

Top Ten Menopause Stories of 2008

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The “Top 10 Stories of 2008” address some of the challenges we face in caring for the total woman and the ongoing balancing act of weighing risks and benefits of our interventions. Focusing first on the ‘greatest good for the greatest number,’ we present new findings and recommendations to identify and prevent cardiovascular disease (CVD) in susceptible women. This was also a blockbuster year from the standpoint of new tools for assessing fracture risk and evolving treatments for bone health. And as we now confidently start hormone therapy (HT) to relieve symptoms in recently postmenopausal women who need it, we gained one more piece of the puzzle from the Women’s Health Initiative (WHI), this time detailing what happens when we stop therapy. Then look for some futuristic food for thought. Take another look at vasomotor symptoms—is a hot flash really just a hot flash? Can we predict the time of menopause? And more...read on!

A New Target for Statin Therapy? The Role of C-Reactive Protein

The results of Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) were presented at the annual American Heart Association (AHA) meeting while simultaneously appearing as the lead article in the *New England Journal of Medicine*¹ and on the front page of the *New York Times*. The results promise to change the way we approach primary prevention of heart disease. The JUPITER trial showed that rosuvastatin therapy (20 mg per day) in ‘apparently healthy’ persons reduced the primary endpoint by 44%; specifically,

the occurrence of a first major cardiovascular event (non-fatal myocardial infarction [MI], nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure or confirmed cardiovascular death) by 44%. From the standpoint of absolute risk, rosuvastatin therapy reduced the primary endpoint from 1.36 events per 100 person-years to 0.77 events per 100 person-years—a difference of 0.59 events per 100 person-years (59 events/10,000 person-years), or less than 1%. Rosuvastatin therapy reduced death from any cause by 20%. The results were just as robust for women as for men, and for all other subgroups evaluated. If risks are projected over an

average 5-year treatment period, the number needed to treat to prevent the occurrence of one primary endpoint is 25.

What makes this statin trial unique are the participants. The subjects were men (≥ 50 years) and women (≥ 60 years) with baseline low-density lipoprotein (LDL) cholesterol < 130 mg/dL (below the threshold for treatment, according to current guidelines) but high-sensitivity C-reactive protein (CRP) levels > 2.0 mg/L. On close examination, approximately 40% of the participants met criteria for the metabolic syndrome, but in subgroup analysis, the results were similar. In order to enroll the 17,802 participants in JUPITER, 89,890 healthy people were screened. One in five persons evaluated qualified for the study; more than half were excluded because of LDL levels > 130 mg/dL, and more than one-third were excluded because CRP was < 2.0 mg/L. At trial baseline, the median LDL was 108 mg/dL and the median CRP was 4.2 mg/L. Of the 17,802 participants, 38% were women (n=6,801).

The trial was stopped after a median follow-up of 1.9 years, when the data and safety monitoring board voted to recommend termination of the trial. Among the subjects assigned to rosuvastatin, the median LDL level (after 12 months of therapy) was 55 mg/dL (a 50% reduction), and the median CRP was 2.2 mg/L (a 37%

decline from baseline). While the focus of this article is CRP, this is an impressive reduction in cholesterol level!

The total number of serious adverse events was similar in the treatment and placebo groups. Protocol-specified measurements showed no difference in fasting blood glucose levels or in newly diagnosed glycosuria. Glycohemoglobin was, however, significantly higher in the rosuvastatin group than in the placebo group (5.9% versus 5.8%; $P = .001$), and physician-reported diabetes was more frequent in the treated participants than in the placebo group (270 cases [3.0%] versus 216 reports [2.4%]; $P = .01$). These events were not adjudicated by the endpoint committee, although they are consistent with findings from previous trials of pravastatin, simvastatin and atorvastatin.

The JUPITER trial results confirm the post hoc analysis you might recall from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),² which showed that statin therapy reduced CVD events in persons with elevated CRP but not hyperlipidemia. The JUPITER trial adds to the growing list of primary prevention statin trials that include adequate numbers of women. How should you incorporate the findings from JUPITER into your practice? The current 2007 AHA recommendations for prevention of CVD in women state, "...the role that novel CVD risk factors (eg, high-sensitivity C-reactive protein)...should play in guiding preventive interventions is not yet defined."³ The 2003 Statement from the Centers for Disease Control and the AHA⁴ regarding markers of inflammation and CVD allows for measurement of CRP in asymptomatic individuals with an intermediate level of risk, if CRP might influence or change the decision to treat. As mentioned in the accompanying New England Journal of Medicine

editorial, "Guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between

or severe vasomotor symptoms. The authors went on to suggest that persistent vasomotor symptoms in older women might signal the need to identify and treat risk factors for CHD



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the benefits of treatment and its long-term safety and cost.⁵ Stay tuned as the dust settles and recommendations emerge to guide you in selecting which women would benefit most from CRP testing and statin therapy.

When is a Hot Flash Not Just a Hot Flash?

Accepted as the *sine qua non* for the menopausal transition, the hot flash has traditionally been viewed as occasionally compromising quality of life, but not posing a threat to life. The intriguing report from the combined analysis of the WHI⁶ pointed out that in women more distant from menopause, the higher coronary heart disease (CHD) risks seen with HT use appeared to be concentrated in the small subset of women with moderate

(or to identify some, as yet, unmeasured risk factors in the future).

How common are hot flashes in older women? At baseline in the Multiple Outcomes of Raloxifene Evaluation osteoporosis trial, 11.8% of 3,167 women in US sites reported hot flashes that were bothersome some, most or all of the time.⁷ Of the women who were within 2 to 5 years after menopause, 44.9% reported hot flashes; the percentage declined in a linear fashion, to 7.8% of women more than 20 years past menopause. Women were more likely to have clinically significant hot flashes if they were less educated, more recently menopausal, had undergone hysterectomy, had previously used estrogen, had higher body mass index, higher serum follicle-stimulating hormone

(FSH) levels and lower high-density lipoprotein levels. Surprisingly, in this study, hot flashes did not correlate with serum estradiol levels. In the Study of Women's Health Across the Nation (SWAN), women with a higher percentage of body fat also had a higher likelihood of reporting hot flashes.⁸

The SWAN study offers additional insights into hot flashes and cardiovascular health. An ancillary heart study conducted at two centers included 492 women (one-third black, two-thirds white) ranging in age from 45 to 58 years.⁹ The women were free of clinical CVD at baseline and had a uterus and at least one ovary. Non-invasive cardiovascular assessments were obtained, hot flash frequency was recorded and estradiol levels were measured. After adjusting for cardiovascular risk factors and estradiol concentrations, hot flashes were associated with significantly lower flow-mediated dilation and increased aortic calcification. Counterintuitively, interactions by age, race, HT use and menopausal stage were not significant. The authors concluded that the presence of hot flashes may mark adverse underlying vascular changes among midlife women, and went on to suggest that the vasculature may play an important role in the physiology of hot flashes.

These very intriguing studies challenge us in a most fundamental way to reevaluate how we think about hot flashes. The findings further compel us to explore these vascular clues with the goal of ultimately elucidating the proposed link between hot flashes and CHD in women. On a day-to-day basis, perhaps we should take a second look at women who present with persistent hot flashes as their time from menopause increases, and make certain to identify and manage cardiovascular risks.

New FRAX Web-based Tool Calculates 10-year Fracture Risk

Deciding who to treat for osteoporosis has been either very clear (those with spine or hip fractures, or osteoporosis diagnosed based on bone mineral density [BMD] determination [T -score ≤ -2.5]) or very controversial (those with low bone mass; T -scores between -1 and -2.5). In the "gray zone" of osteopenia lie relatively young, healthy, often-worried women with a low risk for fracture, as well as older, less healthy, reluctant-to-be-treated women at greater risk. How do we identify the most appropriate women to treat? Since the propensity to fracture reflects the interplay of both risk factors and BMD, the need for a better way to stratify fracture risk and to select persons for treatment has been recognized for some time.

Five years in the making, the widely anticipated fracture prevention algorithm (FRAX) was finally released in February 2008 (www.shef.ac.uk/FRAX, or just Google FRAX). Produced by the World Health Organization (WHO),¹⁰ FRAX provides a method to calculate the 10-year risk of a major osteoporosis-related fracture (hip, spine, forearm and humerus), taking into account both risk factors and BMD of the femoral neck (T - or z -score). This computer-based algorithm factors age (including age 40 years up to 90 years), body mass index, prior fragility fracture, use of oral glucocorticoids, parental history of fracture, current smoking, excess alcohol intake, secondary osteoporosis, and rheumatoid arthritis with (or without) BMD, into a calculated 10-year absolute fracture risk for the categories of "major fracture" and "hip fracture." Country of residence, race and gender are also considered in the calculations.

What to do with the absolute risk once it has been calculated? The

National Osteoporosis Foundation (NOF), in collaboration with WHO, has adapted FRAX to the US population and conducted a cost analysis to recommend which level of risk is most effective to treat.^{11,12} To convey these recommendations, the *NOF Clinician's Guide to Prevention and Treatment of Osteoporosis*¹³ (www.NOF.org) was also updated. According to the new NOF Guide, practitioners should treat postmenopausal women age 50 and older (men are also included in the new guidelines) who have low bone mass at the femoral neck, total hip or spine, if their 10-year hip fracture probability is $\geq 3\%$ or their 10-year major osteoporosis-related fracture probability is $\geq 20\%$. The guidelines appropriately state that clinical judgment and patient preference must remain part of the equation when deciding on a course of action.

FRAX is a straightforward online tool that makes it convenient to sit down with your patient and calculate her risk for an osteoporotic fracture, much as you now calculate her cardiovascular risk with the Framingham Risk Assessment. The FDA has cleared Hologic¹⁴ (and likely other manufacturers) to incorporate FRAX into their bone densitometry systems, which will allow the FRAX-calculated absolute risk to appear concurrently with BMD on the final DXA report.

Like any new technology, FRAX has had some glitches. If you're using FRAX, check out the "FRAX Patch" on the NOF Web site. Stay tuned for other revisions as they arise. Some limitations of the algorithm are also outlined on the FRAX Web site. For example, bone markers are not included, vertebral BMD isn't a component, younger persons aren't included, degree of risk (such as dose/duration of glucocorticoids) can't be stratified, and current treatment of osteoporosis and tendency to fall are not factors. Some of the limitations reflect human nature and

lack of time/interest/ability to use online tools.¹⁵ Nevertheless, the real benefit of FRAX is to encourage you to initiate the conversation about osteoporosis with your patients. By using this validated tool, you can quantify risk and, ultimately, tempered by your clinical judgment, offer therapy to appropriate individuals.

Denosumab: Joining the RANKs of Osteoporosis Therapies

Denosumab is a human monoclonal antibody against the receptor activator of the nuclear factor kappa B (RANK) ligand. The RANK ligand activates osteoclasts and promotes bone resorption; the antibody (denosumab) blocks osteoclast differentiation, proliferation and function, and allows bone formation to proceed.¹⁶

In a 2-year clinical trial with women with low bone density (mean age, 59.4 years),¹⁷ treatment with denosumab (subcutaneous injection every 6 months) increased BMD by 6.5% at the spine and reduced markers of bone turnover by 70%–80%. Denosumab also increased total-body BMD, as well as BMD at the total hip, femoral neck, trochanter and lower radius. Adverse events were similar in the treatment and placebo groups. Bone effects with denosumab are reversible; BMD declines and bone turnover markers increase when therapy is discontinued, and BMD again increases and markers decrease when therapy is restarted.¹⁸ In a head-to-head trial in women with low bone mass,¹⁹ denosumab increased BMD and reduced bone turnover markers to a greater extent than that achieved with weekly alendronate. In postmenopausal women with low BMD who had previously been treated with alendronate, BMD at the hip and spine increased by ~1.0% when denosumab therapy was initiated.²⁰ Women who tried denosumab preferred the twice-yearly injections over daily oral therapy.²¹

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial²² enrolled 7,868 women between 60 and 90 years of age, with BMDs between -2.5 and -4.0; 23% of the women had

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prevalent vertebral fractures at baseline. Treatment included subcutaneous denosumab 60 mg every 6 months along with 1g of elemental calcium and 400–600 international units of vitamin D daily. After 3 years, treatment with denosumab reduced new vertebral fractures by 68% (absolute risk of 7.2% for women in the placebo group compared to 2.3% in the treatment group). Clinical vertebral fractures were reduced by 69%. Nonvertebral fractures were reduced by 20% (8% with placebo versus 6.5% in the treatment group). Hip fractures occurred 40% less frequently (1.2% in the placebo group versus 0.7% in the denosumab group). Adverse events were comparable between the active therapy and placebo groups.

In the “bone community,” there is considerable excitement over this new class of therapeutic agent. Twice-yearly subcutaneous administration simplifies therapy for both patients and providers, likely increasing compliance. If approved, denosumab will also provide an alternative therapy for patients who have already committed to a decade of bisphosphonates and wish to take a break. With a reassuring safety profile in 2- to 3-year trials, denosumab is anticipated to be approved soon. Continued monitoring for possible safety concerns would be prudent.

Screening for Type 2 Diabetes Mellitus in Adults with Hypertension: US Preventive Services Task Force Recommendations

Diabetes ranks high on the list of risk factors for CVD and death, increas-

ing CVD risk 2- to 4-fold; diabetic women suffer a disproportionately higher risk than do diabetic men. The presence of hypertension augments the cardiovascular threat of diabetes, which often goes undetected for years prior to manifestation of common symptoms such as polyuria, polydipsia and polyphagia. Not uncommonly, the initial presentation of diabetes is a cardiovascular event.

Given these concerns, the US Preventive Services Task Force (USPSTF) investigated the benefits of screening asymptomatic persons for diabetes.²³ Their new recommendations state that any adult with sustained blood pressure (treated or untreated) greater than 135/80 mm Hg should be screened for diabetes. How many women in your menopause practice would meet this criterion? According to the AHA, more than one-third of 45- to 54-year-old women are hypertensive; in the age range of 55 to 64 years, more than half of women have high blood pressure.²⁴

Options for diabetes screening include measurement of fasting plasma glucose, 2-hour post-load plasma glucose and hemoglobin A1c. While an argument in support of using the hemoglobin A1c as the preferred screening test has recently been presented,²⁵ the American Diabetes Association (ADA) recommends screening with

fasting plasma glucose (FPG).²⁶ The ADA defines diabetes as FPG \geq 126 mg/dL, and recommends confirmation with a repeated screening test on a separate day.

When it comes to diabetes screening in your hypertensive patients, just do it (as the Nike advertisement used to say). The stakes are high, the potential benefits large, and the cost and effort minimal. As the prevalence of diabetes continues to rise (currently about 9% of the adult US population),²³ this might just be one of the most effective CVD prevention strategies you can incorporate into your practice. And the USPSTF found adequate evidence that lowering blood pressure below conventional target values in adults with diabetes reduces both incidence of CVD events and CVD mortality.²³

What Happens when Women Stop Taking Estrogen plus Progestin? The 3-year Follow-up of the WHI

With the release of the initial findings of the WHI estrogen-plus-progestin (E+P) arm of the trial in July 2002, all participants were advised to discontinue HT. The predefined end of the trial had been set, though, as March 31, 2005, which allowed for a post-intervention phase to extend an average of 2.4 years. Follow-up included 95% of the original women who enrolled in the E+P arm of the trial, and consisted of strict observance of the trial protocol (semiannual endpoint ascertainment and verification, and annual mammogram surveillance).²⁷

What did the investigators learn? The increased risks of cardiovascular events (coronary heart disease, MIs, coronary revascularization procedures, deep vein thrombosis and pulmonary embolism) during the trial in the women assigned to the HT group were no longer evident. Unfortunately, the protective effects of E+P on colon cancer and osteoporotic fractures were

no longer apparent. The annualized event rate for the “all cancer” outcome was, however, increased in the women who had been assigned to E+P during the trial (1.56%), compared to women assigned to placebo (1.26%)—a significant (24%) increase. The difference in risk translates to 30 additional cancer cases per 10,000 women per year of hormone use.

What kind of cancer was increased? The trend of increasing risk for breast cancer during the intervention phase of the trial was not seen to extend beyond the trial’s end, when HT was stopped. While there were 9 additional cases of breast cancer per 10,000 women per year in the post-intervention phase in the group assigned to E+P, the difference did not reach statistical significance. The study lacked statistical power to identify any decrease in breast cancer similar to that previously reported in women who stopped HT.²⁸ Of the remaining increased number of cancers, two were colorectal and 18 were lung cancers.

At the end of the day, the overall risks of E+P in the total population of the WHI, even 3 years after discontinuing, exceeded benefits. It’s not clear why the incidence of lung cancer would be elevated in women who had been assigned to the HT group for an average of 5.6 years. Further analysis providing additional characterization of the women who developed lung cancer would be helpful. If lung cancer is reduced in smokers who use HT, as has been hypothesized by some,²⁹ perhaps the WHI findings represent a “rebound” effect when therapy was halted. If that’s the case, close surveillance for lung cancer would be merited in high-risk women. In the meanwhile, it is reassuring to women (and their clinicians) that CVD risks resort to normal rates once E+P is discontinued. That fracture protection is lost following discontinuation of E+P reminds us that,

depending on risk assessment, BMD could be measured in women who discontinue HT; consideration should be given to initiating other bone-preserving therapy, if indicated.

Aromatase Inhibitors and Breast Cancer: The Good, the Bad and the Ugly

Aromatase is the enzyme that catalyzes the final step in the conversion of androgen to estrogen. Aromatase inhibitors (AIs) interrupt this step, and result in very low levels of endogenous estrogen. A number of clinical trials investigating the use of third-generation AIs (anastrozole, exemestane and letrozole) in women with breast cancer have shown superior efficacy over tamoxifen in the metastatic, neoadjuvant and adjuvant settings. The AIs also improve outcome as extended adjuvant therapy following 5 years of tamoxifen.³⁰ Ongoing trials will assess the value of AIs in primary prevention of breast cancer in high-risk women. And, in an intriguing report from a small retrospective cohort study of 56 healthy postmenopausal women on HT, concurrent prescription of an AI (mostly letrozole, 2.5 mg per day, 3 times per week) significantly reduced mammographic breast density.³¹

On the downside, AIs decrease BMD and increase the risk of osteoporotic fractures. The American Society of Clinical Oncologists recommends that BMD measurement should be obtained at the time AI therapy is initiated and, if BMD is compromised, bisphosphonate therapy should be started. Clinical trials with zoledronic acid,³² risedronate³³ and denosumab³⁴ all reported benefit; BMD was maintained or increased in women on AI therapy.

Symptoms of estrogen deficiency, including arthralgias, can be quite bothersome. In the Arimidex, Ta-

moxifen, Alone or in Combination (ATAC) trial, the major risk factors for developing joint symptoms were previous HT, hormone-receptor-positive status, previous chemotherapy, obesity and treatment with anastrozole.³⁵ In a small prospective study comparing women before and 6 months after AI or tamoxifen therapy, women on AIs complained of more arthralgias and had objective measures of decreased hand-grip strength and evidence of tenosynovial changes on magnetic resonance imaging.³⁶

As a positive twist, in a retrospective analysis of the ATAC trial, the advent of hypoestrogenic symptoms (specifically hot flashes and arthralgias) within the first 3 months of therapy correlated with an absolute 11.4% decrease in breast cancer recurrence after 9 years.³⁷ The authors suggest that new vasomotor or joint symptoms within the first 3 months of therapy constitute a useful biomarker that might reassure patients and possibly improve long-term treatment adherence.

While AI therapy is the new gold standard for adjuvant therapy in women with breast cancer, the need for monitoring BMD and proactively preventing bone loss is well-established. New data on bone sparing agents will expand options for osteoporosis prevention. Finally, turning uncomfortable symptoms into a sign that "the medicine is working" might improve adherence to AI therapy. Ideally, methods to reduce or eliminate bothersome symptoms without interfering with the anti-estrogen effects of AIs would enhance the quality of life for treated women.³⁸

Therapies for Vaginal Symptoms: What's New?

Atrophic vaginitis, recently described as an "untreated epidemic,"³⁹ remains a common clinical concern of women during and after the menopausal transition.⁴⁰ Estrogen therapy (ET)

provides the gold standard for treatment of moderate to severe symptoms of vulvar and vaginal atrophy (dryness and irritation) associated with menopause.⁴¹ According to the FDA's indications for ET (www.fda.gov/cder/

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[drug/infopage/estrogens_progestins/default.htm](http://www.fda.gov/cder/infopage/estrogens_progestins/default.htm) (1/16/08), "when prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, consider topical vaginal products" (creams, tablets and vaginal rings).

A persistent concern is the possible sequelae of increased serum estradiol concentrations, especially during the first several weeks of therapy when atrophic vaginal tissue is most absorptive.⁴² Depending upon the dose and preparation of vaginal estrogens, possible systemic effects include uterine bleeding, breast pain and endometrial over-stimulation.⁴³

In response to these concerns, reports from several recent trials demonstrate safety and efficacy of lower-dose regimens in healthy postmenopausal women. In one trial, 12 weeks of an ultra-low-dose (10 mcg) 17 β -estradiol vaginal tablet was found to be comparable to the approved 25-mcg dose with regard to improvement in scores of vaginal health.⁴⁴ In a year-long trial, the 10-mcg dose, given twice weekly after an initial 2 weeks of daily dosing, effectively reduced vaginal symptoms without endometrial stimulation.⁴⁵

Another trial examined the effects of daily conjugated estrogen vaginal cream (0.5 g, equivalent to conjugated estrogens 0.3 mg), 21 days on and 7 days off or twice-weekly, for 1 year.⁴⁶ The twice weekly regimen was as

effective as daily administration in symptom relief at 12 weeks; at 1-year, endometrial safety was demonstrated with both regimens. In a 12-week study of plant-derived synthetic conjugated estrogens, the twice-weekly

regimen (both 1-g and 2-g doses) was found effective for relieving signs⁴⁷ and patient-reported symptoms of vaginal atrophy.⁴⁸ Vaginal dehydroepiandrosterone (DHEA) was also effective.⁴⁹

Of particular interest to women who may want to avoid estrogen entirely are two new selective estrogen-receptor modulators (SERMs) in phase III trials, lasofoxifene⁵⁰ and ospemifene,⁵¹ both of which improved symptoms of vulvovaginal atrophy.

The good news is that vaginal estrogens are effective at lower doses than traditionally prescribed, even when administered as infrequently as once or twice weekly. The FDA has approved a twice-weekly low-dose version of Premarin vaginal cream, so that intermittent use is no longer off-label. The 10-mcg Vagifem tablet is also scheduled to be approved sometime in 2009. With the availability of creams, tablet and vaginal rings, each woman requiring therapy should be able to find a preparation that is comfortable for her; DHEA might offer a new choice. The advent of new SERMs with vaginal benefits will provide other treatment options for appropriate women.

Are We There Yet? Predicting Time to Menopause

Anti-Mullerian hormone (AMH) is produced in the granulosa cells of ovarian follicles and is thought to be

one of the earliest markers of ovarian aging. It is produced only by the growing ovarian follicles. Serum levels are thought to be a marker for ovarian reserve, representing the quantity of the ovarian follicle pool. Measurement of AMH does not require specific timing within the menstrual cycle.

In two creative longitudinal studies, investigators set out to establish markers to predict women's age at menopause. In the first study, they measured AMH, inhibin B and FSH in 300 follicular-phase blood specimens archived from 50 women with six consecutive annual visits.⁵² Each woman documented her final menstrual period (FMP). The investigators found that the log of AMH longitudinal values declined linearly with time. Very low or undetectable values were highly associated with a time point 5 years prior to the FMP. While inhibin B also fell to the lowest levels approximately 4 years prior to the FMP (at a time when FSH levels were rising), there was no significant association between inhibin B levels and the age at FMP. The authors therefore concluded that AMH was more predictive of age at menopause.

In a separate analysis, the same investigators applied elegant modeling techniques to FSH samples that had been collected from a cohort of 629 women, starting at ages 22 to 44 years over a 14-year period. They identified "four major FSH stages and the FSH levels and ages that clinicians can use, along with menstrual cycle characteristics, to help interpret the likely status of women with respect to reproductive viability and menopause stage."⁵³

Whether it is gaming her remaining time to consider one last pregnancy or weariness at the prospect of several more years of difficult menstrual cycles, a common question from women seeking advice is:

"When will I experience menopause?" The parameters established in these studies might help clinicians answer this question. Future assessments of women curious about reproductive aging will likely include AMH along with FSH, ovarian ultrasound to determine an antral follicle count, and the woman's menstrual history.

A Peek Down the SERM Pipeline...

It has been more than a decade since raloxifene was approved for the prevention of osteoporosis. Since then, raloxifene also has been approved for osteoporosis treatment and prevention of breast cancer in postmenopausal women. The results of several clinical trials investigating three new SERMs were reported last year; they offer a glimpse into agents either currently under FDA review or with submissions anticipated in the near future.

In the 3-year (2-year extension) Postmenopausal Evaluation And Risk-Reduction with Lasofoxifene trial of 8,556 women ages 59 to 80 years, lasofoxifene (0.5 mg/day, P.O.) effectively increased BMD of the spine and hip by 3%, reduced vertebral fractures by 42% and nonvertebral fractures by 24% in women with baseline *T*-scores of -2.5 to -4.5.^{54,55} Lasofoxifene therapy also reduced the risk of estrogen-receptor-positive breast cancer by 81%. The risk of major CHD events was reduced by 32%, and the risk of all stroke events was reduced by 36%. The rates of endometrial cancer or hyperplasia were similar between lasofoxifene and placebo groups, although uterine polyps, endometrial thickening and vaginal bleeding increased on lasofoxifene therapy, necessitating additional uterine procedures. As anticipated, venous thromboembolic events were twice as frequent in the lasofoxifene group. Signs and symptoms of vaginal atrophy, including dyspareunia, improved.⁵⁰

Bazedoxifene, previously shown to reduce vertebral fractures, has now been shown to also decrease the risk of nonvertebral fractures in postmenopausal women at high risk. In the original 3-year trial,⁵⁶ 7,492 women (mean age, 66.4 years) were randomized to bazedoxifene 20 mg or 40 mg, raloxifene 60 mg or placebo. The overall incidence of nonvertebral fractures was similar among treatment groups. In a *post hoc* subgroup analysis of 1,722 women at high risk for fracture (femoral neck *T*-score ≤ -3.0 and/or vertebral fractures at baseline), nonvertebral fracture rates were 4.9% with bazedoxifene 20 mg, 6.5% with bazedoxifene 40 mg, 8.4% with raloxifene, and 9.1% with placebo. Bazedoxifene reduced nonvertebral fractures by 50% compared to placebo, and 44% compared to raloxifene therapy. A separate *post hoc* analysis of baseline and 2-year digitized mammograms⁵⁷ showed no increases in breast density after 24 months of bazedoxifene therapy. Adverse events with bazedoxifene therapy included increased risk of hot flashes, leg cramps and thromboembolism. Endometrial effects did not differ between treatment and placebo groups. Of note, in a small, 12-week clinical trial involving 487 women specifically selected for absence of hot flashes at baseline,⁵⁸ neither bazedoxifene nor raloxifene increased the incidence of hot flashes. Finally, in a 12-week trial with 318 postmenopausal women bothered by frequent hot flashes, the combination of bazedoxifene (20 mg) with conjugated estrogens (0.45 mg or 0.625 mg) controlled hot flashes and improved sleep quality.⁵⁹

In a 2-year, phase-III clinical trial with 331 postmenopausal women (ages 45 to 60 years) with *T*-scores > -2.5 at baseline, treatment with arzoxifene 20 mg significantly increased BMD of the spine (3.2%) and hip

(2.3%), compared to placebo.⁶⁰ Markers of bone turnover decreased by ~30%. Hot flashes did not increase, and endometrial findings were similar between the arzoxifene and placebo groups.

As these compounds advance through years of clinical trials and analysis, we are reminded that the unique structure of each SERM molecule renders unique clinical effects. It is therefore mandatory that each SERM be carefully and fully evaluated. In the years ahead, our challenge will be to carefully match the unique risk and benefit profile of a SERM to the unique concerns of each woman considering SERM therapy. ■

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This article includes discussion of off-label use of medications.

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supplement. Although the optimal supplement formulation remains controversial,⁷⁰ many experts favor supplements containing vitamin D₃ (cholecalciferol) rather than vitamin D₂ (ergocalciferol). Although the current upper “safety limit” for vitamin D intake is 2,000 IU per day,² this is a conservative recommendation, and some experts believe there is little risk of toxicity with doses up to 10,000 IU per day.⁷¹ Indeed, for patients with clear vitamin D deficiency (ie, 25(OH)D <25 nmol/L), administration of 50,000 IU once per week for 8 weeks and every 2 weeks thereafter until 25(OH)D levels no longer indicate deficiency is a reasonable strategy. Subsequent maintenance doses of 800–1,000 IU/day should help most patients achieve the recommended levels of 25(OH)D. ■

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