EDITORIAL

ROBERT L. BARBIERI, MD
■ Editor-in-Chief

OBG MANAGEMENT

Warning: the estrogen product you are about to prescribe...

The status of hormone replacement therapy (HRT) changed forever in July 2002, when the estrogen-progestin arm of the Women's Health Initiative (WHI) was halted. As you undoubtedly recall, that trial concluded that, among postmenopausal women, the risks of HRT—most notably heart disease, stroke, and breast cancer—exceed the benefits.[1]

Under instruction from the US Food and Drug Administration (FDA), Wyeth Pharmaceuticals (*Collegeville, Pa*)—the manufacturer of the estrogen-progestin formulation used in the WHI trial—changed its labeling in August to reflect these findings. But now, thanks to new labeling requirements unveiled by the FDA last month, all menopausal medications that contain estrogen (alone or in combination with a progestin) will have to include a boxed warning—the highest level of warning information—to highlight the increased risk for heart attack, stroke, and breast cancer.

> The agency's position that the findings of the WHI should be extended to all estrogen preparations is shaky scientifically.

A valid decision?

According to an FDA press release, the new labeling was mandated to "emphasize individualized decisions that appropriately balance the benefits and the potential risks of these products."[2] But the agency's position that the findings of the WHI should be extended to all estrogen preparations—whether or not they contain a progestin—is shaky scientifically. After all, the mere fact that the estrogen-only arm of the WHI continues implies that it is associated with a pattern of benefits and risks superior to that of the estrogen-progestin arm.

Based on multiple clinical trials, including the WHI, most experts agree that for menopausal women, oral estrogen—alone or combined with a progestin—should not be used for the primary or secondary prevention of heart disease. However, there is greater complexity and a broader range of opinions concerning the use of estrogen-progestin for the treatment of vasomotor symptoms, vaginal and vulvar atrophy, and osteoporosis. One reason for the complexity is the fact that clinicians and menopausal patients inevitably vary in the values they place on the intricate pattern of benefits and risks associated with HRT.

New treatment recommendations

Operating from a risk-averse viewpoint, the FDA advises the following:

- For menopausal women, when oral estrogen-progestin has been prescribed solely for the prevention of osteoporosis, alternatives such as exercise, vitamin D and calcium, bisphosphonates, raloxifene, and calcitonin should be considered. "Estrogens and combined estrogen-progestin products should only be considered for women with signifi-

CONTINUED

cant risk of osteoporosis that outweighs the risks of the drug," the FDA notes.[2]

- When estrogen-progestins are prescribed solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Estrogens and estrogen-progestins are the best pharmacologic treatments available for vasomotor symptoms and insomnia associated with hypoestrogenism. However, for this indication, clinicians should use the "lowest dose" for the "shortest duration for the individual woman" to reach treatment goals.[2] Prescribers are left to deduce the meaning of "lowest dose" and "shortest duration." Whatever the interpretation, changes in current practice will be required.

Applying the guidelines

For menopausal women with vasomotor symptoms, many clinicians will initiate a standard dose of estrogen, such as conjugated equine estrogen (CEE) 0.625 mg. Let's assume that the dose is effective in relieving vasomotor symptoms. How will the physician know whether it is the lowest effective dose? He or she may need to consider titrating the dose downward—until vasomotor symptoms begin to recur. Alternatively, some clinicians may start with a very low dose (CEE 0.3 mg or less) and titrate upward until sufficient relief from vasomotor symptoms is obtained. These doses are likely to vary considerably among individual patients.

Patient characteristics also will influence the lowest possible dose effective for the treatment of hot flashes. For example, women who drink significant quantities of alcohol can probably adjust their estrogen dose downward by as much as 50%, because ethanol alters the metabolism of oral estrogen. If clinicians and patients widely accept the concept of "lowest possible dose," we are likely to see an increase in the number of women using minimal daily doses of estrogen, such as CEE (0.3 mg), transdermal patches (25 μg), and oral estradiol (0.5 mg).

In the short term, the relabeling of all estrogen and estrogen-progestin hormone replacement regimens is likely to increase the frequency and intensity of patient consultations concerning proper management of the menopause. Individualizing treatment to the unique needs of each woman will continue to be the cornerstone of that management. ■

REFERENCES

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2002;288:321-333.
2. US Food and Drug Administration. FDA approves new labels for estrogen and estrogen with progestin therapies for postmenopausal women following review of Women's Health Initiative data. *FDA News*. January 8, 2003. Available at: www.fda.gov/bbs/topics/NEWS/2003/NEW00863.html. Accessed January 13, 2003.

Next month:
more on the new FDA labeling requirements

Are the new boxed warning label regulations a sound decision in light of recent findings—or an overreaction based on inadequate data? In the March issue of **OBG MANAGEMENT** 2 experts offer opposing views.

SHARE YOUR THOUGHTS!

Do you feel the FDA's decision is a well-founded attempt to protect our patients? Or is the administration jumping to conclusions in the wake of a sensational story?

Send us your thoughts via
E-mail: obg@dowdenhealth.com
Fax: (201) 391-2778
or mail: OBG MANAGEMENT
110 Summit Avenue
Montvale, NJ 07645