Estradiol Therapy Combined With Progesterone and Endothelium-Dependent Vasodilation in Postmenopausal Women

Marie Gerhard, MD; Brian W. Walsh, MD; Ahmed Tawakol, MD; Elizabeth A. Haley, BA; Shelly J. Creager, BSN; Ellen W. Seely, MD; Peter Ganz, MD; Mark A. Creager, MD

Background—Epidemiological studies indicate that estrogen replacement therapy decreases the risk of cardiovascular events in postmenopausal women. Estrogen may confer cardiovascular protection by improving endothelial function because it increases endothelium-dependent vasodilation. It is not known whether progesterone attenuates the beneficial effects of estrogen on endothelial function.

Methods and Results—Seventeen postmenopausal women with mild hypercholesterolemia were enrolled in a placebo-controlled, crossover trial to evaluate the effect of transdermal estradiol, with and without vaginal micronized progesterone, on endothelium-dependent vasodilation in a peripheral conduit artery. Brachial artery diameter was measured with high-resolution B-mode ultrasonography. To assess endothelium-dependent vasodilation, brachial artery diameter was determined at baseline and after a flow stimulus induced by reactive hyperemia. To assess endothelium-independent vasodilation, brachial artery diameter was measured after administration of sublingual nitroglycerin. During estradiol therapy, reactive hyperemia caused an $11.1 \pm 1.0\%$ change in brachial artery diameter compared with $4.7 \pm 0.6\%$ during placebo therapy ($P<0.001$). Progesterone did not significantly attenuate this improvement. During combined estrogen and progesterone therapy, flow-mediated vasodilation of the brachial artery was $9.6 \pm 0.8\%$ ($P=NS$ versus estradiol alone). Endothelium-independent vasodilation was not altered by estradiol therapy, either with or without progesterone, compared with placebo. There was a modest decrease in total and LDL cholesterol during treatment both with estradiol alone and when estradiol was combined with progesterone (all $P<0.001$ versus placebo).

In a multivariate analysis that included serum estradiol, progesterone, total and LDL cholesterol concentrations, blood pressure, and heart rate, only the estradiol level was a significant predictor of endothelium-dependent vasodilation.

Conclusions—The addition of micronized progesterone does not attenuate the favorable effect of estradiol on endothelium-dependent vasodilation. The vasoprotective effect of hormone replacement therapy may extend beyond its beneficial actions on lipids. (Circulation. 1998;98:1158-1163.)

Key Words: endothelium ■ hormones ■ vasodilation ■ women

Epidemiological studies indicate that estrogen replacement therapy decreases the risk of cardiovascular death in postmenopausal women.1-3 Yet, many postmenopausal women require the use of progesterone in addition to estrogen to reduce the risk of endometrial cancer.4 A recent observational report from the Nurses Health Study, which included >63,000 women, suggested that progesterone, when added to estrogen replacement therapy, decreases the risk of cardiovascular events, as does estrogen replacement therapy alone.5 Other, smaller studies have found that progesterone in combination with estradiol had no adverse effect, compared with estradiol alone, on the risk of myocardial infarction and stroke.6-8

An important postulated mechanism whereby estrogen may confer cardiovascular protection is by improving the function of vascular endothelium, specifically by increasing the bioavailability of endothelium-derived nitric oxide.9 Nitric oxide may slow atherogenesis and limit the adverse effects of atherosclerosis by modulating vascular tone; by inhibiting platelet aggregation, synthesis of monocyte chemotactic factors, and monocyte adhesion to the endothelial surface; and by reducing vascular smooth muscle cell proliferation.10-13 Indeed, estrogen administration improves endothelium-dependent vasodilation in coronary and peripheral vessels of ovariectomized animals and postmenopausal women.14-22 Addition of medroxyprogesterone acetate decreases the beneficial effects of estrogen on endothelium-dependent vasodilation in atherosclerotic coronary arteries of cynomolgus monkeys.23 It is not known whether progesterone diminishes the favorable endothelial effects of estrogen on the...
endothelium in postmenopausal women. A counterregulatory action would be inconsistent with the available epidemiological studies.

Oral estrogen also may decrease cardiovascular risk by lowering LDL cholesterol and lipoprotein (a) levels and by raising HDL cholesterol.\cite{24,25} The Postmenopausal Estrogen-Progesterone Intervention (PEPI) trial found that neither medroxyprogesterone acetate nor oral micronized progesterone significantly changed the beneficial effects of conjugated equine estrogen on LDL cholesterol levels.\cite{26} Transdermal administration of estradiol, with or without micronized progesterone, however, has not been shown to significantly alter plasma lipoprotein composition.\cite{24,27}

The objective of this study was to determine whether progesterone, when added to estrogen replacement therapy, attenuates the favorable effects of estrogen on endothelium-dependent vasodilation in postmenopausal women with mild hypercholesterolemia. Specifically, we studied the effect of chronic transdermal estradiol treatment alone and in combination with vaginal micronized progesterone, each administered to achieve physiologically relevant premenopausal levels, on peripheral endothelium-dependent vasodilation in a placebo-controlled, crossover trial.

**Methods**

Seventeen postmenopausal women 48 to 75 years old (mean, 60 years) with mild hypercholesterolemia were recruited via advertisement for participation in the study. Menopause was confirmed by follicle-stimulating hormone levels >40 IU/L and absence of menses for at least 1 year. Exclusion criteria included hypertension, diabetes, cigarette smoking, clinical manifestations of atherosclerosis (coronary artery disease, peripheral artery disease, and cerebrovascular disease), venous thromboembolism, liver disorders, unexplained vaginal bleeding, and personal or family history of breast cancer. All subjects provided a medical history and underwent a physical examination, including gynecological evaluation, and mammography before enrollment. This study was a substudy of a larger trial evaluating the metabolic effects of the restoration of premenopausal hormone levels in postmenopausal women and was approved by the Human Research Committee of Brigham and Women’s Hospital. Each subject gave written informed consent.

**Randomization to Treatment**

This was a double-blind, crossover trial in which subjects received 2 therapeutic regimens, each for a duration of 14 weeks. Nineteen women were enrolled; 17 participated in the vascular reactivity studies. Eight women were randomized to placebo treatment first and received 14 weeks of placebo therapy followed by a 1-month washout period. Then, they crossed over to receive active therapy for 14 weeks. This included estradiol alone for the first 8 weeks, followed by estradiol in combination with 2-week cycles of progesterone during weeks 9 to 10 and 13 to 14. The other 9 women received the opposite treatment order. Estradiol was administered as 0.2 mg estradiol transdermal (two 0.1-mg patches, Estraderm, CIBA-Geigy) placed 2 times per week or corresponding placebo (CIBA-Geigy). The transdermal route of estrogen administration was selected to minimize changes in lipid levels.\cite{24,27} Progesterone was given daily as 300 mg vaginal micronized progesterone (Upjohn) in a nonliquefying base (Unibase, Warner Chilcott Laboratories) to achieve sustained physiological levels.\cite{28} The vaginal route of administration was chosen to administer natural progesterone. Patch and creme medications were administered in the evening, and vascular reactivity studies were performed in the morning. Review of treatment effects was undertaken at each visit by 1 of the authors (B.W.W.). Treatment effects were not made known to the individuals performing and analyzing the vascular reactivity studies.

**Vascular Reactivity Studies**

Vascular reactivity was evaluated during placebo treatment (week 8), during estradiol therapy (week 8), and during estradiol plus progesterone therapy (week 10). Subjects were evaluated at the same time of day for each study in a quiet, temperature-controlled room after resting supine for 15 minutes. To assess vascular reactivity, high-resolution ultrasonography of the brachial artery was performed with a Toshiba 270 SSA ultrasound machine equipped with a 7.5-MHz linear array probe. In brief, as previously described and validated,\cite{20,29-32} the brachial artery was imaged longitudinally at a site just proximal to the antecubital fossa, with the arm abducted 80° from the body and the forearm semipronated. The transducer position was adjusted to obtain optimal images of the anterior and posterior intima. The image was recorded on x-ray film to ensure that the brachial artery was imaged at the identical site and position for each study. All images were recorded on super VHS videotape. After baseline images were recorded, a sphygmomanometric cuff on the upper arm was inflated to suprasystolic pressures for 5 minutes. To determine endothelium-dependent vasodilation, the brachial artery was imaged during reactive hyperemia 1 minute after cuff release. Brachial artery blood flow typically increases 5- to 10-fold during reactive hyperemia, and this is followed by peak brachial artery vasodilation.\cite{20} Flow-mediated vasodilation of the brachial artery is largely an endothelium-dependent process, mediated by nitric oxide and inhibited by the nitric oxide synthase antagonist \textit{N}-monomethyl-\textit{L}-arginine.\cite{30} Moreover, flow-mediated, endothelium-dependent vasodilation of the brachial artery correlates with endothelium-dependent vascular responsiveness of the coronary arteries to acetylcholine in individuals who have undergone both types of testing.\cite{31}

After a minimum of 10 minutes from the time of cuff release and reestablishment of baseline conditions, including baseline diameter, the brachial artery was imaged again. Then, to determine endothelium-independent vasodilation, subjects received 0.3 mg of sublingual nitroglycerin. The brachial artery image was recorded 3 minutes later, a time corresponding to peak vasodilation to nitroglycerin. Forearm blood flow during reactive hyperemia was measured by venous occlusion plethysmography with calibrated mercury-in-Silastic strain gauges as previously described.\cite{32}

**Biochemical Assays**

Serum 17β-estradiol, progesterone level, and lipid concentrations were measured during each treatment period on the day of the vascular reactivity study. An enzymatic method was used to determine total cholesterol and triglyceride levels (Dax 96 analyzer, Bayer). HDL cholesterol was measured by precipitation of apoB-containing lipoproteins by the addition of phosphotungstic acid and magnesium ions. After centrifugation, only HDL cholesterol remained in the supernatant. The cholesterol concentration of the supernatant was measured by the enzymatic method. LDL cholesterol was calculated according to the Friedewald formula.\cite{34} Estradiol and progesterone concentrations were determined by chemiluminescent immunoassays (Bayer).

**Image Analysis**

For each condition (baseline, reactive hyperemia, repeat baseline, nitroglycerin) during each treatment period, 3 end-diastolic frames were selected and digitized for subsequent analysis. Each image was assigned a code. Subject name, date, and time were then removed from the image. Image analysis of the coded frames was then performed by 2 blinded investigators using software that searched for the shortest distance between the points on the arterial wall as previously described.\cite{30,35} This resulted in ~20 paired measurements along a 10- to 15-mm length of artery. Arterial diameter was measured from the intima-lumen interface along the posterior wall to the media-intima interface of the anterior wall. Pixels were converted to millimeters by use of calibration factors from real-time ultrasonography. The average of 3 measurements was used for each determination of brachial artery diameter.
TABLE 1. Effect of Treatment on Heart Rate, Blood Pressure, and Hormone Levels

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Heart rate, bpm</th>
<th>Mean blood pressure, mm Hg</th>
<th>Estradiol, pg/mL</th>
<th>Progesterone, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70±1.9</td>
<td>89±2.2</td>
<td>11.5±0.8</td>
<td>0.2±0.3</td>
</tr>
<tr>
<td>Estradiol</td>
<td>68±2.5</td>
<td>87±2.4</td>
<td>144.5±12.4*</td>
<td>0.2±0.3</td>
</tr>
<tr>
<td>Estradiol + Progesterone</td>
<td>67±2.2</td>
<td>89±2.7</td>
<td>121±10.7*</td>
<td>10.9±1.2*</td>
</tr>
</tbody>
</table>

*P<0.001 vs placebo.

Statistical Analysis

All data are reported as mean±SEM. The effects of estrogen alone and combined with progesterone were analyzed by repeated-measures ANOVA. Post hoc comparisons between the different treatments were made with the Student-Newman-Keuls test. Side effects during treatment were evaluated with the McNemar test. The Spearman rank correlation coefficient was determined for endothelium-dependent vasodilation and total and LDL cholesterol levels. A stepwise multivariate analysis was performed with flow-mediated, endothelium-dependent vasodilation as the dependent variable and 17β-estradiol, progesterone, total cholesterol and LDL cholesterol levels, age, heart rate, and blood pressure as independent variables. Statistical significance was accepted at the 95% confidence level (P<0.05).

Results

The effect of treatment with placebo, estradiol, and estradiol combined with progesterone on heart rate, blood pressure, and serum estradiol and progesterone is described in Table 1. The serum estradiol concentration rose significantly and comparably during both drug treatment periods. The serum progesterone level increased significantly only during the treatment with progesterone on heart rate, blood pressure, and combined with progesterone. Neither heart rate nor blood pressure was altered by active treatment.

During placebo therapy, total cholesterol was 223±7 mg/dL, LDL cholesterol was 141±6 mg/dL, HDL cholesterol was 62±4 mg/dL, and triglycerides were 97±12 mg/dL. Estradiol therapy alone decreased total cholesterol by 6.7±1.8% (P<0.001) and LDL cholesterol by 10.9±2.7% (P<0.001). Estradiol therapy combined with progesterone decreased total cholesterol by 5.8±1.7% (P<0.001) and LDL cholesterol by 8.4±2.4% (P<0.001). Estradiol treatment alone or combined with progesterone did not significantly alter HDL cholesterol or triglyceride concentrations.

There were no significant differences in the degree of symptoms or side effects between placebo, estradiol alone, and estradiol with progesterone therapy. Breast tenderness was noted by 9 subjects during estradiol therapy, by 7 subjects during estradiol with progesterone therapy, and by 5 subjects during placebo therapy. Vaginal bleeding was reported by 4 subjects during estradiol therapy, by 5 subjects during estradiol plus progesterone therapy, and by 2 subjects during placebo therapy. Hot flashes were present in 5 subjects during placebo therapy and were reported by 2 subjects during estradiol therapy. One or 2 subjects reported fatigue, mood change, leg cramps, headache, rash, sweating, insomnia, nausea, urinary frequency, and insomnia during each of the 3 treatment periods.

Effect of Hormonal Treatment on Vascular Reactivity

The baseline brachial artery diameter was 3.61±0.80 mm during placebo treatment, 3.59±0.70 mm during estradiol treatment, and 3.62±0.90 mm during the estradiol plus progesterone treatment (each P=NS versus placebo). Peak reactive hyperemic forearm blood flow, the stimulus for brachial artery flow-mediated vasodilation, was similar for each treatment period (19.5±1.4, 19.7±1.6, and 24.0±1.8 mL·100 mL⁻¹·min⁻¹ during placebo, estradiol alone, and estradiol plus progesterone treatment periods, respectively, P=NS). Flow-mediated, endothelium-dependent vasodilation was greater during estradiol therapy than during placebo therapy. During estradiol therapy, reactive hyperemia caused an 11.1±1.0% increase in brachial artery diameter compared with 4.7±0.6% during placebo therapy (P<0.001) (Figure 1). Flow-mediated endothelium-dependent vasodilation of the brachial artery also was greater during combined estradiol and progesterone treatment (9.6±0.8%) than during placebo treatment (P<0.001 versus placebo) (Figure 1). Progesterone combined with estradiol did not change the magnitude of endothelium-dependent vasodilation compared with treatment with estradiol alone (9.6±0.8 versus 11.1±1.0%, P=NS). Endothelium-independent vasodilation to sublingual nitroglycerin was not affected by treatment (Figure 2). The change in brachial artery diameter after nitroglycerin was 12.7±1.3% during placebo treatment, 12.1±1.0% during estradiol treatment alone, and 11.3±1.2% during the combination of estradiol and progesterone (P=NS).

Figure 1. Flow-mediated, endothelium-dependent vasodilation of brachial artery during placebo therapy, estradiol therapy, and estradiol plus progesterone therapy. Values are mean±SEM. *P<0.001 vs placebo.
oral estradiol administration increases flow-mediated vasodilation of the brachial artery. Studies in animal models have examined the effect of progestin on endothelial function. Miller and Vanhoutte studied canine coronary artery rings and reported that progesterone combined with estrogen attenuated the improvement in endothelium-dependent relaxation seen with estrogen alone. Williams et al found that medroxyprogesterone acetate diminished the endothelium-dependent vasodilator effect of conjugated equine estrogen by up to 50% in coronary arteries of cholesterol-fed monkeys. Recently, Miyagawa et al compared the effects of 2 types of progestin on coronary vasoreactivity in ovariectomized monkeys. Intracoronary administration of serotonin and a thromboxane mimetic induced coronary vasospasm in monkeys treated with 17β-estradiol and medroxyprogesterone acetate but not in monkeys treated with 17β-estradiol and progesterone. Taken together, these studies suggest that the vascular effects of progestins combined with estrogen may be different between synthetic and natural progesterone.

The present study demonstrates that the addition of micronized vaginal progesterone, in a dose that achieved physiological serum concentrations of progesterone, does not attenuate the beneficial effects of estradiol on endothelium-dependent vasodilation in postmenopausal women. Our findings are consistent with those observed in premenopausal women, in whom similar enhancement of endothelium-dependent vasodilation of the brachial artery occurred during the follicular and luteal phases of the menstrual cycle compared with the time of menses. In our study, we achieved estradiol and progesterone levels during active treatment comparable to those found in the follicular (estradiol administration) and luteal (estradiol plus progesterone administration) phases of the menstrual cycle. The use of micronized progesterone, which is less androgenic than medroxyprogesterone acetate, and/or species differences may explain, in part, the findings in women compared with those seen in experimental studies.

**Lipoprotein Effects**

The decrease in total and LDL cholesterol concentrations with both active treatments in this study was modest. This differs from a previous study in which transdermal estradiol concentration used at a lower dose (0.1 mg twice each week) had no effect on these lipoprotein measurements. We chose to use 0.2 mg twice each week to more closely approximate physiological concentrations of estrogen that occur during the menstrual cycle. The higher dose may account for the disparate results on lipoprotein fraction between these 2 studies.

Lowering LDL cholesterol has been shown to improve endothelium-dependent vasodilation in coronary arteries. Therefore, a question has arisen as to whether the effect of estrogen on endothelium-dependent vasodilation is indirect and related to its lipid-lowering properties. If so, this approach would be less appealing than the use of moderate lipid-lowering drugs, which are more potent and more free of side effects. Our findings suggest that improved endothelium-dependent vasodilation with transdermal administration of estradiol is independent of the change in lipid concentra-

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**Factors Associated With Endothelium-Dependent Vasodilation**

Stepwise multiple logistic regression was performed with flow-mediated, endothelium-dependent vasodilation as the dependent variable (Table 2). Estradiol concentration was the only significant predictor of endothelium-dependent vasodilation. A significant correlation between the change in total cholesterol or LDL cholesterol and flow-mediated, endothelium-dependent vasodilation was not detected by rank correlation testing.

**Discussion**

The novel observation made in this study is that the addition of micronized vaginal progesterone to transdermal estradiol does not diminish the benefits of estradiol on endothelium-dependent vasodilation in postmenopausal women. This effect of estradiol therapy, with or without progesterone, on vascular reactivity appears to be independent of its lipid-lowering effect.

**Estrogen and Endothelium-Dependent Vasodilation**

The beneficial effect of estrogen on endothelium-dependent vasodilation was initially elucidated in animal models and subsequently confirmed in postmenopausal women. Replacing estrogen after ovariectomy restores endothelium-dependent relaxation of arteries isolated from rabbits, dogs, and cholesterol-fed swine. Short-term and long-term estrogen administration also improves endothelium-dependent vasodilation of coronary arteries to acetylcholine in vivo in cholesterol-fed ovariectomized monkeys. In postmenopausal women, acute administration of estrogens increases endothelium-dependent vasodilation of coronary arteries and forearm resistance vessels, and chronic estradiol administration increases flow-mediated vasodilation of the brachial artery. Studies in animal models have examined the effect of progestin on endothelial function. Miller and Vanhoutte studied canine coronary artery rings and reported that progesterone combined with estrogen attenuated the improvement in endothelium-dependent relaxation seen with estrogen alone. Williams et al found that medroxyprogesterone acetate diminished the endothelium-dependent vasodilator effect of conjugated equine estrogen by up to 50% in coronary arteries of cholesterol-fed monkeys. Recently, Miyagawa et al compared the effects of 2 types of progestin on coronary vasoreactivity in ovariectomized monkeys. Intracoronary administration of serotonin and a thromboxane mimetic induced coronary vasospasm in monkeys treated with 17β-estradiol and medroxyprogesterone acetate but not in monkeys treated with 17β-estradiol and progesterone. Taken together, these studies suggest that the vascular effects of progestins combined with estrogen may be different between synthetic and natural progesterone.

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**TABLE 2. Stepwise Multivariate Analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-Estradiol</td>
<td>0.562</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔLDL cholesterol</td>
<td>0.101</td>
<td>0.624</td>
</tr>
<tr>
<td>Age</td>
<td>0.075</td>
<td>0.085</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.016</td>
<td>0.554</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>0.056</td>
<td>0.701</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.035</td>
<td>0.809</td>
</tr>
</tbody>
</table>

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**Figure 2. Endothelium-independent vasodilation of brachial arteries during placebo, estradiol therapy, and estradiol plus progesterone therapy. Values are mean±SEM.**
tion. In a multivariate analysis, reduction in total and LDL cholesterol did not correlate with improvement in brachial artery endothelial function. Moreover, in previous studies, intracoronary or intravenous estrogen restored endothelium-dependent vasodilation in the coronary arteries in a matter of minutes, a time duration in which lipid changes could not have occurred.17–19,21,22

Conclusions
The addition of micronized vaginal progesterone does not attenuate the improvement in endothelium-dependent vasodilation that occurs with estradiol treatment. These findings suggest that the increased bioavailability of endothelium-derived nitric oxide achieved with estradiol therapy is not reduced by progesterone. This observation provides insight into a mechanism whereby hormone replacement therapy reduces the risk of cardiovascular events in postmenopausal women and may allay fears about abrogating cardiovascular risk reduction with the addition of progesterone. Moreover, the vasoprotective effects of estradiol and progesterone replacement therapy appear to extend beyond its favorable actions on lipids. Therefore, hormone replacement and lipid-lowering therapies may be complementary, a concept that needs to be explored in future studies.

Acknowledgments
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