MENOPAUSE

Key findings and guidance from the past year on hot flushes, early menopause, and the hormone therapy–venous thromboembolism link. Plus, NAMS updates its position on estrogen-only and estrogen–progestin HT.

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Important developments in the care of menopausal women in the past 12 months include:

• new evidence about the duration, and non-hormonal management, of hot flushes
• new data on the risk of venous thromboembolism when oral and transdermal hormone therapy (HT) are compared
• trends in thinking regarding ovarian conservation at the time of hysterectomy, as well as a new report on the impact of hysterectomy on subsequent ovarian function
• a new Position Statement on HT from the North American Menopause Society.

Hot flushes can last 10 years or longer


Hot flushes are more persistent than has been recognized

Previous reports have suggested that hot flushes, the most prevalent menopausal symptom, persist from 6 months to longer than 5 years. Freeman and colleagues carried out a prospective, population-based study in the Northeastern United States that enrolled more than 250 women (age range at enrollment, 35 to 47 years) who did not use HT. Subjects in this cohort were followed for 13 years as they progressed through menopause.

Surprisingly, the researchers found that the median duration of moderate-to-severe hot flushes was 10.2 years. Hot flushes persisted longer in black women than in white women (P = .02) and longer in non-obese women than in obese women (P = .003). Duration of symptoms was similar in smokers and nonsmokers.

Once again, soy fails to relieve menopausal symptoms

A number of clinical trials performed since the 2002 publication of the initial findings
of the Women’s Health Initiative (WHI) have failed to demonstrate that soy is efficacious for treating menopausal symptoms. Nevertheless, many women remain intrigued by the potential for obtaining symptom relief with over-the-counter supplements.

Investigators in Florida randomized women who had been menopausal for at least 5 years to receive daily soy isoflavones (equivalent to about twice the amount ingested in a typical Asian diet) or placebo for 2 years. Outcomes assessed at baseline and again at 12 and at 24 months included spine and hip bone-mineral density (BMD), menopausal symptoms, and vaginal epithelial maturation. Almost 250 women (mean age, 52 years) were randomized.

At 2 years, researchers found that:
- **BMD had declined** at all sites by about 2% in both groups
- approximately one half of subjects in the soy group and approximately one third who were randomized to the placebo group reported experiencing hot flushes ($P = .02$)
- **vaginal epithelial maturation** did not change appreciably from baseline in either group
- **constipation** was reported by 31% of women in the soy group and 21% in the placebo group—a difference that only marginally achieved statistical significance.

## Hormone therapy and risk of venous thromboembolism

**Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. Menopause. 2011;18(10):1052–1059.**


**Transdermal HT appears to be safer than oral therapy**

Yet another observational study adds evidence that venous thromboembolism (VTE) is less of a risk in women using transdermal estrogen therapy than it is in women taking oral therapy.

To compare oral and transdermal estrogen formulations in regard to the risk of VTE that they pose, Laliberte and colleagues conducted a retrospective cohort study of US and Canadian women, using health insurance claims data from women who were starting transdermal or oral estrogen. In all, 27,018 users of transdermal estrogen were matched with an equal number of oral users.

VTE was diagnosed in 115 women using transdermal estradiol and 164 women using oral estrogen. Compared with the rate in women initiating oral estrogen, **women using transdermal estradiol had a significantly**
lower incidence of VTE than oral estrogen users (adjusted incidence rate ratio, 0.67).

Hysterectomy may accelerate the onset of menopause


Is HT safe for women who have a history of VTE?

In the 2011 OBG MANAGEMENT Update on Menopause, I examined two large observational studies—one from France, the other from Great Britain—that provided convincing evidence that transdermal HT does not, in contrast with oral HT, raise the risk of VTE. These new reports, from North America and France, provide further support for the hypothesis that transdermal HT is safer from the perspective of VTE risk. Although a randomized trial that compares the risk of VTE in women using oral estrogen with the risk in women using transdermal estrogen might put this matter to rest, I don’t anticipate that a trial to address this outcome, with adequate statistical power, will be performed any time soon.

In my practice, most of the estrogen that I prescribe for menopausal women is transdermal. Using transdermal estrogen may be particularly important in patients who are at increased risk of VTE at baseline, including obese women.

The small numbers of thrombotic events in the cohort of women who had a history of VTE limits confidence in the findings of this French report. Nevertheless, this study provides a small measure of reassurance regarding use of transdermal estrogen after VTE.

Only rarely have I prescribed HT to women who have a history of VTE. These exceptional patients have been highly symptomatic and extensively counseled about the risk of recurrent thrombosis as well as the off-label status of hormone use, given their medical history. Certainly, if you consider prescribing HT to such women, the transdermal route (preferably at a dosage of 0.05 mg, or lower) would be more prudent that oral HT.

Hysterectomy may accelerate the onset of menopause


Does hysterectomy hasten ovarian failure?

In a prospective cohort study from North Carolina, Moorman and colleagues followed 406 women who did not have malignancy who underwent hysterectomy, with preservation of at least one ovary and 465 women who had an intact uterus (overall age range, 30 to 47 years). Within 5 years of follow-up, ovarian failure had occurred in 60 women...
ObGyns are more often practicing ovarian conservation in women (particularly younger women) undergoing hysterectomy for benign indications.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Early menopause puts our patients at elevated risk of osteoporosis, cardiovascular disease, neurodegenerative disease (possibly), and sexual dysfunction. We have long suspected that hysterectomy may accelerate the onset of menopause, and the North Carolina cohort study provides strong support for this hypothesis.

The New York State report reveals that ObGyns are more often practicing ovarian conservation in women (particularly younger women) undergoing hysterectomy for benign indications.

In 2008, ACOG revised its guidance on this matter—stating that “strong consideration should be given to retaining normal ovaries in premenopausal women who are not at increased genetic risk of ovarian cancer.”

Evidence that we are increasingly following this prudent guideline is welcome news.

Breaking news: NAMS updates guidance on hormone therapy


Position Statement emphasizes differences in the benefit-risk profile of estrogen–only HT and estrogen–progestin HT

Periodically, NAMS assembles a multidisciplinary panel of clinicians and researchers to evaluate new evidence about HT and reach consensus on guidance about using hormones, and then publishes a Position Statement on the subject. In March, NAMS published its updated (2012) position on HT.

Two recent, and important, analyses of data from the Women’s Health Initiative (WHI) made an impact on the current revision to an earlier (2010) Position Statement; I had summarized those studies in the 2011 OBG MANAGEMENT Update on Menopause.

Recap. Initial findings in the estrogen-progestin arm of the WHI, published in 2002, found that, after participants had used study medications (HT or placebo) for a mean of 5.2 years, their risk of invasive breast cancer was increased (HR, 1.26). This modestly elevated risk was only marginally significant (95% confidence limit, 1.00–1.59).

In 2010, investigators reported on breast cancer characteristics and mortality in WHI participants at a mean follow-up of 11 years. They found that combination HT users had breast cancer histology similar to that of was intact. The likelihood of ovarian failure was higher in the setting of unilateral oophorectomy than when both ovaries had been conserved.

Hysterectomy for benign disease: Are we performing fewer oophorectomies?

Investigators in New York State followed trends in concomitant bilateral oophorectomy among women undergoing hysterectomy for benign disease, from 2000 to 2006. Overall, the rate of concomitant oophorectomy declined by 8% during this period; among women younger than 55 years, the rate of oophorectomy declined by more than 10%. The rate of concomitant bilateral oophorectomy was higher among women who had a family history of breast or ovarian cancer and among those who had a personal history of breast cancer, ovarian cysts, or endometriosis.
Dr. Kaunitz describes his approach to providing hormone therapy

**Estrogen.** Most of my patients who are taking systemic menopausal hormone therapy (HT) use transdermal estrogen, with 0.05 mg the most common starting dose. Given the elevated baseline risk of thrombosis among obese women, I particularly encourage them to use transdermal estrogen when starting systemic HT.

When I prescribe oral estrogen, the formulation I use most often is generic micronized estradiol; the most common starting dosage is a 1 mg tablet.

**Progestin.** To protect the endometrium in menopausal women whose uterus is intact and who are opting for systemic HT, I often use micronized progesterone, 100 mg nightly (provided no peanut allergy is present). My rationale? Progesterone is less likely than other progestational agents to cause unpleasant mood changes, and may offer a safety advantage vis-à-vis breast cancer.

When cost is a concern, generic medroxyprogesterone acetate tablets are well studied and inexpensive (2.5 mg tablets are appropriate when using the dosages of transdermal or oral estradiol given above).

When treating vasomotor symptoms/irregular bleeding in perimenopausal women, symptomatic relief may be more likely if HT formulations with sufficient progestin to consistently suppress ovulation are employed. Therefore, in such patients, I often use approaches such as femHRT 1/5 (also available as a generic) and Activella (also available as a generic).

Last, my experience is favorable using a combination of transdermal estrogen and the progestin-releasing IUD in symptomatic perimenopausal women.

Note: Using any sex steroids to manage perimenopausal symptoms constitutes an off-label use.

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subjects assigned to placebo, but that the tumors were more likely to be node-positive in combination HT users (23.7%, compared with 16.2% among placebo users). In addition, breast cancer mortality was slightly higher among users of HT (2.6 deaths, compared with 1.3 deaths, for every 10,000 woman-years of use) (HR, 1.96; 95% confidence interval [CI], 1.00–4.04); again, this elevated risk reached only marginal statistical significance.

Then, in 2011, WHI investigators reported their findings from the estrogen-alone arm of the study, in which postmenopausal, hysterectomized women were randomized to oral estrogen or placebo and took study medications for a mean of 6.8 years. (Recall that initial findings from the estrogen-only arm of WHI, published in 2004, found that the risk of invasive cancer was lower in women randomized to estrogen [HR, 0.77]—a reduction in risk that approached, but did not achieve, statistical significance [95% CI, 0.59–1.01].) In the 2011 report, the lower risk of breast cancer in the estrogen group persisted; with almost 11 years mean follow-up, this prevention was found to be robust and statistically significant (HR, 0.77; 95% CI, 0.62–0.95).

The sobering increased risk of advanced-stage tumors and the marginally higher likelihood of fatal breast cancer associated with use of estrogen–progestin HT stands in stark contrast with the significant reduction in breast cancer associated with estrogen-only HT.

Accordingly, NAMS has modified its guidance. To step back for a moment, in the abstract of its 2010 Position Statement, NAMS had concluded that:

Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable for women who initiate HT close to menopause but decreases in older women and with time since menopause in previously untreated women.

Contrast that with the conclusion in the abstract of the Society’s 2012 Position Statement:

Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms and to prevent osteoporosis in women at high risk of fracture. The more favorable benefit-risk ratio for ET allows more flexibility in extending duration of use compared to EPT where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years.
Very-long-term users often focus on either 1) their greater sense of well-being with HT or 2) the benefit of the prevention of osteoporosis in the face of their desire to avoid long-term bisphosphonate therapy.