HORMONE THERAPY IN MENOPAUSE

Menopause is the permanent cessation of menses that is a period of time marked by loss of ovarian follicular activity, inadequate estradiol production, and the subsequent cessation of menses. The median age for a woman to experience menopause is 52 years. Some other factors that may be associated with early menopause include low body weight, increased menstrual cycle length, nulliparity, and smoking. Smokers generally experience menopause approximately 2 years earlier than nonsmokers.

The usual transitional period prior to menopause, known as perimenopause or the *climacteric*, is a period when hormonal and biologic changes begin to occur. These changes may begin 2 to 8 years prior to menopause and eventually lead to irregular menstrual cycles, an increase in cycle interval, and a decrease in cycle length.

❖ PHYSIOLOGY

The physiologic changes that occur during the perimenopausal and menopausal periods are caused by the decrease and eventual loss of ovarian follicular activity. As women age, the number of ovarian follicles decreases, and the remaining follicles require higher levels of FSH for maturation and ovulation. During perimenopause, anovulatory cycles are more likely, and the lack of progesterone production leads to irregular and unpredictable menses. During menopause, FSH concentrations increase 10- to 15-fold, LH concentrations increase fivefold, and levels of circulating estradiol decrease by more than 90%.

❖ CLINICAL PRESENTATION AND DIAGNOSIS

Common symptoms of menopause include vasomotor symptoms (hot flashes, night sweats), vulvovaginal atrophy, vaginal dryness, and dyspareunia. Women less commonly may experience mood swings, depression, insomnia, arthralgia, myalgia, urinary frequency, and decreased libido. These symptoms diminish females' quality of life.

The diagnosis of menopause is primarily a clinical one and is made after a woman experiences amenorrhea for 12 consecutive months. The loss of ovarian follicular activity leads to an increase in follicle-stimulating hormone (greater than 40 mIU/mL (40 IU/L)), which, on laboratory examination, may help to confirm the diagnosis.

❖ TREATMENT

⇨ Desired Outcomes

Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms and vulvovaginal atrophy and can be considered, especially for women experiencing moderate to severe symptoms.

The goals of treatment are to alleviate or reduce menopausal symptoms and to improve the patient's quality of life (QOL) while minimizing adverse effects of therapy. The appropriate route of administration should be chosen based on individual patient symptoms, and therapy should be continued at the lowest dose for the shortest duration consistent with treatment goals for each patient.

⇨ General Approach to Treatment

Women suffering from vasomotor symptoms should attempt lifestyle or behavioral modifications before seeking medical treatment. *Women should receive a thorough history and physical examination, including assessing for coronary heart disease (CHD) and breast cancer risk factors and contraindications, before HT is considered. They should be informed of the risks and the benefits of HT and encouraged to be involved in the decision-making process. If a woman does not have any contraindications to HT, including CHD or significant CHD risk factors, and also does not have a personal history of breast cancer, HT could be an appropriate therapy option.*

Women who have undergone a hysterectomy need only be prescribed estrogen. A progestogen should be added to the estrogen only for women with an intact uterus.

Alternative and nonhormonal treatment options are available for women who are not candidates for HT, but they have limited effectiveness and may also have adverse effects.

⇨ Nonpharmacologic Therapy

Due to the minimal adverse effects of these interventions, patients should try lifestyle or behavioral modifications before and in addition to pharmacologic therapy. The most common nonpharmacologic interventions for vasomotor symptoms include the following,

•• Smoking cessation
•• Limit alcohol and caffeine
•• Limit hot beverages (eg, coffee/tea, soups)
•• Limit spicy foods
•• Keep cool, and dress in layers
•• Stress reduction (eg, meditation, relaxation exercises)
•• Increase exercise (demonstrated an improvement in QOL but did not improve vasomotor symptoms.)
•• Paced respiration (a form of deep, slow breathing, improved vasomotor symptoms in a small group of patients.)

Dyspareunia may result from vaginal dryness. Water-based lubricants may provide relief for several hours after application.

A decline in estrogen concentrations also may be associated with urinary stress incontinence. Kegel exercises are recommended as a first-line intervention for stress incontinence, although pharmacologic therapy also may be necessary.

⇨ Pharmacologic Therapy

»» *Estrogens*

Estrogen is indicated for the treatment of moderate to severe vasomotor symptoms and vulvovaginal atrophy associated with menopause. In addition, it is indicated for the prevention of postmenopausal osteoporosis in women with significant risk.

Oral or transdermal estrogen products should be prescribed at the lowest effective dose and for the shortest duration possible to provide relief of vasomotor symptoms. Topical vaginal products in the form of creams, tablets, or rings should be prescribed for women exclusively experiencing vulvovaginal atrophy.

»» *Progestogens*

Women who have an intact uterus should be prescribed a progestogen in addition to estrogen in order to decrease the risk of endometrial hyperplasia and endometrial cancer. Progestogens should be prescribed for at least 12 to 14 days of the month and often are prescribed continuously.

»» Adverse Effects

Therapy with estrogen with or without a progestogen should be initiated at the lowest dose in order to minimize adverse effects. Because the adverse effects of these preparations can be similar, it may be difficult to assess whether the estrogen or the progestogen is the cause.

These most commonly include resumption of vaginal bleeding and breast tenderness. Nausea, weight gain, edema, headache, premenstrual syndrome-like symptoms, and increased vaginal discharge have also been reported. Skin irritation may occur with the use of transdermal products. Frequently, these side effects diminish with time or may respond to a change in dosage or product.

»» Contraindications

HT should not be prescribed to women with a history of or active thromboembolic disease, breast cancer or estrogen-dependent neoplasm, pregnancy, liver disease, or undiagnosed vaginal bleeding. It also should not be used for the prevention or treatment of cardiovascular disease, cerebrovascular disease, or dementia.

»» Methods of Administration

Cyclic Estrogen and Progestogen: Estrogen is administered daily, and progestogen is administered for 12 to 14 days of the month. The disadvantage of this method of administration is the return of monthly menses in approximately 90% of women 1 to 2 days following the last progestogen dose.

Continuous Combined Estrogen and Progestogen: Estrogen and progestogen are administered daily and result in endometrial atrophy. Therefore, women do not experience a withdrawal bleed but may experience unanticipated breakthrough bleeding or spotting during the month. Although this may sound more appealing than a withdrawal bleed, women may view the unpredictable bleeding or spotting as a disadvantage to this type of administration. If bleeding persists beyond 6 to 12 months, women should seek medical attention to rule out endometrial hypertrophy or carcinoma.

»» Low-Dose HT

Several trials demonstrated that lower doses of conjugated equine estrogen (CEE) ± medroxyprogesterone acetate (MPA) (CEE 0.45 mg or 0.3 mg ± MPA 2.5 mg or 1.5 mg) decreased hot flashes comparable with standard HT, improved vulvovaginal atrophy, increased bone mineral density (BMD) at the spine and hip, and provided sufficient endometrial protection.

»» Benefits of HT

Vasomotor Symptoms: HT remains the most effective treatment for vasomotor symptoms, and systemic HT should be considered only in women experiencing these symptoms.

If it is decided to use HT, it should be prescribed at the lowest dose that relieves or reduces menopausal symptoms and should be recommended only for short-term use (generally less than 5 years). Women should be reassessed every 6 to 12 months, and discontinuation of therapy should be considered.

Vulvovaginal Atrophy: Vulvovaginal atrophy is associated with vaginal dryness and dyspareunia and also may be associated with recurrent urinary tract infections, urethritis, and urinary urgency and frequency.

Topical vaginal preparations generally should be prescribed as first-line therapy unless the patient is also experiencing vasomotor symptoms. Local vaginal estrogen has demonstrated increased efficacy over systemic estrogen and generally does not require supplementation with a progestogen in women with an intact uterus using low or ultralow doses. Women using regular or high doses of topical estrogen products may require intermittent treatment with a progestogen.

Osteoporosis Prevention: *Because HT should be maintained only for the short term, traditional therapies such as bisphosphonates should be considered as first-line therapy for the prevention of postmenopausal osteoporosis, in addition to appropriate doses of calcium and vitamin D.* Because of the associated risks, HT should not be prescribed solely for the prevention of osteoporosis.

»» Risks of HT

Cardiovascular Disease: Results of randomized trails demonstrate that HT does not prevent or treat CHD in women and that it actually may cause an increase in CHD events. An increased risk of CVD has been noted in women over the age of 60 years who initiated HT more than 10 years postmenopause.

Breast Cancer: A study demonstrates an increased risk of invasive breast cancer among women taking HT (estrogen therapy increases this risk less than estrogen progestogen therapy). Therefore, women with a personal history of breast cancer and possibly even a strong family history of breast cancer should avoid the use of HT and could consider alternative or nonhormonal therapies for the treatment of vasomotor symptoms.

Venous Thromboembolism: HT use increases the overall risk for venous thromboembolic disease, including deep venous thrombosis (DVT) and pulmonary embolism (EP), twofold.

»» Discontinuation of HT

When treating moderate to severe postmenopausal symptoms, the benefit-to-risk ratio appears to be best when HT is started close to the time of menopause. Therapy should be tapered before discontinuation in order to limit the recurrence of hot flashes.

Slowly discontinuing HT over 3 to 6 months may be associated with less risk of symptom return. Tapering HT may be done by a dose taper or day taper. The dose taper involves decreasing the dose of estrogen over several weeks to months and monitoring closely for symptom return. If symptoms recur, the next reduction in dose should not occur until symptoms resolve or stabilize on the current dose. The day taper involves decreasing the number of days of the week that a woman takes the HT dose, for example, decreasing a daily dose of 0.3 mg estrogen to 0.3 mg estrogen 5 days a week. Again, if symptoms recur, continue on the current dose until symptoms resolve or stabilize before trying a subsequent decrease.

»» Nonhormonal and Alternative Treatments

There has been an increase in the use of alternative and nonhormonal therapies for the management of menopausal symptoms, particularly for women with CHD and/or breast cancer risk factors. A wide range of therapies, both prescription and herbal, have been studied with limited success for symptomatic management of vasomotor symptoms.

SSRIs and venlafaxine are theorized to reduce the frequency of hot flashes by increasing serotonin in the central nervous system and by decreasing LH. Of the SSRIs, paroxetine has the most published data demonstrating a reduction in hot flashes while treating other symptomatic complaints such as depression and anxiety. Other SSRIs such as fluoxetine, citalopram, and sertraline may also be effective. These antidepressant medications offer a reasonable option for women who are unwilling to or cannot take hormonal therapies, particularly those who suffer from depression or anxiety.

Phytoestrogens are plant sterols that are structurally similar to human and animal estrogen. Soy protein is a common source of phytoestrogens. There are differences among classes of phytoestrogens and biologic potencies vary, making it difficult to recommend specific dosing. The most commonly studied phytoestrogen is the isoflavone class. Because the effect of phytoestrogens on breast cancer and other female-related cancers is unknown, these products should not be considered in women with a history of estrogen-dependent cancers.

Black cohosh has been one of the most studied alternative therapies for vasomotor symptoms, but it has not demonstrated a substantial benefit over placebo. The mechanism of action, safety profile, drug–drug interactions, and adverse effects of black cohosh remain unknown. However, there have been case reports of hepatotoxicity with its use. Caution should be exercised when considering the use of this product, and it is not recommended for more than a 6-month period of time.

Gabapentin and *clonidine* have also been studied for the management of menopausal symptoms.

Overall, alternative and nonhormonal therapies are less effective in treating vasomotor symptoms than HT but do offer another option for women experiencing menopausal symptoms who cannot or are unwilling to take HT. SSRIs and phytoestrogens have the best evidence for efficacy.

In summary, HT improves overall well-being and mood in women with vasomotor symptoms, but it has not demonstrated an improvement in QOL in women without vasomotor symptoms. Combined estrogen plus progestogen should not be used for the prevention of chronic diseases because it increases the risk of CHD, stroke, breast cancer, and VTE. However, rates of fracture were reduced with combined hormonal treatment.