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OBG MANAGEMENT

From the Women's Health Initiative to clinical practice: A 5-point plan

A seasoned physician offers practical guidance on postmenopausal use of estrogen and progesterone.

After our usual Saturday morning match, my tennis partner asked if I still prescribed estrogen and progestin therapy (EPT) for menopausal women. He had, of course, seen recent reports of the Women's Health Initiative (WHI) findings (**TABLES 1 and 2**).[1]

I replied that most of my symptomatic postmenopausal patients continued taking estrogen therapy (ET) or EPT. Still, I understood the concern that prompted the question.

After the WHI findings became widely publicized, many women discontinued EPT—only to resume therapy 8 to 10 weeks later because of persistent vasomotor symptoms. A number of other postmenopausal women, however, were able to cope with the transient recurrence of menopausal symptoms. I was happy to encourage them to permanently discontinue ET/EPT, since the primary reason for starting the therapy (vasomotor symptoms) was no longer an issue and the secondary reason (long-term benefits originally attributed to therapy with estrogen and progestin) had been seriously challenged.

This article discusses the American College of Obstetricians and Gynecologists guidelines on ET/EPT,[2] and includes 5 specific pointers on managing menopausal women at risk for osteoporosis, breast cancer, and cardiovascular disease.

The bottom line: The WHI has significantly affected clinical practice, but hormone use is not precluded in symptomatic postmenopausal women, whose distressing symptoms and quality of life are improved by EPT.

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1. Individualize treatment

In the realm of estrogen therapy, 1 size does not fit all. Women tolerate and respond differently to various preparations and doses. I

KEY POINTS

- Give estrogen and estrogen-progestin therapy only for the relief of significant vasomotor symptoms, and halt the therapy in all asymptomatic women.
- Prescribe natural estrogens and progesterone whenever possible and measure serum levels to assess response and compliance.
- Initiate therapy at a dose of 0.3 mg for conjugated equine estrogen, 0.5 mg for oral estradiol, and 0.035 mg for transdermal estradiol and progressively increase, if necessary, to no more than twice these amounts.
- Give progesterone cyclically rather than continuously to reduce risk of cardiovascular disease, breast cancer, other adverse events.
- Reassess regimens annually in each patient.

tend to use estradiol and micronized progesterone as much as possible because I believe they may be safer. With natural hormones it also is easier to measure serum levels; this helps me assess a patient's response to and compliance with therapy.

I prefer the transdermal preparation consisting of estradiol/norethindrone acetate (CombiPatch) because it is more physiologic and yields constant serum levels throughout the 24-hour day. In addition, it avoids the first pass through the liver, which is associated with nonphysiologic alteration of hepatic enzymes and proteins—especially binding globulins for steroids, thyroid and sex hormones, and coagulation factors.

2. Use the lowest effective dose to achieve benefits and avoid side effects

This is a critical recommendation. Although this rule should apply to all therapies, it is especially important for ET/EPT, which can be associated with life-threatening side effects.

In a prospective, observational study conducted in healthy postmenopausal women, Grodstein et al[3] explored primary prevention of cardiovascular disease. They found that the relative risk of stroke rose with each incremental increase in the dose of unopposed conjugated equine estrogen (CEE). The relative risk of stroke with CEE at a daily dose of 0.3 mg, 0.625 mg, and 1.25 mg was 0.54 (95% confidence interval [CI], 0.28–1.06), 1.35 (95% CI, 1.08–1.68), and 1.63 (95% CI, 1.18–2.26), respectively. Thus, the lowest effective dose at initiation would be 0.3 mg for CEE. Comparable doses for oral estradiol and transdermal estradiol are 0.5 mg and 0.035 mg, respectively.

This dose may be progressively increased according to the patient's response, but seldom should exceed double the starting dose. Similar guidelines should be followed for progestins.

TABLE 1

Relative risk of selected adverse events in women taking estrogen-progestin therapy[1]

EVENT	RELATIVE RISK	CONFIDENCE INTERVAL	STATISTICAL SIGNIFICANCE
Coronary heart disease	1.29	1.02–1.63	Yes
Stroke	1.41	1.07–1.85	Yes
Breast cancer	1.26	1.00–1.59	Yes
Pulmonary embolism	2.13	1.39–3.25	Yes
Endometrial cancer	0.83	0.47–1.47	No
Hip fracture	0.66	0.45–0.98	Yes
Colorectal cancer	0.63	0.43–0.92	Yes
Deep venous thrombosis	2.07	1.49–2.87	Yes
Vertebral fractures	0.66	0.44–0.98	Yes
Other osteoporotic fractures	0.77	0.69–0.86	Yes
Global index	1.15	1.03–1.28	Yes

3. Consider minimizing duration of progestin treatment

Prescribe ET for hysterectomized women and EPT for those with a uterus. This may seem like old advice, since all gynecologists know the importance of using EPT in women with a uterus. But the optimal formulation and administration of EPT remain elusive. It is now clear that not all progestins have the same physiologic effects—especially on cardiovascular health (see page 74). For this reason, the type, sequence, dose, and duration of progestin administration should be carefully reevaluated.

Daily progestin is not physiologic. When it first became evident that unopposed estrogen causes endometrial cancer in women with a uterus, progestins were administered for 7, 10, or 12 days each month, usually in the form of medroxyprogesterone acetate (MPA), mimicking the cyclic production of progesterone by the premenopausal ovary. Although this regimen was effective in protecting against endometrial cancer, the cyclic administration of EPT induced undesirable uterine bleeding, which caused many women to stop the therapy. To avoid cyclic bleeding and improve compliance, continuous combined EPT preparations were introduced, which involved daily exposure to progestin—a level that is clearly not physiologic.

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TABLE 2

Number of selected adverse events per 10,000 woman-years[1]*

EVENT	PLACEBO (N = 8,102)	CEE/MPA (N = 8,506)	DELTA
Coronary heart disease	30	37	7
Stroke	21	29	9
Breast cancer	30	38	8
Pulmonary embolism	8	16	8
Endometrial cancer	6	5	-1
Hip fracture	15	10	-5
Colorectal cancer	16	10	-6
Deep venous thrombosis†	3	26	16
Vertebral fractures†	15	9	-6
Other osteoporotic fractures†	170	131	-49
Global index	151	170	19

CEE = conjugated equine estrogen
MPA = medroxyprogesterone acetate
*Absolute risk
†Not included in global index

Has estrogen changed? Why the Women's Health Initiative confounded expectations

Prior to the Women's Health Initiative (WHI), estrogen therapy (ET) and estrogen-progestin therapy (EPT) were widely assumed to protect against cardiovascular disease. This assumption had been substantiated by epidemiologic studies, as well as experimental and clinical trials, which consistently reported that ET/EPT had beneficial effects on the lipid profile. Also noted were direct effects on vessel walls, evident in decreasing arteriosclerosis and increased vasodilatation.[1] Were all these studies erroneous? Or is there an explanation for both pre- and post-WHI findings?

Observational studies are somewhat notorious for selection and compliance biases. Women who take hormones generally are healthier, better educated, and wealthier than nonusers; they also have fewer coronary risk factors. Thus, the favorable outcomes observed with ET and EPT may have simply reflected these women's greater health at baseline. But I don't think so.

Although these confounding factors may have exaggerated the benefits of ET/EPT, it is unlikely that they masked the increased risk observed with the WHI and other recently published prospective, randomized studies, such as the Heart and Estrogen/progestin Replacement Study (HERS)[2] and the Women's Estrogen for Stroke Trial (WEST).[3] Moreover, the other benefits (osteoporosis and colon cancer protection) and risks (thromboembolic events and breast cancer) previously reported in observational studies have been appropriately confirmed by prospective, randomized studies. Only the cardiovascular benefits have not. Instead, they have been completely negated. Why?

There is no clear answer, but 1 explanation may be that the significant improvement in cardiovascular health care for women over the past 2 decades has obscured the cardiovascular benefits of EPT manifested 15 years ago in epidemiologic studies.

Indeed, 20 and 30 years ago, cardiovascular disease was considered a disease of men; very few women were evaluated or treated for hypertension or hyperlipidemia, 2 major cardiovascular disease risk factors. In women, ET/EPT may have been therapeutic, either indirectly by improving the lipid profile or directly by decreasing plaque formation and inducing vasodilatation through regulation of nitric oxide, prostaglandin synthetase, and membrane ionic permeability.[1]

During the past 15 years, women's health care has changed greatly. Women who have hypertension or hyperlipidemia—especially those who participate in clinical trials[2-4]—are commonly treated with potent lipid-lowering agents and antihypertensive medications. These agents' protective effects against cardiovascular disease would obscure any potential vascular benefits of ET/EPT. Consequently, only the adverse vascular effects of ET/EPT would be noted, since its potential benefits would have been usurped by the stronger cardiotropic statins and antihypertensive drugs.

Consider this corollary: Had the WHI patients at risk for fracture been treated with bisphosphonates, I doubt very much that the protective effects of ET/EPT on bone would have been noted. This hypothesis is supported by the recent Estrogen in the Prevention of Atherosclerosis Trial.[5] In this prospective study, 222 postmenopausal women with low-density lipoprotein

Because it appears from the WHI study that progestins may be mostly responsible for the increased risks of cardiovascular disease, stroke, and breast cancer—since the estrogen-alone arm of the trial continues—it may be prudent to minimize the duration of progestin treatment in postmenopausal women. Several studies have demonstrated that the cyclic administration of progestin for 2 weeks every 2 to 3 months may be as protective against endometrial cancer as monthly administration.[4-6] Moreover, if they receive the lowest effective dose of daily estrogen (as outlined above) and bi- or tri-monthly cyclic

cholesterol levels in excess of 130 mg/dL were randomized to receive either 17-ß estradiol or placebo and were angiographically monitored for progression of coronary atherosclerosis.

The results revealed that the women randomized to 17-ß estradiol experienced significantly less progression of atherosclerosis than the placebo group. However, in those study patients who were also taking lipid-lowering therapy (statins), 17-ß estradiol did not confer additional benefits on coronary atherosclerosis.

It appears, then, that ET/EPT served its purpose for cardiovascular protection when there was a need for it—prior to the widespread use of cardioprotective agents. Now, with vastly improved women's health care, ET/EPT for cardiovascular protection is neither needed nor safe.

Role of progestin. The fact that the estrogen-only arm of the WHI has not been interrupted supports the hypothesis that the progestin in the EPT preparation is mostly responsible for the increased risk of breast cancer and atherosclerosis, including coronary heart disease and stroke.

Moreover, medroxyprogesterone acetate (MPA)—the progestin used in the WHI—may be key to the cardiovascular risks[6] observed in the trial. A different progestin, such as micronized progesterone or norethindrone acetate, may not confer similar risks.[7] Indeed, the Postmenopausal Estrogen/Progestin Interventions study found that the addition of MPA to conjugated equine estrogen in postmenopausal women negated some of the beneficial effects of conjugated equine estrogen on the lipid profile, whereas the addition of micronized progesterone did not.[8]

Moreover, animal studies have found that MPA[6]—but not norethindrone acetate[9] or micronized progesterone—negates the beneficial effects of estrogen on coronary plaque formation. Thus, it appears that different progestins have variable effects on atherosclerosis and that, among the various clinically available progestins, MPA may be particularly deleterious to cardiovascular health. Unfortunately, the results of these animal studies may not apply to humans. Still, they should serve as hypotheses for future prospective, randomized clinical trials.

Whether the WHI findings can be generalized to other hormone preparations is unclear. At present, the burden of proof for greater safety and efficacy lies with the sponsors of the other products.

REFERENCES

1. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. *FASEB J*. 1996;10:615-624.
2. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in menopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;280:605-613.
3. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen replacement therapy after ischemic stroke. *N Engl J Med*. 2001;345:1243-1249.
4. 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 control trial. *JAMA*. 2002;288:321-323.
5. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis. *Ann Intern Med*. 2001;135:939-953.
6. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Artherioscler Thromb Vasc Biol*. 1997;17:217-221.
7. Riis BJ, Lehmann HJ, Christiansen C. Norethisterone acetate in combination with estrogen: effects on the skeleton and other organs. *Am J Obstet Gynecol*. 2002;187:1101-1116.
8. Alexanderson P, Haarbo J, Sandholdt I, Shalmi M, Lawaetz H, Christiansen C. Norethindrone acetate enhances the antiatherogenic effect of 17-beta-estradiol: a secondary prevention study of aortic atherosclerosis in ovariectomized cholesterol-fed rabbits. *Arterioscler Thromb Vasc Biol*. 1998;18:902-907.
9. The Writing group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA*. 1995;273:199-208.

progesterone, most women will experience little or no bleeding.

4. Stop long-term, fixed-dose EPT in asymptomatic women

Also eliminate its use for cardiovascular protection. Asymptomatic women do not need—nor will they benefit from—ET/EPT, so there is no reason to use it. EPT's potential benefit in terms of bone loss and fractures can be achieved with other agents that are FDA-approved for the prevention of osteoporosis but carry less risk of breast cancer, cardiovascular disease, or thromboembolic events.

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Overview and implications of Women's Health Initiative data

During an interim analysis of the Women's Health Initiative (WHI) estrogen-progestin arm, the data safety monitoring board determined that estrogen and progestin therapy (EPT) had a greater potential for harm than for benefit. So on July 9, 2002, after an average of 5.2 years of observation, that arm was halted.[1]

The other arm of the trial continued to examine the use of unopposed estrogen in hysterectomized women. The fact that it continues suggests that its global index is still not definitively unfavorable.

At the time the EPT arm was halted, its participants had an increased incidence of 26% for breast cancer, 41% for stroke, 29% for coronary heart disease events, and 110% for thromboembolic events, compared with the placebo group. On the benefit side, they experienced a 37% reduction in colorectal cancer and a 34% reduction in hip fractures. These reductions were not sufficient to offset the increased risk **(TABLES 1 and 2)**. There was no difference in mortality rates between the EPT and placebo groups.

Absolute versus relative risk. Because relative risks are confusing and often misunderstood, the results were also reported in absolute values, expressed in the number of additional events for treated woman-years, which is more meaningful to individual women. Thus, among 10,000 women taking EPT for a year, there will be 8 more cases of invasive breast cancer, 8 more strokes, 8 more pulmonary embolic events, and 7 more myocardial infarctions, but 6 fewer cases of colorectal cancer and 5 fewer hip fractures.

The absolute risk for an individual woman remains quite small (less than 0.1% per year). When this risk was calculated for all events over the 5.2 years of the trial, approximately 100 more women in the hormone group experienced an adverse event than in the placebo group. If this figure is extrapolated to the population at large and to a longer treatment duration, the use of EPT could account for tens of thousands of additional adverse events.

Study excluded women with hot flashes. The WHI did not evaluate the relief of vasomotor symptoms. In fact, women with severe hot flashes were excluded from the study. This means that the major benefits and most common indication for EPT were not considered in the risk-benefit ratio. Had they been included, that ratio might have yielded different results.

Value of the data. Nevertheless, the WHI data do provide important information, which allows us to discuss the benefits and risks of EPT more precisely and more objectively, especially for asymptomatic postmenopausal women.

REFERENCE

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 control trial. *JAMA*. 2002; 288:321-323.

• **The bisphosphonates**—alendronate and risedronate—are safe, effective, convenient (weekly dosing), and not associated with life-threatening side effects.

• **Raloxifene,** the selective estrogen receptor modulator, is another good alternative for prevention and treatment of osteoporosis in patients not at risk for thromboembolic events. Unlike ET/EPT, raloxifene is not associated with an increased risk of either breast cancer or cardiovascular events. In fact, data from the Multiple Outcomes of Raloxifene Evaluation study suggest that, besides protecting against bone loss and vertebral fractures,[7] raloxifene may reduce the risk of breast cancer[8] by as much as 75%.[9] Nor was raloxifene found to increase the risk or incidence of cardiovascular disease.[8] In fact, in a group of 1,035 postmenopausal women at high risk for cardiovascular disease, raloxifene

reduced the incidence of all cardiovascular events by 40%.[9]

5. Annually reassess the ratio of benefit to risk

At every patient's annual visit, weigh the reasons for hormone therapy against current knowledge of the benefit-risk ratio, which evolves along with the patient's needs and status. When all the data from the WHI studies are available and reassessed, the benefit-risk ratio is likely to change again, further altering our recommendations. In my practice I explain the current data and remind patients that the most important—if not the only—reason for ET/EPT is to control menopausal symptoms.

To determine whether the menopausal symptoms have resolved or have become more tolerable, I invite the patient to discontinue the therapy for 4 to 8 weeks. If the symptoms recur and are intolerable, or if the patient concludes that the ratio of benefits to risks is positive, we resume therapy. If she feels that ratio is negative, we stop and consider alternatives.

Our role should be helping the patient arrive at her own conclusions based on the scientific data that we provide, as well as the symptoms she experiences.

Recommendations for initiating therapy

As has been stated, the only indications for EPT in menopausal women are vasomotor symptoms and associated quality-of-life issues. When the therapy is given for these reasons, women should be advised to take the lowest effective dose of the more physiologic preparations for as short a time as possible.

Again, the duration of therapy must be individualized and regularly assessed. This may require periodic interruption of the therapy to evaluate symptom recurrence and the patient's tolerance of and response to safer alternatives.

Estrogen. I favor estradiol—either orally or transdermally—starting at daily doses of 0.5 mg or 0.035 mg, respectively. If symptoms are not adequately controlled and serum estradiol levels remain below 50 pcg/mL, I increase the daily dose to 0.75 mg or 0.075 mg, respectively. If necessary, I will increase it again to a maximum of 1 mg or 0.100 mg, respectively.

Asymptomatic women do not need—nor will they benefit from—ET/EPT.

Progestin. For the progestin component, I recommend 200 mg of oral micronized progesterone, to be taken at bedtime for 2 weeks of each or every other month to confer endometrial protection. If patients cannot tolerate micronized progesterone, I recommend norethindrone acetate in combination with estradiol, to be administered orally (Activella) or transdermally (CombiPatch). ■

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 control trial. *JAMA*. 2002;288:321-323.
2. American College of Obstetricians and Gynecologists. *Response to Women's Health Initiative Study Results by the American College of Obstetricians and Gynecologists*. Washington, DC: ACOG; 2002.
3. Grodstein F, Manson JE, Golditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133:933-941.
4. Williams DB, Voigt BJ, Fu YS, Schoenfeld MJ, Judd HL. Assessment of less than monthly progestin therapy in postmenopausal women given estrogen replacement. *Obstet Gynecol*. 1994;84:787-793.
5. DeLeo V, La Marca A, Morgante G, Lanzetta D. Comparison of 2 HRT regimens with bimonthly and monthly progestin administration in postmenopause. *Maturitas*. 1999; 31:171-177.
6. Ettinger B, Selby J, Citron JT, Vangessel A, Ettinger VM, Hendrickson MR. Cyclic hormone replacement using quarterly progestin. *Obstet Gynecol*. 1994;83:693-700.
7. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282:637-645.
8. Cauley JA, Norton L, Lippman ME, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from MORE trial. Multiple Outcomes of Raloxifene Evaluation. *Breast Cancer Res Treat*. 2001;65(2):125-134.
9. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: Four-year results from the MORE randomized trial. *JAMA*. 2002;287:847-857.

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