MENOPAUSE

A closer look at WHI data on hormone therapy and breast cancer risk is reassuring, and a new paradigm for osteoporosis treatment is on its way

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Dr. Kaunitz has received funding from Barr Laboratories, Berlex, Medical Diagnostic Laboratories, Organon, and Warner Chilcott. He is a speaker or consultant for the American College of Obstetricians and Gynecologists, Barr Laboratories, Berlex, Johnson & Johnson, Merck, Noven Organon, and Warner-Chilcott. He holds stock with Barr, Johnson & Johnson, Procter & Gamble, Roche, and Sanofi-Aventis.

ObGyns and their patients are the beneficiaries of a steady stream of scientific data on issues relating to menopause. In last year's Update, I focused on the question of whether menopausal hormone therapy (HT) increases the risk of breast cancer.[1] Because breast cancer continues to top the list of women's concerns, I will use this year's Update to assess what we have recently learned about HT and breast cancer, and to explore the latest data on nonhormonal management of vasomotor symptoms.

I am delighted that Dr. Michael McClung, an internationally recognized expert in skeletal health, has agreed to review current evidence on the prevention of osteoporotic fractures in menopausal women in the latter part of this article.

New WHI analysis confirms safety of short-term combination HT

Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen and progestin. Maturitas. 2006;55:103–115.

At the annual San Antonio Breast Cancer Symposium in December, investigators presented data showing that the incidence of breast cancer in US women decreased by 7% from 2002 to 2003, a striking decline that was most prominent among women aged 50 to 69 years. The presenters speculated that the plummeting rates of HT use following publication of the initial Women's Health Initiative (WHI) findings in the summer of 2002 (in regard to the estrogen–progestin arm[2]) might be responsible for this decline.[3]

The major media attention that followed this presentation makes one thing clear: Concerns about developing breast cancer with HT use continue to fuel anxiety among women. Although secular trend data on the national breast cancer incidence can help generate hypotheses, they cannot explain the trends. What can shed light on the association between estrogen–progestin HT and breast cancer are important new data recently released by WHI investigators.

Women new to HT had no increased risk of breast cancer

In the 2006 subgroup analysis of WHI participants in the estrogen–progestin

arm, investigators focused on HT use before enrollment in the trial. Recall that in this part of the WHI, 16,608 women with an intact uterus were randomized to conjugated equine estrogen plus medroxyprogesterone acetate or placebo. Use of the study medication was stopped after a mean follow-up of 5.6 years (mean exposure to HT: 4.4 years). Overall, the risk of invasive breast cancer was slightly higher with combination HT than placebo (hazard ratio [HR] 1.24; 95% confidence interval [CI] 1.01–1.54).[2]

In the 2006 report from the 2002 WHI study of estrogen–progestin HT versus placebo, investigators compared the risk of being diagnosed with breast cancer in 12,297 women who had not used HT prior to study enrollment with the risk in 4,311 participants who had previously used HT. Of the previous users, 42% reported less than 2 years of use prior to WHI enrollment, and 36% reported more than 4 years of HT prior to WHI enrollment.

The findings: Among WHI participants who had never before used HT, the use of estrogen–progestin HT in the study was not associated with an elevated risk of being diagnosed with breast cancer (HR 1.02; 95% CI 0.77–1.36). However, among previous HT users, the additional use of HT in the WHI study was associated with a risk nearly double that of placebo users (HR 1.96, 95% CI 1.17–3.27).

The reassuring results of this WHI subgroup analysis received little media attention in the United States, probably because the report appeared in a journal that has low readership in this country. WHI and other findings allow us to reassure women who have undergone hysterectomy that use of unopposed estrogen has little, if any, impact on breast cancer risk in menopausal women.[4,5] This new WHI subgroup analysis, along with a recent review of European and North American data,[6] allows ObGyns to counsel women with an intact uterus that up to 5 years of combination estrogen–progestin hormone therapy also has little, if any, impact on breast cancer risk.

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Among women who had never before used hormones, the use of combination HT did not increase the risk of breast cancer

Not much to recommend among nonhormonal therapies

Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy or placebo. Ann Intern Med. 2006;145:869–879.

Grady D. Clinical practice. Management of menopausal symptoms. N Engl J Med. 2006;355:2338–2347.

Grady D, Cohen B, Tice J, et al. Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol. 2007;109:823–830.

Loprinzi CL, Kugler JW, Barton DL, et al. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. J Clin Oncol. 2007;25:308–312.

Since publication of the initial WHI findings in 2002,[2] interest in nonhormonal management of vasomotor symptoms has increased among menopausal women and their clinicians. The botanical black cohosh and "nutraceutical" soy or isoflavone supplements represent the nonprescription remedies most widely used for relief of hot flashes. Unfortunately, accumulating evidence does not support the efficacy of these popular remedies.

In a recent NIH-funded, randomized, double-blind, placebo-controlled clinical trial, Newton and colleagues compared the following interventions:

- black cohosh, 160 mg daily
- daily multibotanical supplement that included 200 mg of black cohosh and 9 other ingredients
- the multibotanical supplement plus

counseling regarding dietary soy
- conjugated equine estrogen, 0.625 mg daily (with or without 2.5 mg of medroxyprogesterone acetate)
- placebo

The study involved 351 perimenopausal or postmenopausal women aged 45 to 55 years with 2 or more vasomotor symptoms daily.

The findings: At 3, 6, and 12 months, women allocated to estrogen (with or without progestin) had statistically significant relief of symptoms. In contrast, women allocated to botanical and/or herbal supplements experienced minimal relief, comparable to the effects of placebo.

The findings of this important study, as well as those of Grady, are discouraging: Black cohosh, botanicals, and encouraging increased soy intake are ineffective in the treatment of vasomotor symptoms.

Evidence on antidepressants is inconclusive

Selective serotonin reuptake inhibitors (SSRIs) and the antidepressant venlafaxine have been assessed for their effects on menopausal vasomotor symptoms, particularly in breast cancer survivors. In a recent review and also a randomized trial, Grady reports that the SSRIs citalopram and sertraline do not appear to be effective, and the findings in regard to the SSRI fluoxetine and venlafaxine have been inconsistent. Compared with placebo, the SSRI paroxetine has eased vasomotor symptoms to a modest degree in breast cancer survivors, but had little effect in women who have not had the disease.

Breast cancer survivors often take tamoxifen or aromatase inhibitors, medications that can induce or aggravate hot flashes. Breast cancer survivors also have a higher prevalence of mood disorders. These factors suggest that the experience and treatment of menopausal symptoms differ between breast cancer survivors and the general population.

Overall, Grady notes, for women with bothersome vasomotor symptoms who have no history of breast cancer, clinical trials of antidepressants have not been encouraging.

Gabapentin is more effective than antidepressants, but with a price

Clinical trials of gabapentin suggest that this anticonvulsant is moderately effective in the nonhormonal treatment of vasomotor symptoms, and the phase III trial by Loprinzi and colleagues finds it to be more effective therapy for vasomotor symptoms than antidepressants.

The drawback? This drug must be taken 2 or 3 times daily, and side effects (including fatigue) limit its attractiveness.

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When deciding whom to treat, consider risk as well as BMD

Sanders KM, Nicholson GC, Watts JJ, et al. Half the burden of fragility fractures in the community occur in women without osteoporosis. When is fracture prevention cost-effective? Bone. 2006;38:694–700.

The diagnosis of osteoporosis in postmenopausal women is now based on a threshold bone mineral density (BMD) T-score of –2.5. However, BMD is only one of several important risk factors for fracture, and most patients who experience a fracture related to osteoporosis do not have BMD values in the range consistent with osteoporosis, as Sanders and colleagues observe. Therefore, clinicians are faced with this question: Which patients who do not have osteoporosis should be treated to prevent fracture?

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The World Health Organization (WHO) task force on fracture risk assessment, under the leadership of Professor John Kanis, has developed an algorithm to estimate fracture probability in individual patients.[7] This algorithm is based on a sophisticated analysis of almost all of the large epidemiological studies performed worldwide that have assessed relationships between clinical risk factors and fracture risk. By including the 3 major risk factors (age, BMD, and fracture history), as well as weaker risk factors (family history of hip fracture, current smoking, excess alcohol intake, and history of chronic glucocorticoid use), the absolute risk of developing a fracture of the spine, wrist, hip, or shoulder over the next 10 years will be estimated. This information will be the basis for revised guidelines by the National Osteoporosis Foundation (NOF) and other organizations. The new guidelines will include recommendations for treating patients at or above a certain threshold of fracture risk rather than a certain BMD threshold. The new treatment threshold will be based on a combination of cost- and clinical effectiveness.

The WHO algorithm and revised NOF guidelines are expected later this year.

New paradigm will shift focus to older women

This revised approach will shift the focus of therapy from young postmenopausal women at low fracture risk toward older women who do not have osteoporosis but do have an increased risk of fracture by virtue of their age and other factors.[8] This will direct therapy more appropriately to patients who stand to gain the most and in whom therapy has been proven to reduce fracture risk.

Despite concerns, bisphosphonates appear to be safe for the long term

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Bone-turnover marker data do not suggest progressive suppression of bone remodeling with continued use of bisphosphonates

Bisphosphonates are the most extensively studied and widely used treatment for osteoporosis. Alendronate, the first bisphosphonate approved for the treatment of osteoporosis in the United States, has been available for more than 11 years. In general, all 3 of the currently approved bisphosphonates are well tolerated, and studies following patients for 7 to 10 years have not demonstrated significant adverse events or evidence of skeletal harm with long-term use.[9–11] However, because the drugs accumulate in the skeleton, there is a theoretical concern that long-term use will lead to oversuppression of bone turnover.

Small series of patients receiving bisphosphonates have described unusual fractures, evidence of low formation, and poor fracture healing, suggesting skeletal harm in at least some patients.[12] Bone biopsies performed in patients who received alendronate for 10 years or risedronate for 5 years showed evidence of bone remodeling in all the biopsy samples.[11,13] There was no progressive inhibition of bone metabolism in those biopsies compared with biopsies taken from patients who had received shorter-term treatment.

These findings are consistent with bone-turnover marker data suggesting no progressive suppression of bone turnover with continued use.[10,11,13] Biochemical indices of bone resorption are reduced to the lower half of the normal premenopausal range within about 3 months of beginning therapy, and values remain at that new level as long as patients receive the drug.

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Risk of osteonecrosis of the jaw is low in general population

Woo SB, Hellstein JW, Kalmar JR. Narrative review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144:753–761.

Bilezikian JP. Osteonecrosis of the jaw—do bisphosphonates pose a risk? N Engl J Med. 2006;355:2278–2281.

An association between bisphosphonate therapy and nonhealing lesions of the jaw (so-called osteonecrosis of the jaw) has been observed, but primarily affects patients with cancer-related bone diseases who receive high doses of intravenous therapy in addition to chemotherapy. Patients receiving oral doses of bisphosphonates for osteoporosis in Paget's disease have also had these lesions, as Woo and colleagues point out.

There is much that we do not know about this clinical problem, including its pathogenesis, whether the risk increases with longer-term use, and whether stopping therapy reduces the risk of developing lesions or improves the outcome of lesions already present. We do know that the incidence of exposed bone in the jaw in patients receiving bisphosphonate therapy for osteoporosis is low, estimated to range from 1 in 1,000 to 1 in 100,000 patients, according to Bilezikian.

Risk is very small, compared with potential benefits

It is important to put this risk in perspective. Based on data from the alendronate Fracture Intervention Trials (FIT), we have estimates of hip and spine fracture risk in certain types of patients. For example, for women age 68 with a femoral neck T-score of –2.5 or lower and no vertebral fractures, the likelihood of a clinical fracture over a mean treatment interval of 4.2 years was 19.6%.[14] In women age 71 with a femoral neck T-score of –2.5 and 1 or more vertebral fractures, spine and hip fractures occurred in 15% and 2.2% of subjects, respectively, over 2.9 years.[15] In these populations, alendronate reduced the risk of both hip and spine fracture by about 50%. For women without a vertebral fracture, the absolute reduction in the risk of clinical fracture over 4.2 years was 6.5% (number needed to treat [NNT] = 15). In patients with a vertebral fracture, the absolute reduction in the incidence of further spine and hip fracture was 8.6% over 2.9 years (NNT = 12).

This information argues strongly that the concern about osteonecrosis of the jaw does not justify withholding bisphosphonate therapy from patients with osteoporosis. The risk of such lesions in otherwise healthy patients with osteoporosis is very low (much lower than the risk of fracture), and most lesions heal spontaneously when treatment is stopped.

Clinical recommendations

For patients using or considering bisphosphonate therapy for osteoporosis, the following measures may be helpful:

- Have regular dental checkups and routine preventive dental care.
- If invasive dental procedures are planned, such as tooth extraction or implants, complete the dental work and allow the bone to heal before beginning bisphosphonate therapy.
- If a patient on bisphosphonate therapy plans invasive dental work, stop treatment for 3 months before the procedure and do not restart it until the jaw lesion is healed. Although there is no firm evidence that this strategy is helpful, it is certain that discontinuing bisphosphonate for a few months does not harm the skeleton.
- If a patient on bisphosphonate develops exposed bone, stop the drug and consult a dentist or oral surgeon experienced in the care of these lesions.

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The risk of osteonecrosis of the jaw in bisphosphonate users is much lower than the risk of fracture, and most lesions heal when treatment stops

Some can take a holiday from bisphosphonate therapy

Black DM, Schwartz AV, Ensrud KE, et al, for the FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-Term Extension (FLEX): a randomized trial. JAMA. 2006;296:2927–2938.

There is evidence that bone metabolism continues to be affected for some time when alendronate is stopped after 2 to 5 years of treatment, as Black and colleagues found in the Fracture Intervention Trial Long-Term Extension (FLEX) and others have demonstrated.[10] This raises the possibility that patients can take a "drug holiday" after several years of treatment. (This study was also reported in the March issue of OBG MANAGEMENT in "Examining the Evidence," with a commentary by Steven R. Goldstein, MD. Visit www.obgmanagement.com and click on "Past Issues" to see the article.)

The FLEX trial attempted to determine whether it is better to continue or stop alendronate after several years' exposure. One thousand ninety-nine women who had taken alendronate for 3 to 6 years in the FIT trials were randomly assigned to 5 or 10 mg of alendronate daily or placebo. All subjects received 500 mg of calcium and small vitamin D supplements and were followed for an additional 5 years.

The 2 alendronate groups were pooled for the analyses. Patients who switched to placebo for 5 years had declines in BMD at the total hip (2.4%) and spine (3.7%), compared with those who continued alendronate. However, values at the end of 5 years without therapy remained at or above pretreatment levels. Indices of bone turnover increased modestly when therapy was discontinued, but again the rates of bone turnover remained substantially lower than pretreatment values.

Fractures were collected as an exploratory endpoint. Compared with women who stopped treatment, women who continued alendronate reduced their risk of developing a clinical vertebral fracture by 55% (from 5.3% in the placebo group to 2.4% in the alendronate group). No difference was observed in the incidence of nonvertebral fractures between the 2 groups.

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It may be appropriate to stop bisphosphonate therapy for a time in women who are not at high risk of fracture

Who should take a holiday, and who can stay put?

Unfortunately, this study does not clearly answer the question. Patients at high risk for spine fracture, including those with a previous fracture, appeared to fare better if they continued treatment. Patients at lower risk did equally well whether they stopped or continued alendronate. This suggests that it would be appropriate to stop treatment in women who are not at high risk, including women who do not have osteoporosis by BMD criteria and have not experienced a fragility fracture since menopause.

The reason for stopping therapy in patients at low risk is because there was no added benefit observed with continued treatment, not because of concerns about risk.

When should the holiday end?

If treatment is stopped, the clinical question of whether and when to restart treatment becomes a challenge. The changes in bone density after treatment is stopped are too small to discern in individual patients. In theory, monitoring one or more bone-turnover markers is a more sensitive way to determine when the effects of bisphosphonates on skeletal remodeling are dissipating, but this approach is backed by very little clinical experience.

Another unresolved issue is whether the response after stopping treatment is the same in patients taking risedronate, ibandronate, or lower doses of alendronate. ■

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"Operative vaginal delivery: 10 components of success," by Michael A. Belfort, MD, PhD (February)

Obesity complicates the operative-delivery decision

Dr. Belfort outlined a strategy for determining the likelihood of success of operative vaginal delivery: "the rule of fifths." I agree that this rule can be very helpful at the time of abdominal palpation, but it can be difficult to apply when the patient is obese. This is discouraging because the incidence of obesity is especially high in the United States, and obese women have an increased incidence of macrosomia and difficult operative delivery.

Another way to determine the likelihood of success is to ask the patient to bear down as you perform a vaginal examination. If the fetal head exhibits mobility and some descent, success is more likely. A "tight fit" would be an indication for a trial of forceps in the operating room.

In some cases, an ultrasound scan may help determine the position of the fetal head.

The most important determination is whether forceps delivery can be performed in the labor and delivery suite or is better limited to a trial of forceps in the operating room. The proper application of the forceps is vital to avoid maternal and fetal injury.

Raymond Michael, MD
Marshall, Minn

Dr. Belfort responds:

Informative abdominal exam is possible even in the obese

I agree that determining the number of fifths of the fetal head above the maternal symphysis pubis may be more difficult in an obese patient. However, even in an extremely obese woman, it is still possible to elevate the pannus and feel the symphysis in most cases (even if an assistant has to help). If there is any doubt that the head is palpated, further efforts may be appropriate to ensure that the fetal head is engaged, including, as Dr. Michael suggested, use of ultrasound.

While I agree in theory that descent of the fetal head with maternal pushing efforts is important, I would not

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