

## Current Concepts in Postmenopausal Hormone Replacement Therapy

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As more women are living longer, there is an increasing need for women to discuss hormone replacement therapy (HRT) with their physicians. This task is complicated by areas of scientific uncertainty and evolving data concerning the risks and benefits of HRT. Benefits of HRT that are supported by strong scientific evidence include relief from menopausal symptoms such as hot flashes, prevention of osteoporosis, cardioprotective effects, relief of urogenital atrophy, and decreased urinary incontinence. Benefits supported by observational evidence include improvement of emotional lability and depression, improved sense of well-being in patients with rheumatoid arthritis, increased dermal and total

skin thickness, improved verbal memory skills, and decreased risk of colon cancer. Risks to consider include a possible increase in the incidence of breast cancer and an increase in endometrial cancer in women who have an intact uterus and do not receive a progestin. Women in various risk groups, such as those at risk for coronary artery disease, osteoporosis, or breast cancer, must consider the risk-to-benefit ratio for their own individual circumstances.

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A growing number of women are living longer after their reproductive years, and physicians find themselves increasingly needing to intelligently discuss the issue of hormone replacement therapy (HRT). Scientific uncertainty and evolving data concerning some of the risks and benefits of replacement therapy make this task difficult. Physicians must carefully discuss the risks and benefits and address four major areas of concern about HRT with their patients: "How will HRT help me?" "How will it hurt me?" "Is it right for me?" and "How do I take it?" After informed consideration, patients can reasonably decide whether to use HRT and, if so, select an appropriate regimen.

### Background

Two hundred years ago, only 30% of women lived long enough to reach menopause, whereas 90% of today's women will experience the climacteric.<sup>1</sup> Although menopause is not a disease, it is an estrogen-deficient state and, as such, has many adverse health consequences. Estrogen replacement therapy (ERT) and combination estrogen and progesterone therapy, also known as HRT, will ameliorate many of these adverse consequences but also may increase other risks.

The menopausal period is not just a point in time defined by the cessation of menses; it is a period in a woman's life that extends from the cessation of menses until her death and involves distinct and evolving health issues. Menopause is diagnosed by amenorrhea of greater than 12 months or amenorrhea combined with a follicle-stimulating hormone (FSH) level above 40 pg/mL. Hot flashes and emotional lability may become apparent before the cessation of menses. Other changes such as bone loss, coronary artery disease, and urogenital atrophy may not become evident for years. When considering whether to use HRT, it is important

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to remember that good health is not the same as absence of disease. Hormone replacement therapy can improve a woman's quality of life and prevent the long-term effects of estrogen deficiency.

## Benefits: How Will HRT Help Me?

Our understanding of the benefits of HRT has expanded greatly in the last 5 years. Effects of HRT can be measured in the potential for lives saved or lost, but it also may improve many harder to measure quality-of-life factors. Estrogen replacement therapy has been shown to decrease overall mortality in users, especially with long-term use.<sup>2,3</sup> It is important for physicians to provide as complete a picture of benefits as possible so that patients can make a truly informed decision.

### *Benefits Supported by Strong Scientific Evidence*

#### HOT FLASHES

Along with emotional lability, hot flashes are one of the main perimenopausal symptoms that lead women to seek HRT. Although the mechanism of hot flashes and how HRT prevents them is not well understood, new evidence suggests that estrogen may cause relaxation of vascular smooth muscle.<sup>5</sup> Studies by Gilligan et al<sup>4</sup> have demonstrated that estrogen reverses postmenopausal impairment of acetylcholine-mediated vasodilatation and potentiates endothelium-dependent vasodilatation.

#### OSTEOPOROSIS

The strongest evidence for long-term physical benefits of HRT is the prevention of osteoporosis. In fact, estrogen is often considered the drug of choice for treating osteoporosis.<sup>6</sup> Hormone replacement therapy stops excessive loss of bone matrix that occurs in women with low-estrogen states and, if started within 3 years of the onset of menopause, may actually reverse bone loss.<sup>4,6</sup> Continued bone loss and risk of vertebral and hip fractures are significantly reduced with HRT, but bone loss resumes upon discontinuation of therapy.<sup>4,7</sup> The greatest benefit is obtained in the first 5 to 7 years postmenopause.<sup>4,8</sup> Estrogen also seems to decrease the bone loss associated with thyroid hormone replacement therapy.<sup>9</sup>

#### CARDIOVASCULAR DISEASE

An unfavorable cholesterol profile in a postmenopausal woman can be favorably altered with HRT. Estrogen use results in increased high-density lipoproteins (HDL) and decreased low-density lipoproteins (LDL).<sup>6,7,10</sup> Both low

HDL and high LDL levels are independent risk factors for coronary artery disease (CAD) and stroke. The recently reported Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial was a multicenter, placebo-controlled, double-blinded, randomized study designed to assess the effect of estrogen alone and estrogen/progestin combinations (including continuous-dose medroxyprogesterone) compared with placebo on cardiac risk factors such as low HDL and elevated LDL, systolic blood pressure, insulin levels, and fibrinogen levels.<sup>10</sup> There was no significant demonstrated effect on insulin levels or blood pressure. All the regimens, however, showed favorable effects on lipids and fibrinogen, with estrogen alone having the greatest effect on HDL cholesterol, and estrogen plus micronized progesterone showing the next most substantial improvement. A significant increase in triglycerides was found in all estrogen users, but this increase did not reach levels usually associated with pancreatitis.

The combination of increased HDL, decreased LDL, increased vasodilatation, and decreased fibrinogen levels could potentially lower a woman's risk of CAD and stroke.<sup>4,10</sup> Overall, ERT is associated with a 40% to 60% reduction in CAD and a 31% decrease in the incidence of stroke.<sup>3,4,11</sup> Although the addition of progestins may somewhat lower some cardioprotective effects, HRT still conveys a protective effect.<sup>7,10,12</sup>

#### UROGENITAL ATROPHY

Urogenital atrophy is another common postmenopausal problem that is relieved by HRT and commonly overlooked by physicians. Sexual activity may continue late into life, but genital changes caused by relative estrogen deficiency can compromise sexual functioning. Under the influence of estrogen, the vaginal epithelium is thicker, more elastic, has greater lubricating ability, and contains more glycogen stores.<sup>13</sup> Hormone replacement therapy also relieves the urethral syndrome and decreases the frequency of urinary tract infections.<sup>4</sup>

Atrophic vaginal or cervical epithelium may also cause Papanicolaou (Pap) smears to be abnormal. Colposcopists often prescribe estrogen for 2 to 4 weeks before a colposcopic examination in order to "normalize" the epithelium before the examination. This therapy is generally assumed to be safe even if dysplasia or cancer is present because the duration of therapy is short and these lesions do not express any more estrogen receptors than does normal cervical tissue.<sup>14</sup>

#### INCONTINENCE

Urinary incontinence affects 15% to 35% of noninstitutionalized women over the age of 60 years. Meta-analysis of available trials of postmenopausal estrogen on urinary

incontinence demonstrate a significant improvement in subjective symptoms in all patients and in patients with genuine stress incontinence. There was no significant change in the quantity of fluid lost, but there was a significant effect on maximal urethral closure pressure.<sup>13</sup>

### *Benefits Supported by Observational Evidence*

#### DEPRESSION

Emotional lability, depression, and a decreased sense of well-being are common during the perimenopausal period, but HRT can decrease these potential stress responses in women with ovarian failure.<sup>15</sup> Many studies also have shown an increase in the sense of well-being, energy level, and sleep patterns in patients treated with HRT.<sup>4,16,17</sup> Ditkoff et al<sup>17</sup> reported a double-blind, placebo-controlled trial that demonstrated a significant increase in well-being, as measured on the Profile of Adaptation to Life test ( $P < .05$ ) and a decrease in depressed mood on the Beck Depression Inventory ( $P < .05$ ) in women on HRT. All these factors may contribute to an improved quality of life for treated patients.

#### RHEUMATOID ARTHRITIS

Hormone replacement therapy has been shown to decrease osteoporosis, increase articular index, and improve sense of well-being in patients with rheumatoid arthritis.<sup>16,18</sup> In these patients, the decrease in bone loss is most evident in the vertebral spine.<sup>18</sup> No changes have been demonstrated in indicators of disease such as C-reactive protein or sedimentation rate.<sup>16,18</sup> Unlike studies in animal models, human studies do not show that HRT prevents rheumatoid arthritis.<sup>19</sup>

#### MISCELLANEOUS

With billions of dollars spent each year on antiaging products, it is important to note any drug effect that improves skin appearance. Estrogen has been shown to significantly increase dermal and total skin thickness, which may decrease the appearance of wrinkles.<sup>20</sup> Estrogen replacement therapy has also been shown to improve verbal memory skills in healthy postmenopausal women.<sup>21</sup> Hormone replacement therapy may lower the risk of colon cancer<sup>22</sup> and delay the onset of diabetes mellitus.<sup>7</sup>

### **Risks: How Could HRT Hurt Me?**

Since fear is a stronger human motivator than long-term gain, patients often decide whether to use a therapy such as HRT based more on the risks and possible side effects

than on the benefits. There is no evidence that HRT increases hypertension or clotting abnormalities.<sup>4,6,7</sup> Common possible side effects, however, include withdrawal bleeding with cyclic dosing; spotting during the first 3 to 6 months or longer with combined continuous therapy; mastalgia; edema; abdominal bloating; and increase in the size of uterine leiomyomata. Hormone replacement therapy rarely aggravates symptoms of anxiety and depression.<sup>6</sup> Although there is no increase in asymptomatic gallstones, a 2.7-fold increase (3.4% to 9.8%) in the number of cholecystectomies performed in women using HRT has been noted.<sup>7</sup>

### *Breast Cancer*

A possible increase in the incidence of breast cancer in women on HRT has long been a concern. This issue is very controversial because most studies are observational, the number of subjects is generally small, there are conflicting results from many of the studies, and the number of women who develop breast cancer is so great that even a small change in the incidence of the disease will affect a large number of women. Although some early studies, especially those performed in Europe, demonstrated an increase in breast cancer risk in current users of HRT, many of these studies used unopposed estrogens of types not commonly prescribed in the United States. There have been many studies since then that have shown no increase or possibly a decreased risk of breast cancer.<sup>1,2,3,24</sup>

Unfortunately, the role of HRT as a cause of breast cancer is still unclear. There is no consistent or conclusive effect in women with surgical menopause, benign breast disease, family history of breast cancer, or prolonged estrogen use.<sup>6,23</sup> Only one of three major meta-analyses performed on HRT effects on breast cancer in 1991 and 1992 has shown an increased risk, and this was only after at least 14 years of use. Another study that spanned 22 years found no increase in risk.<sup>4,24,25</sup> Two new studies were published in 1995, but they have not further clarified the situation. The follow-up to the Nurses Health Study found an increase in the relative risk of breast cancer for current users who have been using HRT for more than 5 years, especially in older women.<sup>26</sup> Another study found no increase in the incidence of breast cancer among current users and that HRT may be protective in women after 8 or more years of use.<sup>27</sup>

### *Endometrial Cancer*

Unopposed estrogen therapy has been associated with endometrial cancer in women with an intact uterus. Endometrial hyperplasia, which is thought to be a precursor

to cancer, occurs in 20% to 30% of patients who receive unopposed estrogen therapy. Although women who develop endometrial carcinoma while on estrogens have a more favorable prognosis compared with untreated women who develop this disease, some cancers are still invasive.<sup>4</sup> Adding 10 to 15 days of a progestin per month, or continuous progestin, actually carries a lower risk of hyperplasia and carcinoma than not using estrogens.<sup>4,6,7,10,28</sup>

## Patient Selection: Is HRT Right for Me?

Good health is more than just the absence of disease. Part of the decision to use estrogen may be based on the improvement in well-being and quality of life that have been demonstrated in most HRT studies. Decision analysis has shown, however, that estrogen replacement<sup>29</sup> and estrogen and progestin replacement<sup>29,30</sup> result in substantial increases in life expectancy. If the patient has no contraindications to therapy and is willing to assume the effort and cost of long-term therapy, all of the beneficial effects of HRT should be considered. Women in different risk groups, such as those at risk for coronary artery disease, osteoporosis, or breast cancer, must factor their personal risk-to-benefit ratio into their decision.

Hormone replacement therapy may be started anytime in a woman who has ceased menstruating, or it may be used when a patient starts experiencing symptoms related to menopause. Estrogen and progestin supplementation has long been prescribed for mid-period spotting and for dysfunctional uterine bleeding. For these purposes, postmenopausal HRT doses may be continued in women who do not respond to short courses of therapy. For menstruating women who develop hot flashes, low-dose estrogen may ameliorate this symptom.

Contraindications to HRT include pregnancy, undiagnosed abnormal genital bleeding, impaired liver function, acute thromboembolic disease, history of thromboembolic disease with hormone use, and a history of breast or endometrial carcinoma. Cyclic estrogen is relatively contraindicated in women with a history of endometriosis because of possible reactivation of the disease. It is also not recommended in women with active gallbladder disease because of changes in the bile and should be used cautiously in patients with uterine leiomyomata or a history of menstrual migraines.<sup>4</sup>

### *Survivors of Breast Cancer*

The standard of care in the United States is to discourage the use of HRT in survivors of breast cancer, and the

American College of Obstetrics and Gynecology considers breast cancer to be a contraindication to HRT. Many researchers postulate that when a patient is "cured" of breast cancer, there are actually minimal micro-metastases at "immunologic peace" with the body. This explanation would account for the long disease-free intervals associated with this disease.<sup>1</sup> It is feared that adding HRT could upset this balance. There is, however, some observational evidence that HRT may be safe after a 5-year disease-free interval.<sup>31</sup> Some researchers have called for further outcomes research, since this concern is based more on theoretical considerations than clinical findings and most of the research does not address the lifesaving noncancer effects of HRT.<sup>1,31,32</sup> There is currently insufficient information to justify definitive statements.

## Dosage and Administration: How Do I Take It?

Estrogens from animal sources have been widely available in oral form for many years. Now oral forms are also derived from plant sources or are chemically synthesized. Oral estrogens must pass through the liver after absorption, which causes measurable changes in clotting factors, but these changes are unlikely to result in any clinically significant effect.<sup>4,6</sup> There is no major demonstrable advantage to other dosing routes for the typical patient except patient preference and convenience. Typical starting dosages are shown in the Table.

Oral estrogens were first derived from pregnant mares' urine, which continues to be a major source. Some animal rights groups object to conjugated equine estrogens on the grounds that collection of the mares' urine is cruel to the animals because it requires they be stabled several months of the year. Veterinary and Canadian animal welfare organizations dispute the position of the animal rights groups, stating that the mares are at least as well cared for as other horses in similar circumstances.<sup>33</sup>

Transdermal estrogen patches relieve hot flashes and improve cholesterol levels and bone density without causing blood clotting changes. Their positive cholesterol effects may be less than with oral estrogens<sup>6</sup> but they have almost no effect on serum triglycerides.<sup>4</sup> The patches also may cause skin irritation, but this problem can be avoided by placing the patch on the buttocks and regularly rotating application sites.

Intravaginal estrogens are effective in relieving local symptoms of estrogen deficiency but do not have a major effect on other factors except in long-term or large doses. Histologic and cytologic changes associated with estrogen deficiency, which can be misinterpreted as inflammation or dysplasia, are greatly reduced after only a few

Table. Commonly Used Hormone Replacement Drugs, Typical Dosage Ranges, and Costs

Replacement Hormone (Trade Name)	Dosage	Cost Per Month, \$*
<b>Estrogens</b>		
Conjugated equine estrogens (Premarin)	0.625–1.25 mg/d	11.05
Esterified estrogens (Estratab, Menest)	0.625–1.25 mg/d	8.11
Estradiol—Micronized (Estrace)	1–2 mg/d	9.56
Estradiol—Transdermal (Estraderm)	0.05–0.1 twice weekly	18.38
Estropipate (Ogen, Ortho-Est)	0.625–1.25 mg/d	15.37
<b>Progestins</b>		
Medroxyprogesterone acetate (Provera, Cycrin, Amen)	5–10 mg daily	8.64–15.58
Medroxyprogesterone acetate (Provera, Cycrin, Amen)	10 mg for 10–14 days/mo	3.08–5.57
Norethindrone acetate (Aygestin)	5–10 mg for 10–14 days/mo	10.27
<b>Combined</b>		
Conjugated equine estrogens (Premphase)	0.625 mg estrogen (28 pills) with 5 mg medroxyprogesterone acetate added to 14 of the 28 pills	16.39
Conjugated equine estrogens (Prempro)	0.625 mg estrogen and 2.5 mg medroxyprogesterone acetate (28 pills)	17.88

\*Average wholesale cost to the pharmacy for a 1-month supply of the medication.

Data in table from The 1996 Drug Topics Red Book, Medical Economics Inc, Montvale, NJ, 1996.

weeks of estrogen therapy. Short-term application of intravaginal estrogens after a minimally abnormal Pap smear is often used to “normalize” the cervical epithelium.

### Estrogen

Commonly used estrogens are shown in the Table. It was once thought that cyclic estrogens, ie, estrogens given for 25 days each month with a 5-day drug-free period, might prevent an increased risk of breast cancer, but subsequent studies showed no such benefit.<sup>23,24</sup> The justification for cyclic administration was the belief that this regimen simulated a “normal cycle”; however, the amount of estradiol in the blood from HRT is usually below the amount present during menses in a premenopausal woman. Today, many physicians advocate the use of continuous estrogen therapy because there are no proven benefits to the drug-free intervals, the cyclic regimen is more complex and harder to comply with, and symptoms may recur during this period.<sup>35</sup>

### Progesterone

Since unopposed estrogens are associated with endometrial hyperplasia and carcinoma, women with an intact uterus should also be given a progestin.<sup>6,28,34,35</sup> Regardless of the regimen, the lowest possible dose of progestin that protects against endometrial hyperplasia should be used in order to minimize adverse cardiovascular effects.<sup>6</sup> In the perimenopausal period (approximately 2 years before and after menses cessation), cyclic progestins given for 10 to 14 days each cycle are the preferred method of

therapy. Typical starting dosages are shown in the Table. In women who have had a hysterectomy, progestins should not be added.<sup>34,35</sup>

Beyond the perimenopausal period, amenorrhea can be achieved with continuous progestin therapy. Therefore, progestins can be given cyclically or continuously every day.<sup>36</sup> Although spotting is common during the first 6 months of combined continuous HRT, 75% to 90% of users will experience amenorrhea within 1 year.<sup>36</sup> Studies have shown that continuous combined estrogen and progestin therapy provides equal endometrial protection and increases patient compliance as compared with cyclic dosing of progestins.<sup>4,6,28,37,38</sup> Continuous therapy is beneficial in treating hot flashes, alleviating urogenital atrophy, lowering LDL cholesterol, and halting the development of osteoporosis.<sup>6,28,37,38</sup> The most commonly used progestin in the United States is medroxyprogesterone acetate at a dose of 2.5 mg or 5 mg daily. Because there is a slightly higher rate of spotting and fewer women achieve amenorrhea at 1 year with the 2.5 mg dose, the 5 mg dose is sometimes preferred.<sup>37</sup> The PEPI trial demonstrated that micronized progesterone has the most beneficial effect on HDL cholesterol, but this preparation is not widely available in the United States.<sup>10</sup> If a woman on continuous combined therapy experiences uterine bleeding beyond 6 months after cessation of menses, an endometrial biopsy is mandatory.<sup>35,39</sup>

Studies have been conducted using progestins every 2 to 3 months instead of monthly or continuously.<sup>7,40</sup> Although there are minimal side effects with this regimen and endometrial hyperplasia rates are less than with ERT,

hyperplasia is more common than with typical HRT regimens.

### Androgens

Although the addition of supplemental androgens to ERT has received much attention in the lay press, there is little scientific information in the medical literature to support it. There are concerns about correct dosing, patient selection, and adverse side effects, especially on lipids and cardiovascular disease. Small, placebo-controlled, crossover studies comparing the estrogen-androgen combination with estrogen alone and with placebo have demonstrated increases in energy levels, sense of well-being, rates of sexual desire, and sexual arousal.<sup>41,42</sup> Another recent study showed a significant increase in spinal bone mineral density and improvement in menopausal symptoms but also revealed decreases in HDL cholesterol.<sup>43</sup> There is a recent trend to use lower doses of androgens, ie, 2.5 mg of methyltestosterone every day, in postmenopausal replacement therapy.

### Alternative Therapies

Not all women will accept or tolerate HRT. For these women, there are alternative treatments for menopausal symptoms. Alternative drugs for treating hot flashes include clonidine<sup>4</sup> and progestins, such as megestrol acetate.<sup>44</sup> Lubricants can counteract vaginal dryness, and Kegel exercises or surgery may help with incontinence. Regular weight-bearing exercise coupled with 1500 mg of calcium and 400 IU of vitamin D per day can decrease bone loss. The drugs alendronate sodium (Fosamax) and calcitonin-salmon nasal spray (Miacalcin Nasal Spray) have recently been approved for the treatment of osteoporosis. Regular exercise, good diet, and not smoking will help prevent heart disease and are recommended for all patients, regardless of the use of HRT.

### Conclusions

Hormone replacement therapy offers many potential health and quality-of-life benefits to postmenopausal women. A woman's health care provider must carefully discuss the risks and benefits of HRT with each patient so that she can weigh the facts for herself. By considering personal disease risk factors and potential life-saving and quality-of-life benefits, each patient can then make an appropriate informed choice.

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