

## A Review of Hormone Replacement Therapy for Disease Prevention

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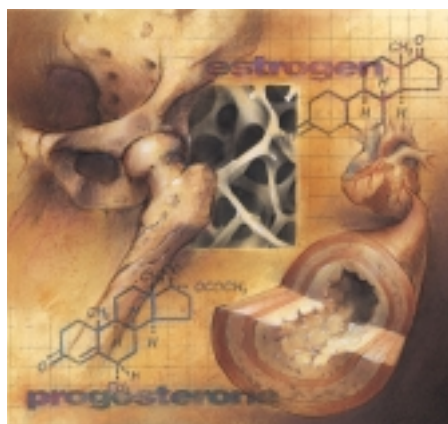
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**E**strogen replacement therapy and hormone replacement therapy (HRT) have received much media attention in recent years, and postmenopausal women frequently ask their physicians about the benefits of these therapies. Increasing awareness of women's health issues in the medical community and the general public necessitates that physicians have a working knowledge of HRT.

HRT is currently used for three main indications: prevention of osteoporosis, prevention of coronary artery disease (CAD), and treatment of climacteric symptoms. This article focuses on the evidence supporting the use of HRT for prevention of disease. The use of HRT to prevent osteoporosis is supported by extensive experience (**Table 1**). HRT has been shown to be effective in both maintaining bone mineral density (BMD) and preventing fractures. The use of HRT to prevent CAD also has strong support from the literature. However, a landmark study by Hulley et al<sup>1</sup> in 1998, the Heart and Estrogen/Progestin Replacement Study (HERS), raised significant questions regarding whether HRT should be started for secondary prevention of CAD.

New forms of HRT that may not increase the risk of breast and endometrial cancer are now available in the form of raloxifene and other "designer estrogens." However, raloxifene has not been shown to be as effective as traditional HRT in the prevention of osteoporosis or CAD. Increasing the confusion about how and when to use different regimens of HRT, the United States Food and Drug Administration (FDA) recently approved micronized progesterone, adding another hormone to the armamentarium for HRT. This article and review of



the literature aims to elucidate these topics. A discussion of the complications of HRT and the effects of HRT on cognitive function is also presented.

### OSTEOPOROSIS

Osteoporosis is a major public health problem in the United States. Approximately 150,000 hip fractures occur annually in women older than age 65 years. Hip fractures cause significant morbidity and mortality, and as many as 30% of women with hip

fracture die in the year following the fracture. In addition, 40% of 80-year-old women experience osteoporotic vertebral crush fractures. Women of Northern European and Asian descent are at particular risk for osteoporosis, although a significant number of African American women also experience this disease. Other risk factors for osteoporosis include a family history of the disease, a low body weight, and a diet low in calcium.

Women with multiple risk factors for osteoporosis should be screened and treated with HRT unless contraindicated (**Tables 2** and **3**). Several screening tests exist for osteoporosis, and dual energy x-ray absorptiometry (DEXA) is the most frequently used screening test. Estrogens have traditionally provided the mainstay

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**Table 1.** Select Recent Trials of Hormone Replacement Therapy and Estrogen Replacement Therapy for Prevention of Osteoporosis

Study	Study Type	Therapy	Conclusions
Lufkin et al 1992	Randomized	HRT	BMD increased at lumbar spine, femoral trochanter, and mid-radius; no difference seen in the BMD of the femoral neck; RR of vertebral fracture, 0.3 (0.16–0.95)
Felson et al 1993	Prospective cohort	ERT	Only women who used ERT for more than 7 years had significantly increased BMD: BMD increased 11.2% in women younger than age 75 years and 3.5% in women older than 75 years
Cauley et al 1995	Prospective cohort	ERT and HRT	Current ERT and HRT use decreased wrist fractures (RR 0.39 [0.24–0.64]), non-spinal fractures (RR 0.66 [0.54–0.8]), and hip fractures (RR 0.6 [0.36–1.02]); previous use of ERT and HRT had no effect
Michaelsson et al 1998	Case control	ERT and HRT	Current HRT users had RR of 0.35 (0.24–0.53) for hip fracture; equally strong risk reduction was noted when therapy started 9 or more years after menopause.

BMD = bone mineral density, ERT = estrogen replacement therapy, HRT = hormone replacement therapy, RR = relative risk.

Lufkin EG, Wahner HW, O'Fallon WM, et al: Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;117:1–9.

Felson DT, Zhang Y, Hannan MT, et al: The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993;329:1141–1146.

Cauley JA, Seeley DG, Ensrud K, et al: Estrogen replacement therapy and fractures in older women. *Ann Intern Med* 1995;122:9–16.

Michaelsson K, Baron JA, Farahmand BY, et al: Hormone replacement therapy and risk of hip fracture: population based case-control study. The Swedish Hip Fracture Study Group. *BMJ* 1998;316:1858–1863.

of therapy in prevention of osteoporotic fractures in postmenopausal women, although bisphosphonates may provide an attractive alternative for women who are unable or unwilling to take HRT.

### Bone Mineral Density

Estrogen decreases normal bone resorption and promotes mineralization of the remodeling space, yielding the 5% to 10% increase in BMD that occurs in HRT users. Numerous studies have demonstrated this increase in BMD. One study assessed both estrogen and etidronate and noted a 7% increase in BMD in the lumbar spine and a 4.8% increase in the femoral neck. This effect is additive when etidronate is used.<sup>2</sup> However, estrogen may need to be used for as long as 7 years for a significant benefit to be seen, and this increase is maintained only as long as estrogen is continued.<sup>3</sup> Therefore, once HRT is started for prevention of osteoporosis, continuing therapy for life is reasonable because the benefits of therapy disappear within a few years after cessation of therapy.

### Fractures

Because low BMD has been shown to increase the risk of fractures, the assumption has been that increas-

ing BMD should decrease the incidence of osteoporotic fractures. Surprisingly, only one randomized, placebo-controlled study that used fracture and not BMD as an end point has been conducted.<sup>4</sup> Lufkin et al<sup>4</sup> studied HRT in women with established osteoporosis and vertebral fractures. The study evaluated 75 women with a history of vertebral fractures secondary to osteoporosis who were randomized to receive HRT or placebo for 1 year. New vertebral fractures were reduced in the HRT group with a relative risk of 0.39 (95% confidence interval, 0.16 to 0.95). This study was limited by its small sample size (75 subjects total, 39 in the HRT group) and short duration (only 1 year). However, numerous observational studies have concluded that the benefits of HRT increase with duration of use, which suggests that the benefits of HRT were likely to have been greater if the study had continued.

New data suggest that it may never be too late to start HRT to prevent osteoporosis. Although the traditional thinking was that HRT must be started in the perimenopausal period to be effective, Michaelsson et al<sup>5</sup> showed that starting therapy even as late as 9 or more years after menopause provided equally strong protection against hip fracture. This finding is important because the risk for fracture increases with age.

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**Table 2.** Risk Factors for Osteoporosis

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Postmenopausal state
Surgically induced menopause
Northern European descent
Low body weight
Low calcium intake
Excess alcohol consumption
Smoking
Drinking carbonated beverages
Sedentary lifestyle
Family history of osteoporosis
Medications
Glucocorticoids
Anticonvulsants
Heparin
Hyperthyroidism
Hyperparathyroidism
Anorexia nervosa
Hypogonadism
Hyperprolactinemia
Cushing's syndrome

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This case-controlled study used a postal questionnaire sent to patients hospitalized for fracture in a region in Sweden.<sup>5</sup> The study also demonstrated a risk reduction of 6% for every year of use of HRT.<sup>5</sup> The protective benefits of HRT were largely lost within 5 years of cessation of therapy. The method of drug administration did not matter: both transdermal and oral estrogen conferred equal benefit. HRT (estrogen and progesterone) provided a slightly better effect on BMD than estrogen alone. Finally, low-dose estrogen (1 mg estradiol or 0.325 mg conjugated estrogens) did not reduce the risk of hip fracture; doses of 2 mg estradiol or 0.625 mg conjugated estrogens were required to reduce this risk.

**Summary**

The available evidence supports the use of both estrogen replacement therapy and HRT to increase BMD and prevent osteoporotic fractures. Although it is prudent to start therapy in women at risk in the perimenopausal period, some evidence suggests that initiation of therapy later in life may also be effective. The method of administration (oral versus transdermal) does not change the efficacy of treatment, but low-dose regimens may not be as effective. Finally, the benefits of treatment are lost within 5 years of cessation of therapy.

**Table 3.** Contraindications to Hormone Replacement Therapy

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Personal history of breast cancer
Personal history of endometrial cancer
Personal history of thromboembolic disease
Active liver disease
Pregnancy
Undiagnosed abnormal genital bleeding

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**CARDIOVASCULAR DISEASE**

**Theoretical Basis**

The physiologic effects of estrogen and progesterin are noted in **Table 4**. A summary of the results of select recent trials of HRT and estrogen replacement therapy for prevention of cardiovascular disease are noted in **Table 5**.

**Estrogen.** Estrogen has numerous beneficial effects on the cardiovascular system. First, this hormone improves the patient's cholesterol profile through five mechanisms:

- 1) Increases the number of hepatic apolipoprotein B and E receptors, which increases the uptake of low-density lipoprotein (LDL) and chylomicrons
- 2) Increases the synthesis of apolipoprotein A-1
- 3) Reduces hepatic lipoprotein lipase levels
- 4) Decreases Lp(a) lipoprotein levels
- 5) Increases the level of high-density lipoprotein (HDL)

Because these changes are all mediated by the liver, only oral estrogen, rather than transdermal estrogen, provides these favorable lipid effects.

Estrogen also decreases the risk of cardiovascular disease by the effects of the hormone on endothelial cell function. Estrogen increases production of prostacyclin, raising the half-life of prostacyclin, and blocks calcium channels. These changes usually result in a reduction of blood pressure. Finally, estrogen is known to improve sensitivity to insulin and to enhance fibrinolytic activity.<sup>6</sup>

**Progestins.** In contrast, progestins alone tend to oppose many of the beneficial effects of estrogen. Progestins decrease HDL levels, increase LDL levels, and oppose the dilatory effect of estrogen on arteries.<sup>7</sup> Nevertheless, the combination of estrogen and progesterone appears to retain many of the beneficial secondary endpoints for patients.

**Table 4.** Physiologic Effects of Estrogen and Progestin

**Estrogen**

Increases hepatic apolipoprotein B and E receptors  
Increases synthesis of apolipoprotein A-1  
Increases high-density lipoprotein levels  
Increases endothelial prostacyclin  
Blocks endothelial calcium channel  
Improves insulin sensitivity  
Enhances fibrinolytic activity  
Increases nitric oxide bioavailability  
Prevents low-density lipoprotein oxidation

**Progestin**

Decreases high-density lipoprotein levels  
Increases low-density lipoprotein levels  
Opposes arterial dilation caused by estrogen

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**Observational Studies**

By 1998, more than 30 major observational studies of estrogen therapy and the risk of cardiovascular disease had been conducted, all of which indicated that estrogen therapy reduces the risk of cardiovascular disease by approximately 50%.<sup>6</sup> McLaughlin et al<sup>8</sup> used electron beam tomography to assess the coronary arteries of 914 women who were referred to a clinic. Women taking HRT had significantly lower amounts of coronary artery plaque compared with women who were not taking HRT. Cross-sectional studies of women undergoing cardiac catheterizations have similarly documented less stenosis among women who were taking estrogen therapy.

In the mid- to late 1990s, evidence continued to mount in support of the use of HRT to decrease the risk of cardiovascular disease. In 1996, Grodstein et al<sup>7</sup> reported data from the Nurses' Health Study, a prospective cohort study. Using myocardial infarction, cerebrovascular accidents, and death as endpoints, the study found that the cardioprotective effects of estrogen therapy were preserved with the addition of progestin. Compared with women who do not use HRT, women using combination HRT were found to have a relative risk of cardiovascular event of 0.39 (confidence interval, 0.19 to 0.78) and women using estrogen alone were found to have a relative risk of 0.60 (confidence interval, 0.43 to 0.83).<sup>7</sup>

Also in 1996, researchers from Kaiser Permanente Medical Care Program (Oakland, CA) reported that long-term estrogen therapy (greater than 5 years) in

postmenopausal women was associated with a 50% reduction in risk of death and 60% reduction in CAD.<sup>9</sup> These reductions occurred without a concomitant increase in cancer mortality.

Both of these studies also suggest that HDL cholesterol is the best predictor of CAD in women.<sup>6,9</sup> Each 4 to 5 mg/dL increment in HDL cholesterol is associated with an estimated 20% to 25% decrease in the risk of CAD in women. However, the addition of a progestin to estrogen therapy has been shown to lessen the beneficial effects of estrogen on HDL cholesterol and atherosclerosis.<sup>10-12</sup> In the landmark study by Hulley et al,<sup>1</sup> as discussed later in this article, HRT users achieved decreases in LDL of 11% and increases in HDL of 10%.

Use of HRT for secondary prevention of CAD has also been supported by the literature. Positive effects on mortality were reported by Sullivan et al,<sup>6</sup> who evaluated estrogen therapy in 1098 women who had undergone coronary artery bypass grafting. The study found a 5-year survival rate among estrogen users of 98.8% versus 82.3% in non-users. All of these studies were observational, however, and the first randomized controlled clinical trial published in 1998 produced shockingly different results.<sup>1</sup>

**A Cautionary Note: The HERS Study**

In August 1998, Hulley et al<sup>1</sup> reported results from the HERS study, the first randomized controlled trial of HRT in women with CAD. The study assessed 2763 women with known CAD who were given either 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (MPA) daily or placebo. Primary endpoints of coronary revascularization, congestive heart failure, cerebrovascular accident, peripheral artery disease, and death were followed for 5 years. Despite the study's finding of benefits in terms of cholesterol, as discussed earlier in this article, the HRT and placebo groups had similar outcomes in terms of the primary endpoints. In addition, the HRT group had a higher rate of cardiovascular events in the first year of the study, but lower rates in the fourth and fifth years of the study. The HRT group also had a significantly higher rate of thromboembolic events, as well as gallbladder disease. Hulley et al<sup>1</sup> therefore concluded that they would not recommend starting HRT for secondary prevention of CAD, but that women who had already started HRT for that purpose might consider continuing therapy.

The significant amount of evidence in favor of HRT that was supported by previous studies complicates the results of the HERS study. As a randomized trial, the HERS study avoided the selection bias that was inherent in the prior observational studies. In the HERS

**Table 5.** Select Recent Trials of Hormone Replacement Therapy and Estrogen Replacement Therapy for Prevention of Cardiovascular Disease

Study	Study Type	Prevention	Therapy	Conclusions
Grodstein et al 1996	Longitudinal	Primary	HRT	HRT RR 0.39 (0.19–0.78); ERT RR 0.60 (0.43–0.83)
Ettinger et al 1996	Matched	Primary	ERT	Long-term users with RR 0.40 (0.16–1.02)
Sullivan et al 1997	Cohort	Secondary	ERT	Following coronary artery bypass graft, the 5-year survival rate is 98.8% in ERT users versus 81.4% in non-users
Hulley et al 1998	Randomized	Secondary	HRT	Overall no difference, HRT users had an increased rate in year one, and placebo users had an increased rate in years four and five

ERT = estrogen replacement therapy, HRT = hormone replacement therapy, RR = relative risk.

Grodstein F, Stampfer MJ, Manson JE, et al: Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453–461.

Ettinger B, Friedman GD, Bush T, Quesenberry CP Jr: Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet Gynecol* 1996;87:6–12.

Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB: Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am J Cardiol* 1997;79:847–850.

Hulley S, Grady D, Bush T, et al: Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–613.

study, patients who were taking HRT may differ from patients who were not taking HRT in characteristics that are not easily measured. For example, patients not taking HRT may differ in terms of their willingness to seek medical attention. The design of randomization in the study attempts to account for these unmeasured differences by allocating patients equally to both groups. Differences found between the therapy and placebo groups are more likely to truly be a result of the therapy being tested. Thus, the findings of the HERS study are impossible to ignore. In addition, the results of the HERS study do not necessarily conflict with the advancing knowledge of CAD. Although, over time, the progression of plaque correlates with infarction, myocardial infarction is most often the result of acute clot formation and rupture.

Estrogen is known to be thrombogenic in the short term, thus many authorities have concluded that the increase in first-year mortality is likely the result of early clot formation. This view is supported further by the increased rate of thromboembolism found in the HRT group of the HERS study. Thus, the later benefits noted in the HERS study could be the result of the beneficial physiological effects described previously. For secondary prevention therefore, the current thinking is best summarized by: “Don’t start, but don’t stop.” Women who have survived the early risk of mortality

can perhaps be assumed to be benefiting from their therapy at this point.

For primary prevention, substantial evidence continues to favor use of HRT in postmenopausal women, especially when considering the noncardiovascular benefits. Results from randomized trials for women without established CAD, however, should be appearing in the next 5 years.

## COMPLICATIONS

### Endometrial Cancer

The increased incidence of endometrial cancer is the most well established complication of HRT in women who have not had a hysterectomy. The lifetime incidence of endometrial cancer in the general population is approximately 3%. The risk of endometrial cancer among estrogen-only users with an intact uterus is estimated to be 4 to 10 times the risk of non-users. However, no corresponding increase in mortality from endometrial cancer has been reported, perhaps because of increased surveillance and earlier detection. Women taking estrogen replacement therapy also have a higher incidence of well differentiated and less invasive cancers.

Whereas women who have had a hysterectomy can be treated with estrogen only, women with an intact uterus must be treated with both estrogen and progestogen

HRT because of the increased relative risk of endometrial cancer. This risk is greatly reduced by the addition of progestogen, either cyclic or continuous administration. In some studies, the risk of endometrial cancer with estrogen and progestogen HRT (versus estrogen replacement therapy alone) was shown to be essentially eliminated. However, one study showed a relative risk greater than 3 (confidence interval, 1.7 to 5.7) in women who had taken HRT for more than 5 years with fewer than 10 days of progestogen each month.<sup>13</sup> This study also showed decreasing risk when progestogens were given for increasing numbers of days each month. The risk of endometrial cancer was not increased in women using HRT for less than 5 years who received 10 to 21 days of progestogens each month. The risk of endometrial cancer with continuous daily dosing of both estrogen and progestogen has not been clearly defined. This regimen is particularly popular among patients because of the cessation of withdrawal bleeding after 6 months of therapy in most women.

#### **Breast Cancer**

Fear of breast cancer is one of the primary reasons patients stop taking HRT and why many physicians are reluctant to prescribe HRT; however, the evidence about the relationship between HRT and breast cancer is conflicting. Although it has become increasingly clear that HRT does not reduce the risk of breast cancer, a consensus has not yet been reached on whether or how much HRT increases the risk of breast cancer. The Nurses' Health Study, a prospective cohort study, showed a relative risk of 1.32 (confidence interval, 1.14 to 1.54) in current estrogen-only users.<sup>14</sup> The relative risk increased slightly to 1.46 (confidence interval, 1.22 to 1.74) in women who had been taking estrogen replacement for 5 or more years. The addition of progestins did not significantly change the reported relative risks.

**Personal history.** A personal history of breast cancer remains an absolute contraindication to HRT. The role of HRT in women with a personal history of breast cancer has been investigated by only a small number of studies because of the perceived theoretical risk. One study followed 49 women with a history of breast cancer on HRT for a median of 31 months.<sup>15</sup> Only one patient had a recurrence of estrogen receptor-negative breast cancer. The small size and short duration of this study clearly limit its clinical usefulness in general practice today. Now that many other viable new therapies for osteoporosis are available, it is unnecessary and unwise to expose women with a personal history of breast cancer to the potential risk of exogenous estrogens.

**Family history.** A family history of breast cancer is not

a contraindication to HRT. Although patients with a family history of breast cancer may be reluctant to take HRT, this therapy probably does not dramatically increase their risk of breast cancer. One study found a small but not statistically significant increase of breast cancer in estrogen replacement therapy users with a family history of breast cancer and a significant reduction in overall total mortality rate.<sup>16</sup> This reduction in total mortality has been noted in numerous other studies; however, this reduction must be interpreted with caution. Possibly, healthier women are more likely to take HRT, as discussed earlier in this article in reference to the HERS study.

#### **Thrombosis**

Until recently, HRT was generally thought not to significantly increase the risk of thrombosis, unlike oral contraceptives. As the term *hormone replacement therapy* implies, only replacement doses of estrogens are used. Only one fourth to one sixth of the dose of estrogens that are used in oral contraceptive pills are used in HRT. It seems logical that, if thrombosis is a dose-related side effect, the incidence of thrombosis associated with HRT would be much lower than the incidence associated with oral contraceptives; however, two case-control studies recently published in *Lancet* both found an increased risk of thromboembolism in users of HRT.<sup>17,18</sup> Both studies found that the relative risk of thrombosis was approximately 3 in users of estrogen replacement therapy. However, these studies were small and their findings had very wide confidence intervals, which means that their statistical reliability is questionable. No prospective, randomized, controlled trials have addressed this issue. Until the risk of thrombosis is more definitely resolved, it is not prudent to prescribe HRT to women with a history of thromboembolic disease.

#### **Other Complications**

As with any drug, the number of reported complications are long and varied. One of the more common complications is gallstones caused by changes in bile cholesterol content. Also reported are increases in blood pressure, fluid retention, recurrent uterine bleeding, breast tenderness, headaches, and glucose intolerance. Several different dermatologic complications have been reported, the most common of which is local irritation at the site of the estrogen patch. The contraindications for HRT are listed in Table 3.

#### **RECENT DEVELOPMENTS**

##### **Selective Estrogen Receptor Modulators**

Selective estrogen receptor modulators (SERMs) are a class of compounds that possess tissue-specific

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estrogen-agonist and -antagonist properties. The tissue selectivity of SERMs has been attributed to the presence of different estrogen receptor types in different tissues and the activation of distinct post-receptor binding pathways. Originally developed as antagonists of estrogen-dependent tumors of mammary tissue, the two most familiar SERMs are tamoxifen and raloxifene.

**Tamoxifen.** Tamoxifen is a pure estrogen antagonist in breast tissue, an estrogen agonist in bone, and a partial agonist in uterine tissue. Although tamoxifen is used as a treatment for breast cancer, this drug has also been found to increase the incidence of endometrial cancer because of its partial agonist effect in the uterus.

**Raloxifene.** Raloxifene is a benzothiophene derivative that has emerged as an alternative to standard HRT. Several studies have shown that raloxifene prevents bone loss and lowers serum cholesterol in postmenopausal women.<sup>19-21</sup> Studies in animal models have established that raloxifene acts as an estrogen antagonist in breast tissue. Similarly, studies in humans have shown that raloxifene does not stimulate uterine tissue.<sup>19,20</sup> Hence, raloxifene offers some of the benefits of estrogen without the side effects of breast tenderness, increased risk of breast cancer, and vaginal bleeding. The most common side effect of raloxifene is hot flashes (25% in the raloxifene group versus 18% in placebo group);<sup>22</sup> therefore, raloxifene is not useful for the treatment of menopausal symptoms.

The effect of raloxifene on the lipoprotein profile and BMD is not as favorable as the effect of estrogen. Compared with placebo, raloxifene significantly increases BMD but not to the same extent as HRT or alendronate.<sup>20,23</sup> Regarding lipoproteins, Walsh et al<sup>21</sup> found that raloxifene significantly lowered total cholesterol, LDL cholesterol and Lp(a) lipoprotein in postmenopausal women; however, raloxifene had no effect on HDL cholesterol. The study also found that HRT with conjugated equine estrogens and MPA resulted in a significant increase in HDL cholesterol and a significantly larger decrease in Lp(a) lipoprotein.

The effect of raloxifene on atherosclerosis and CAD in women remains unclear; however, the effect of raloxifene in animals has been studied. In a 2-year study, Clarkson et al<sup>24</sup> showed that, in postmenopausal monkeys treated with raloxifene, coronary artery plaque size did not differ from postmenopausal monkeys treated with placebo, whereas estrogen treatment resulted in a 70% reduction in plaque size. Bjarnason et al<sup>25</sup> found that postmenopausal rabbits treated with

raloxifene had 33% less aortic atherosclerotic disease than placebo-treated controls. The study also found that rabbits treated with unopposed estrogen had 66% less aortic atherosclerosis than the placebo group. Overall, it appears that the favorable effect of raloxifene on lipids and atherosclerosis is not as potent as the effects of estrogen.

In summary, raloxifene clearly exerts estrogen-like effects on bone and serum lipids without stimulating breast or uterine tissue. However, estrogen and raloxifene differ significantly, and the clinical implications remain unclear. HRT should be the first-line therapy for women for primary prevention of CAD and/or the prevention or treatment of osteoporosis. Although raloxifene has not been proven to be as effective as HRT, raloxifene appears to be a reasonable alternative for women who cannot tolerate the side effects of estrogen or who want to avoid the increased risk of breast cancer.

#### **Micronized Progesterone**

As previously discussed, HRT in women who have not had a hysterectomy must include a progestogen, either a synthetic progestin or natural micronized progesterone. MPA is the progestin most widely used for HRT in the United States. MPA is a chemical analogue of progesterone that is naturally produced by the ovaries. Natural progesterone, derived from extracts of soybeans or Mexican yams, is chemically identical to the progesterone of ovarian origin. Oral bioavailability of natural progesterone is increased through micronization. In December of 1998, the FDA approved an oral form of micronized progesterone for use in combination with estrogen for HRT.

The Postmenopausal Estrogen Progestin Intervention (PEPI) Trial showed that the addition of MPA to estrogen resulted in significantly smaller increases in HDL cholesterol than either unopposed estrogen or estrogen plus micronized progesterone.<sup>10</sup> Specifically, when 200 mg of micronized progesterone was given sequentially for 12 days per 28-day cycle, the drug prevented endometrial hyperplasia as effectively as MPA and preserved more of the beneficial effect of estrogen on HDL cholesterol. The clinical significance of increasing HDL levels remains unclear in the absence of randomized clinical trials. As noted previously, however, observational studies have demonstrated a strong inverse association between HDL cholesterol and cardiovascular disease; therefore, when possible, increasing HDL levels in women is desirable. Micronized progesterone combined with conjugated equine estrogen

promises to be an attractive alternative that may have more favorable effects on lipoproteins than the current standard HRT regimens.

#### EFFECTS ON COGNITIVE FUNCTION

The epidemiologic evidence for an association between estrogen and cognitive function in postmenopausal women is inconsistent. Numerous mechanisms have been proposed to explain how estrogen may affect cognition: increased activity of acetyl-transferase, increased density of dendritic spines, and improved cerebral blood flow are only a few. However, a recent meta-analysis by Yaffe et al<sup>26</sup> concluded that, although estrogen may improve cognitive performance in postmenopausal women with menopausal symptoms, there is no clear beneficial effect in asymptomatic women. Yaffe et al<sup>26</sup> suggest a 29% decreased risk of developing dementia among estrogen users but caution that the findings of the studies are heterogeneous and have substantial methodological problems. Until large randomized clinical trials have been completed, HRT is not recommended for the prevention or treatment of dementia.

#### SUMMARY

A number of recent advances have occurred in the understanding of how to use HRT intelligently. HRT remains the mainstay of treatment for the prevention of osteoporosis and osteoporotic fractures. The understanding of the use of HRT for the prevention of CAD is evolving, and HRT continues to be indicated for primary prevention of CAD in women with multiple risk factors. Based on the results of the HERS study, HRT should be initiated with great caution for secondary prevention.<sup>1</sup> For patients already taking HRT for secondary prevention, there is no need to discontinue therapy because the increased mortality in the HERS study largely occurred in the first year.<sup>1</sup> The Women's Health Initiative, a large clinical trial in progress, will further elucidate the role of HRT in the prevention of CAD. These study results are expected in 2005.

The arrival of both raloxifene and micronized progesterone provides exciting treatment options. For now, raloxifene should be used for the treatment of osteoporosis only when traditional HRT is contraindicated. The evidence is insufficient to support the use of raloxifene for either primary or secondary prevention of CAD. Micronized progesterone is an attractive alternative to MPA and may prove to be more effective in the prevention of CAD because of its more favorable lipoprotein profile. HP

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