

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In part 1 of this forum, two of our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations. (The remaining responses will appear in the May/June issue.)

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

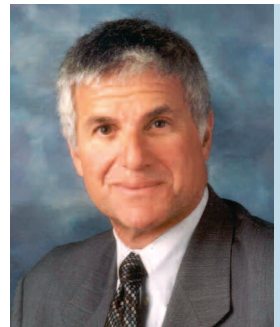
Question: Given your review of The North American Menopause Society's March 2007 Position Statement on estrogen and progesterone use in peri- and postmenopausal women, together with recent epidemiologic data suggesting a reduction in the incidence of breast cancer since the termination of the Women's Health Initiative, what might you consider as changes in your clinical practice with regard to hormone usage after menopause?

Answers:

Certainly, the release of news from the 29th San Antonio Breast Cancer Symposium (12/14/06), showing a 7% drop in the incidence of new-onset breast cancer for 2003,¹ created quite a stir. In my hometown newspaper (*The New York Times*) it was the lead story in the far-right column "above the fold"! The analysis suggested that there was a link (cause and effect) between the enormous number of women who stopped

hormone therapy (HT) after the Women's Health Initiative (WHI) news initially broke in July 2002, and this huge drop in breast cancer (7%) 6–18 months later.

The only real "news" here was good news for all—that is, that 14,000 fewer women were diagnosed with breast cancer in 2003 than in 2002. Has any of this caused me to consider changes in my clinical practice with hormone usage after menopause? Absolutely not. But, then again, I had changed much of my clinical management practices with regard to hormone use prior to July 2002. I was already aware that the use of HT (then still called HRT) was not appropriate for primary or secondary prevention of heart disease.² The increased risk of breast cancer was also not a surprise and had been foreshadowed.^{3,4} Even the differences in breast cancer rates in women on estrogen plus progesterone versus those on estrogen alone, highlighted by the hysterectomized arm of the WHI,⁵ was clearly foreshadowed.^{3,4} Thus, since well before July 2002 my clinical mantra for the use of HT to relieve disruptive transitional symptoms has been to employ the lowest effective dose for the shortest possible period of time consistent with the patient's treatment goals. The current report does nothing to change that. In the past women were given HT so they would not be "inconvenienced" by menopause. If they felt well it was renewed year in and year



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out. That is clearly not my approach. However, individual women whose symptoms are sufficiently disruptive can and should be offered HT within the guidelines discussed above.

There are, however, two things that came out of the estrogen-only arm of the WHI that have swayed my clinical thought process. The first is the 20% reduction (although not statistically significant) in breast cancer in the hysterectomized women receiving Premarin 0.625 mg daily⁶ compared with the 26% increased risk (statistically significant) in the Premarin/Provera arm of the WHI in women with a uterus.⁷ Since we use progestogen only to confer endometrial protection, I have been able to utilize transvaginal ultrasound to reduce and sometimes eliminate progestogen exposure. Space does not allow me to fully develop this thesis,⁸ but suffice it to say that we currently treat 100% of women with a uterus to protect the 7% who will develop simple hyperplasia after 6 months on unopposed Premarin (0.625 mg daily).⁹ Transvaginal ultrasound is the key to success in preventing the unnecessary treatment of so many women with progestogen. The second finding from

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the estrogen-only arm of the WHI is that there were statistically significant reductions in the rates of hip (35%), clinical vertebral (36%) and total fractures (29%), compared with placebo.¹⁰

Thus, you can appreciate that my level of concern for patients who require HT, whether with daily or monthly progestogens, is somewhat different from those who are taking ET only. Perhaps this is best underscored by a patient who called the day after *The New York Times* published the article about the San Antonio conference. She said her husband

insisted that she stop taking hormones. This patient had been taking Premarin 0.45 mg daily since her hysterectomy. I told her that the data being written about simply did not apply to her particular situation, explained the estrogen-only issues involved, and “deputized” her to pass the information on to her husband.

—Steven R. Goldstein, MD

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The incidence of new breast cancer cases in the United States decreased 7% between 2002 and 2003, with 14,000 fewer cases in 2003, according to a research report at the San Antonio Breast Cancer Symposium.¹ A similar finding was reported by the Northern California Cancer Center and Kaiser Permanente's Division of Research.² These declines are temporally associated with the 50% decrease³ in the use of HT that occurred across the country following the release of results from the WHI estrogen-plus-progestin study.⁴

Estrogen-receptor-positive tumors declined more than estrogen-negative tumors, leading to concern that there might be a causal relationship between stopping HT and declining detection of new breast cancers, although this epidemiologic data do not provide direct evidence of causality.

Does this information change what we tell patients? Since the release of the WHI results

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– JoAnn V. Pinkerton, MD

in 2002, The North American Menopause Society (NAMS) has developed position statements to address the changing information about the risks and benefits of HT. The most recently released (2007) NAMS HT position statement⁵ confirms earlier assessments, but provides more clarity regarding the risks and benefits of HT in light of the WHI.

It is important to remember that the WHI studies did not address women with premature menopause or women in early menopause with significant hot flashes. For these women, estrogen is the most effective treatment. The WHI and other studies support the use of HT to relieve menopausal symptoms.

Based on the 2007 NAMS Position Statement and including the new epidemiologic data described above, our current recommendations for women seen at the Midlife Health Center at the University of Virginia include the following:

- The primary indication for HT remains the treatment of symptomatic menopausal women.
- Progestogen therapy is needed to protect against the risk of endometrial cancer in women who have a uterus and are taking estrogen.

- For women taking HT, NAMS's recommendation remains the same. Women who need HT should take the lowest dose possible for the shortest time possible to attain their treatment goals.
- We will continue to individualize the decision about whether to recommend HT, how long to continue therapy, and what type of therapy and what regimen or dose to use. We will also continue to reevaluate risk-benefit at each visit.
- Lower doses of both ET and HT should be considered, as these doses appear equally effective for relief of hot flashes and vaginal dryness, and for preserving bone. They may be better tolerated and theoretically are safer, although they have not been tested in long-term studies.
- Consider local vaginal estrogen for vaginal dryness, including creams, a vaginal ring or tablets.
- For persistent menopausal symptoms that affect quality of life, weigh the possibility of a small increased risk of breast cancer caused by the use of ET or HT versus potential benefits with regard to vasomotor symptoms, sleep, skin, sexuality and prevention of bone loss, taking into account underlying risk of heart disease, stroke, venous thrombosis or other conditions.
- For women who are taking HT long-term (>5 years) for "quality of life reasons," the decision to continue or discontinue therapy should be rethought annually in terms of risks and benefits, including discussion of other treatment options.
- ET and HT are not currently recommended to protect against heart disease, stroke or Alzheimer's disease. Research continues on the "window-of-time" theory, in which the timing of treatment initiation may be critical for prevention.
- Women who were taking HT for the sole reason of preventing heart disease or dementia should have already discontinued it.
- With regard to the new epidemiologic data showing decreased breast cancer events the year after release of the WHI-EP data, women who are symptomatic with moder-

ate to severe hot flashes should not be alarmed. They are, it is hoped, already on the lowest effective dose that relieves their symptoms. They are younger and are therefore at lower risk of breast cancer, and most will probably taper or wean off after 3–5 years of use.

- Non-oral therapy has some advantages and some disadvantages: it may be associated with less venous thrombosis risk but it appears to confer the same risk of breast cancer as does oral therapy.
- For older women who continue on very low doses of hormones (quarter doses of estrogen only, with or without intermittent progestogen), the risk of breast cancer is theoretically less, although lower doses have not been proven to be safer.
- Longer-term or extended use of HT may be the best decision if women are persistently symptomatic and at high risk for osteoporotic fracture, or are unable to tolerate other therapies.
- In depressed perimenopausal women, some studies have shown HT to be effective;⁵ HT should not, however, be used for the treatment of depression in general.
- Regarding bioidentical hormones, it is important for patients to understand that FDA-approved products must meet certain standards of scientific testing and quality production. Caution is recommended in the use of compounded products because regulatory oversight (that is, the FDA) is lacking for quality, purity and batch-to-batch consistency of ingredients. In addition, safety and efficacy data are lacking. Claims that customized “bioidentical hormones” are safer and more effective are not supported by scientific data. Educational information on risks and benefits needs to be provided to patients.
- Regardless of whether or not women are taking hormones, breast exams and annual mammograms are recommended.

The new epidemiologic data suggest the possibility that discontinuation of HT leads to at least an initial decrease in detectable breast can-

cers. However, before we can intelligently interpret or discuss these findings we will need to wait until we see the results of the currently ongoing National Institutes of Health-sponsored follow-up studies of the WHI participants who discontinued HT.

Although lifetime exposure to estrogen has been shown to increase risk for breast cancer, there continues to be disagreement on whether estrogen administered at menopause confers the same risk. Timing, dose, duration and effect of progestogen in combination with estrogen may all affect the risk. How much risk is present, even with long-term use, remains controversial.

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Look for additional responses to this important question in the next issue of *Menopause Management*.