

More than 25 years ago, investigators began studying gynecologic applications for mifepristone, the selective progesterone receptor modulator (SPRM) also known as RU-486. In 1993, Samuel Yen's group in San Diego reported that treatment with 50 mg of RU-486 induced amenorrhea and resulted in a 50% reduction in fibroid volume over 12 weeks of treatment.[1] Unfortunately, despite promising initial results, the politics of abortion largely stymied interest and limited funds by pharmaceutical companies to develop SPRMs as treatments for benign gynecologic problems such as fibroids and endometriosis.

Although mifepristone has been available in the United States since 2000, its use has been restricted to first trimester abortion. Some providers have expanded the off-label use to include second trimester abortion, but the high cost and limited availability of the drug has made other off-label uses in gynecology essentially impossible. Since mifepristone is now almost synonymous with medical abortion, it is naïve to believe it would ever find a place on pharmacy shelves in many parts of the country even if a supportive labeling for a gynecologic indication was approved.

Enter ulipristal acetate. Developed by the National Institutes of Health, this SPRM has been extensively tested in a number of gynecologic applications and as a contraceptive. It has not been studied or tested as an abortifacient. Ulipristal recently received FDA approval as a single-dose oral pill for emergency contraception (EC), after initial approval for the same indication by European regulatory authorities.[2] Not only is UPA more effective than levonorgestrel (LNG) EC, it has an expanded window of use, up to 5 days after unprotected intercourse. Although the availability of a more effective EC is great news for American women, this indication unfortunately helps to link UPA with medical abortion in the minds of those opposed to family planning. Even though all of the available evidence support that both LNG and UPA act as emergency contraceptives by delaying or preventing follicle rupture, science seems to take a back seat to religious faith in the pursuit of truth regarding mechanism of action.[3,4]

Unencumbered by this anti-science culture, our European colleagues have moved ahead and will soon have approval for UPA for the treatment of fibroids. The results of these two studies demonstrate conclusively that UPA is a safe, effective oral treatment that shrinks fibroids and

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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

reduces bleeding. It works as well as a GnRH antagonist, but without the unpleasant side effect of hot flushes. Furthermore, it appears that UPA could be a long-term medical treatment that is not limited by bone loss, vaginal dryness, or other menopausal symptoms. One concern with long-term treatment is the presence of so-called progesterone receptor antagonist-associated benign endometrial changes.[5] These do not appear to be associated with hyperplasia or endometrial cancer, but we will need to follow this story if long-term use becomes routine. ■

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Platelets and Cancer: Friend or Foe?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Paraneoplastic thrombocytosis is supported by a paracrine circuit initiated by tumor-derived cytokines and is responsible for poor survival in ovarian cancer patients. Amelioration of these factors through targeted agents may provide a new avenue of systemic therapy for these patients.*

Source: Stone RL, et al. Paraneoplastic thrombocytosis in ovarian cancer. *New Engl J Med* 2012;366:610-618.

It has been long recognized that thrombocytosis (defined as a platelet count > 450,000/mm^3) frequently accompanies the diagnosis of advanced cancer and has been associated with poor outcomes. How platelets illicit this effect is not well understood and was systematically explored in this study. Clinical data from 619 patients with epithelial ovarian cancer were interrogated to explore the relationship between platelet counts and disease outcome. In addition, human samples and mouse models of epithelial ovarian cancer were investigated to clarify the underlying mechanisms of paraneoplastic thrombocytosis, including the effects of platelets on tumor growth and angiogenesis. The authors found that thrombocytosis was a common phenomena of patients presenting with ovarian cancer, occurring in nearly one-third. Thrombocytosis was significantly associated with advanced disease and shortened survival. In addition, plasma levels of thrombopoietin and interleukin-6 were significantly elevated in these patients and strongly correlated with thrombocytosis.

To determine the origin and temporal relationship of these factors on the tumor phenotype, mouse models of ovarian cancer were studied. In these models, increased hepatic thrombopoietin synthesis occurred in response to interleukin-6, which was specifically derived from ovarian tumors. Blocking these factors, either exogenously or via genetic manipulation of the murine model, reversed thrombocytosis. This was associated with reduced tumor growth. In addition, neutralizing interleukin-6 in mouse models of epithelial ovarian cancer significantly enhanced the therapeutic efficacy of paclitaxel. Of interest, these platelets were found to preferentially localize in tumors (as compared to peritoneum or areas of inflammation). Treatment with an antiplatelet antibody (dosed to reduce platelet counts by 50%) was associated with significantly reduced tumor growth and angiogenesis. Similarly, patients treated with the anti-interleukin-6 antibody, siltuximab, in an ongoing Phase 1/2 clinical trial, demonstrated significantly reduced platelet counts. These novel findings strongly support the existence of a feed-forward paracrine circuit driven by tumor-derived interleuin-6, which subsequently drives hepatic production of thrombopoietin promoting thrombocytosis and tumor infiltration of secretory platelets. Understanding this mechanism may now lead to rationally targeted therapy approaches for women with ovarian cancer.

■ COMMENTARY

It is estimated that as many as 40% of patients who present with asymptomatic thrombocytosis in the absence of iron deficiency anemia or benign inflammatory conditions will be diagnosed with cancer. Similarly, as many as 25% of patients presenting with a vascular thrombotic event (VTE), without an antecedent history, will be diagnosed with a malignancy.[1] The relationship is not new; the prognostic impact has been well known for more than a

century (Trousseau, 1867). However, the mechanism underlying these observations is not well understood. Previously, platelets have been suspected as promoting cancer progression through, among others, tumor cell immune escape, stimulation of angiogenesis, and prevention of tumor cell apoptosis. The current report provides new evidence as to "why" the condition exists and, perhaps more importantly, "how" the paraneoplastic cycle may be disrupted. The latter appears to lead to tumor regression in animal models, and, as such, a new modality of cancer therapy. Indirect clinical observations already support the merit of this contention. For instance, the use of low molecular-weight heparin improves survival among patients with cancer, independently of morbidity/mortality associated with VTE.[2] In addition, daily aspirin use among patients with colorectal cancer is associated with decreased all-cause and cancer-specific mortality.[3] Nevertheless, much more work is necessary to clearly understand how abrogation of these effectors will impact outcome and toxicity for women with ovarian cancer. ■

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Operative Delivery

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Data from a New York City Birth Registry involving deliveries between 1995-2003 show a surprisingly lower incidence of seizures, depressed Apgar scores, and combined neonatal morbidity with forceps delivery compared with vacuum extraction.*

Source: Werner EF, et al. Mode of delivery in nulliparous women and neonatal intracranial injury. *Obstet Gynecol* 2011;118:1239-1246.

MANAGING LABOR IS AN ART, WHILE THE ACTUAL DELIVERY process requires the addition of skill and experience. Yet, the decision of which route of delivery to employ may have the greatest impact on outcome. A recent article deals with neonatal morbidity, including an important contributor, intracranial injury, and its association with various forms of operative delivery.

Werner at al reviewed hospital discharge data from New York City between 1995 and 2003. The authors were interested in the relationship of a variety of neurological and cranial injuries to vacuum extraction, forceps delivery, and cesarean section. More than 1 million births occurred during this time in New York City, but they narrowed their investigation to the 120,541 patients who had operative deliveries.

In the study, 72.2% of the operative deliveries were done by cesarean section, 15% by vacuum, and 12.8% by forceps (The type of forceps application — outlet, low, or mid pelvis — was not defined). Only 1.5% had more than one method attempted, and were excluded. The dependent variables were various types of intracranial and facial injuries, seizures, fractures, brachial plexus injuries, and low Apgar scores.

The trends over time were not unexpected. For instance, while the cesarean section rate went from 20.4% in 1995 to 23.4% in 2003, the vacuum extraction rate rose from 4.0% to 5.8%, and the forceps rate went from down from 5.6% to 2.1%. Cesarean section was associated with higher rates of seizures and lower Apgar scores (5-minute score of < 7), and there was a trend toward an increased rate of intraventricular hemorrhage. Vacuum deliveries had higher rates of subdural hematomas (0.19%) than forceps (0.14%), while cesarean section had the lowest rate of this complication (0.09%). Not surprisingly, brachial plexus and facial injuries were greatest in the forceps group. When comparing vacuum and forceps with regard to combined neurological morbidity, forceps was the surprising winner (0.26% vs 0.45%, respectively), and the rate was even lower for forceps than cesarean section (0.44%).

■ COMMENTARY

It may be unfair to compare combined neurological morbidity (and especially seizures) between cesarean section and operative vaginal delivery because the cesarean section group, who had the highest rate of these outcomes, undoubtedly contained more mothers whose fetuses were judged to be incapable of tolerating labor. However, the two operative vaginal delivery groups were probably roughly similar and some of the outcomes should have been expected: cephalo-hematomas with vacuum extraction and facial and brachial plexus injuries with forceps. However, I was somewhat surprised that the combined

neonatal morbidity, Apgar scores, and the incidence of seizures were lower with forceps than with vacuum extraction.

It is interesting that the sample included delivery data that dated back to 1995 when operators were probably more skilled in the application of forceps. Currently, there seems to be less enthusiasm for forceps training in the face of trends in the medico-legal climate, since one rarely gets sued for doing an expeditious cesarean section instead of attempting an operative vaginal delivery. Perhaps the study will provide some incentive to reconsider operative vaginal delivery as an acceptable option to what must still be considered a major operation, cesarean section. ■

Postoperative LNG-IUS for Chronic Pelvic Pain

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *Postoperative use of a levonorgestrel intrauterine system effectively manages pelvic pain and improves quality of life in women with moderate to severe chronic pelvic pain found to have endometriosis at laparoscopy.*

Source: Tanmahasamut P, et al. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: A randomized controlled trial. *Obstet Gynecol* 2012;119:519-526.

The authors conducted a double-blind, randomized, controlled trial to determine whether the postoperative use of a levonorgestrel intrauterine system (LNG-IUS) was an effective treatment for chronic pelvic pain in women with endometriosis. Subjects with moderate-to-severe dysmenorrhea (defined as a visual analog scale [VAS] score of > 50 mm) and/or chronic pelvic pain for ≥ 6 months who were scheduled to undergo conservative surgery were eligible if they had ASRM Stage 1-4 endometriosis and no other gynecologic abnormalities at the time of surgery. Women were excluded if they had had prior treatments (other than analgesics) for endometriosis, contraindications to the LNG-IUS, planned pregnancy within a year, or would be intolerant of menstrual changes. Women meeting eligibility criteria were randomized to receive the LNG-IUS while under anesthesia or no additional treatment (expectant management). Subjects were not informed as to their treatment group. The study protocol was written to maintain blinding by using a study nurse to collect all information about pain and quality of life (QOL). The primary outcome was the change in dysmenorrhea VAS score from baseline. Secondary outcomes included changes in pelvic pain and dyspareunia VAS scores, QOL (as measured using the Short Form [SF]-36 score), and adverse effects.

A total of 55 women were randomized (LNG-IUS: n = 28, expectant management: n = 27), and the two groups were comparable in age, body mass index, parity, and baseline pain scores. It is notable that most women in both groups were found to have Stage 3 (11% LNG-IUS, 19% expectant) or 4 (57% LNG-IUS, 50% expectant) endometriosis at the time of surgery. At 12 months, compared with the control group, the LNG-IUS group had greater VAS reductions in dysmenorrhea (-81.0 compared with -50.0 mm, $P = 0.006$) and pelvic pain (-48.5 compared with -22.0 mm, $P = 0.038$). There was a comparable reduction in dyspareunia (-15.0 compared with -19.0 mm, $P = 0.831$); however, a significantly higher proportion of the LNG-IUS-treated subjects reported being sexually active at baseline (21/28, 75% compared to 9/26, 33%). In the expectant management group, 39% had recurrent dysmenorrhea (defined as a pain score of > 50 mm occurring after 3 months of postoperative pain relief) within 1 year postoperatively, compared to only 7.4% of those managed with the LNG-IUS ($P = 0.014$). QOL improved in the LNG-IUS group, but did not change in the expectant management group. The vast majority (25/27, 93%) of LNG-IUS-treated women correctly guessed that they had received the device, and about half (52%) of the expectant group falsely believed that they had received the active treatment. No adverse effects of treatment were reported, but two women in the expectant group underwent repeat surgery for endometriotic cysts at 6 and 9 months after surgery, compared to none in the LNG-IUS group. Four subjects in the LNG-IUS group requested device removal after 1 year due to unacceptable bleeding.

The results of this study add to previous research that demonstrates the LNG-IUS is an effective and well-accepted long-term treatment option for women with moderate-to-severe pain related to endometriosis.

■ COMMENTARY

The levonorgestrel intrauterine system has moved beyond contraception to become a reliable and proven nonsurgical treatment for many gynecologic problems. Although the FDA-approved labeling for the LNG-IUS only lists intrauterine contraception and treatment of heavy menstrual bleeding (in women who choose to use intrauterine contraception) as approved indications, the literature is full of descriptive series and controlled studies demonstrating the utility of this local hormone delivery device for a variety of gynecologic complaints.[1] The absence of a labeling indication is not a barrier to the prescription of most medications, as law does not bar

the physician from using the state of the science rather than the label to guide practice. However, the laws and regulations promoted by some religious groups and members of congress that would allow employers to prohibit insurance coverage of contraception would compromise our ability to provide these important gynecologic therapies to many of our patients. The arguments raised against contraceptive coverage make no sense to me. It seems that opposition to any type of logical health care reform has become an orthodoxy that trumps any logic. The evidence clearly shows that universal contraceptive coverage makes sense from an economic standpoint[2] and reduces unintended pregnancy and abortion. Furthermore, religious women are no less likely to use contraception than the general population.[3] The important noncontraceptive and therapeutic benefits of hormonal contraception as treatments for serious gynecologic conditions, such as heavy menstrual bleeding and endometriosis, provide additional reasons to oppose any effort to restrict access to these important medicines.

The paper by Tanmahasamut provides further evidence documenting the benefit of the LNG-IUS in the treatment of pelvic pain and dysmenorrhea due to endometriosis. These results are not intuitive as endometriosis is a pelvic disease, and the action of the LNG-IUS is primarily local with the circulating level of LNG low in comparison to other delivery systems. Although the authors attempted to maintain blinding of the subjects, most correctly guessed whether they had received an IUS. While we cannot determine whether this influenced the perception of pain, the robust improvement seen in the LNG-IUS-treated women suggests a powerful treatment effect, particularly since more than half of the subjects presented with ASRM Stage 4 endometriosis. Other randomized studies of the LNG-IUS in women with moderate-to-severe endometriosis have shown a similar reduction with a GnRH analogue[4] and with Depo-Provera[5] as comparators. Biopsies obtained during second look laparoscopies have demonstrated that the ameliorative effect of the IUS on pain symptoms is associated with down regulation of estrogen and progesterone receptors in the ectopic endometrium, a "systemic effect."[6]

Clinicians should embrace these findings as further evidence that medical therapy effectively manages the symptoms of endometriosis. The LNG-IUS provides a great option to manage women with chronic pelvic pain and endometriosis. A surgical diagnosis of endometriosis is not needed prior to starting medical therapy, and laparoscopy should be avoided unless a pelvic mass is suspected. In my experience, women with high baseline levels of pelvic pain have more insertion-related discomfort, and often complain of post-insertion pain lasting more than 1 to 2 weeks. They should be followed closely to rule out the low likelihood of endometritis or expulsion, and encouraged to continue with the device. Strong analgesic medication may be needed to bridge this time. The prolonged bleeding and spotting common after insertion confuse the situation, but the vast majority of women will experience significant improvement of symptoms within several weeks. ■

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Special Feature

How Often Should Healthy Women Be Screened for Osteoporosis?

By Elizabeth Micks, MD, and Alison Edelman, MD, MPH

Dr. Micks is a Fellow in Family Planning, Department of Obstetrics and Gynecology, Oregon Health & Science University; and Dr. Edelman is Associate Professor, Assistant Director of the Family Planning Fellowship, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland

Dr. Micks and Dr. Edelman report no financial relationships relevant to this field of study.

Synopsis: *In a prospective study of nearly 5000 postmenopausal women, it was determined that it would take 16.8 years to develop osteoporosis in 10% of women*

with normal bone mineral density. The authors conclude that repeat screening in women without new risk factors can be delayed for at least 15 years.

Source: Gourlay ML, et al. Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med* 2012;366:225-233.

In this study, 4957 women aged 67 and older were followed prospectively for up to 15 years. Statistical models were used to calculate the bone mineral density (BMD) testing interval for women with normal BMD and those with mild, moderate, or advanced osteopenia. The BMD testing interval was defined as the number of years it would take for 10% of women to develop osteoporosis, before having a hip or vertebral fracture and before any treatment for osteoporosis was initiated. For women with normal BMD, the BMD testing interval was determined to be 16.8 years (95% confidence interval [CI] 11.5-24.6). For women with mild osteopenia (T score -1.01 to -1.49), the interval was 17.3 years (95% CI 13.9-21.5). More frequent testing intervals were found for those with moderate (T score -1.5 to -1.99, 4.7 years, 95% CI 4.2-5.2) and advanced (T score -2.0 to -2.49, 1.1 years, 95% CI 1.0-1.3) osteopenia.

■ COMMENTARY

Osteoporosis, diagnosed by low BMD on dual-energy x-ray absorptiometry (DEXA) scan, is well known to cause significant morbidity and mortality in postmenopausal women.[1] BMD accounts for at least three-fourths of the variation in bone strength, and is by far the strongest predictor of fracture risk.[2] The American Congress of Obstetricians and Gynecologists (ACOG) and other organizations recommend that all women have DEXA scans starting at age 65, or sooner if they have risk factors for osteoporosis.[3] In terms of subsequent screening, however, there has been little evidence for when to recommend the next DEXA scan. The U.S. Preventive Services Task Force[4] and ACOG[3] currently recommend only that the screening interval should be no more than every 2 years. This important new study provides data on the optimal screening intervals for women with normal BMD, and those with varying degrees of osteopenia.[5]

To review, The World Health Organization (WHO) uses the T score in its widely used definitions of osteoporosis and osteopenia.[6] Osteopenia is diagnosed if hip T score is between -1 and -2.5, meaning between 1 and 2.5 standard deviations below the mean peak BMD in a young adult population. A patient with a T score of ≤ -2.5 has osteoporosis. The main outcome for this particular study was "BMD screening interval," defined as the amount of time it would take for 10% of women to develop osteoporosis after a baseline screening test. The study is not a cost-benefit analysis of DEXA screening for osteoporosis, and the authors don't provide any clear justification for this definition.

The BMD screening interval was found to be 16.8 years for those with normal BMD, and 17.3 years for those with mild osteopenia. Surprisingly, less than 1% of women with normal BMD (T score > -1.00) and 5% of women with mild osteopenia (T score -1.01 to -1.49) actually developed osteoporosis during the 15-year study period. The study found 2.4% of subjects had a hip or vertebral fracture before osteoporosis was diagnosed. Even without critiquing the statistics used by the study authors, we can reassure our patients with normal BMD or mild osteopenia that it is safe to delay repeat screening for much longer than previously thought.

The data were not as reassuring for those with moderate (T score -1.50 to -1.99) or advanced osteopenia (T score -2.00 to -2.49). About 20% of women with moderate osteopenia, and more than 62% of those with advanced osteopenia, developed osteoporosis during the study period. The BMD testing interval for moderate osteopenia was found to be 4.7 years, and just 1.1 years for advanced osteopenia.

Analysis also was performed stratifying by significant clinical risk factors including age, BMI, and baseline

Clinical Tips

- Osteoporosis screening should be initiated at age 65 in healthy women with no risk factors for osteoporosis.
- Younger women should undergo screening if their fracture risk is equivalent to that of a 65-year-old woman.
  - Risk factors include family history of osteoporosis, Caucasian race, smoking, early menopause (less than 45 years), and certain medications. See ACOG Practice Bulletin No. 50: Osteoporosis for a complete list of medical conditions, medications, and other factors that increase a woman's fracture risk: (www.acog.org/Resources_And_Publications/Practice_Bulletins)
  - Use the FRAX Fracture Risk Assessment Tool to calculate a patient's 10-year fracture risk and timeframe for screening (www.shef.ac.uk/FRAX/).
- Osteoporosis develops slowly in women with normal bone density or mild osteopenia.
  - For women with normal BMD and no new risk factors, repeat screening can likely be safely delayed for 15 years.
- Women with moderate or severe osteopenia warrant more frequent screening.

estrogen use. Within a specific T-score group, younger women were found to have a longer time interval to osteoporosis. For women with osteopenia, estrogen use during the baseline exam was associated with a longer time interval to osteoporosis. Unfortunately, this did not apply to women who reported prior estrogen use, indicating that the positive effect of estrogen on BMD is not long lasting. For women with advanced osteopenia, higher BMI was associated with a longer time interval to osteoporosis. Other risk factors — including smoking, glucocorticoid use, rheumatoid arthritis, and any fracture after age 50 — were not significant predictors of osteoporosis in this study, even among women with osteopenia at baseline.

When actual fracture risk rather than osteoporosis was examined as the outcome, it was determined that it would take more than 15 years for 2% of women with normal BMD or mild osteopenia to have a femoral or clinical vertebral fracture.

An earlier analysis of the Study of Osteoporotic Fractures (SOF), the same study population as the current publication, in 2007 showed that repeat BMD screening at up to 8 years did not contribute to better prediction of fracture risk beyond the baseline screening.[7] To date, these are the only longitudinal studies addressing the optimal frequency of DEXA scans.

For the SOF, 9704 women aged 65 or older in four sites within the United States participated in at least one study examination. From this initial group, 8497 women had adequate baseline BMD data. Of these, about 25% were excluded because they were found to have osteoporosis, and 200 were excluded because they already had a femoral or vertebral fracture or had taken calcitonin. An additional thousand subjects were excluded because they were lacking follow-up data. A total of 4957 subjects were included in the present analysis. Subjects underwent study examinations at year 2, year 6, year 8, year 10, and year 16. Based on T scores, cumulative incidence curves for the time to osteoporosis were developed.

This large prospective, longitudinal study provides much needed evidence for the optimal interval between DEXA scans in women with normal BMD or osteopenia. While we await revised guidelines from ACOG and the U.S. Preventive Services Task Force, we can counsel our patients that osteoporosis develops slowly. ■

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CME Questions

1. **Ulipristal acetate in a daily oral dose in women with symptomatic fibroids was:**
   a. more effective than placebo in decreasing fibroid size.
   b. associated with prolonged spotting after 12 weeks of use.
   c. poorly tolerated due to headache.
   d. effective only with the highest dose (10 mg).

2. **Based on their experiments and observations, Stone et al posit that paraneoplastic thrombocytosis is the result of which of the following?**
   a. Hepatic derived interleukin-6 stimulating bone marrow platelet production
   b. Tumor-derived thrombopoietin production
   c. Platelet-induced escape from immune surveillance
   d. A feed-forward paracrine tumor-hepatic-bone marrow-platelet circuit

3. **Although the cesarean section rate rose steadily during the study period (1995-2003), the rates of both forceps and vacuum extraction diminished.**
   a. True
   b. False

4. **According to current ACOG guidelines, how often should women with normal bone mineral density (BMD) and no new risk factors for osteoporosis undergo BMD screening?**
   a. Every 10 years
   b. Every 5 years
   c. Not more frequently than every 2 years
   d. Not more frequently than every year

5. **All of the following are risk factors for osteoporotic fractures in postmenopausal women, *except*:**
   a. obesity.
   b. alcoholism.
   c. smoking.
   d. family history of osteoporosis.

6. **Most women with mild osteopenia will develop osteoporosis within 15 years.**
   a. True
   b. False

In Future Issues: Fetal DNA Testing

PHARMACOLOGY WATCH

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

Statins and the Risk of Diabetes

In this issue: Statins and diabetes risk; new treatment guideline for diabetes; new pertussis vaccine recommendation; antibiotics and rhinosinusitis; fluoroquinolones and cystitis; and FDA actions.

Do statins increase the risk of diabetes?

Studies have suggested that statins may increase the risk of diabetes in the elderly, women, and Asians. A new study reviews data from the 162,000 postmenopausal women enrolled in the Women's Health Initiative to investigate whether the incidence of new onset diabetes mellitus (DM) is associated with statin use among these women. This study reviewed records from women who were enrolled between 1993 and 1998 through 2005. More than 7% of the women in the study reported taking statins. Statin use at baseline was associated with an increased risk of DM (hazard ratio, 1.71; 95% confidence interval, 1.61-1.81). This association remained after adjusting for other potential confounders, including obesity, and was observed for all types of statin medications. The authors conclude that statin medication use in postmenopausal woman is associated with an increased risk for DM and that this may be a medication class effect (*Arch Intern Med* 2012;172:144-152). As pointed out in a brief comment in the same issue, observational data are potentially susceptible to "bias (confounding) by indication." In other words, women who would be prescribed statins may be inherently at risk for DM. This study did a good job of evaluating women with and without a history of cardiovascular disease and found that there was still an increased risk of DM. This finding "may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality." The FDA has issued a new warning about statins and the risk of diabetes (see FDA actions). ■

Oral medications for diabetes

The American College of Physicians has published a new guideline for the "Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus" in the February 21 issue of the *Annals of Internal Medicine*. The guideline suggests that if diet, exercise, and weight loss fail to improve hyperglycemia, oral drug therapy should be initiated. Most diabetes medicines lower HbA_{1c} levels to a similar degree, and none of the medications have compelling outcomes data to suggest one class is superior to another class with regard to cardiovascular or all-cause mortality. But metformin "was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases)." Therefore, the guideline recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy for most patients with type 2 diabetes. Metformin is effective at reducing glycemic levels and is not associated with weight gain. Additionally, the drug helps reduce LDL cholesterol and triglyceride levels. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart

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failure, and any conditions that might lead to lactic acidosis. For patients with persistent hyperglycemia despite metformin, a second drug should be added. No good evidence supports one combination over another. Sulfonylureas have a higher risk for hypoglycemia and thiazolidinediones are associated with an increased risk for heart failure. There are no specific recommendations for the use of the glinides (nateglinide or repaglinide) or the DPP-4 inhibitors (linagliptin, saxagliptin, or sitgliptin). The guideline does not make a recommendation for combinations of more than two oral agents. Injectables, such as the various insulins and GLP-1 analogs, were not addressed in the guideline. (*Ann Intern Med* 2012; 156:218-231). ■

New recommendation for Tdap vaccine

The Advisory Committee on Immunization Practices, a division of the Centers for Disease Control and Prevention, is recommending that all adults get immunized against pertussis (whooping cough). Previously the committee had recommended that only adults who spend time around infants or young children should be immunized. The goal of the expanded recommendation is to prevent teenagers and adults from spreading the disease to infants. In 2010, California experienced a pertussis outbreak that infected 9000 people and resulted in 10 infant fatalities. The adult vaccine combines tetanus, diphtheria, and acellular pertussis (Tdap). ■

Antibiotics not needed for rhinosinusitis

Physicians now have more ammunition for not treating patients with acute rhinosinusitis with antibiotics, based on the results of a new study that shows amoxicillin is of no benefit in these patients. Researchers at Washington University in St. Louis randomized 166 adults with uncomplicated, acute rhinosinusitis to a 10-day course of amoxicillin 500 mg three times a day or matching placebo. The main outcome (change in the Sinonasal Outcome Test) was not significantly different between the two groups at day 3 or day 10. There was a slight improvement in the antibiotic group at day 7. The authors conclude that "treatment with amoxicillin for 10 days offers little clinical benefit for patients clinically diagnosed with uncomplicated acute rhinosinusitis." Patients with symptoms indicative of serious complications were excluded from the trial (*JAMA* 2012;307:685-692). ■

Fluoroquinolones for cystitis

Cefpodoxime is inferior to ciprofloxacin for short-course treatment of acute uncomplicated cystitis in women, according to new study. In a randomized, double-blind trial, 300 women ages 18-55 with uncomplicated cystitis were randomized to ciprofloxacin 250 mg orally twice daily for 3 days or cefpodoxime 100 mg twice daily for 3 days. The overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were considered as having a clinical cure was 93% for ciprofloxacin compared to 82% for cefpodoxime. For the intent-to-treat approach in which patients lost to follow-up were considered as not having responded to treatment, the clinical cure rate was 83% for ciprofloxacin compared to 71% for cefpodoxime. The microbiological cure rate was 96% for ciprofloxacin compared with 81% for cefpodoxime. At follow-up, 16% of women in the ciprofloxacin group had vaginal *Escherichia coli* colonization compared with 40% in the cefpodoxime group. The authors conclude that cefpodoxime did not meet criteria for non-inferiority to ciprofloxacin for treating uncomplicated cystitis in women (*JAMA* 2012;307:583-589). The study is somewhat disappointing given the increasing rates of fluoroquinolone resistance in the community and the need for effective alternatives. ■

FDA actions

The FDA has issued a new warning and is requiring label changes to all statins regarding the risk of elevated blood sugar and reversible cognitive changes. The agency is making these changes after a comprehensive review of multiple studies that show increases in blood sugar associated with the drugs. A separate labeling change warns that cognitive effects have been reported with statin use, including transient memory loss and confusion — symptoms that are reversible with stopping the medication. There is no evidence that statins are associated with long-term cognitive changes or dementia. Statins affected by these warnings include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In a separate warning, lovastatin is now contraindicated with strong CYP3A4 inhibitors, such as itraconazole and erythromycin. This is a similar warning to that issued for simvastatin in 2011.

In one of the strangest stories of the year, the FDA is warning oncologists that a counterfeit version of bevacizumab (Avastin) may have been purchased and used by some medical practices in the United States. The counterfeit version does not contain any active drug and may have resulted in patients not receiving needed therapy. Counterfeit bevacizumab was purchased from a foreign supplier known as Quality Specialty Products or Montana Health Care Solutions. The FDA is recommending that physicians stop using bevacizumab purchased from the suppliers and call the FDA immediately. ■