

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

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Question: What are the four most significant new things you have learned from the literature and from The North American Menopause Society meetings over the past several years?

Answers:

I have been asked to describe four things that I have learned in the last few years, either

from the NAMS meetings or from the literature. It is an interesting choice of word: "learned." I would like to modify that to be "things I have come to know," because the longer I am in academic medicine, the more I truly believe we do not "learn" linearly. We come to know things. Sometimes, hearing it presented once or reading it once is enough. Other times, such knowledge comes over a longer period of time with multiple hearings or readings, all with slightly different aspects or nuances. So, here are four things that I have come to know, which I think are increasingly important in my clinical practice.



Steven R. Goldstein, MD

1. Progestogen, hormone therapy, and breast cancer

The exact role of hormone therapy (HT) and the risk of developing breast cancer is not clearly understood. Much has been written, studied and hypothesized about the relationship, without total consensus. Over the last several years, and in many studies, many presentations and after much discussion, I have become firmly convinced that progestogens are the main culprit in the small but real increase in breast cancer seen with HT. Various reports seem to indicate that, compared with estrogen therapy (ET), estrogen-progestogen therapy (EPT) is associated with two to three times the risk of invasive breast cancer. In the Breast Cancer Detection Demonstration Project¹ the relative risk (RR) of breast cancer with ET use within the previous 4 years was 1.2 (95% CI = 1.0–1.4), while the RR for EPT was 1.4 (95% CI = 1.1–1.8). That epidemiologic study involved more than 46,000 women followed over a 15-year period. The Women's Health Initiative (WHI) stopped its EPT arm early because of a 26% increase in the incidence of invasive breast cancer compared with placebo, which reached prearranged levels of significance.² The ET-only arm was also stopped, but not because of any increase in invasive breast cancer.³

The actual risk of invasive breast cancer was $RR = 0.77$ (95% CI, 0.59–1.01). Furthermore, the Million Women Study in Britain,⁴ although observational in nature, involved almost 1.1 million women. Current users of ET had a 30% increase in risk ($RR = 1.30$; CI = 1.22–1.40), while users of EPT had a 100% increase in risk

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over never-users ($RR = 2.0$; CI = 1.88–2.12). Thus, while it appears that the addition of progestogen to ET significantly reduces endometrial cancers, it would also appear to increase the risk of invasive breast cancer over that associated with the use of estrogen alone.

2. Raloxifene

In spite of a recent \$36 million settlement by Eli Lilly for “off-label” promotion, as a clinician who carefully follows category I literature, I cannot ignore the power of the MORE trial and the CORE trial when counseling my patients. Realize, in a double-blind, randomized, placebo-controlled trial of more than 7,700 postmenopausal women, those treated for 4 years with raloxifene had a 72% reduction in the incidence of new-onset breast cancers compared to placebo.⁵ That study was designed for osteoporosis *treatment* (although the NHANES III correction resulted in a sizable number being only osteopenic). The CORE extension of the MORE trial⁶ resulted in 8-year data. This held firm with a 66% reduction in new-onset breast cancer in raloxifene-treated patients versus placebo. Of course, the thromboembolic risk seen in MORE (approximately twofold) also held in CORE. Still, although raloxifene is *approved* as a medication for the prevention and treatment of osteoporosis, these extraskeletal

effects—mainly the huge reduction in new-onset breast cancers—must be factored in when choosing pharmacologic agents.

3. Shortcomings of bone mineral density measurements

Bone mass measurement, done by central dual-energy x-ray absorptiometry (DXA) scanning of the hip and spine, is used to diagnose osteoporosis. It is true and often quoted that for every reduction of one standard-deviation (SD) of bone mass (one number on the *T*-score) there will be a doubling of fracture risk. But this is the *relative risk* of fracture. If that is very low to start with, a doubling may still be quite low. Absolute fracture risk will be very age-dependent. For a number of reasons beyond the scope of this short piece, increasing age may arguably be among the most significant of risk factors for fracture. The 10-year probability of sustaining an osteoporotic fracture is about the same in a 50-year old with a *T*-score of -3 (something almost everyone would treat pharmacologically) as it is for an 80-year old with a *T*-score of -1 (something that many would triumphantly tell a patient is “normal bone”).^{7,8} Furthermore, *T*-score definitions of normal, osteopenic, and osteoporotic categories were developed by the World Health Organization to be used in *postmenopausal* women. They simply tell us bone mass, not necessarily bone quality. Thus, a 38-year-old who has convinced her primary care practitioner to inappropriately order a DXA scan and has a *T*-score of -2 has the same bone mass as a 65-year old with a *T*-score of -2, but entered menopause at age 50 with a *T*-score of 0. The bone mass of both of these patients is the same, but bone quality and fracture risk is very, very different. The bottom line is that we are not treating *T*-scores. We are trying to prevent fragility fracture.

4. The loss rate for amniocentesis

Although obviously not related to menopause, this fact is so new and clinically important, and so many physicians interested in menopause are obstetrician/gynecologists, that I could not help but include it. For 25 years we have quoted the loss rate associated with diagnostic

midtrimester amniocentesis as 1 in 200.⁹ I have always felt that amniocentesis was a safer, more forgiving procedure, dating back to the 1971 National Institutes of Health (NIH) consensus study in which the pregnancy loss rate for amniocentesis in 1,040 women was 3.2%. The pregnancy loss rate in 996 matched controls was also 3.2%. Thus, there was no increased loss. The 1 in 200 number (0.5%) comes from an averaging of the NIH consensus trial, the Canadian Collaborative study (0% increase) and the United Kingdom collaborative study (1.5% loss over baseline). Recently, in the FASTER trial, the amniocentesis associated loss rate was 0.15% (1 in 667).¹⁰ This corroborates something I have suspected for nearly 3 decades but had no modern data to support. I believe the potential clinical implications are huge. If amniocentesis is truly that safe, then the balance may shift once again toward its use, because amniocentesis yields actual chromosomes; the newly developed first trimester screening test assesses risk through ultrasound of the nuchal translucency, maternal age, and a finger-stick blood test of free human chorionic gonadotropin and pregnancy-associated plasma protein A. A report of a 1-in-1,000 risk of Down syndrome is not the same as seeing “normal chromosomes” on an amniocentesis report!

– Steven R. Goldstein, MD

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I've been asked to discuss the top four items that I have learned in the last several years from journals and from NAMS meetings. I would say that the number-one issue that was most important to me and my practice in that time period was Marion Limacher's point in her talk at the 2004 NAMS meeting that if one uses “years from menopause” instead of chronological age when assessing the risk of adverse cardiac events in the WHI, the results are quite different. Women who began their therapy with combined estrogen and progestin within 9 years of their last menstrual period actually had an 11% decrease in cardiac events rather than an increase. As about 99% of the estrogen plus progestin that I prescribe for women is initiated within that time period, this has made a difference in discussions of risk and benefit with patients. I have made a slide of Marion Limacher's data and use it when teaching.

A second and related concept, presented by Tom Clarkson at NAMS, also shows that the time of initiation of estrogen or estrogen plus progestin is of utmost importance when predicting outcome. He has presented basic science research showing that timing affects whether plaque will be prevented or will become unstable. This depends on many factors, but with HT, time of initiation is critical.

The third concept I would name is the excellent Quality of Life Index that Wulf Utian developed and presented at the NAMS meeting in 2002.¹ He published it in *Menopause* as



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well, which was most generous and helpful. For women in the postmenopausal years the issue of quality of life and the interpretation of their individual quality of life becomes one of the most important factors in their care.

Last, I would have to combine the presentations by Pauline Maki in 2004 and Victor Henderson and Kristine Yaffe (both in 2005)

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at NAMS meetings, which clarified many scientific findings to present a clearer picture of the difficult area of cognition and the effects of hormone therapy on cognition. Again, time of initiation of therapy seems to be an important consideration. It seems that before damage is done, in the brain as well as in the coronary vessels, prevention can occur with estrogen; once the cerebral vessels are changed, estrogen will not help, and might be harmful.

In general, I have found the NAMS meetings always to be up to date and timely. I've never missed a meeting and have always felt they are incredibly worthwhile.

– Lila E. Nachtigall, MD

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Thinking about the four most significant new things I have learned in the last several years about menopause has been a lot of fun as well as a challenge. The time limit in the question was especially difficult as I find it harder and harder to place things in time (in both my clinical and personal life). For me, learning about menopause has been a continuous process, combining what I learn from my patients, colleagues and the medical literature. In any case, here are my four choices:

1. Results of the estrogen-only arm of the WHI

The results of the estrogen-only arm of the WHI were published in April 2004.¹ Although this study did not get as much press as its predecessor study of estrogen and progesterone, the fact that estrogen alone did not increase the risk of either heart disease or breast cancer in study participants demanded that we reconsider what we thought we learned from the original WHI data. The estrogen-only study supported the notion that we do not yet know all there is to know about estrogen's role in the human female body. Although the women in the estrogen-only arm of the WHI are distinguished by the fact that they had had hysterectomies, this study guaranteed that there is more conversation to come about the risks and benefits of estrogen and progesterone. And for me, as a clinician, using estrogen alone over the long-term in women with hysterectomies now seems less scary.



Marcie K. Richardson, MD

2. Removing the ovaries in perimenopausal or postmenopausal women at hysterectomy

Many years ago at a NAMS meeting, Rogerio Lobo made a statement in a workshop that he did not generally remove the ovaries in a perimenopausal or postmenopausal woman at the time of hysterectomy. He justified this recommendation, which flew in the face of standard gynecologic teaching at the time, by pointing

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out that postmenopausal ovaries produce testosterone. In August 2005 Parker et al² published an article in *Obstetrics and Gynecology* that concluded: “Ovarian conservation until at least age 65 benefits long term survival for women of average risk for ovarian cancer at the time of hysterectomy for benign disease,” supporting this practice.

3. Ultra low-dose estrogen and bone effects

Published studies of low-dose estrogen first appeared in the 1990s and they continue to crop up. Several new low-dose formulations have made it onto the market. Bruce Ettinger and colleagues’ article about ultra low-dose estrogen and bone effects nudged this trend further.³ In practice, individual women can identify the dose of hormones that gives them the desired symptomatic relief and this is not infrequently less than the doses that have been studied. This does always involve patience, trial and error.

Ettinger summarized the data on lower-dose estrogen in his recent article in the *American Journal of Medicine*.⁴ Using lower and lower doses of estrogen with an individualized approach is the future of HT.

4. Postmenopausal sexuality

Learning about postmenopausal sexuality has been an exercise in frustration. Our understanding of the physiology of female sexuality is primitive. And a woman’s sexual experience is enormously complicated by psychological and social factors. As Ann Landers, among others, has said, “For women, the most important sex organ is the brain.” Postmenopausal female sexuality is always on the program at the

NAMS annual meetings, but the wonderful supplement in the journal *Menopause*, which was edited by Rosemary Basson,⁵ is a resource with which anyone interested in this field should familiarize themselves. It has taught me a lot.

Finally, I want to thank Dr. Utian and *Menopause Management* for giving me this opportunity to think about what I have learned, and I encourage our readers to do the same—and to come to the NAMS meeting this fall.

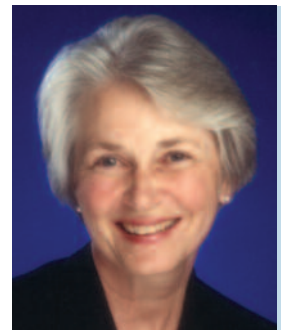
– Marcie K. Richardson, MD

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One of the important aspects of menopause I have come to realize over the last few years is that its timing and progression is driven not only by the ovary but also by central nervous system (CNS) mechanisms.¹ The recent Study of Women’s Health Across the Nation (SWAN) report,² which suggests that hypothalamic-pituitary sensitivity to estrogen feedback becomes blunted as women approach menopause, represents a unique contribution to this literature from a healthy population of women, and supports earlier findings in animal models.

This important finding, together with evidence pointing to the influence of severe stress exposure (abuse) on the timing of



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menopause,³ leads to the second significant new issue I wish to highlight: the mechanisms by which the social environments of women's lives may accelerate their reproductive aging

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processes via the CNS. Although one may not be inclined to link the experience of menopause to a growing body of literature on health disparities, I find myself wondering about how some of the differences in women's experiences of this transition may be better explained by integrative biobehavioral and social models than by biology alone.⁴

Recent research on symptoms has stimulated curiosity about those associated with chronic disease and disability—for example, joint pain and stiffness. Although these symptoms are not associated with progression through the menopausal transition,⁵ their prevalence is significant in the studies of community-based populations, including SWAN⁶ and the WHI participants.⁷ Moreover, these symptoms were among those that were significantly alleviated by the use of HT in the WHI treatment trial⁷ and in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.⁸ When women who were participants in the WHI trial discontinued HT, they experienced an increase in moderate or severe symptoms of pain and stiffness.⁹ Coupled with the earlier findings, these should encourage us to think about menopause as a period of transition that occurs within a much larger framework—that of aging.⁵ For this reason, NAMS' emphasis on

studying menopause *and beyond* seems extremely important.

Finally, we need to explore the symptom-management strategies that women use—and their inclination to adopt complementary and alternative medicine, despite a lack of efficacy data.^{10,11} We need to understand what there is about these therapies that make women see them as safe, natural and accessible in contrast to the traditional allopathic remedies. As black cohosh, soy products and other nutritional supplements become more commonly adopted for symptom management, we should be considering the impetus for women to choose these agents.

– Nancy F. Woods, PhD, RN, FAAN

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