EDITORIAL

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

OBG MANAGEMENT

Unique hormone regimens, unique clinical effects

Recent reports from the Women's Health Initiative (WHI) amply confirm the long-held suspicion that different postmenopausal regimens (eg, estrogen-progestin and estrogen-only) have unique clinical effects.

Regimens vary by the specific chemistry of the estrogen (estradiol, estrone, estrone sulfate, equine estrogens, etc) and/or progestin (C-19 progestin, C-21, etc), dosage, route (oral, topical, vaginal, injection, nasal) and timing (continuous, cyclic, sequential).

Although the WHI final data are not yet published or available for detailed review and critique, the available summary indicates that an estrogen-only regimen of 0.625 mg daily conjugated equine estrogen has dramatically different clinical effects than an estrogen-progestin regimen containing the same estrogen given in the same dose, by the same route. **In July 2002, the WHI stopped the estrogen-progestin arm**, in which 0.625 mg daily of conjugated equine estrogen and 2.5 mg daily of medroxyprogesterone acetate were administered to menopausal women who were an average age of 63 years at entry. The trial was stopped because, at that point, it demonstrated that, compared with placebo, estrogen-progestin treatment was associated with a significant increase in the rate of breast cancer (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.00-1.59) and an increase in the rate of coronary heart disease events (HR 1.29, 95% CI 1.02-1.63).[1] Follow-up analyses indicated that an increased rate of breast cancer was observed for both total breast cancer (HR 1.24, 95% CI 1.02-1.50) and invasive breast cancer (HR 1.24, 95% CI 1.01-1.54). The invasive breast cancers in the estrogen-progestin group were larger (1.7 cm versus 1.5 cm, $P = .04$) and more likely to be lymph-node positive (26% versus 16%, $P = .03$) at diagnosis than in the placebo group.[2]

In March 2004, the WHI stopped the estrogen-only arm (conjugated equine estrogen 0.625 mg daily) because the 7 years of follow-up demonstrated no cardioprotective effects. Also, a slight increase in the risk of stroke was observed. A noteworthy finding was that estrogen-only treatment was not associated with either an increased risk of breast cancer or an increased risk of coronary heart disease.

The estrogen-only arm of the WHI had sufficient statistical power to detect differences in breast cancer and heart disease as small as those observed in the estrogen-progestin study—which suggests that estrogen-only has a relatively benign side-effect profile on the heart and breast compared to estrogen-progestin treatment. It appears that it is the progestin or an interaction between estrogen and progestin—not estrogen alone—that is responsible for the increase in the risk for breast cancer and heart disease in women receiving estrogen-progestin.

This finding has important implications for Food and Drug Administration (FDA) policy and challenges clinicians to reexamine the hormone treatment they use in practice.

TABLE

Clinical effects of oral estrogen-progestin and oral estrogen-only therapy based on the Women's Health Initiative findings

	ORAL ESTROGEN-PROGESTIN*	ORAL ESTROGEN-ONLY†
Breast cancer	Significant increased risk	Study did not detect an increased risk
Coronary heart disease events	Significant increased risk	Study did not detect an increased risk
Hip fractures	Decreased risk	Decreased risk
Stroke	Increased risk	Increased risk

*Conjugated equine estrogen 0.625 mg/2.5 mg medroxyprogesterone acetate daily
†Conjugated equine estrogen 0.625 mg daily

Revised FDA warning needed. In August 2002, the FDA required all menopausal medications that contain estrogen (alone or in combination with a progestin) to carry a black box warning—the highest level of warning—that menopausal hormone treatment is associated with an increased risk for heart attack, stroke, and breast cancer.

When the FDA adopted this policy, we noted that the agency's decision to extend the estrogen-progestin findings to all estrogen-only regimens and all progestin medications was not scientifically sound. Based on the most recent WHI findings, the FDA should limit the warning about heart attack, stroke, and breast cancer to estrogen-progestin combinations, and develop alternative language to balance the benefits and risks of estrogen-only treatment.

Implications of recent WHI findings. For clinicians, the recent findings require a thorough reassessment of hormone regimens used in practice. It seems the estrogen-only regimen has a safety profile that is superior to the estrogen-progestin regimen (TABLE). Consequently, it would appear that all hysterectomized women who are using hormone therapy should consider using an estrogen-only regimen, not an estrogen-progestin regimen.

In addition, the WHI provides clear support for the hypothesis that each preparation of estrogen and each estrogen-progestin regimen may have unique clinical effects.

The search is far from over for the estrogen and progestin preparations with the greatest safety and efficacy and for the lowest effective dose. Meanwhile, in light of these findings, clinicians will continue to individualize hormone treatment to each woman's unique clinical situation, and will continue to rely on the time-tested tenet: Treat with the lowest effective dose for the shortest time needed to relieve symptoms.

obg@dowdenhealth.com

REFERENCES

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2. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. *JAMA*. 2003; 289:3243-3253.