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## Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society

### Abstract

**Objective**—To update for both clinicians and the lay public the evidence-based position statement published by The North American Menopause Society (NAMS) in March 2007 regarding its recommendations for menopausal hormone therapy (HT) for postmenopausal women, with consideration for the therapeutic benefit-risk ratio at various times through menopause and beyond.

**Design**—An Advisory Panel of clinicians and researchers expert in the field of women's health was enlisted to review the March 2007 NAMS position statement, evaluate new evidence through an

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evidence-based analysis, and reach consensus on recommendations. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees as an official NAMS position statement. The document was provided to other interested organizations to seek their endorsement.

**Results**—Current evidence supports a consensus regarding the role of HT in postmenopausal women, when potential therapeutic benefits and risks around the time of menopause are considered. This paper lists all these areas along with explanatory comments. Conclusions that vary from the 2007 position statement are highlighted. Addenda include a discussion of risk concepts, a new component not included in the 2007 paper, and a recommended list of areas for future HT research. A suggested reading list of key references is also provided.

**Conclusions**—Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable close to menopause but decreases with aging and with time since menopause in previously untreated women.

### Keywords

Menopause; Perimenopause; Estrogen; Progestogen; Hormone therapy; Hormone replacement therapy; Vasomotor symptoms; Vaginal atrophy; Sexual function; Urinary health; Quality of life; Osteoporosis; Coronary heart disease; Venous thromboembolism; Stroke; Total mortality; Diabetes mellitus; Endometrial cancer; Breast cancer; Mood; Depression; Dementia; Cognitive decline; Premature menopause; Premature ovarian failure; Bioidentical hormones; Postmenopause; Women's Health Initiative; NAMS

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The North American Menopause Society (NAMS), a nonprofit scientific organization, published position statements on the role of menopausal hormone therapy (HT) in October 2002 (*Menopause* 2003;10:6–12), September 2003 (*Menopause* 2003;10:497–506), October 2004 (*Menopause* 2004;11:589–600), and March 2007 (*Menopause* 2007;14:168–182). The goal of these position statements was to clarify the benefit-risk ratio of HT—as either estrogen therapy (ET) or combined estrogen-progestogen therapy (EPT)—for both treatment of menopause-related symptoms and disease prevention at various times through menopause and beyond.

Because of the rapidly evolving data affecting the benefit-risk ratio of HT and clinical management of aging women, the NAMS Board of Trustees recognized a need to update its position statement and convened a fifth Advisory Panel to provide recommendations and also place therapeutic risks into perspective for both clinicians and the lay public. The Panel's recommendations were reviewed and approved by the 2007–2008 NAMS Board of Trustees.

The Society's position statements provide expert analysis of the totality of the data, including the most recent scientific evidence, in an attempt to assist healthcare providers in their practices. They do not represent codified practice standards as defined by regulating bodies and insurance agencies.

### METHODOLOGY

An Advisory Panel of clinicians and researchers expert in the field of women's health was enlisted to review the March 2007 NAMS position statement, evaluate literature published subsequent to the previous position statement of 2007, conduct an evidence-based analysis, and attempt to reach consensus on recommendations.

A comprehensive literature search was conducted using the database MEDLINE with appropriate search words—including menopause, perimenopause, postmenopause, estrogen, progestogen, hormone therapy, hormone replacement therapy, vasomotor symptoms, vaginal atrophy, sexual function, urinary health, quality of life, osteoporosis, coronary heart disease, venous thromboembolism, stroke, total mortality, diabetes mellitus, endometrial cancer, breast cancer, mood, depression, dementia, cognitive decline, premature menopause, premature ovarian failure, natural hormones, bioidentical hormones, and Women’s Health Initiative—to identify all new papers published subsequent to the 2007 position statement. Some relevant papers were also provided by the panelists. Limitations included a scarcity of randomized prospective study data on the consequences of long-term use of HT when prescribed for symptom management or disease risk-reduction outcomes. In addition, evidence-based medicine implies that recommendations be limited to the women for whom the studies are relevant. Although this goal is ideal in principle, it is impossible in practice, given that there will never be adequate randomized, controlled trials (RCTs) to cover all populations, eventualities, drugs, and drug regimens. The practice of medicine is ultimately based on the interpretation at any one time of the entire body of evidence currently available.

NAMS recognizes that no trial data can be used to extrapolate clinical management recommendations for all women and that no single trial should be used to make public health recommendations. There are many observational studies, but, because the trials within the Women’s Health Initiative (WHI) are for some outcomes the only large, relatively long-term RCTs to date of postmenopausal women using HT, there was a necessity to give these findings prominent consideration among all the studies reviewed in the development of this paper. It is also recognized that the WHI trials have several characteristics that limit the ability to generalize the findings. These include the use of only one formulation of estrogen (conjugated estrogens [CE]), alone or with one progestin (medroxyprogesterone acetate [MPA]), and only one route of administration (oral). Moreover, women studied in the WHI were older (mean age, 63 y)—mostly more than 10 years beyond menopause, with more risk factors than younger women who typically use HT for menopause symptoms. They were also largely without menopause-related symptoms.

After considering all the evidence, the Panel provided its recommendations, which were reviewed and approved by the NAMS 2007–2008 Board of Trustees as an official NAMS position statement.

This position statement focuses on the use of HT products available by prescription in the United States and Canada. A current listing of these products is posted on the NAMS Web site (<http://www.menopause.org/edumaterials/hormoneprimer.aspx>). This paper does not include other hormones, such as estrogen agonists/antagonists (formerly called selective estrogen-receptor modulators), those available without a prescription (including phytoestrogens), and testosterone therapy, the latter having been addressed in a previous NAMS position statement (*Menopause* 2005;12:497–511).

The most current published references regarding HT use are found at the end of this statement.

## Terminology

NAMS strongly recommends use of uniform and consistent terminology when describing HT (see Table 1). Definitions for additional potentially confusing terminology used in this paper are found in Table 2.

## Understanding risk

Confusion can arise among healthcare providers, the lay public, and the media when general concepts of risk are discussed. Understanding HT risks in particular is critical to clinical decision making around menopause and beyond. Since these issues are crucial to a discussion of the role of HT in an individual woman, this position statement addresses risk concepts in a special addendum to this paper (see Addendum A).

## BENEFITS AND RISKS OF HT

Use of HT should be consistent with treatment goals, benefits, and risks for the individual woman. The benefit-risk ratio for an individual woman continually changes with her age and her menopause-related symptoms (eg, vasomotor symptoms, sleep disturbance, vaginal atrophy, dyspareunia, or diminished libido), any of which may have an adverse impact on quality of life (QOL). Risk factors are related to a woman's baseline disease risks; her age; age at menopause; cause of menopause; time since menopause; prior use of any hormone; types, routes of administration, and doses of HT used; and emerging medical conditions during treatment. Potential benefits and risks are described below for the relevant clinical outcomes.

### Vasomotor symptoms

ET, with or without the use of a progestogen, is the most effective treatment for menopause-related vasomotor symptoms (ie, hot flashes and night sweats) and their potential consequences (eg, diminished sleep quality, irritability, and reduced QOL). Treatment of moderate to severe vasomotor symptoms remains the primary indication for HT. Every systemic ET and EPT product has regulatory agency approval for this indication.

### Vaginal symptoms

ET is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy (eg, vaginal dryness, dyspareunia, and atrophic vaginitis). Many systemic ET and EPT products and all local vaginal ET products have regulatory agency approval for treating these vaginal symptoms. When HT is considered solely for this indication, local vaginal ET is generally recommended.

### Sexual function

Relief of moderate to severe vaginal atrophy with systemic ET/EPT or local ET can be effective in relieving dyspareunia, a common cause of intercourse avoidance. One oral systemic ET product is approved in the United States for the treatment of pain with intercourse. HT is not recommended as the sole treatment of other problems of sexual function, including diminished libido.

### Urinary health

Local ET may benefit some women with urge incontinence who have vaginal atrophy. Whether ET by any route is effective in treating overactive bladder is unclear. There is controversy as to whether local ET can improve certain cases of pure stress incontinence. On the other hand, systemic HT may worsen or provoke stress incontinence, perhaps related to changes in uterine volume or periurethral collagen.

The use of local ET may help reduce the risk of recurrent urinary tract infection (UTI) by a direct proliferative effect on the urethra and bladder epithelia helping to restore the acidic environment and normal lactobacillus-predominant flora of the vagina, thus discouraging colonization of the vagina by pathogens associated with UTI. Clinically, only ET administered by the vaginal route has been shown in an RCT to be effective in reducing the risk of recurrent

UTI. However, no ET/EPT product has regulatory agency approval for any urinary health indication.

### Change in body weight/mass

Body mass index (BMI) increases with age in midlife, with the peak BMI occurring between ages 50 and 59. At this time of life, other factors may also contribute to weight gain, including a decrease in energy expenditure and an increase in energy intake coupled with a decrease in metabolic rate. In women, the hormonal changes associated with the menopause transition can affect body composition and add to the tendency to gain weight. No statistically significant difference in mean weight gain or BMI has been demonstrated between women who use HT and those who do not.

### Quality of life

Although no HT product has regulatory agency approval for enhancing QOL, an improvement in health-related quality of life (HQOL) can result with HT use because of decreased menopause symptoms and perhaps other mechanisms, including a possible elevation of mood that leads to a feeling of well-being. Whether HT improves HQOL in asymptomatic women is unknown. Nor are data available to determine the effect of HT on global QOL, the sense of well-being whether symptoms or physical impairments are present or absent.

### Osteoporosis

Bone strength depends on both bone quality and bone mineral density (BMD). Changes in BMD alone may not always reflect fracture risk. There is RCT evidence that HT reduces postmenopausal osteoporotic fractures, including hip fractures, even in women without osteoporosis, although no HT product has regulatory agency approval for treatment of osteoporosis. Many systemic ET-containing products have regulatory agency approval for prevention of postmenopausal osteoporosis through long-term treatment; a current list of these products can be found on the NAMS Web site (<http://www.menopause.org/edumaterials/otcharts.pdf>).

Extended use of HT is an option for women who have established reduction in bone mass, regardless of menopause symptoms, for prevention of further bone loss and/or reduction of osteoporotic fracture when alternate therapies are not appropriate or cause side effects, or when the benefit-risk ratio of the extended use of alternate therapies is unknown.

### Cardiovascular effects

Three primary cardiovascular effects are discussed: coronary heart disease (CHD), stroke, and venous thromboembolism (VTE).

**Coronary heart disease**—Most observational and preclinical studies support the potential benefits of systemic ET/EPT in reducing the risk of CHD. Most RCTs do not. However, it is now understood that the characteristics of women participating in observational studies are markedly different from those of women enrolled in RCTs, and that these demographic or biologic differences, or both, influence baseline cardiovascular risks and the effects of HT on cardiovascular risk.

**Timing of initiation:** Data indicate that the disparity in findings between observational studies and RCTs is related in part to the timing of initiation of HT in relation to age and proximity to menopause. Most women studied in observational studies were younger than age 55 and within 2 to 3 years after menopause at the time HT was initiated. On the other hand, women enrolled in RCTs were an average of 63 to 64 years old and more than 10 years beyond menopause.

When analyzed by age and time since menopause at initiation of HT, RCTs are in general agreement with observational studies indicating that HT may reduce CHD risk when initiated in younger and more recently postmenopausal women. In a secondary analysis of WHI data, there was a statistically significant reduction in the composite endpoint of myocardial infarction, coronary artery revascularization, and coronary death in women who were randomized to ET during ages 50 to 59. Combined data from both the ET and EPT trials of the WHI showed a statistical trend of an HT effect relative to placebo on CHD by time since menopause, indicating that women who initiate HT more than 10 years beyond menopause are at increased risk for CHD, and those women who initiate HT within 10 years of menopause tend to have a decreased risk for CHD.

**Duration of therapy:** Observational studies suggest that longer duration of HT use is associated with reduced risk of CHD and mortality. The WHI RCTs and the WHI observational study suggest a pattern of lower risk of CHD among women who used HT for 5 or more years, but this is not conclusive.

Analysis of age groups in the WHI indicates that women younger than age 70 at the time of initiating HT have no increased risk of CHD with HT relative to placebo for up to the years of follow-up provided in this study. Although observational studies show decreased risk of CHD with much longer HT use, it is unlikely that RCTs will be conducted for these long periods of time to confirm these findings. This is not unique to HT and is true for other therapies used to prevent CHD, such as statin therapy, for which there are RCT data in women up to an average of only 5 years of use.

In contrast, in the short term, HT may possibly be associated with an increase in CHD risk among women who are more distant from menopause at the time of HT initiation.

**Coronary artery calcium:** Observational studies show that long-term use of HT is associated with less accumulation of coronary artery calcium, which is strongly correlated with atheromatous plaque burden and future risk of clinical CHD events. In an ancillary substudy of younger women (<60 y) in the WHI ET trial, after an average of 7 years of treatment, women who had been randomized to ET had lower levels of coronary artery calcium than those randomized to placebo. These findings suggest that ET commenced in recently postmenopausal women may slow the development of atherosclerotic plaque.

**Stroke**—Results of observational studies of the risk of stroke with HT have been inconsistent. Several indicated an increased risk of ischemic stroke (including the Nurses' Health Study [NHS], the largest prospective study of HT and stroke), whereas others showed no effect on stroke risk. The WHI EPT and ET trials demonstrated an increased risk of ischemic stroke and no effect on risk of hemorrhagic stroke. In these trials, there were 8 additional strokes per 10,000 women per year of EPT use and 11 additional strokes per 10,000 women per year of ET use when the entire cohort was analyzed. In recent analyses that combined results from the WHI EPT and ET trials, younger women aged 50 to 59 years at study entry had no significant increase in risk of stroke (relative risk [RR], 1.13; 95% confidence interval [CI], 0.73–1.76).

In women randomized in the WHI within 5 years of menopause, there were 3 strokes per 10,000 women per year of EPT, which is not statistically significant. The excess risk of stroke observed in the WHI studies would fall into the rare category of risk. Stroke risk was not increased in the Heart and Estrogen/progestin Replacement Study (HERS) and Women's Estrogen for Stroke Trial (WEST) secondary prevention trials. These observations are largely driven by effects of HT on ischemic stroke as neither ET nor EPT seems to affect the risk of hemorrhagic stroke. However, with few women in that age group in the WHI trials, the CI was wide, which means that there was insignificant statistical power to reach a conclusion. In the NHS, among

women aged 50 to 59 years, the relative risk of stroke for current EPT users was elevated (RR, 1.34; 95% CI, 0.84–2.13), and was significantly increased for current users of ET (RR, 1.58; 95% CI, 1.06–2.37). Lower doses of estrogen (eg, 0.3 mg CE) were not associated with an increased risk in the NHS, although this was based on the relatively few women who were taking lower doses.

All studies indicate that postmenopausal HT is not effective for reducing the risk of a recurrent stroke among women with established cardiovascular disease (CVD) or for prevention of a first stroke, and may increase the rate of first strokes. HT cannot be recommended for the primary or secondary prevention of stroke.

**Venous thromboembolism**—Data from both observational studies and RCTs suggest an increased risk of VTE with oral HT. In the WHI trials, there were 18 additional VTEs per 10,000 women per year of EPT use and 7 additional VTEs per 10,000 women per year of ET use when the entire cohort was analyzed. VTE risk in RCTs emerges soon after HT initiation (ie, during the first 1–2 y), and the magnitude of the excess risk seems to decrease somewhat over time. In the WHI trials, the absolute excess VTE risk associated with either EPT or ET was lower in women who were younger than age 60 when randomized to HT than in older women who initiated HT after age 60. There were 7 additional VTEs per 10,000 women per year of EPT use and 4 additional VTEs per 10,000 women per year of ET use in women aged 50 to 59 years when randomized to HT. These risks fall into the rare category of risk.

Growing evidence suggests that women with a prior history of VTE or women who possess factor V Leiden are at increased risk for VTE with HT use. There are limited observational data suggesting lower risks of VTE with transdermal than with oral ET, but there are no RCT data on this subject. Lower doses of oral ET may also confer less VTE risk than higher doses, but no RCT data are available to confirm this assumption.

**Cardiovascular effects conclusion**—Pending additional data, HT is currently not recommended as a sole or primary indication for coronary protection in women of any age. Initiation of HT by women aged 50 to 59 years or by those within 10 years of menopause to treat typical menopause symptoms (eg, vasomotor, vaginal) does not seem to increase the risk of CHD events. There is emerging evidence that initiation of HT in early postmenopause may reduce CHD risk.

## Diabetes mellitus

Aging is associated with an increased risk of non-insulin-dependent diabetes mellitus (DM), also known as adult-onset DM or type 2 DM. Although no HT product has regulatory agency approval to treat DM, large RCTs suggest that HT use reduces the new onset of type 2 DM. Women who received active treatment in the WHI EPT arm had an annualized incidence of DM requiring treatment of 0.61% versus 0.76% in placebo-treated women. This translates into a 21% reduction (hazard ratio [HR], 0.79; 95% CI, 0.67–0.93) in incident-treated DM, or 15 fewer cases per 10,000 women per year of therapy. A similar risk reduction was also noted in the HERS trial (HR, 0.65; 95% CI, 0.48–0.89). In the WHI ET trial, there was a 12% reduction (HR, 0.88; 95% CI, 0.77–1.01) in incident DM, or 14 fewer cases per 10,000 women per year of ET use. It is presently unclear whether the mechanism for this benefit is through lesser centripetal weight gain, reduced insulin resistance in women receiving combined EPT, or some other factor. Meta-analysis data suggest that HT is associated with an improvement in insulin resistance in postmenopausal women. There is inadequate evidence to recommend HT as the sole or primary indication for the prevention of DM in peri- or postmenopausal women.

Optimal glucose control is a prime goal of therapy in postmenopausal women who have type 2 DM. Some data suggest that postmenopausal women with type 2 DM who use ET may require lower doses of medications for glycemic control.

In women with type 2 DM, measures to reduce CHD risk are probably of greatest concern. If HT is prescribed, the specific agent, dose, regimen, and route of administration are especially important. Transdermal ET administration may offer advantages over the oral route. Serum triglyceride levels, which are often increased in patients who have DM, are not increased further with transdermal HT. Moreover, adverse alterations in blood pressure in both nonhypertensive and hypertensive women (although viewed as being a rare, if not idiosyncratic, reaction) have been reported only with oral therapy.

### **Endometrial cancer**

The use of unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the ET dose and duration of use. Standard-dose therapy (0.625 mg/d CE or the equivalent), when used for more than 3 years, is associated with up to a fivefold increased risk of endometrial cancer; if used for 10 years, the risk increases up to tenfold. This increased risk persists for several years after ET discontinuation. Because abnormal uterine bleeding usually brings the disease to medical attention early in its course, most cases do not reduce life expectancy. To negate this increased risk, adequate concomitant progestogen use is recommended for women with an intact uterus (see Progestogen indication, below, for more). There is limited evidence to support the use of HT in women with a history of early-stage (stages I and II) endometrial cancer.

### **Breast cancer**

Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years. In the WHI, this increased risk, in absolute terms, was in the rare category, being four to six additional invasive cancers per 10,000 women per year of EPT use for 5 or more years. In this trial, the increase in breast cancer risk was significantly related to EPT use before enrollment in the trial. Studies have not clarified whether the risk differs between continuous and sequential use of progestogen. Women in the ET arm of the WHI demonstrated no increase in risk of breast cancer after an average of 7.1 years of use, with six fewer cases of invasive breast cancer per 10,000 women per year of ET use, which is not statistically significant. The decrease in risk was observed in all three age groups studied (ie, starting ET at 50–59, 60–69, and 70–79 y). Available evidence suggests that ET for fewer than 5 years has little impact on breast cancer risk. Specific subgroups may be affected in different ways.

EPT and, to a lesser extent, ET, increase breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms.

The question of HT use in women with a history of breast cancer is unresolved. The limited epidemiologic evidence is mixed; there are no completed long-term RCTs.

### **Mood and depression**

Several, but not all, studies of midlife women suggest that depressive symptoms are no more common after the menopause transition than before, and most midlife women do not experience more depressive symptoms than younger women do. However, the menopause transition itself, as well as early postmenopause, may be times of heightened vulnerability for a subgroup of women. For women without a history of prior depression, several community-based longitudinal studies have observed an increased risk for the onset of major or minor depression during perimenopause or early postmenopause compared with premenopause.



For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood. Several small, short-term trials among middle-aged women suggested that HT use improves mood, whereas other trial results showed no change.

Progestogens in EPT may worsen mood in some women, possibly in those with a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression.

Only a few RCTs have examined the effects of HT in middle-aged or older women who have depression. Two small RCTs support the antidepressant efficacy of short-term ET in depressed perimenopausal women, whereas one RCT failed to demonstrate the antidepressant efficacy of ET in depressed women who were 5 to 10 years postmenopause. It is controversial whether ET might in some circumstances augment antidepressant effects of selective serotonin reuptake inhibitors.

In conclusion, although HT might have a positive effect on mood and behavior, HT is not an antidepressant and should not be considered as such. Evidence is insufficient to support its use for the treatment of depression.

### **Cognitive aging/decline and dementia**

The term “cognition” describes the group of mental processes by which knowledge is acquired or used. It encompasses such mental skills as concentration, learning and memory, language, spatial abilities, judgment, and reasoning. Cognitive abilities change throughout life. With advancing age, performance tends to decline on many, but not all, cognitive tests. Dementia is the progressive decline in cognitive function due to damage or disease in the brain beyond what might be expected from normal aging. Alzheimer’s disease (AD) is the most common cause of dementia.

Memory complaints are common in midlife, but findings from well-characterized cohorts suggest that natural menopause has little effect on memory performance or other areas of cognitive function.

Limited, short-term clinical trial data among younger postmenopausal women suggest that EPT does not have a substantial impact on cognition after natural menopause. As inferred from very small, short-term clinical trials, ET initiated promptly after bilateral oophorectomy may improve verbal memory. Several observational studies report no association between age at menopause and AD. However, a case-control study found that bilateral oophorectomy before menopause was associated with an elevated risk of cognitive impairment or dementia, and this risk increased with younger age at oophorectomy.

For postmenopausal women over age 60, findings from several large, well-designed clinical trials indicate that ET/EPT does not improve memory or other cognitive abilities. One trial within WHI—the Women’s Health Initiative Memory Study (WHIMS)—of women aged 65 to 79 reported an increase in dementia incidence with ET and EPT use. The estimate of dementia cases attributed to HT was 12 per 10,000 persons per year of ET use and 23 per 10,000 persons per year of EPT use.

By way of contrast, a number of observational studies have reported associations between HT use and reduced risk of developing AD. HT exposure in observational studies is more likely to involve use by younger women closer to the age of menopause than by women eligible for the WHIMS trial. Speculatively, this difference implies an early window during which HT use might reduce AD risk. However, recall bias and the healthy-user bias may account for protective associations in the observational studies, many of which are difficult to interpret because of fairly small numbers of study participants. The window of opportunity perspective

is supported by limited evidence, but no clinical trial data address long-term cognitive consequences of ET/EPT exposure during the menopause transition and early postmenopause. For women with AD, limited clinical results suggest that ET has no substantial effect on dementia symptoms or progression.

Based on these considerations, HT cannot be recommended at any age for the sole or primary indication of preventing cognitive aging or dementia. HT seems to increase the incidence of dementia when initiated in women age 65 and older. Similarly, HT should not be used to enhance cognitive function in younger postmenopausal women with intact ovaries, although very small clinical trials support the use of ET initiated immediately after menopause induced by bilateral oophorectomy. Available data do not adequately address whether HT used soon after menopause increases or decreases later dementia risk. Limited data do not support the use of HT as treatment of AD.

### **Premature menopause and premature ovarian failure**

Women experiencing premature menopause ( $\leq 40$  y) or premature ovarian failure are a distinctly different group than women who reach menopause at the typical age of 51.3 years. Premature menopause and premature ovarian failure are associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD. There are inadequate data regarding HT in these populations. Most reports suggesting an increased risk of CHD with early natural or surgical menopause also suggest a protective effect of HT. The existing data regarding HT in women experiencing menopause at the typical age should not be extrapolated to women experiencing premature menopause and initiating HT at that time. The risks attributable to HT use by these young women receiving HT are likely smaller and the benefits potentially greater than those in older women who commence HT at or beyond the typical age of menopause, although no trial data exist.

### **Total mortality**

The WHI trials are consistent with observational studies indicating that HT may reduce total mortality when initiated soon after menopause. The WHI suggests that both ET and EPT reduce total mortality by 30% when initiated in women younger than age 60, and when data from the ET and EPT WHI RCTs were combined, that reduction with HT use was statistically significant. In contrast, HT was not associated with mortality reduction among women who initiated HT at age 60 or older.

## **PRACTICAL THERAPEUTIC ISSUES**

### **Class versus specific product effect**

Estrogens and progestogens share some common features and effects as well as potentially different properties. However, the current gold standard for determining the net clinical outcome for any given agent (alone or in combination) is through RCTs. In the absence of rigorous, head-to-head RCTs of various estrogens and progestogens, which are unlikely to be conducted, clinicians will be required to generalize the clinical trial results for one agent to all agents within the same hormonal family. On a theoretical basis, however, there are likely to be differences within each family based on factors such as relative potency of the compound, androgenicity, glucocorticoid effects, bioavailability, and route of administration.

### **Progestogen indication**

The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use. All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen. Postmenopausal women without a uterus should generally not be prescribed a progestogen with systemic ET. A progestogen is generally

not indicated when ET at the recommended low doses is administered locally for vaginal atrophy. Concomitant progestogen may improve the efficacy of low-dose ET in treating vasomotor symptoms. Some women who use EPT may experience undesirable side effects from the progestogen component.

## Dosages

The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman should be the therapeutic goal, with a corresponding low dose of progestogen added to counter the adverse effects of systemic ET on the uterus. Lower ET and EPT doses are better tolerated and may have a more favorable benefit-risk ratio than standard doses. However, lower doses have not been tested in long-term trials. Among the lower daily doses typically used when initiating systemic ET are 0.3 mg oral CE, 0.5 mg oral micronized 17 $\beta$ -estradiol, and 0.014 to 0.025 mg transdermal 17 $\beta$ -estradiol patch. The progestogen dose varies based on the progestogen used and the estrogen dose, typically starting at the lowest effective doses of 1.5 mg MPA, 0.1 mg norethindrone acetate, 0.5 mg drospirenone, or 50 to 100 mg micronized progesterone. Different doses may have different health outcomes. Some women may require additional local ET for persistent vaginal symptoms.

## Routes of administration

There is currently no clear benefit of one route of administration versus another for systemic ET. Nonoral routes of administration may offer both advantages and disadvantages compared with the oral route, but the long-term benefit-risk ratio has not been demonstrated. Differences would be related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of ingredients. There is observational evidence that transdermal ET may be associated with a lower risk of deep vein thrombosis (DVT) than oral administration but no RCT evidence. Local ET administration is preferred when treating solely vaginal symptoms. Although minimal systemic absorption is possible, there are no reports of adverse effects.

Systemic progestogen is required for endometrial protection from unopposed ET. Topical progesterone is not recommended. (For more, see Progestogen indication, above.)

## Regimens

There are multiple dosing regimen options for endometrial safety when adding progestogen to estrogen (see Table 3). Research is inadequate to endorse one regimen over another. Current data support the recommendation to minimize progestogen exposure through one of various options. There is insufficient evidence regarding endometrial safety to recommend as an alternative to standard EPT regimens the off-label use of long-cycle regimens, vaginal administration of progesterone, the contraceptive levonorgestrel-releasing intrauterine system, or low-dose estrogen without progestogen. If any of these approaches is used, close surveillance of the endometrium is recommended pending more definitive research, much of which is currently in progress.

There are also multiple dosing regimen options from which to choose when using ET alone for women after hysterectomy; no data provide guidance on which regimen is best for all women.

## “Bioidentical” hormones

NAMS recognizes that one area of confusion in clinical practice is so-called “bioidentical” hormone preparations. This term has been used to refer to many well-tested, regulatory agency–approved, brand-name HT products containing hormones chemically identical to hormones

produced by women (primarily in the ovaries), such as  $17\beta$ -estradiol or progesterone. However, the term is most often used to describe custom-made HT formulations (called “bioidentical hormone therapy,” or BHT) that are compounded for an individual according to a healthcare provider’s prescription.

Custom-compounding of HT may provide different doses, ingredients (eg, estriol), and routes of administration (eg, subdermal implants) that are not commercially available, and therapies without nonhormonal ingredients (eg, dyes, preservatives) that some women cannot tolerate. Use of BHT has escalated in recent years, often with the dose determined by salivary hormone testing, a procedure that has not been proven accurate or reliable. There may be risks to the patient. Custom-compounded formulations, including BHT, have not been tested for efficacy or safety; safety information is not consistently provided to patients with their prescription, as is required with commercially available HT; and batch standardization and purity may be uncertain. Custom-compounded drug formulations are not approved by any regulatory agency, although some active ingredients meet the specifications of the *United States Pharmacopeia*. Expense is also an issue, as many custom-compounded preparations are viewed as experimental drugs and are not covered by third-party payers, resulting in higher cost to the patient.

The US Food and Drug Administration (FDA) has ruled that compounding pharmacies have made claims about the safety and effectiveness of BHT unsupported by medical evidence and considered to be false and misleading (see statement at: [www.fda.gov/cder/pharmcomp/default.htm](http://www.fda.gov/cder/pharmcomp/default.htm)). Pharmacies may not compound drugs containing estriol without an investigational new drug authorization. The FDA also states that there is no scientific basis for using saliva testing to adjust hormone levels.

NAMS recommends that filled prescriptions for BHT should have a patient package insert identical to that required for products that have regulatory agency approval. In the absence of efficacy and safety data for any specific prescription, the generalized benefit-risk ratio data of commercially available HT products should apply equally to BHT. There are individual women for whom the positives outweigh the negatives, but for the vast majority of women, regulatory agency–approved HT will provide appropriate therapy without assuming the risks and cost of custom preparations.

## TREATMENT ISSUES

### Pretreatment evaluation

HT should be considered only when an indication for therapy has been clearly identified, contraindications ruled out, and the potential individual benefits and risks adequately discussed with the woman so that an informed decision can be made. Before initiating HT, a comprehensive history and physical examination are essential. Mammography should be performed according to national guidelines and age, but preferably within the 12 months before initiation of therapy. Other specific examinations, such as bone densitometry, may be considered on a case-by-case basis.

### Timing of initiation

Emerging data reveal that the timing of HT initiation in relation to proximity to menopause is important. How soon treatment is begun after menopause seems to have a strong impact on long-term health outcomes (eg, early initiation may reduce total mortality rates and CHD risk; see Coronary heart disease and Total mortality).

Women older than age 60 who experienced natural menopause at the typical age and have never used HT will have elevated baseline risks of CHD, stroke, VTE, and breast cancer, and

HT should therefore not be initiated in this population without a compelling indication and only after appropriate counseling.

Premature menopause and premature ovarian failure are conditions associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD, but there are no clear data as to whether ET or EPT will affect morbidity or mortality from these conditions. Despite this, it is logical and considered safe to recommend HT for these younger women, at least until the typical age of natural menopause. Younger women with premature menopause might also require higher doses of HT for menopause symptom relief than the doses currently recommended for women aged 50 to 59 years.

### Duration of use

One of the most challenging issues regarding HT is the duration of use. Existing data do not provide a clear indication as to whether longer duration of therapy improves or worsens the benefit-risk ratio.

Since the effects of HT on risk of breast cancer, CHD, stroke, total CVD, and osteoporotic fracture in perimenopausal women with moderate to severe menopause symptoms have not been established in RCTs, the findings from trials in different populations should, therefore, be extrapolated with caution. For example, data from large studies such as WHI and HERS should not be extrapolated to symptomatic postmenopausal women who initiate HT younger than age 50, as these women were not studied in those trials. WHI and HERS involved predominantly asymptomatic postmenopausal women aged 50 years and older (with mean ages of 63 y and 67 y, respectively), most of whom were 10 years or more beyond menopause, and HERS was conducted solely among women with known coronary artery disease. Results obtained from RCTs among women with established disease should not be extrapolated to women without such conditions. The data also should not be extrapolated to women experiencing premature menopause ( $\leq 40$  y) and initiating HT at that time.

Extending HT use beyond the years around menopause may be a concern for healthcare providers and their patients. The benefits outweigh the risks in some women, whereas the reverse is true for others. Treatment recommendations are different for women experiencing premature menopause, those who are first users of HT, or women who are in their 60s and have previously used HT for several years.

Provided that the lowest effective dose is used, that the woman is well aware of the potential benefits and risks, and that there is clinical supervision, extending HT use for an individual woman's treatment goals is acceptable under some circumstances, including:

- The woman for whom, in her own opinion, the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop HT
- Regardless of symptoms, for further prevention of osteoporotic fracture and/or preservation of bone mass in the woman with established reduction in bone mass when alternate therapies are not appropriate, cause unacceptable side effects, or when the benefit-risk ratio of the extended use of alternate therapies is unknown.

### Symptom recurrence

Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use. The decision to continue HT should be individualized on the basis of severity of symptoms and current benefit-risk ratio considerations, provided the woman in consultation with her healthcare provider believes that continuation of therapy is warranted.

## Discontinuance

Current data suggest that the rates of vasomotor symptom recurrence are similar when HT is either tapered or abruptly discontinued.

Data regarding breast cancer incidence after discontinuance are conflicting. An initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries showed that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 6.7%) in 2003, as compared with the rate in 2002. The decrease was evident only in women who were aged 50 years or older and was more evident in cancers that were estrogen-receptor positive than in those that were estrogen-receptor negative. It was theorized that the drop could be related to the large number of women discontinuing HT following the termination of the EPT arm of the WHI. However, women in the WHI who had been assigned to EPT had an equivalent rate of cardiovascular events, fractures, and colon cancers as women who had been assigned to placebo when followed for 3 years after stopping HT. The only statistical difference was an increase in the rates of all cancer in women who had been assigned to EPT, with an excess of 30 cancers per 10,000 women per year of EPT, including a number of fatal lung cancers. There is an obvious disparity in these two reports; in the absence of any current conclusion, neither report should influence clinical decisions regarding current HT usage beyond those reported in this NAMS position statement.

## Individualization of therapy is key

An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks, but it cannot be assumed that benefits and risks of HT apply to all age ranges and durations of therapy. Women's willingness to accept risks of HT will vary depending on their individual situations, particularly whether HT is being considered to treat existing symptoms or to lower risk for osteoporotic fractures that may or may not occur. Moreover, because incidence of disease outcomes increases with age and time since menopause, the benefit-risk ratio for HT is more likely to be acceptable for short-term use for symptom reduction in a younger population. In contrast, long-term HT or HT initiation in older women may have a less acceptable ratio. Women experiencing premature menopause, whether natural or induced, have a different situation, including increased risk of osteoporosis and CVD, and often more intense symptoms, than women reaching menopause at the typical age. Recommendations would be different for women who are first users of HT or women who are in their sixties and have previously used HT for several years. Each woman is unique, having her own risk profile and preferences. When HT is desired by patients, individualization of therapy is key to bringing health benefits with minimal risks, thereby enhancing QOL.

## Variations from the May 2007 position statement

Each section of the May 2007 position statement has been updated using new studies and findings. The outline and contents have been reorganized, and the statement has been expanded to include additional areas of attention as indicated below.

### Benefits and risks of HT

Vaginal symptoms (**new**)

Sexual function (**new**)

Urinary health (**new**)

Change in body weight/mass (**new**)

Cardiovascular effects (expanded and modified)

Breast cancer (expanded and modified)  
 Endometrial cancer (**new**)  
 Mood and depression (**new** and expanded)  
 Cognitive aging/decline and dementia (expanded)  
 Total mortality (**new**)

#### Practical therapeutic issues

Dosages (**new**)  
 Routes of administration (**new**)  
 Regimens (**new**)  
 “Bioidentical” hormones (expanded)

#### Treatment issues

Timing of initiation (**new**)  
 Duration of use (**new**)  
 Discontinuance (**new**)  
 Individualization of therapy (**new**)

#### Explaining HT risk (**new**)

### Summary

The potential absolute risks published thus far for use of HT are low, particularly for the WHI ET trial, which provided evidence of considerable safety for 0.625 mg/day of oral CE. The risks in the WHI EPT trial were rare by the criteria of the Council for International Organizations of Medical Sciences (CIOMS), except for stroke, which was above the rare category. For women younger than age 50 or those at low risk of CHD, stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk or benefit from ET or EPT is likely to be even smaller than that demonstrated in the WHI, although the relative risk at different ages may be similar. There is a growing body of evidence that each type of estrogen and progestogen, route of administration, and timing of therapy have distinct beneficial and adverse effects. Further research remains essential.

### ADDENDUM A: EXPLAINING HT RISK

One lesson learned since the first announcement of WHI results is that healthcare providers see how vulnerable patients are to fear, leading to mistrust of healthcare providers and pharmaceutical products. Any fear is difficult to reason away, but ongoing communication of accurate information is essential to assist women in navigating the maze of information.

It is mandatory that clinicians caring for postmenopausal women understand the basic concepts of risk in order to communicate the potential benefits and risks of HT and other therapies. Risk is defined as the possibility or chance of harm; it does not indicate that harm will occur.

### Calculating risk

Studies comparing outcomes with exposures attempt to identify or calculate the degree to which the outcome is associated with the exposure. But a statistical association between an exposure and an outcome does not necessarily mean that the exposure caused the outcome. A weak association or an association found only in a single study, particularly if it is not an RCT, should

not be taken as concrete evidence of a true cause-and-effect relationship. For example, if a woman using EPT for a short length of time is diagnosed with breast cancer, EPT is unlikely to be the initiator of the breast cancer. It has been postulated that EPT may stimulate a preexisting cancer to grow more quickly, thereby being diagnosed earlier than if no hormone is used.

Risk calculations provide a basis by which healthcare providers and patients can weigh the pros and cons of initiating or continuing therapy. Understanding the concepts “relative risk,” “absolute risk,” and “statistical significance” is essential to interpreting risk.

**Relative risk**—Relative risk (RR) is a ratio—the rate of disease or of the outcome of interest in a group exposed to a potential risk factor or treatment divided by the rate of disease or outcome of interest in an unexposed group.

Rate describes the number of events, per number of individuals, per time interval (eg, 50/10,000/year). For example, if the annual rate of DVT in postmenopausal women who use oral ET is 22 per 10,000, and the annual rate in those who do not use ET is 11 per 10,000, the RR associated with ET use is:

$$RR = \frac{22}{10,000/y} \div \frac{11}{10,000/y} = 2.0$$

This means that compared with postmenopausal women not using ET, the risk of DVT for those using ET is twice that of a nonuser in the study.

RR *less than 1.0* suggests that the exposure lowers risk. For example, an RR of 0.50 means there is a 50% less chance (or risk) of the outcome studied for those with versus those without the exposure. An RR of 0.3 means a 70% lower risk for the exposed group.

RR *greater than 1.0* suggests the exposure increases risk. For example, an RR of 1.2 means there is a 20% increase in risk in the group with the exposure versus the group without the exposure. An RR of 2.0 means double the risk.

RR *equal to 1.0* suggests that the exposure is associated with neither harm nor benefit versus the group without the exposure.

**Absolute risk**—The impact of RR on both a population and an individual basis depends on incidence (ie, the number of new cases). This can be quantified by the absolute risk (AR), which is the difference between the incidence rates in the exposed and unexposed groups—in other words, the risk difference. The AR quantifies the effect of an exposure on a population basis, providing a measure of its public health impact. AR is more clinically useful than RR in explaining risk to patients. For example, for the calculation presented above about the risk of DVT in women using oral ET, the AR is:

$$AR = \frac{22}{10,000/y} - \frac{11}{10,000/y} = \frac{11}{10,000/y}$$

This means that for every 10,000 postmenopausal women who use ET, there would be 11 additional cases of DVTs per year of ET use.

**Statistical significance**—When the statistical significance is, for example,  $P = 0.05$ , this means that there is a 5% chance that the study’s results are due to chance or coincidence and



a 95% chance that they are truly related to the intervention being studied. Practical (or clinical) significance—whether the results are worth acting on—is entirely different. For example, a 6-month study of a weight loss treatment that includes a large number of patients might show statistically significant weight loss of 1 pound, which is not practically significant for someone who needs to lose 30 pounds. Thus, statistical significance does not always imply clinical relevance.

### Risk levels

These numbers are often difficult to place in practical and personal perspective for many women and even for health professionals. The World Health Organization convened a panel of experts to develop standardized nomenclature for the description of risk for adverse events in recognition of this problem. In 1998, the CIOMS Task Force provided a strict form of risk categorization to assist healthcare professionals and the public when interpreting risk. CIOMS definitions are as follows:

- Rare = Less than or equal to 10 per 10,000 per year
- Very rare = Less than or equal to 1 per 10,000 per year

### Numerical data

Using numerical data to understand and explain health risks can be extremely helpful, but can also be very confusing. Consider the following suggestions:

- Instead of saying to the patient that there is a 20% chance of a side effect, say that 2 of every 10 women experience the side effect.
- Avoid presenting data with different denominators (eg, “Headache developed in 6 of 500 women without the drug versus 20 in 1,000 with the drug”). Use the same denominator, such as 1,000 or 10,000 (eg, “Headache developed in 12 of every 1,000 women without the drug, compared to 20 of 1,000 women with the drug”).
- Be aware of the hazard for the condition in the baseline population. Two times a very rare event is still a very rare event.
- Recognize that even in the absence of an exposure (eg, HT use), there is a risk of development of all the diseases and other adverse health outcomes under consideration. In RCTs, that background inherent risk is represented by the rate of occurrence of the adverse health outcome in the placebo group.
- Be careful not to overstate the risk, especially if the studied population has a low rate. Try to use the AR, not the RR (eg, instead of saying that a drug increases the risk of heart attack about twofold, say that 4 out of every 1,000 drug users have a heart attack per year compared to 2 out of every 1,000 nonusers).
- Be aware that the meanings of high, moderate, low, very low, and minimal risk are not universal, so using these terms can lead to confusion.
- Recognize that a woman’s values, education, needs, preferences, and emotions affect the way she considers risk, so data alone may not influence her. She may, for instance, view menopause as a natural event not calling for any medical intervention.
- Understand that different adverse health outcomes may have the same risk, but women may fear certain outcomes more. For example, the risks of stroke and breast cancer from EPT are similar. However, although stroke may be more disabling, some women will fear breast cancer more.

- Recognize that media reports of new medical research can lead to possible misunderstanding of the reported risks, often due to the practice of delivering news in small incomplete portions. Reported risks are often difficult to interpret by the media, sometimes because the findings are not clearly written by the researchers. Use tables or diagrams to help patients put risk into perspective.
- Learn to communicate to different patients in different ways. Be sensitive as to whether patients seek numerical information, the healthcare provider's honest opinion, or both.

## **ADDENDUM B: FUTURE RESEARCH**

During this review, the following areas requiring further research were identified:

### **Pharmacology**

- Head-to-head comparison of different formulations, regimens, and doses of both estrogens and progestogens
- Mechanism for the possible early harm from HT, including pharmacogenomics, polymorphisms, and prothrombotic markers
- Endometrial effects from alternatives to standard progestogen regimens, such as a progestin-releasing intrauterine system or long-cycle progestogen regimens
- Role of progestogens (eg, type and regimen) in breast cancer, CHD, and other disease outcomes
- Benefits and risks of the most commonly used formulations of custom-compounded hormone therapy
- Identification of the mechanisms that lead to the differential effects of HT on cardiovascular risk in younger, recently postmenopausal women versus older women well past menopause
- Comparison of health outcomes of HT to other common long-term therapies

### **HT for women with underlying disease**

- Effects of estrogen on mood and interactions of estrogens with mood-altering drugs
- Effect of simultaneous use of some estrogen agonists/antagonists with ET to modulate the long-term safety profile of ET
- Incidence and course of potential influence of HT on CHD, breast cancer, dementia, and other health outcomes in women experiencing premature menopause
- Short- and long-term effects of HT on neuropsychiatric disorders, such as Parkinson's disease, depression, and schizophrenia
- Short- and long-term effects of HT on sleep in general and sleep disorders, such as sleep apnea
- Long-term effects of HT on primary and secondary prevention and progression of hearing loss and ophthalmologic disorders, such as cataract and age-related macular degeneration
- Role of HT in postmenopausal women with underlying disease, such as DM and hypertension, and evaluation of the effects of HT on the adverse events associated with the disease itself

- Factoring of other health outcomes, including QOL issues, into the composite benefit-risk ratio for HT
- Determination of how women at risk of DVT and pulmonary embolism can best be identified as well as how hypercoagulability responsiveness to estrogens in general can be measured
- Determination of any relationship between the menopause transition, HT, and various forms of arthritis and joint pain
- Stricter evaluation of and potential influence of HT on domains of QOL through the menopause transition
- Treatment of symptomatic perimenopause

### Health outcomes for HT over the long term (>10 y)

- Timing of initiation of HT relative to menopause with regard to cardiovascular, cognitive, and other health outcomes
- Cause of the increase in stroke with HT and of increased CHD and breast cancer with EPT to better understand the pathophysiology of these events, to identify potential new treatments and ways to prevent their occurrence, and to identify a subgroup for whom HT would be less toxic
- Long-term effects of HT on risk of AD and other forms of dementia, particularly when therapy is initiated before age 65
- Health outcomes with osteoporosis drugs over the long term (>10 y)
- Identification of subgroups of women for whom ET or EPT might be beneficial with regard to cardiovascular, DM, cognitive, and overall health outcomes
- Creation of validated instruments for determining the impact of HT on both overall QOL and HQOL

### Discontinuance

- Benefit-risk ratio associated with an abrupt versus a tapering discontinuation of HT regimens, including the impact on bone density in the first 2 or 3 years after termination
- Effects of HT discontinuation on health outcomes influenced by HT
- Identification of the outcomes with differing schedules of withdrawal from HT (ie, abrupt vs tapered) and predictors of adverse effects of HT discontinuation

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## SUGGESTED READING

Suggested Reading is categorized into primary headings.

### Position statements and guidelines

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**TABLE 1**

## NAMS Menopausal HT Terminology

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- ET—Estrogen therapy
  - EPT—Combined estrogen-progestogen therapy
  - HT—Hormone therapy (encompassing both ET and EPT)
  - Progestogen—Encompassing both progesterone and progestin
  - Systemic therapy—HT administration that results in absorption in the blood high enough to provide clinically significant effects; in this paper, the terms ET, EPT, HT, and progestogen are presented as systemic therapy unless stated otherwise
  - Local therapy—Vaginal ET administration that does not result in clinically significant systemic absorption
  - Timing of HT initiation—The length of time after menopause when HT is initiated
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**TABLE 2**

## NAMS Menopause Terminology

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•	Spontaneous/natural menopause—The final menstrual period (FMP), confirmed after 12 consecutive months of amenorrhea with no obvious pathologic cause
•	Induced menopause—Permanent cessation of menstruation after bilateral oophorectomy (ie, surgical menopause) or iatrogenic ablation of ovarian function (eg, by chemotherapy or pelvic radiation therapy)
•	Perimenopause/menopause transition—Span of time when menstrual cycle and endocrine changes occur a few years before and 12 months after the FMP resulting from natural menopause
•	Premature menopause—Menopause reached at or under age 40, whether natural or induced
•	Early menopause—Natural or induced menopause that occurs well before the average age of natural menopause (51 y), at or under age 45
•	Premature ovarian failure—Ovarian insufficiency experienced under age 40, leading to permanent or transient amenorrhea
•	Early postmenopause—The time period within 5 years after the FMP resulting from natural or induced menopause

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**TABLE 3**

Terminology defining some types of EPT regimens

<b>Regimen</b>	<b>Estrogen</b>	<b>Progestogen</b>
Cyclic	Days 1–25	Last 10–14 d of ET cycle
Cyclic-combined	Days 1–25	Days 1–25
Continuous-cyclic (also called continuous-sequential)	Daily	10–14 d every mo
Continuous-cyclic (also called continuous-sequential; long-cycle)	Daily	14 d every 2–6 mo
Continuous-combined	Daily	Daily
Intermittent-combined (also called pulsed-progestogen; continuous-pulsed)	Daily	Repeated cycles of 3 d on, 3 d off