

New estrogen guidelines: 2 experts give opposing views

Drs. Love and Notelovitz articulate different positions
and offer practice recommendations.

The decision by the US Food and Drug Administration (FDA) to put warning labels on all estrogen and estrogen-progestin products prescribed for postmenopausal women is startling—especially when you consider that barely a year ago, estrogen was viewed as a remedy or preventive for all kinds of ills.

This reversal in the official status of estrogen has created shock waves among Ob/Gyns still struggling to answer patients' questions and counsel them appropriately.

The FDA's role has been anything but passive; early this year, it issued several recommendations on the use of estrogen and estrogen-progestin hormone replacement therapy (HRT) by postmenopausal women. The FDA:

- acknowledged that estrogen and estrogen-progestin formulations remain the most effective treatment for hot flashes and night sweats caused by menopause, but counseled doctors to prescribe the lowest possible dose for the shortest duration.
- advised against using HRT to prevent cardiovascular disease.
- urged clinicians to consider approved non-estrogen



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agents when prescribing HRT to prevent menopause-induced osteoporosis, reserving estrogen for cases in which the risk of osteoporosis is greater than the risks associated with the therapy. (See related article "New options in osteoporosis therapy: combination and sequential treatment" on page 60.)

• recommended that, until more data become available, all estrogens—with or without a progestin—be presumed to carry risks similar to those observed for conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) in the Women's Health Initiative (WHI).

The best advice came from FDA Commissioner Mark McClellan, MD, PhD, who encouraged women to consult their physicians about the clinical implications of the WHI findings.

Although concrete data on the risks and benefits of estrogen have never been so substantial, considerable disagreement remains over how to proceed from here. To provide our readers with additional perspective

and insight, OBG MANAGEMENT asked 2 international experts, Dr. Morris Notelovitz and Dr. Susan Love, to offer their views on the WHI findings and other aspects of postmenopausal estrogen use.

—Robert L. Barbieri, MD
Editor-in-Chief

Beware of widespread preventive therapies

The recent FDA decision to require warning labels on all estrogen and estrogen-progestin products prescribed for postmenopausal women is a vindication for all of us who have been worried about the widespread use of these drugs for prevention. (Note that this article is not about symptom relief; short-term use of hormone therapy for this indication is a different discussion.)

Although many women and doctors were shocked by the data from the long-overdue randomized, controlled trials on the use of HRT for prevention, there were many others who cheered—not because of the findings, but because at last we were doing the kind of studies that would tell us whether the commonly held hypothesis about these drugs was true.

Those who are holding on to the fact that the WHI's estrogen-alone study has not yet been halted as evidence that progestin is the culprit should note that an increase in heart attacks and strokes has been seen in this cohort as well. The breast cancer risk may be less without the progestin, but many studies suggest that it certainly is not zero. Plus, the smaller size of the study means it would take longer to reach the same stopping goals. The risk-benefit ratio is likely to be similar to that for estrogen-progestin for most endpoints.

An abundance of observational data

Prior to the Heart and Estrogen-progestin Replacement Study (HERS) and WHI trials, only 1 long-term randomized, controlled trial had explored postmenopausal HRT, and it was too small to yield definitive data.^{1,3} The rest of the many studies looking at the benefits and risks of hormone therapy for prevention were based on observation. Indeed, the overwhelm-

ing majority of them demonstrated that HRT decreased heart disease.^{4,5} But these studies were still observational. Observational studies cannot prove cause and effect.

As we now know all too well, women who took postmenopausal HRT were, in general, of a higher socioeconomic level, better educated, and healthier than the women who did not.⁶ It was not a matter of hormones making women healthy, but rather, healthy women taking hormones.

Women who can generate as little as 5 pg/mL of their own estrogen have almost no fractures; these data suggest that we probably do not have to “replace” hormones in most women. —Dr. Love

In itself this is not surprising. Confounding is common in observational studies and is one of the reasons this research is better at driving hypotheses than proving cause and effect. Somehow, however, the number and consistency of these studies clouded our collective judgment and caused us to get ahead of the data. It is not the first time we have let this happen, and I am sure it will not be the last.

In breast cancer, for example, the use of high-dose chemotherapy with stem-cell rescue became the standard of care before there were any randomized data demonstrating its value. When the randomized studies did finally come in, many clinicians were surprised to find that this aggressive regimen was no better than standard therapy and had worse side effects.⁷ Now, the use of this therapy has virtually ceased.

It would behoove us to follow this lead in

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Exercise prescriptions should replace hormones, and weight should be monitored rather than bone density in a woman in her 50s. —Dr. Love

the use of hormones for prevention. In a recent analysis at the National Cancer Institute meeting on HRT, Deborah Grady could find no subgroup, including women with an osteoporotic fracture, where the benefits outweighed the risk.⁸

Risks of rushing to substitute

What should we do? Many clinicians may wish to quickly find something else to give women—be it selective estrogen receptor modulators, bisphosphonates, or bio-identical hormones. In my view, that misses the point. This new data on postmenopausal hormone therapy should cause us to question the hypothesis upon which its use was based.

Perhaps we do not have to treat postmenopausal women with anything. Rather than equate menopause with ovarian failure or estrogen deficiency, perhaps we can regard it as the natural progression of a woman's life. New studies indicate that postmenopausal women who are able to generate as little as 5 pg or more of their own estrogen per milliliter of serum have almost no fractures; these data suggest that we probably do not have to "replace" hormones in the majority of women.⁹

In addition, the data suggest that age is a more potent predictor of fracture risk than bone density.¹⁰ Many experts are suggesting that osteopenia should not be treated and that bone density should not be measured until age 65.

Deaths from heart disease are at all-time lows due mostly to improved treatment techniques rather than prevention.¹¹

Lifestyle changes are still the best prevention

I would suggest that the warning label on the estrogen and estrogen-progestin formulations be viewed as a caution against the whole

concept of widespread use of drugs in healthy women for prevention. Lifestyle changes remain the best way to maintain quality of life and prevent the diseases of aging. Weight control, exercise, diet, and not smoking are still the safest approaches to a healthy life.

Rather than continue this debate, we should put our energies into devising strategies to help women achieve healthy lifestyle goals. Exercise prescriptions should be the replacement for hormones, and weight should be monitored rather than bone density in a woman in her 50s. Advice about smoking cessation needs to take the place of discussions of breast self-exam.

My hope is that this warning will serve as a wake-up call for all who care for women.

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Estrogen is a valid option when prescribed correctly

Women are living longer, but not necessarily better. Increases in longevity are partially offset by a greater prevalence of chronic conditions such as osteoporosis, cardiovascular disease, cognitive dysfunction, and breast cancer—all of which impact a woman's quality of life. HRT is a logical outgrowth of this increased longevity.

Unfortunately, while it represents an attempt to improve the health and well-being of postmenopausal women, HRT is based upon a faulty premise: that all women are biologically equal and react similarly to the menopausal transition. Equally erroneous are 2 corollaries: that all menopausal women will respond to the same dose of HRT and that all estrogen formulations are comparable.

As has become clear, this generic approach to menopause is inappropriate. The convenient but simplistic strategy of treating all women at and beyond menopause with a standard dose of the same estrogen-progestin formulation is ill-founded. Estrogen offers the postmenopausal patient numerous benefits and needs to remain an important part of the Ob/Gyn's options. However, it can no longer be prescribed in the "traditional" manner.

The trouble with tradition

Here are 2 problems with the conventional approach:

- Every woman synthesizes estrogen differently, depending on the endocrinology of her nonreproductive organs in the premenopausal, perimenopausal, and postmenopausal periods; the pathogenesis of conditions such as cardiovascular disease and their relationship to estrogen and androgen synthesis and metabolism; and the pharmacokinetic and pharmacodynamic variance between HRT formulations.^{1,2}

- Women are encouraged to have annual examinations, yet a review of the type and dose of HRT rarely takes place at these exams.

New strategy: *Replenish hormones to age 65, maintain thereafter*

Women need "individualized and adjusted hormone therapy." This is relevant for patients 35 to 65 years of age and is based on our ability to tailor the type and route of hormone therapy to approximate the hormonal milieu of women at a given age. The term "HRT"—which I define as the attempt to replicate a premenopausal woman's hormonal milieu—should be restricted to women who are between the ages of 35 and 45 who need hormone therapy. After that, hormone *replenishment* should be practiced until age 65. Based on the pharmacokinetics of estrogen, HRT is best achieved by non-oral estradiol; hormone replenishment relies on the bioconversion of estradiol to estrone after oral estrogen and the "normal" postmenopausal estrone:estradiol ratio. Hormone *maintenance* refers to women who have been stabilized on a prior hormonal regimen. They should be left on their current medication as long as there is still an indication for hormone therapy.

The type, dose, and route of this therapy should be regularly reviewed and adjusted, if necessary, as a woman's needs change over time.

Estrogen synthesis and metabolism.

Only 2 bioavailable estrogens are synthesized in postmenopausal women: estradiol and estrone. Both are derived from the aromatization of androgens in adipose tissue and muscle and are further metabolized by the liver. The aromatization of androgens to estrogens occurs in tissues such as breast, bone, and coronary artery, and the local concentration far ex-

ceeds that measured in the peripheral circulation. The estrogen synthesized locally and the metabolites produced by the liver can have protective effects (increased bone density) or potentially harmful effects (breast cancer), even though serum estradiol may be within a “normal” range (i.e., less than 20 pg per deciliter).

The synthesis and metabolism of estrogen are genetically controlled. For example, the genes determine whether a woman has a high risk of breast cancer. Therefore, clinicians should select the dose and route of estrogen administration that would optimize the benefit and limit the risk of hormone therapy. This will be different in each woman. (Although most postmenopausal women can safely take hormones, some may have an endogenous abnormality that precludes the therapy.)

Fraction of dose may relieve symptoms. The estrogen threshold for the relief of hot flashes—HRT’s main indication—also varies among women. One half to one quarter of the “standard” dose (0.625 mg per day of CEE)—the amount prescribed in the WHI³—has been shown to be effective.

The long trajectory of ‘menopausal’ diseases

The pathogenesis of osteoporosis and cardiovascular disease—conditions for which long-term HRT has been advocated—commences with the first menstrual period (FIGURE). Thus, primary prevention should begin in early adulthood. This includes diet and lifestyle modifications and exercise. Normal ovarian function is essential, as anovulatory hypoestrogenic disorders predispose young women to a greater risk of these conditions later in life.

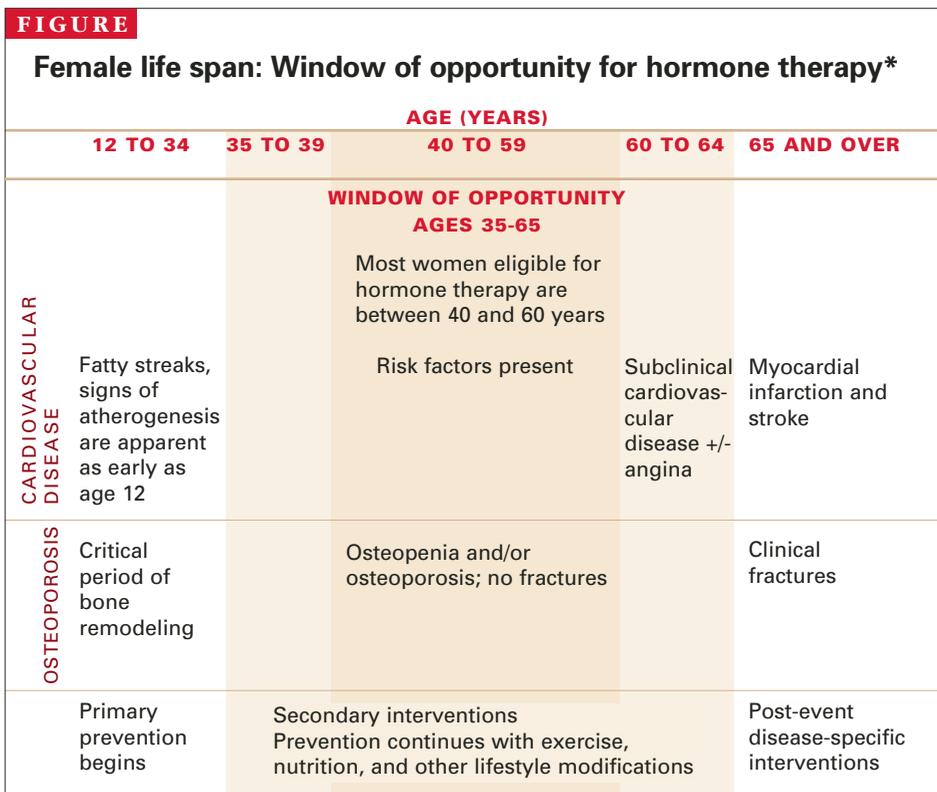
Endogenous estrogen’s protective effect is based on the presence of estrogen—and androgen—receptors in bone (e.g., osteoblasts, osteoclasts)

and in the coronary artery (e.g., endothelium, smooth muscle) and liver. As estrogen levels decline, bone remodeling accelerates and bone mineral is lost; the process of atherothrombosis also accelerates. Given the multifactorial nature of these conditions, estrogen therapy plays an important role in stabilizing bone loss and halting the progression of atheromatosis, both at menopause and at other times when a lack of estrogen is a relevant causative factor. When bone loss is due to hyperthyroidism or when cardiovascular disease is associated with dyslipidemia, hypertension or diabetes, disease-specific treatment is needed.

Individualizing HRT to condition and severity

As for HRT, the dosage and type need to be judged according to each clinical situation and degree of abnormality. For example, a lower dose of estrogen is required when a woman has osteopenia than when she has osteoporosis. Transdermal estrogen is the best option for a woman with elevated serum triglycerides or C-reactive protein (a cardiac

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*Shaded area shows window of opportunity.

inflammatory biomarker). Women with low levels of high-density-lipoprotein cholesterol will benefit from oral estrogen.

Measurement is central to this approach. Without a mammogram, breast density (a sign of local estrogen biosynthesis) cannot be documented or quantified. A bone-density test (with bone markers) is needed to assess bone health; a fasting lipid profile (including glucose) and possibly a C-reactive protein assay are the only means of assessing the patient's cardiovascular disease risk status.

Prescribe lowest dose and monitor.

Clinicians should prescribe the lowest estrogen dose and then monitor therapy. This entails measuring baseline serum estradiol and conducting meaningful posttreatment monitoring, best achieved with 17 β -estradiol-based products (oral or transdermal). A total serum estradiol value of 40 to 80 pg per milliliter has been found effective in controlling bone loss, coronary artery vasoreactivity, and cognition. The late initiation of hormone therapy is not recommended, since estrogen may disrupt the fibrin capsule of arterial intimal plaques and precipitate thrombosis with vascular luminal occlusion and myocardial infarction or stroke.

Not all hormones are the same

Not all estrogens or progestins are equal in their formulation, pharmacologic properties, or function. As noted previously, nonpregnant women synthesize only 2 bioavailable estrogens: estradiol and estrone. Pharmacologic preparations of 17 β -estradiol have properties similar to those of endogenous estrogen. Depending on the dose and route of administration, they can, to a certain degree, replicate a premenopausal or postmenopausal estrogen milieu. CEE, the preparation used in the WHI, contains 10 estrogens and 200 metabolites, with varying degrees of estrogenic and antiestrogenic activity. Thus, it is not possible to monitor posttreatment estradiol values.

It is significant that only the estrogen-progestin arm of the WHI was suspended.

This suggests that MPA, the progestin in the combination therapy used in the trial, may be responsible for the unwanted results. There are a number of pharmacologic differences between MPA, natural progesterone, and the 19-nor-testosterone-derived progestins (e.g., norethindrone acetate [NETA]). In addition, the half-life of MPA (24 hours) greatly exceeds that of progesterone (12 hours) and NETA (6 to 8 hours), thus potentially down-regulating estrogen receptors in vital blood vessels that may already be compromised.

Putting the WHI in perspective

The WHI was planned as a primary cardiovascular-disease-prevention trial. Of the women enrolled in the study, 45.3% were 60 to 69 years of age, and 21.3% were 70 to 79. Thus, given the pathogenesis of cardiovascular disease, most subjects had some degree of coronary artery disease at the start of the study. Yet only 37 hormone-group subjects versus 30 placebo-group subjects per 10,000 women annually experienced an adverse clinical cardiovascular event. Except for year 5, the ratio of such adverse events in the hormone group decreased over time, compared with women in the placebo group. The HRT:placebo ratios of these events for years 1 through 6 were 1.78, 1.15, 1.06, 0.99, 2.38, and 0.78, respectively. (The unexpected jump in the event ratio in year 5 was due to an unexplained paucity of events in the placebo group and not an increase in the group of subjects treated with hormone therapy.)

The WHI definition of “healthy postmenopausal woman” ignored the heterogeneity of the climacteric by assuming that all women were biologically equal and that age had not added its toll in organ damage. In a parallel observational arm of the WHI, C-reactive protein independently predicted vascular events among healthy postmenopausal women, but this was related to baseline levels of the inflammatory biomarkers and not to the hormone-therapy-related increase in C-reactive

protein. The same is true for the stated increased risk of HRT-related breast cancer: 35 versus 30 events annually per 10,000 women on HRT and placebo, respectively. What differentiated the 35 who developed breast cancer from the 9,965 who did not?

Clinical challenge: Not to withhold HRT, but to identify women at risk

As clinicians, we must strive not to deny HRT to women who could safely benefit from it, but to develop cost-effective strategies to differentiate healthy women from those with metabolic dysfunction (e.g., premammographic breast cancer) and asymptomatic latent disease (e.g., silent atherosclerosis). “Normal” women will benefit from selective HRT; the latter require medications specific to their underlying disorder.

In the aftermath of the WHI, the scope of the HRT problem has been overblown. When the absolute-risk numbers for HRT-related cardiovascular disease and breast cancer are extrapolated to the nation, the perceived size of the problem—which is only a mathematical projection and estimate—can assume troubling proportions. But physicians in clinical practice have only 1 responsibility: ensuring the health and well-being of their patients, 1 at a time. Thus, the question of HRT must be resolved between the physician and the patient. This takes time—time to talk with, examine, and test the patient; time to think through the problem; and time to prescribe and educate the patient regarding her therapeutic needs. This is time well spent. ■

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