A Fresh Look at HORMONE THERAPY

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NEEDS STATEMENT
In the aftermath of the early end of the estrogen and the estrogen plus progestin arms of the Women’s Health Initiative (WHI), use of hormone therapy (HT) dropped dramatically.1 Half a decade later, the tide is turning as research indicates that the risks and benefits of HT may depend on the formulation, dosage, mode of administration, time elapsed since menopause or patient age at initiation of therapy, and duration of treatment.2 Clinicians are again recommending HT, with its proven beneficial effects on vasomotor and urogenital symptoms, to selected patients, recognizing that many women rely on HT for effective relief of life-disrupting menopausal symptoms. They can also point to the fact that further review of WHI data provides reassurance about the use of HT in women who are younger and closer to menopause than the average WHI study participant—women who are more likely to require management for the vasomotor symptoms, urogenital changes, and other aspects of menopause.

Effective symptom management and appropriate patient care mean that it is critical for clinicians who care for menopausal women to be familiar with the available options for HT—agents, dosages, and routes of administration—and the distinctions among them, including their side-effect profiles.3 This includes an understanding of not only the estrogen component of HT but also the progestogens that are required for endometrial protection in women with intact uteri.

Knowledge about the differences between natural products and synthetic analogs, for instance, can help clinicians make prescribing decisions that suit their patients’ expectations of HT and their medical needs.4 Further, the question of bioidentical hormones—a term that may mean one thing to clinicians and another to patients—is currently subject to some confusion and controversy, so clinicians require clarifying evidence-based information.5,6 As the authors of a recent editorial in the journal Circulation noted, “…HT is not a singular entity; we need to consider route, type, and dose of these complex agents in practice and in future research.”

An educational initiative that clearly outlines the role, utility, and safety of HT in women’s health, with evidence-based guidance on the distinctions among available HT products and how best to use these agents, will help clinicians in women’s health improve and personalize the care and counseling they provide for their patients.

References

PROGRAM OBJECTIVES
After participating in this educational activity, clinicians should be better able to:
• Evaluate the risks and benefits of hormone therapy (HT) for each patient, according to her specific needs and treatment goals
• Differentiate among the available hormone formulations, dosage levels, and routes of administration to identify appropriate options for each patient
• Identify the effect of progestogens on the endometrium
• Counsel patients on how the benefits and risks of therapy may affect them individually, based on women’s needs for menopausal symptom management
• Discuss current evidence-based expert opinion on bioidentical hormones

TARGET AUDIENCE
Obstetrician-gynecologists, primary care physicians, and nurse practitioners in women’s health

FACULTY DISCLOSURES
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John J. Vogel, DO, has no relationships to disclose with regard to the content of this program.

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CREDIT STATEMENTS
This activity meets Type I criteria for mandatory continuing education requirements towards relicensure as established by the Texas Board of Nursing. This activity is approved for 1 Contact Hour. To receive a certificate of successful completion, nurses are required to read the activity, achieve a 70 percent or better score on the posttest and complete and return the credit request form and activity evaluation form at the end of the activity. Duration of this CME/CNE activity is May 2008 through May 31, 2009.

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Estradiol deficiency, the hallmark of menopause, can diminish a woman’s quality of life. Manifestations include vasomotor symptoms (hot flashes and night sweats) and sexual dysfunction (vaginal dryness, pain at intromission, postcoital burning, and dyspareunia).\textsuperscript{1,2} Sleep disturbances, including arousals, awakenings, and mood alterations, are also associated with menopause.\textsuperscript{3}

Hormone therapy (HT), either estrogen alone or with progestin, can markedly diminish the severity and frequency of these symptoms.\textsuperscript{4} Reports from studies including the Women’s Health Initiative (WHI) have stoked fears that HT presents an unacceptable health risk, especially with regard to breast cancer. This monograph reviews these issues and takes a fresh look at HT during menopause.

**RISK PERCEPTION: ESTROGEN, HEART DISEASE, AND BREAST CANCER**

Most women tend to underestimate their risk of heart disease, which accounts for 39% of deaths among US women. Compared
with all forms of cancer—including breast cancer—heart attacks, strokes, and other cardiovascular diseases kill nearly twice as many women, according to the American Heart Association. One-third of all adult women have some form of cardiovascular disease (CVD).

Women are often surprised to hear these statistics. We face a challenge in educating women about their true risks of heart disease and breast cancer and about appropriate risk-reducing interventions.

**ESTROGEN AND CARDIOPROTECTION**

Epidemiologic and observational studies demonstrate that estrogen lowers coronary heart disease (CHD) rates by 40% to 50% (*Figure 1*). Further, these studies, which included women who took estrogen only (ET) as well as women taking estrogen plus a progestin (E+P), showed little or no difference between the two regimens in the relative risk of CVD. Unopposed estrogen lowers cardiovascular risk, and the addition of a progestin (required for endometrial protection in women with a uterus) did not offset the benefit in these observational studies.

We face a challenge in educating women about their true risks of heart disease and breast cancer and about appropriate risk-reducing interventions.

Several plausible mechanisms may explain estrogen's cardioprotective effects. Estrogen might reduce low-density lipoprotein (LDL) and lipoprotein A levels and/or increase high-density lipoprotein (HDL) levels. Estrogen may have antioxidant effects, thereby decreasing lipid oxidation. The hormone has
also been linked to upregulation of endothelial nitric oxide synthase and vasodilation. Estrogen may inhibit platelet aggregation and may increase prostacyclin, eg; cyclo-oxygenase-2 activity. Estrogen may also decrease cell adhesion molecules and decrease inflammatory factors such as tumor necrosis factor alpha, interleukin-6, monocyte chemotactic protein-1, and fibrinogen.

**WHI AND NHS**

In the 1990s, a series of chronic disease prevention trials started, most notably the Women’s Health Initiative (WHI). The goals included gaining further understanding of observational data on the effects of estrogen on the cardiovascular system, cardiovascular risk, bone health, and mental health. The WHI included a randomized controlled clinical trial that enrolled more than 16,000 postmenopausal women aged 50 to 79 years. In the estrogen-only arm, women received conjugated equine estrogen (CEE) 0.625 mg/d or placebo. Women in the estrogen plus progestin arm were given CEE, 0.625 mg/d, plus medroxyprogesterone acetate (MPA), 2.5 mg/d or placebo.

In July 2002, the WHI Hormone Therapy Estrogen + Progestin (WHI-E+P) treatment arm was stopped ahead of schedule, which resulted in revised US Food and Drug Administration (FDA) treatment recommendations and HT labeling. In March 2004, the WHI estrogen-only (WHI-E) arm also ended early. Data from both treatment arms continue to be reevaluated and published.

It’s fair to say that most women have at least heard of the WHI and are generally aware of the media hubbub that surrounded the results (Figure 2). Headlines that came out in the wake of the study’s publication told women that HT was associated with

- 41% increase in strokes
- 29% increase in heart attacks
- 100% increase in venous thromboembolism (VTE)
22% increase in total CVD
26% increase in breast cancer
37% decrease in colorectal cancer
33% decrease in hip fracture
24% decrease in total fractures
No difference in all-cause mortality.

WHI results stand in contrast to those of the Nurses’ Health Study (NHS), a prospective, observational cohort study that included 70,533 postmenopausal women and ran from 1976 to 2006. In the NHS, current HT use was associated with substantially decreased risk for coronary events. Among women who were taking oral conjugated estrogens, two daily dosages—0.625 mg and 0.3 mg—were associated with cardiac risk reductions in women with no history of heart disease. The risk reductions associated with these estrogen dosages were similar. An increased risk of stroke was observed, however, in women taking estrogen at a daily dosage of 0.625 mg or higher in combination with progestin.

Although both the NHS and the WHI were designed to examine primary prevention of CVD, the populations under study differed markedly. WHI patients were generally older at study onset than NHS participants. Patients in the NHS had started HT at about the time of menopause, but WHI participants initiated therapy at an average age of 63, or more than 10 years later than the average age of natural menopause. Compared with women enrolled in the NHS, WHI participants were 7 times more likely to smoke, were less likely to take aspirin, and were more overweight, with 34% having a body mass index (BMI) of 30 kg/m² or higher. The two study groups were comparable in the prevalence of hypertension and diabetes. 

In short, the NHS population was healthier and younger than the WHI population. Relative risk of CHD among NHS hormone users was lower than among never-users of HT (Figure 3). In the WHI-E+P arm, women taking CEE/MPA had a slightly elevated relative risk, with an adjusted confidence interval.
that crossed 1.0. An analysis by Prentice and colleagues in 2005 concluded that “adjustment for confounding factors and time from hormone therapy initiation can bring estrogen-plus-progestin hazard ratios (HRs) from the WHI observational study into fairly close agreement with those from the clinical trial for CHD and venous thromboembolism and, to a lesser extent, for stroke.”

It is interesting to note that when Prentice and colleagues compared the WHI clinical trial with the WHI observational study, it was clear that the estimated HR was 39% to 48% lower in the observational study compared to that in the clinical trial for CHD, stroke, and VTE, and consistent with the findings in the NHS for these end points.

**WHI: A CLOSER LOOK**

In the WHI’s E+P arm, the absolute risk of breast cancer was 8 per 10,000 women per year, which places it in the “rare” category of a World Health Organization classification scheme. The risk of stroke was similar, at 7 per 10,000 women per year. The risk of VTE associated with E+P was considerably higher, at 18 per 10,000 women per year. Contrast this with the benefit in terms of total fractures associated with E+P, at 47 per 10,000 women per year. The data were similar in the WHI-E arm (Table 1). Breast cancer was actually reduced in the groups receiving estrogen; strokes, VTE, and pulmonary embolism (PE) were rare occurrences. Again, the total number of fractures was greatly reduced.

The impact of E+P on CHD risks compared to placebo in various WHI subgroups illustrates several important points (Figure 4). Mean follow-up was 5.2 years. E+P was associated with a CVD HR of 1.24 overall, with the most striking effect in the first year of treatment (HR, 1.81). Note that all of the

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**TABLE 1. WHI E+P and WHI-E and selected health events**

<table>
<thead>
<tr>
<th>Health Event</th>
<th>Absolute Risk per 10,000 Women/Year</th>
<th>Absolute Benefit per 10,000 Women/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHI E+P</td>
<td>WHI-E</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Total fractures</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

HRs cross 1.0. These data demonstrate that the risk of CHD is reduced among women taking E+P who have been in menopause for fewer than 10 years. When more time has passed since menopause, E+P seemed to be associated with an increased risk of CVD in this cohort, with the highest risk in women 20 or more years postmenopause. When age subgroups were considered, women aged 70 to 79 years (who roughly corresponded to 20 years past menopause), also had the highest risk of CVD. E+P increased the HR by 44% over that in the placebo group. The authors believe that statins may have attenuated any increased risk posed by E+P.15

In a secondary analysis, the WHI investigators took a closer look at the association between HT and CVD risk according to age and years since menopause. More than 10,000 women who had had a hysterectomy were randomized to receive CEE or placebo, and 16,000 women with a uterus were randomized to CEE/MPA or placebo. During the follow-up of the combined trials, 396 CVD cases and 327 strokes occurred among women taking hormones; 379 incidents of CVD and 239 strokes occurred among women in the placebo groups. The HR associated with CEE was 0.63 for women aged 50 to 59 years at randomization, and 0.94 for those aged 60 to 69 years at randomization. Among women aged 70 to 79 years at randomization, the HR was 1.11. Based on these and other findings, the investigators concluded that CHD risk did not increase with the use of HT among women close to menopause.18

**FIGURE 4.** Risk of CHD with use of estrogen plus progestin in various subgroups.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Estrogen + Progestin</th>
<th>Placebo</th>
<th>Hazard Ratio for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>No. of cases of CHD (annualized %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>37 (0.22)</td>
<td>27 (0.17)</td>
<td>1.27</td>
</tr>
<tr>
<td>60–69</td>
<td>75 (0.35)</td>
<td>68 (0.34)</td>
<td>1.05</td>
</tr>
<tr>
<td>70–79</td>
<td>76 (0.78)</td>
<td>52 (0.55)</td>
<td>1.44</td>
</tr>
<tr>
<td><strong>Years Since Menopause</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>31 (0.19)</td>
<td>34 (0.22)</td>
<td>0.89</td>
</tr>
<tr>
<td>10–19</td>
<td>63 (0.38)</td>
<td>51 (0.32)</td>
<td>1.22</td>
</tr>
<tr>
<td>≥20</td>
<td>74 (0.75)</td>
<td>44 (0.46)</td>
<td>1.71</td>
</tr>
<tr>
<td><strong>Statin Use</strong></td>
<td></td>
<td></td>
<td>P&lt;.07 for trend</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (0.78)</td>
<td>23 (0.80)</td>
<td>0.99</td>
</tr>
<tr>
<td>No</td>
<td>164 (0.36)</td>
<td>124 (0.29)</td>
<td>1.27</td>
</tr>
</tbody>
</table>

CHD includes nonfatal myocardial infarction and death due to CHD.


The NHS followed 121,700 nurses for 3 decades. During 2 of these decades, HT use was tracked, and biennial questionnaires asked each participant about HT duration and type. An analysis of NHS data published in 2006 asked: Does the timing of HT initiation relative to menopause affect...
the onset of CHD? The findings showed that women who started HT soon after the menopause experienced a significantly reduced risk of CHD. Among women taking unopposed estrogen, CHD risk was reduced by 34% (relative risk [RR], 0.66). In those taking estrogen with a progestin, risk was decreased by 28% (RR, 0.72). In a subgroup of women the authors described as “demographically similar” to WHI participants and who had started HT 10 or more years after menopause, there was no relationship between HT and CHD risk (RR, 0.87 for estrogen; 0.90 for E+P). The findings were similar even in older women, with a possible trend toward lower CHD risk among women taking E+P.¹⁹

**BREAST CANCER AND THE WHI**

In a study published in 2002 by the Writing Group for the Women’s Health Initiative Investigators, HRs for breast cancer were higher in prior HT users compared to HRs in women who had not used HT (HR, 1.06).¹⁴ For women with less than 5 years of HT exposure, the HR was 2.13; for those with 5 to 10 years of exposure, the HR was 4.61. In women with more than 10 years of HT exposure, the HR was 1.81.¹⁴ The investigators concluded that the overall health risks exceeded the benefits of using E+P.

What is the effect of HT discontinuation on assessments of breast cancer risk found in the WHI? To determine the rate of persistence with HT, Pilon and colleagues conducted a study (prior to reports of the WHI) of 4,527 women from the Quebec health insurance database with a mean age of 50.2 years.²⁰ All had a low chronic disease score and were on social assistance. All women took estrogen orally, at a mean initial dosage of 0.625 mg/d. In this cohort, 57% of women discontinued treatment by the end of the first year, 43% continued with treatment for more than 1 year, and 20% continued treatment for more than 4 years. The investigators concluded that the persistence rate associated with HT is poor and that few women take it long enough to derive a preventive health benefit from it. Discontinuation of treatment was most commonly associated with adverse events, especially with higher-dose formulations and with resolution of menopausal symptoms. Lower-dose formulations are associated with a lower incidence of adverse events and are recommended to improve patient compliance.²⁰ As few women typically continue HT longer than a few years, and generally fewer than 5 years, the increased rates of breast cancer found in the WHI study, if real, would apply to a very small percentage of women starting HT.

**VENOUS THROMBOEMBOLISM**

Exogenous estrogen use is associated with an increased risk of VTE. This association, originally noted among women using oral contraceptives, was later found in women taking HT.²¹ In a systematic review and meta-analysis conducted for the US Preventive Services Task Force in 2002, Miller and coworkers confirmed the elevated risk of VTE in women on postmenopausal HT and also found evidence suggesting that the risk was highest during the first year of HT use.²¹ They estimated that current estrogen use was associated with a 2-fold increased risk for VTE.²¹ Results of the Estrogen and Thrombo-
Embolism Risk (ESTHER) Study Group were published in 2003. This case-control study was conducted in France and initially included 155 cases with VTE and 381 controls. Among women who had VTE, 21% were currently using oral HT compared with just 7% of women in the control group. In contrast, 19% of women with VTE and 24% of the control group were using transdermal estrogen. An odds ratio (OR) of 3.5 was associated with the use of oral and transdermal estrogen compared with nonuse of estrogen. Compared to users of transdermal estrogen, users of oral estrogen had 4 times the risk of VTE.

Canonico and colleagues recently performed a final analysis of the ESTHER trial with a larger pool of patients that included 208 hospital cases and 63 outpatient cases (271 total cases) from 1999 through 2006. Once adjusted for confounding factors including obesity, family VTE history, history of varicose veins, education, age at menopause, hysterectomy, and cigarette smoking, the OR of VTE with oral estrogen was found to be 4.2 (confidence interval [CI], 1.5-11.6), compared with 0.9 (CI, 0.4-2.1) for transdermal estrogen. Note that 12 cases and 7 controls who used oral estrogen combined with nortestosterone derivatives were excluded from this analysis of VTE risk.

Two additional multicenter case-control studies, both including postmenopausal women aged 45 to 70 years, were conducted among ESTHER participants. The impact of the route of estrogen administration on the association between a prothrombotic mutation (factor V Leiden or prothrombin G20210A mutation) and VTE risk was evaluated. During a 5-year period, 235 patients with a first documented episode of idiopathic VTE (128 with PE and 107 with deep venous thrombosis [DVT]) were recruited and matched with 554 controls. Patients with VTE were more likely than controls to have a higher BMI and a history of varicose veins. In the case group, 22% of patients were current users of oral estrogen and 25.5% were current users of transdermal estrogen.

Among women without a prothrombotic mutation, the adjusted OR for VTE associated with current use of transdermal estrogen was 1.2 (CI, 0.8-1.8), compared with 4.1 (CI, 2.4-7.1) for oral estrogen. Compared with nonusers without a prothrombotic mutation, the OR for a combination of current use of oral estrogen and the presence of 1 prothrombotic mutation was 25.5 (CI, 6.9-95.0). The OR for current users of transdermal estrogen with a prothrombotic mutation and for nonusers with a mutation were similar at 4.4 (CI, 2.0-9.9) and 4.1 (CI, 2.3-7.4), respectively. Thus, in women with a prothrombotic mutation included in this study, transdermal estrogen use did not increase the risk of VTE.

The impact of the route of administration on the association between an elevated BMI and VTE risk was evaluated in the second study. Over a 6-year period, 253 women with a first documented episode of idiopathic VTE (136 with PE and 117 with DVT) were recruited and matched with 597 controls. Mean BMI was higher among cases than controls (26.8 vs 24.5, respectively). Patients with VTE were more likely than controls to have a family history of VTE and varicose veins and to use oral estrogen. The most common estrogen therapy among current users was 17 beta-estradiol.
Compared with normal-weight nonusers, the OR for VTE risk further increased with a combination of oral estrogen use and overweight or obesity to 10.2 (CI, 3.5-30.2) and 20.6 (CI, 4.8-88.1), respectively. The risk for VTE in transdermal users with elevated BMI was similar to that of nonusers with increased BMI: OR = 2.9 (CI, 1.5-5.8) and OR = 2.7 (CI, 1.7-4.5), respectively. The OR for overweight was 5.4 (CI, 2.1-14.1) and for obesity, 4.0 (CI, 2.1-7.8).

THE CLINICAL PERSPECTIVE ON HT

The incidence of osteoporotic fracture in women is far greater than the incidence of heart attack, stroke, and breast cancer combined. Osteoporotic fractures are 3 times more common than heart attacks, 6 times more common than strokes, and 8 times more common than breast cancer. The WHI analyses may have undervalued the seriousness of osteoporotic fractures.

While there was no mortality increase in the WHI, 2 points should be noted. The mortality associated with colon cancer is greater than that with breast cancer. The 6-month mortality associated with hip fracture is greater than the 10-year mortality associated with stage 1 breast cancer. It is clear that the mortality improvement associated with HT and both colon cancer and hip fracture would more than offset any increased mortality from breast cancer.

CLINICAL APPLICATION

What do these findings mean in clinical practice? Patients with vasomotor symptoms can be treated with estrogen or E+P, as appropriate, after considering individual risks and benefits. Keep symptom amelioration in mind as the major goal of HT. An increased risk of breast cancer from HT should not be an issue for at least 5 years among women on HT and for at least 7 years for women taking only estrogen.

When determining whether to treat menopausal symptoms with HT, a clinician should first determine the patient’s CVD risk factors. HT is unlikely to increase CVD risk in a recently menopausal woman with slightly elevated lipid levels and no other CVD risk factors. Use of HT does not appear to pose a significant CHD risk in women who are less than 10 years post-menopausal. As time since menopause increases, so does risk for atherosclerosis and coronary events. The risk of thrombosis should be considered paramount, and patient age is a critical factor in determining risk for thrombotic stroke.

If a patient has no systemic symptoms, local therapy is preferred; for example, topically applied agents may be sufficient for vaginal atrophy, which can worsen over time. Using nonoral estrogen therapy, which includes patches, lotions, gels, and vaginal rings, among others, appears to greatly reduce the risk of thrombosis, which is the major risk associated with HT. Note, however, that the long-term benefits and risks of nonoral agents are unknown. To prevent osteoporosis, consider alternatives to HT, but individualize treatment.

Oral agents, which are metabolized primarily in the liver, are associated with increases in HDL cholesterol, decreases in LDL cholesterol, and increases in triglycerides. Low-dose oral HT has a slower
onset of symptom relief compared with standard dosages, but the risk of adverse events may be decreased. Nonoral HT agents bypass first-pass hepatic metabolism. Transdermal patches provide rapid symptom relief, with peak concentrations generally attained in 2 to 8 hours, after which levels tend to decrease.\textsuperscript{34} Patch location may affect absorption. Low levels have been reported in some patch users, possibly related to individual differences in skin and hair follicle characteristics.\textsuperscript{35} Patch-related skin irritations or adhesion problems have been reported in 20% to 40% of users.\textsuperscript{36}

Percutaneous gels are dispensed from a dose pump or individual packets or sachets and contain 17 beta-estradiol. Once applied, the gel is absorbed quickly without residue. Significant symptom relief is rapid. Steady systemic estradiol levels are maintained. Vaginal rings deliver 3-month supplies of HT and maintain stable serum concentrations. Circulating plasma estradiol levels are generally in the premenopausal range and are sufficient to maintain normal mucosa and prevent vaginal atrophy. The ring may be expelled and may cause local irritation.\textsuperscript{37-39}

Dosage, route of administration, and duration of therapy must be tailored to the patient. Guidelines from authoritative sources emphasize that HT should be used at the lowest effective dose for symptom relief over the shortest period of time (vasomotor symptoms generally subside within a few years).\textsuperscript{40,41}

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REFERENCES


A variety of hormone therapy (HT) options are available to help manage menopausal symptoms. These agents vary by formulation, dosage, and route of administration, as well as side-effect profiles.\textsuperscript{1-3} Research conducted since the Women’s Health Initiative findings first raised safety concerns about HT\textsuperscript{4} indicates that the relative risks and benefits of HT depend on the time elapsed since menopause, patient age at initiation of therapy, and duration of treatment.\textsuperscript{1,5,6}

We now understand that there are many reasons to individualize HT, including a woman’s age, her global health status, the age at which menopause occurred, and her specific symptoms and their severity. Other factors to be considered include comorbid conditions, family medical history, and other individual risk factors. Idiosyncratic reactions to specific formulations may cause a clinician to deviate from usual formulary preferences. Some patients express strong preferences for or against certain brands based on their beliefs or the experiences of friends and family. Cost must also be considered for patients who have limited or no pharmacy benefits.

The following clinical vignettes illustrate an evidence-based approach to selecting HT based on individual patient needs, including approaches to patients who request the so-called bioidentical hormones.

**VIGNETTE 1**

A 46-year-old woman with severe vasomotor symptoms has been treated with 0.625 mg of conjugated equine estrogen (CEE) daily and 5 mg of medroxyprogesterone acetate (MPA) 14 days a month for the past year. She has experienced good symptom relief but complains of irritability, anxiety, and breast tenderness beginning on the eighth day of her MPA cycle and increasing until 1 day after her last dose of MPA. She refers to MPA as “PMS in convenient tablet form.”

Her clinician switches her from cyclic MPA to continuous oral micronized progesterone (OMP) at a dosage of 100 mg each morning. When she returns 2 months later, her mood changes and breast tenderness have resolved. But now, despite good sleep patterns and regular exercise, she struggles with late-morning fatigue, which interferes with her work. While waiting for her follow-up visit, she conducted Internet research for a “natural” alternative to progesterone. She asks about advice she found on the Web site...
of an advocacy group called the Feminist Women’s Healthcare Center, which states: “…if you find you feel pretty good when you’re taking the estrogen but then really crummy when you start the Provera (a synthetic progesterone), you might want to switch to a natural, generic progesterone such as Pro-Gest cream (derived from Mexican wild yams).”

**The most effective way to mitigate progestin intolerance is to change progestins empirically.**

*Comment.* The simplest and most effective way to mitigate this patient’s progestin intolerance is to change progestins empirically, eg, by switching from MPA to OMP or norethindrone acetate (NETA). Studies that compared the side-effect profiles of MPA and OMP on mood and constitutional symptoms have had equivocal results. In the author’s experience, OMP is favored by the largest percentage of patients, followed by NETA. Combination formulas containing norgestimate or dros- pirenone may also be well tolerated but are available only in fixed combinations, so flexible dosing must be sacrificed. When progestin side effects continue despite drug changes, other approaches include:

- Decreasing the progestin cycle to 10 to 12 days
- Switching to progestin exposure once every 3 months
- Changing the timing of progesterone delivery
- Changing the route of progesterone delivery.

Although vaginal progesterone products such as tablets, bioadhesive gels, and capsules are not FDA-approved for menopausal HT, there is evidence that vaginal administration decreases adverse effects of OMP."10 Certain progesterone metabolites with unique pharmacologic activities are associated with the side effects observed with OMP (**Figure 1**). Allopregnanolone and its isomer allosteri-
cally modify the gamma-aminobutyric acid A (GABA_A) receptor in a manner analogous to that of benzodiazepines, and its activity is responsible for adverse central nervous system effects such as excessive sedation, dizziness, foggy head, and negative mood (paradoxical irritability or depressed mood). An agonist of the aldosterone receptor, 11-deoxycorticosterone, has been associated with edema. Circulating levels of progesterone and its pharmacologically active metabolites are strongly influenced by route of administration. Vaginal administration of progesterone sharply diminishes side effects caused by enteral progesterone metabolism. Because this route of administration is not FDA-approved and generally has lower patient acceptability, it is not recommended as a first-line method.

If percutaneous progesterone is used, transvaginal ultrasound or endometrial sampling is recommended at 6-month intervals.

On the basis of short-term studies in small numbers of patients, percutaneous progesterone has been investigated for HT, although data are not yet adequate to recommend its use. Further, even if long-term data in larger numbers of patients were available, the progesterone concentrations and formulations in the topical creams and gels have not been standardized. Over-the-counter progesterone products are categorized as cosmetics, and thus are not subject to meaningful external regulation. If percutaneous progesterone is used, transvaginal ultrasound or endometrial sampling is recommended at 6-month intervals.

**VIGNETTE 2**

A 48-year-old woman presents with severe vasomotor symptoms and sleep disruption. She has tried black cohosh root, wild yam cream, soy tablets, and dong quai for her symptoms, without relief. Last week she attended a seminar given by a local pharmacy and is now convinced that she wants to use bioidentical hormone replacement therapy (BHRT). She asks you to prescribe it for her.

**Comment.** The first step in individualizing therapy for this patient is good communication. What is she really asking for? Why is she asking for it? It is important to help her understand the scientific evidence surrounding BHRT and the FDA position on this therapy.

Patients typically define BHRT as nonsynthetic therapy that is custom-made in a compounding pharmacy. BHRT is usually promoted as HT that employs only the estrogen(s) naturally found in women, as well as natural progesterone and testosterone. Patients therefore perceive BHRT to be less dangerous than commercial HT preparations, especially CEE.

Patients often assume that compounded hormone formulations are better because they are custom-prepared for the individual rather than mass-produced. Patients who
have received a prescription for BHRT have commonly received a detailed pre- and post-therapy measurement of hormone levels (salivary or serum) to determine the proper prescribing levels and achieve “hormone balance.” BHRT advocates promote the scientifically unsubstantiated position that obtaining a proper ratio of hormones is as important as obtaining symptomatic relief. BHRT has been most visibly promoted by celebrity Suzanne Somers in her best-selling book The Sexy Years. Her endorsement of BHRT promises antiaging effects, restoration of a youthful appearance, fabulous sex, increased energy, and greater mental acuity. Many health care providers, including physicians, nurses, and pharmacists, also tout the superiority of BHRT.

Estriol is the linchpin of BHRT promotional efforts, and the component that most sharply differentiates it from conventional HT in the United States. Mass-market books, magazines, and local lectures tell women that estriol is the primary human estrogen, present in much greater serum concentrations than estradiol or estrone, even in nonpregnant women. BHRT most often consists of one of two estrogen combinations:

- Bi-est, 80% estriol + 20% estradiol
- Tri-est, 80% estriol + 10% estradiol + 10% estrone.

Data from 2 well-conducted studies, however, demonstrate that serum estriol levels are consistently present in lower levels than estradiol and estrone throughout the menstrual cycle.\(^{15,16}\)

The other major claim made by BHRT advocates is that estriol carries no risk of breast cancer—or even protects breast tissue against cancer.\(^{17}\) A comprehensive survey of more than 40 years of research on estriol found no evidence that it is a safer or breast-protective estrogen. All studies that have investigated the relationship of estriol and breast cancer in humans are population studies, and most of the studies intended to demonstrate a protective effect of estriol have failed to do so.\(^{18,19}\) Epidemiologic data show no benefit, or even adverse effects, associated with higher urinary estriol excretion in breast cancer patients compared to controls.\(^{20}\) Although research on estriol was abandoned 20 years ago, promoters continue to justify its clinical use based on 2 or 3 studies that are not representative of the total collected data.

The FDA calls estriol a misbranded drug because of unsubstantiated claims of efficacy, superiority, and bioidentity. Estriol is classed as an unapproved new drug under section 505 of the Food, Drug, and Cosmetic Act.\(^{21}\) In a warning letter to one of several compounding pharmacies, the agency wrote, "Compounding follows a practitioner’s deci-

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**TABLE 1. Transdermal vs. oral estradiol on lipid parameters**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>TC</th>
<th>LDL-C</th>
<th>TG</th>
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<tbody>
<tr>
<td>Oral estradiol 2 mg/d</td>
<td>32</td>
<td>-4.9%</td>
<td>-12.5%</td>
<td>+40.5%</td>
</tr>
<tr>
<td>Transdermal estradiol 50 µg/d</td>
<td>30</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>

LDL-C = low-density lipoprotein cholesterol; NS = not significant; TC = total cholesterol; TG = triglyceride. Bard JM, et al. 7th Congress Eur Assoc Ob Gyn; Helsinki, Finland; Abstract 28, 1992.
Even the lower doses of CEE now commonly used have a pronounced effect on triglyceride levels.

A Fresh Look at Hormone Therapy

VIGNETTE 3
A 38-year-old woman who had a total abdominal hysterectomy with bilateral salpingo-oophorectomy 5 months ago returns for a follow-up visit. After her surgery, she was started on oral estradiol, 1 mg/d. Her only other medication is hydrochlorothiazide, 12.5 mg/d. Her medical history is significant for hypertension and non–insulin-dependent diabetes, diagnosed 2 years ago, which she controls with diet and lifestyle changes. Her body mass index is 34 kg/m², and she has difficulty losing weight.

Between visits, she has seen her internist, who is upset that her previously normal triglyceride level now exceeds 220 mg/dL. Her diet and glucose control are unchanged. Although fully recovered from surgery, she complains of persistent diminished sexual interest and increased difficulty with orgasm. Her pelvic exam is normal and shows well-estrogenized vaginal epithelium.

Comment. Lipid metabolism begins in the hepatocyte, where apoproteins such as apo B-100 are synthesized and then undergo lipidation by cholesterol and triglycerides from intracellular lipid stores. After lipid and protein are assembled into lipoproteins, the particles can travel through the bloodstream to target tissues. Through the hepatic first-pass effect, oral administration of estrogen can dramatically increase hepatic triglyceride synthesis and very-low-density lipoprotein (VLDL) cholesterol production. Women with certain metabolic phenotypes are especially prone to triglyceride and VLDL excess. These include women with diabetes, metabolic syndrome, or a personal history of polycystic ovary syndrome, among others. Estradiol delivery routes may have differential effects on the lipid profile (Table 1).

Although oral estradiol lowers LDL-C levels, a dramatic increase in triglyceride-rich lipoproteins can also occur. In contrast, while transdermal estradiol does not lower LDL-C, it has neutral effects on triglyceride levels. Oral estrogen products should be avoided in patients with known hypertriglyceridermia, and women at increased cardiovascular risk require monitoring of the lipid profile after initiation of estrogen treatment. Even the lower doses of CEE now commonly used have a pronounced effect on triglycerides.

Sex steroid hormone-binding globulin (SHBG) synthesis, along with several other hepatic proteins, is also strongly induced by oral estrogen. Transdermal estrogen usually produces no significant changes, however. Since SHBG is the primary serum-binding and transport protein for testosterone, the increase in SHBG seen with oral estrogen lowers free testosterone levels.
women report clinical sensitivity to these changes and experience diminution of sexual arousability and difficulty with orgasm. Clinical studies of testosterone supplementation have shown mixed results, and no FDA-approved testosterone treatment for women exists. After a thorough evaluation, one initial approach to women with arousal difficulties is to consider the possible iatrogenic effects of oral estrogen. Replacing it with transdermal estrogen should increase free testosterone levels. Success is determined by patient self-report after a trial of several months.

VIGNETTE 4
A long-standing 41-year-old patient says she is fed up with the “crazy periods” she has had over the past 6 months. Her menstrual cycle has decreased to 23 days and she has spotting between periods. She also has a long history of menstrual migraine without focal neurologic signs, and she now has several headaches a month, rather than her typical one. Between her erratic bleeding and headaches, she feels as though she can hardly find a day when she feels like being with her new sexual partner.

Comment. Combined oral contraceptive pills (COCPs) offer many noncontraceptive benefits, including decreased risk of uterine and ovarian cancer, suppression of ovarian cysts and fibroids, menstrual cycle control, and prevention of dysmenorrhea. The benefits may be even more numerous in perimenopause, which is characterized by frequent and unpredictable variations in sex hormone levels, especially estrogen. By suppressing ovarian steroidogenesis, a COCP can dampen the hyperestrogenic states common in early perimenopause and may facilitate a symptom-free transition into the hypoestrogenic environment of late perimenopause. Large fluctuations in circulating estrogen levels, as occur in perimenopause, are a known migraine trigger in susceptible women. COCPs have a bad reputation with migraine patients, but this may be attributable to previous experience with 21/7 formulations. Recent prospective data have shown that migraine frequency is diminished when women use COCP continuously, or with a pill-free interval of no more than 3 days. COCPs should not be given to women with a history of focal neurologic events associated with migraine, such as vision loss or limb weakness. Additionally, women with risk factors for cardiovascular disease should be evaluated and treated before consideration of COCP use. Many perimenopausal women are very receptive, especially after a lifetime of periods, to long-cycle or continuous use of COCPs. However, breakthrough bleeding is a common and vexing problem. A single 3-day
break in pill use is 90% effective in resolving breakthrough bleeding, with only a transient increase in vaginal bleeding.

COCPs continue to provide highly effective contraception, an important consideration for perimenopausal women. In 2001, 70,000 unintended pregnancies occurred in women above 40 years of age in the United States. It is critical to explain this to women who may believe that irregular periods and hot flashes mean they cannot get pregnant.

The increasing number of hormonal therapy options for menopausal symptoms enhances the physician's ability to individualize treatment recommendations that minimize potential risk and diminish the likelihood of side effects. Careful clinical evaluation and good communication with patients predict successful outcomes for patients who require and want hormone therapy.

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REFERENCES

CME/CE Questions
A Fresh Look at Hormone Therapy

1. Which statement is true?
   A. Women overestimate their risk of coronary heart disease (CHD).
   B. Women underestimate their risk of CHD.
   C. Women underestimate their risk of breast cancer.
   D. Women don’t think about CHD or breast cancer risk.

2. When looking at the association between cardiovascular disease and use of hormone therapy (HT) according to age and years since menopause, Women’s Health Initiative (WHI) investigators found that cardiovascular disease risk did not increase with the use of HT among women
   A. Close to menopause
   B. 10 years past menopause
   C. 12 years past menopause
   D. 15 years past menopause

3. The WHI and Nurses’ Health Study (NHS)
   A. Had similar study populations.
   B. Had similar findings about the benefits of estrogen.
   C. Differed with respect to their study populations and findings.
   D. Were both designed to examine primary prevention of breast cancer.

4. The major risk associated with HT is
   A. Thrombosis
   B. Breast cancer
   C. Stroke
   D. Migraine

5. The major goal of HT is:
   A. CVD prevention
   B. Symptom amelioration
   C. Fracture reduction
   D. Venous thromboembolism (VTE) prevention

6. Data indicate that the elevated risk of VTE associated with HT use is attributable to:
   A. Route of administration
   B. Amount of estrogen
   C. Type of estrogen
   D. Time of day dose taken

7. Which of the following is NOT a recommended management strategy for a patient who does not tolerate progestin well?
   A. Switching from one type of progestin to another.
   B. Eliminating progestin from the regimen, since evidence in favor of its use is equivocal.
   C. Decreasing the length of the progestin cycle.
   D. Changing the route of progesterone delivery.

8. Which of the following statements is false?
   A. Allopregnanolone is responsible for the CNS effects associated with oral micronized progestin.
   B. The vaginal route of progesterone administration is associated with fewer side effects than the oral route.
   C. The vaginal route of progesterone administration is approved by the FDA.
   D. An agonist of the aldosterone receptor, 11-deoxy-corticosterone, has been associated with edema.

9. Bioidentical hormone therapy is
   A. Typically promoted as having only natural equine hormones.
   B. Approved by the FDA.
   C. Perceived by patients as being less dangerous than commercially available hormone preparations.
   D. Supported by robust efficacy data.

10. Oral administration of estrogen can
    A. Increase hepatic triglyceride synthesis and very-low-density lipoprotein cholesterol production.
    B. Decrease hepatic triglyceride synthesis and very-low-density lipoprotein cholesterol production.
    C. Decrease hepatic triglyceride synthesis and high-density-lipoprotein-cholesterol production.
    D. Decrease both hepatic triglyceride synthesis and very-low-density-lipoprotein-cholesterol production.
**Answer Sheet**

A Fresh Look at Hormone Therapy

**Instructions:** Please complete this form and return it to the address or fax number below.

**Scale:** P = Poor; F = Fair; G = Good; VG = Very Good; E = Excellent

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<td>1 Evaluate the risks and benefits of hormone therapy (HT) for each patient, according to her specific needs and treatment goals</td>
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<td>2 Differentiate among the available hormone formulations, dosage levels, and routes of administration to identify appropriate options for each patient</td>
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<td>3 Identify the effect of progestogens on the endometrium</td>
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<td>4 Counsel patients on how the benefits and risks of therapy may affect them individually, based on women’s needs for menopausal symptom management</td>
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<td>5 Discuss current evidence-based expert opinion on bioidentical hormones</td>
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**Post-Test Responses**

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