CHAPTER 85

Hormone Therapy in Women

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KEY CONCEPTS

1. Estrogen-based postmenopausal hormone therapy should be used for treatment of menopausal symptoms (e.g., vasomotor and urogenital symptoms) and, when specifically indicated, for osteopenia and osteoporosis prevention.
2. A progestogen should be added for endometrial protection when estrogen therapy is prescribed. Thus, women with an intact uterus should not receive unopposed estrogen, whereas women who have undergone hysterectomy always should receive estrogen alone.
3. Lower doses of hormone therapy than previously used should be considered as standard initial therapy. Clinicians should prescribe hormone therapy at the lowest effective dose for the shortest duration, carefully and individually weighing treatment goals and risks for each woman.
4. The major indication for estrogen-containing hormone therapy is the relief of menopausal symptoms. The benefits of short-term perimenopausal and postmenopausal hormone therapy for the relief of severe menopausal symptoms outweigh the risks in many women.
5. Osteoporosis prevention remains an approved indication for estrogen-based hormone therapy, but alternative strategies are available and should be considered as first-line agents for asymptomatic women. Vitamin D deficiency should be excluded before any other treatment is prescribed for the prevention or treatment of bone loss, and adequate calcium intake should be ensured.
6. Postmenopausal hormone treatment with oral combined estrogen plus progestogen has no benefit for cardiovascular disease prevention and increases the risk of breast cancer, coronary heart disease events, stroke, and venous thromboembolic events. However, it reduces the rates of hip fracture.
7. Hormone therapy improves mood and well-being primarily in women with hot flushes, night sweats, and sleep disturbance, but it does not improve gross quality-of-life measures in postmenopausal women who do not experience vasomotor symptoms.
8. Evaluation of each individual woman is essential in determining the appropriateness of perimenopausal and postmenopausal hormone therapy, and collaboration between a woman and her primary care provider in the decision-making process is essential. The benefits and risks of hormone therapy should be reassessed annually.
9. Results from randomized trials of hormone therapy in postmenopausal women cannot be extrapolated to premenopausal women with ovarian dysfunction. Women with premature ovarian failure (i.e., those younger than 40 years) need exogenous sex steroids to compensate for the decreased production by their ovaries.

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Menopause is the permanent cessation of menses following the loss of ovarian follicular activity.[1] By definition, it is a physiologic event that occurs after 12 consecutive months of amenorrhea, so the time of the final menses is determined retrospectively. Women who have undergone hysterectomy must rely on their symptoms to estimate the actual time of menopause.

Many women seek therapy for alleviation of symptoms that arise from loss of ovarian function at the time of menopause. However, since 2002, use of hormone therapy (estrogen with or without progestogen) for the prevention of diseases of aging has attracted considerable public attention as a result of the premature termination of the estrogen–progestogen arm of the Women's Health Initiative (WHI) trial due to increased risk of coronary heart disease and breast cancer.[2] The estrogen-alone arm of the trial also was discontinued after 7 years of followup because the study found that estrogen alone did not affect (either increase or decrease) heart disease.[3] Breast cancer risk was not increased during the study period.[3]

The median age at the onset of menopause in the United States is 51 years, whereas the average life expectancy for women is 81 years. Thus, American women can expect to be postmenopausal for more than one third of their lives.

Although the age at menarche has declined steadily throughout the centuries, probably as a result of improved nutrition, the age at menopause onset appears to be relatively stable. However, on average, cigarette smokers experience menopause 2 years earlier than do nonsmokers. Women who have undergone hysterectomy also are more likely to have an earlier menopause despite preservation of their ovaries.

Since the publication of the WHI trial results, many women have either stopped or become reluctant to use hormone therapy.[4] The WHI trial was a chronic disease prevention trial designed to evaluate the role of hormone therapy in reducing the risks of cardiovascular disease in older women and at the same time to investigate the effects on the risk of breast cancer.[2,3] The trial was conducted in a total of 16,607 mainly asymptomatic women who were an average 12 to 13 years postmenopausal (mean age 63 ± 7.11 years).[2,3] No randomized controlled clinical trials of the population of women normally targeted for hormone therapy (i.e., symptomatic perimenopausal or early postmenopausal women) have been reported. Although hor-

mone therapy is not indicated for prevention of chronic diseases of aging, it remains the most effective treatment for vasomotor symptoms, impaired sleep quality, and urogenital symptoms of menopause. Regulatory authorities expressed major concerns about hormone therapy use following the results of the WHI trial.[5,6]

Approved indications of postmenopausal hormone therapy include treatment of menopausal symptoms (e.g., hot flushes, night sweats, and urogenital atrophy) and osteoporosis prevention.[5] Although it has been proposed that hormone therapy should be prescribed at the lowest possible dose for the shortest possible time,[5] evidence that new low-dose regimens are safer than traditionally prescribed doses is lacking. Weighing the risks and benefits, the Food and Drug Administration (FDA) mandated the addition of new safety warnings to the labels of all systemic estrogens (regardless of route or dosage form), including estrogen-only and combined estrogen–progestogen products.[6] The labels now caution that use of estrogen-containing hormone therapy regimens by postmenopausal women may be associated with an increased risk of myocardial infarction, stroke, breast cancer, and thromboembolism.[6]

MENOPAUSE AND PERIMENOPAUSAL AND POSTMENOPAUSAL HORMONE THERAPY

PHYSIOLOGY

Characteristics of the human menstrual cycle throughout reproductive life are well described.[7] A woman is born with approximately two million primordial follicles in her ovaries. During a normal reproductive life span, she ovulates fewer than 500 times. The vast majority of follicles undergo atresia.

The hypothalamic–pituitary–ovarian axis dynamically controls reproductive physiology throughout the reproductive years. The pituitary is regulated by pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), produced by the pituitary in response to GnRH, regulate ovarian function. These gonadotropins also are influenced by negative feedback from estradiol and progesterone. Ovarian follicular activity is reflected by the circulating concentrations of sex steroids and by peptide hormones (e.g., inhibin and activin). The sex steroids include estradiol, produced by the dominant follicle; progesterone, produced by the corpus luteum after maturation of the dominant ovarian follicle; and androgens, primarily testosterone and androstenedione, secreted by the ovarian stroma. Sex steroids are important for the healthy functioning of many organs, including the bones, brain, skin, and reproductive and urogenital tracts. They act primarily by regulating gene expression.

Pathophysiologic changes associated with menopause are caused by loss of ovarian follicular activity.[1] Ovarian primordial follicle numbers decrease with advancing age, and at the time of the menopause, few follicles remain in the ovary. Hence the postmenopausal ovary is no longer the primary site of estradiol or progesterone synthesis. The postmenopausal ovary secretes primarily androstenedione and testosterone. In contrast to the acute fall in circulating estrogen at the time of menopause, the decline in circulating androgens commences in the decade leading up to the average age of natural menopause and closely parallels increasing age.[8] Androgens are secreted by both the ovaries and the adrenal glands. Following menopause, direct ovarian androgen secretion appears to account for as much as 50% of testosterone production, with the adrenal gland being a less important source. Hypertrophy of the ovarian stroma may develop after menopause, probably secondary to high LH concentrations, thereby resulting in increased ovarian testosterone production. Alternatively, the ovaries may become fibrotic and a poor source of sex steroids.

No endocrine event clearly signals the time just prior to final menses.[9] Nonetheless, as women age, a progressive rise in circulating FSH[10] and a concomitant decline in ovarian inhibin[9] are observed. In women who continue to experience menstrual bleeding, FSH determinations on day 2 or 3 of the menstrual cycle are considered elevated when concentrations exceed 10 to 12 international units/L, an indication of diminished ovarian reserve. Clear elevations in serum FSH are seen in women at age approximately 40 years.[9] When ovarian function has ceased, serum FSH concentrations are greater than 40 international units/L.

The perimenopause is the period immediately prior to the menopause and the first year after menopause. The menopausal transition is the period of time when the endocrinologic, biologic, and clinical features of the approaching menopause commence.[9] The menopausal transition usually begins approximately 4 years prior to menopause and is characterized by menstrual cycle irregularity caused by increased frequency of anovulatory cycles. Vasomotor symptoms (hot flushes and night sweats), psychological symptoms (anxiety, mood swings, and depression), and disturbances of sexuality are increased markedly in the perimenopause. Menopause is characterized by a 10- to 15-fold increase in circulating FSH concentrations compared with concentrations of FSH in the follicular phase of the cycle, a fourfold to fivefold increase in LH, and a greater than 90% decrease in circulating estradiol concentrations.[9] During the perimenopause, FSH concentrations may rise to the postmenopausal range during some cycles but return to premenopausal levels during subsequent cycles. Thus, high concentrations of FSH should not be used to diagnose menopause in perimenopausal women. However, vasomotor symptoms in perimenopausal women may require treatment despite the presence of menstrual bleeding. Abnormal thyroid function and other conditions that may cause similar symptomatology should be excluded first. Dysfunctional uterine bleeding may occur during the perimenopausal years because of anovulatory cycles, but other gynecologic causes also should be considered. Treatment options for dysfunctional uterine bleeding include progestogens or low-dose oral contraceptives.

An observational study of more than 9,000 postmenopausal women examined the relationship between endogenous estrogens and bone mineral density, bone loss, fractures, and breast cancer.[11–14] Women with detectable serum estradiol concentrations (5–25 pg/mL) had a 6% to 7% higher bone mineral density at the total hip and spine compared with women with undetectable levels (less than 5 pg/mL).[11] They also had significantly less bone loss at the hip than women with undetectable levels.[12] Women with undetectable serum estradiol concentrations had a relative risk of 2.5 for subsequent hip and vertebral fractures.[13] However, women with the highest estradiol serum concentrations had the greatest risk of developing breast cancer.[14]

CLINICAL PRESENTATION OF PERIMENOPAUSE AND MENOPAUSE

Symptoms

- Vasomotor symptoms (hot flushes and night sweats)
- Sleep disturbances
- Mood changes
- Sexual dysfunction
- Problems with concentration and memory
- Vaginal dryness and dyspareunia

Signs

- *Perimenopause:* Dysfunctional uterine bleeding as a result of anovulatory cycles (other gynecologic disorders should be excluded)
- *Menopause:* Signs of urogenital atrophy

Laboratory Tests

- *Perimenopause:* FSH on day 2 or 3 of the menstrual cycle greater than 10–12 international units/L
- *Menopause:* FSH greater than 40 international units/L

Other Relevant Diagnostic Tests

- Thyroid function tests
- Iron stores

CLINICAL PRESENTATION OF MENOPAUSE

Vasomotor symptoms, hot flushes, and night sweats are common symptoms of estrogen withdrawal. Hot flushes are the classic sign of menopause and the major clinical complaint of American women during the perimenopausal and early menopausal years. Hot flushes are a sensation of warmth, frequently accompanied by skin flushing and perspiration. A chill may follow as the core body temperature drops. Hot flushes may occur in women of any age who experience acute estrogen withdrawal. They can be occasional or frequent, can last from seconds to 1 hour, and are characterized by symptoms ranging from mild warmth to profuse sweating. For some women, hot flushes are a minor nuisance, but for other women, they are a disturbing symptom that disrupts their sense of well-being and causes problems in their social and professional lives. They usually occur spontaneously but often are increased in frequency or severity in hot or humid weather or after ingestion of caffeine, alcohol, or spicy foods. The prevalence of hot flushes is higher in the first 2 postmenopausal years. Women who have undergone surgical menopause tend to have more intense menopausal symptoms than those who experience a natural menopause.

Vaginal dryness is directly related to estrogen insufficiency, but some women can find adequate relief from nonestrogenic vaginal creams. Most women with significant vaginal dryness require local or systemic estrogen therapy to replenish moisture. Vaginal dryness should be differentiated from lack of lubrication during sexual stimulation. The latter is an impaired arousal response and may not improve with simple vaginal estrogen therapy.

Although some accept a range of other symptoms to be typical of estrogen deficiency (e.g., mood swings, tiredness, poor concentration, depression, insomnia, migraines, formication, arthralgia, myalgia, and urinary frequency), the relationship between these symptoms and the absolute decline in estrogen is more controversial. Many women, nonetheless, experience relief of such symptoms with estrogen therapy.

TREATMENT

Menopause

Postmenopausal hormone therapy is a subject of major interest in the field of women's health. In some women, menopausal symptoms can be managed effectively with lifestyle modifications, including exercise, weight control, smoking cessation, and a healthful diet. More recently, however, dietary supplements and nonpharmacologic therapies have been promoted as "complementary medicine" alternatives to hormone therapy. To date, little evidence supports the use of such nonprescription products, which include various herbal remedies and soy-based supplements.

PHYTOESTROGENS

Phytoestrogens have physiologic effects in humans.[15] They are plant compounds with estrogen-like biologic activity and relatively weak estrogen receptor–binding properties. Epidemiologic studies suggest that consumption of a phytoestrogen-rich diet, which is common in traditional Asian societies, is associated with a lower risk of breast cancer.[16]

The biologic potencies of phytoestrogens vary. Most of these compounds are nonsteroidal and are less potent than synthetic estrogens. The three main classes of phytoestrogens are isoflavones, lignans, and coumestans, all of which are found in plants or their seeds.[15] The most commonly studied phytoestrogen is the isoflavone class. Genistein and daidzein are the most abundant active components of isoflavones. The concentration of isoflavones per gram of soy protein varies considerably among preparations. Also, a single plant often contains more than one class of phytoestrogen. Common food sources of phytoestrogens include soybeans (isoflavones), cereals, oilseeds such as flaxseed (lignans), and alfalfa sprouts (coumestans).

Mild estrogenic effects have been seen in postmenopausal women,[15] but current data suggest that phytoestrogen supplementation is no more effective than placebo in relieving hot flushes or other symptoms of menopause in postmenopausal women.[17]

Phytoestrogens decrease low-density lipoprotein (LDL) cholesterol and triglyceride concentrations with no significant change in high-density lipoprotein (HDL) cholesterol concentrations.[18] Furthermore, phytoestrogens have the ability to inhibit LDL oxidation and normalize vascular reactivity in estrogen-deprived primates.[18] In addition, bone density may be improved by phytoestrogens.[15] Common adverse effects include constipation, bloating, and nausea.[19]

Larger, long-term studies are needed to document the effects of phytoestrogens on the breast, bone, and endometrium. Furthermore, differences among classes of phytoestrogens must be identified clearly, including dosing and biologic activity, before phytoestrogens can be considered an alternative to conventional hormone therapy in postmenopausal women.

Black cohosh (*Cimicifuga racemosa*), a widely used herbal supplement, may not offer substantial benefits for relief of vasomotor symptoms as suggested by earlier trials.[20] This substance does not appear to have strong intrinsic estrogenic properties but may act through the serotonergic system. Long-term effects of black cohosh are unknown.

HORMONAL REGIMENS

Approved indications of hormone therapy include treatment of menopausal symptoms and osteoporosis prevention. Therapy directed at menopausal symptoms, such as hot flushes, often is short term. However, therapy directed at prevention of osteoporosis should be long term. For osteoporosis prevention, the advantages of hormone therapy must be weighed against the risks, including thrombosis and the increased incidence of cardiovascular disease and breast cancer,[2] and consideration should be given to approved nonestrogen alternatives.

In women with an intact uterus, hormone therapy consists of an estrogen plus a progestogen. In women who have undergone hysterectomy, estrogen therapy is given unopposed by a progestogen.

The WHI randomized controlled trial was a chronic disease prevention trial designed to evaluate the role of hormone therapy in diseases of aging.[2,3] The continuous combined oral estrogen–progestogen arm of the WHI trial was terminated prematurely. This arm included 16,608 relatively healthy postmenopausal women aged 50 to 79 years at enrollment (mean age 63.2 years). The primary outcome was coronary heart disease events, defined as nonfatal myocardial infarction and coronary artery disease death, with invasive breast cancer as the primary adverse outcome.[2] The study also examined secondary outcomes, including stroke, thromboembolic disease, fractures, colon cancer, and endometrial cancer.[2] After a mean followup of 5.2 years (planned duration 8.5 years), the Data and Safety Monitoring Board recommended stopping this arm of the trial because of the occurrence of a prespecified level of invasive breast

cancer. That is, women who received the active drug had an increased risk of invasive breast cancer (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1–1.59), and the overall risks exceeded benefits.[2] The study also found increased coronary disease events (HR 1.29, 95% CI 1.02–1.63), stroke (HR 1.41, 95% CI 1.07–1.85), and pulmonary embolism (HR 2.13, 95% CI 1.39–3.25). Beneficial effects included decreases in hip fracture (HR 0.66, 95% CI 0.45–0.98) and colorectal cancer (HR 0.63, 95% CI 0.43–0.92).[2] Results from this study indicated that short-term use (<1 year) has risks for coronary heart disease and thromboembolic disease events. The number of deaths was similar among the groups.

After a mean followup of 7 years, the Data and Safety Monitoring Board also recommended stopping the oral estrogen-alone arm of the study. This arm consisted of 10,739 women who had undergone hysterectomy. Estrogen-only therapy had no effect on coronary heart disease risk and was not associated with increased breast cancer risk.[3]

Among women in the estrogen–progestogen arm, one serious adverse event occurred in every 100 women treated for 5 years. Specifically, the study suggested that for every 10,000 women taking combined hormone therapy, there would be eight more cases of breast cancer, seven more cases of myocardial infarctions, eight more cases of stroke, and eight more cases of pulmonary embolism. However, six fewer colorectal cancers and five fewer hip fractures would be expected.[2] For the majority of women who had never used hormone therapy before enrolling in the study (6,280 treated with estrogen–progestogen and 6,024 treated with placebo), the HR for breast cancer was 1.06 (95% CI 0.81–1.38), indicating that the burden of risk for breast cancer resulted from use of hormone therapy for more than 5 years. Subsequently, a large epidemiologic study reported a greater risk estimate for combined estrogen–progestogen use as well as increased risk for estrogen-only therapy and tibolone.[21] However, interpretation of these findings is limited by selection bias because the risk profiles of women who used hormone therapy were significantly different from the those of nonusers.[21] Whether the type of estrogen compound or the dose, route, or administration method could be at least partly responsible for the risks observed in the WHI trial is unclear.

ESTROGEN AND PROGESTOGEN TREATMENT

Estrogens

1 The primary accepted indication for estrogen-based hormone therapy is the relief of vasomotor symptoms, and the initial dose should be the lowest effective dose for symptom control. Estrogens are naturally occurring hormones or synthetic steroidal or nonsteroidal compounds with estrogenic activity. Various systemically administered estrogens (typically oral and transdermal) are suitable for replacement therapy (Table 85–1). Estrogens can be administered orally, transdermally (patches and other topical products), intravaginally (creams, tablets, or rings), intranasally, intramuscularly, and even subcutaneously in the form of implanted pellets. The choice of estrogen delivery (product, route, and method) should be determined in consultation with the patient to ensure acceptability and enhance compliance. In general, the oral and transdermal routes are used most frequently, with oral conjugated equine estrogens (CEEs) particularly popular in the United States. No evidence indicates that one estrogen compound is more effective than another in relieving menopausal symptoms or preventing osteoporosis.

Oral Estrogen Oral CEE has been available for more than 50 years. CEE is prepared from the urine of pregnant mares and is composed of estrone sulfate (50%–60%) and multiple other equine estrogens such as equilin and 17α-dihydroequilin.[22]

Estradiol is the predominant and most active form of endogenous estrogens. A micronized form of estradiol (produced by a technique that yields extremely small particles of the pure hormone) is readily absorbed from the small intestines.[22] When given orally, estradiol is metabolized by the intestinal mucosa and the liver during the first hepatic passage, and only 10% reaches the circulation as free estradiol. Metabolism of estrogen is partly mediated by the cytochrome P450 3A4 isoenzyme. Gut and liver metabolism converts a large proportion of estradiol to the less potent estrone. Thus, measurement of serum estradiol is not useful for monitoring oral estrogen replacement. The principal metabolites of micronized estradiol are estrone and estrone sulfate. Administration of estradiol via the oral route results in estrone concentrations that are three to six times those of estradiol. Ethinyl estradiol is a highly potent semisynthetic estrogen that has similar activity following administration by the oral or parenteral route.

Orally administered estrogens stimulate the synthesis of hepatic proteins and increase the circulating concentrations of sex hormone–binding globulin, which, in turn, may compromise the bioavailability of androgens and estrogens.

Other Routes Parenteral estrogens (including transdermal, intranasal, and vaginal) bypass the gastrointestinal tract and thereby avoid first-pass liver metabolism. Parenteral routes of estrogen delivery result in a more physiologic estradiol-to-estrone ratio (estradiol con-

TABLE 85-1 Selected Systemic Estrogen Products[a,b]

Estrogen	Dosage Strength	Comments
Oral estrogens		
Conjugated equine estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg	Orally administered estrogens stimulate synthesis of hepatic proteins and increase circulating concentrations of sex hormone–binding globulin, which, in turn, may compromise the bioavailability of androgens and estrogens
Synthetic conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg	
Esterified estrogens	0.3, 0.625, 1.25, 2.5 mg	
Estropipate (piperazine estrone sulfate)	0.625, 1.25, 2.5, 5 mg	
Micronized estradiol	0.5, 1, 1.5, 2 mg	
Estradiol acetate	0.45, 0.9, 1.8 mg	
Parenteral estrogens		
Transdermal 17β-estradiol (patch)	14, 25, 37.5, 50, 60, 75, 100 mcg per 24 h	Women with elevated triglyceride concentrations or significant liver function abnormalities may benefit from parenteral therapy
Estradiol vaginal ring	0.05, 0.1 mg per 24 h (replaced every 3 months)	
Estradiol topical emulsion	4.35 mg of estradiol hemihydrate per foil-laminated pouch	Single approved dose is 8.7 mg of estradiol hemihydrate per day (two pouches)
Estradiol topical gel	0.25 to 1 mg of estradiol per dose	Apply to skin once daily
Estradiol topical solution	1.53 mg of estradiol per spray	Spray on inner surface of forearm once daily
Intranasal estradiol[c]	One spray per nostril delivers 150 mcg	

[a]Systemic oral and transdermal estrogen and progestogen combination products are available in the United States.
[b]Systemic oral estrogen and androgen combination products are available in the United States.
[c]Not available in the United States.

TABLE 85-2 Estrogen for Treatment of Menopausal Symptoms and Osteoporosis Prevention

Regimen	Standard Dose	Low Dose	Route	Frequency
Conjugated equine estrogens	0.625 mg	0.3 or 0.45 mg	Oral	Once daily
Synthetic conjugated estrogens	0.625 mg	0.3 mg	Oral	Once daily
Esterified estrogens	0.625 mg	0.3 mg	Oral	Once daily
Estropipate (piperazine estrone sulfate)	1.5 mg	0.625 mg	Oral	Once daily
Ethinyl estradiol	5 mcg	2.5 mcg	Oral	Once daily
Micronized 17β-estradiol	1–2 mg	0.25–0.5 mg	Oral	Once daily
Transdermal 17β-estradiol	50 mcg	25 mcg	Transdermal (patch)	Once or twice weekly
Intranasal 17β-estradiol[a]	150 mcg per nostril	–	Intranasally	Once daily
Implanted 17β-estradiol	50–100 mg pellets	25-mg pellets	Pellets implanted subcutaneously	Every 6 months
Percutaneous 17β-estradiol	0.04 mg (gel) 0.05 mg (emulsion)		Transdermal (emulsion, gel)	Once daily

[a]Not available in the United States.

centrations greater than estrone concentrations), as seen in the normal premenopausal state. Parenteral estrogen therapy also is less likely to affect sex hormone–binding globulin compared with oral therapy. Parenteral regimens produce little or no change in circulating lipids, coagulation parameters, or C-reactive protein levels.[23]

Transdermal estrogens share the advantages of other parenteral estrogen routes. Transdermal systems have the added advantage of delivering estradiol to the general venous circulation at a continuous rate. Reactions at the application site occur in approximately 10% of women who use reservoir (alcohol-based) patches. The newer matrix systems (estrogen in adhesive) generally are better tolerated, and fewer than 5% of women experience skin reactions.[24] The incidence of skin irritation diminishes when the application site is rotated. Topical antiinflammatory products can be applied for managing the rashes, and switching to another transdermal patch is often a viable option.

Percutaneous preparations (gels, creams, and emulsions) are convenient, but variability in drug absorption is common. This form of estrogen is used for systemic therapy. Topical emulsion and gel formulations are approved for use in the United States.

Estradiol pellets (implants) containing pure crystalline 17β-estradiol have been available for more than 50 years. They are inserted subcutaneously into the anterior abdominal wall or buttock. Pellets are difficult to remove and may continue to release estradiol for a long time after insertion. Implantation should not be repeated until serum estradiol concentrations have fallen to values similar to those at the midfollicular phase of the menstrual cycle. Estradiol pellets have not gained popularity in the United States.

Intranasal 17β-estradiol spray, which enables single-daily or twice-daily dosing, has been shown to have clinical therapeutic equivalence to oral and transdermal estradiol and is associated with significantly lower reports of mastalgia.[25]

Vaginal creams, tablets, and rings are used for treatment of urogenital (vulval and vaginal) atrophy. However, this route of administration can have more than just a local effect. Systemic estrogen absorption is lower with the vaginal tablets and rings (specifically Estring) compared with the vaginal creams. Nonetheless, local application of the cream at low doses can reverse atrophic vaginal changes and avoid significant systemic exposure. Nonestrogen vaginal moisturizers and lubricants also may provide local symptom relief. These products can be used alone or in combination with locally acting vaginal estrogens. Vaginal rings are a sustained-release delivery system composed of a biologically inert liquid polymer matrix with pure crystalline estradiol that can maintain adequate estradiol concentrations. One such vaginal ring product (Femring) is designed to achieve systemic concentrations of estrogen and is indicated for treatment of moderate-to-severe vasomotor symptoms.

The standard dose of estrogen previously believed to be effective in alleviating vasomotor symptoms is equivalent to 0.625 mg CEE,[26] but new evidence indicates that lower doses of estrogen also are effective in controlling postmenopausal symptoms and reducing bone loss (Table 85–2).[27–30] Even ultralow doses of 17β-estradiol delivered by a vaginal ring (Estring) improved serum lipid profiles and prevented bone loss in elderly women.[31] In general, if adverse effects such as breast tenderness occur with initial doses, lowering the dose may resolve the problem and improve patient compliance. Alternatively, if vasomotor symptoms are not controlled adequately with a lower-dose regimen, increasing the estrogen dose may be a reasonable option.

Adverse Effects Common adverse effects of estrogen include nausea, headache, breast tenderness, and heavy bleeding. More serious adverse effects include increased risk for coronary heart disease, stroke, venous thromboembolism, breast cancer, and gallbladder disease.

Initiating therapy with low doses of estrogen often will minimize breast tenderness, unscheduled bleeding, and potentially other adverse effects. Transdermal estrogen is less likely than oral estrogen to cause nausea and headache. Also, transdermal estrogen is associated with a lower incidence of breast tenderness and deep-vein thrombosis than is oral estrogen.[32,33] In many cases changing from one estrogen regimen to another can alleviate certain adverse effects.

Progestogens

2 Because of the increased risk of endometrial hyperplasia and endometrial cancer with estrogen monotherapy (unopposed estrogen), women who have not undergone hysterectomy should be treated concurrently with a progestogen in addition to the estrogen.[34] Progestogens reduce nuclear estradiol receptor concentrations, suppress DNA synthesis, and decrease estrogen bioavailability by increasing the activity of endometrial 17-hydroxysteroid dehydrogenase, an enzyme responsible for converting estradiol to estrone.[35]

Several progestogen regimens designed to prevent endometrial hyperplasia are available (Table 85–3). Progestogens must be taken for a sufficient period of time during each cycle. A minimum of 12 to 14 days of progestogen therapy each month is required for complete protection against estrogen-induced endometrial hyper-

TABLE 85-3 Progestogen Doses for Endometrial Protection (Oral Cyclic Administration)

Progestogen	Dose
Dydrogesterone[a]	10–20 mg for 12–14 days per calendar month
Medroxyprogesterone acetate	5–10 mg for 12–14 days per calendar month
Micronized progesterone	200 mg for 12–14 days per calendar month
Norethisterone[a]	0.7–1 mg for 12–14 days per calendar month
Norethindrone acetate	5 mg for 12–14 days per calendar month
Norgestrel[a]	0.15 mg for 12–14 days per calendar month
Levonorgestrel[a]	150 mcg for 12–14 days per calendar month

[a]Not available in a progestogen-only oral dosage form in the United States.

plasia.[36] Of note, use of even low-dose estrogen, including some vaginal preparations, requires progestogen coadministration for endometrial protection in women with an intact uterus.[37] However, rarely is progestogen administration needed in women who have undergone hysterectomy.

Four combination estrogen and progestogen regimens currently in use are continuous-cyclic (sequential), continuous-combined, continuous long-cycle (or cyclic withdrawal), and intermittent-combined (or continuous-pulsed) hormone therapy.[38] The latter two were introduced during the past decade. Sequential hormone therapy results in scheduled vaginal withdrawal bleeding but often is scant or completely absent in older women. For many women, the scheduled withdrawal bleeding is one of the main reasons for avoiding or discontinuing hormone therapy. Because there is no physiologic need for bleeding, new hormone therapy regimens that reduce monthly bleeding (e.g., continuous long-cycle regimens) or prevent monthly bleeding (e.g., continuous-combined and intermittent-combined regimens) have been developed. Various hormone therapy regimens that combine an estrogen and a progestogen are available (Table 85–4).

The first generation of progestogens included the C-19 androgenic progestogens norethisterone, norgestrel, and levonorgestrel. More recent preparations have included the C-21 progestogens dydrogesterone and medroxyprogesterone acetate, which are less androgenic. Drospirenone, a synthetic progestogen analog of the potassium-sparing diuretic spironolactone, has both antiandrogenic and antialdosterone properties. Micronized progesterone also has become available for use in postmenopausal women. The most commonly used oral progestogens are medroxyprogesterone acetate, micronized progesterone, and norethisterone acetate. The latter now can be administered transdermally in the form of a combined estrogen–progestogen patch.

Adverse Effects Common adverse effects of progestogens include irritability, depression, and headache. Changing from a cyclic to a continuous-combined regimen or changing from one progestogen to another may decrease the incidence or severity of untoward effects. Adverse effects of progestogens are difficult to evaluate and can vary with the agent administered. Some women experience "premenstrual-like" symptoms, such as mood swings, bloating, fluid retention, and sleep disturbance. New methods and routes of progestogen delivery (e.g., parenterally by an intranasal spray or locally by an intrauterine device that releases levonorgestrel or a progesterone-containing bioadhesive vaginal gel) may be associated with fewer adverse effects. Women who are unable to tolerate a progestogen may be given unopposed estrogen if they are informed of the significant increased risk for endometrial cancer and have endometrial biopsy annually or whenever breakthrough vaginal bleeding occurs.

TABLE 85-4 Common Combination Postmenopausal Hormone Therapy Regimens

Regimen	Doses
Oral continuous-cyclic regimens	
CEE + MPA[a]	0.625 mg + 5 mg; 0.625 mg + 10 mg
Oral continuous-combined regimens	
CEE + MPA	0.625 mg + 2.5 mg; 0.625 mg + 5 mg; 0.45 mg + 2.5 mg; 0.3 mg + 1.5 mg/day
17β-Estradiol + NETA	1 mg + 0.1 mg;1 mg + 0.25 mg; 1 mg + 0.5 mg/day
Ethinyl estradiol + NETA	1 mcg + 0.2 mg; 2.5 mcg + 0.5 mg; 5 mcg + 1 mg; 10 mcg + 1 mg/day
Transdermal continuous-cyclic regimens	
17β-Estradiol + NETA[a]	50 mcg + 0.14 mg; 50 mcg + 0.25 mg
Transdermal continuous-combined regimens	
17β-Estradiol + NETA	50 mcg + 0.14 mg; 50 mcg + 0.25 mg; 25 mcg + 0.125 mg

CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate.

Other oral (drospirenone and norgestimate) and transdermal (levonorgestrel) progestogens also are available in combination with an estrogen.

[a]Estrogen alone for days 1–14, followed by estrogen–progestogen on days 15–28.

Methods of Estrogen and Progestogen Administration

Continuous Cyclic Estrogen/Progestogen (Sequential) Treatment Estrogen typically is administered continuously (daily). A progestogen is coadministered with the estrogen for at least 12 to 14 days of a 28-day cycle.[36] The progestogen causes scheduled withdrawal bleeding in approximately 90% of women. With this regimen, bleeding usually begins 1 to 2 days after the last progestogen dose. Occasionally, bleeding begins during the latter phase of progestogen administration.

Continuous Combined Estrogen–Progestogen Treatment Continuous-combined estrogen–progestogen administration results in endometrial atrophy and the absence of vaginal bleeding. However, initially it causes unpredictable spotting or bleeding, which usually resolves within 6 to 12 months. Decreasing the estrogen dose or increasing the progestogen dose usually decreases or stops the spotting. Occasionally, a drug-free period of 1 or 2 weeks is useful to stop the bleeding.

Women who recently have undergone menopause have a higher risk for excessive, unpredictable bleeding while receiving continuous therapy; thus, this regimen is best reserved for women who are at least 2 years postmenopause. Continuous-combined hormone therapy is more acceptable than traditional cyclic therapy.

Continuous Long-Cycle Estrogen–Progestogen Treatment To decrease the incidence of uterine bleeding, a modified sequential regimen has been developed.[38] In the continuous long-cycle (or cyclic-withdrawal) estrogen–progestogen regimen, estrogen is given daily, and progestogen is given six times per year, every other month for 12 to 14 days, resulting in six periods per year. Bleeding episodes may be heavier and last for more days than withdrawal bleeding with continuous-cyclic regimens. The effect of continuous long-cycle estrogen–progestogen treatment on endometrial protection is unclear.

Intermittent Combined Estrogen–Progestogen Treatment The intermittent combined estrogen–progestogen regimen, also called *continuous-pulsed estrogen–progestogen* or *pulsed-progestogen*, consists of 3 days of estrogen therapy alone, followed by 3 days of combined estrogen and progestogen, which is then repeated without interruption.[38] This regimen is designed to lower the incidence of uterine bleeding. It is based on the assumption that pulsed-progestogen administration will prevent downregulation of progesterone receptors that can be produced by continuous-combined regimens. The lower progestogen dose induces fewer side effects and can be better tolerated. The long-term effect of intermittent-combined regimens in endometrial protection is undetermined.

CLINICAL CONTROVERSY

Although some clinicians believe that estrogen can be used safely at lower doses to treat postmenopausal women with severe and protracted vasomotor symptoms, others caution that such long-term therapy, even with lower doses of estrogen, may be associated with unacceptable risks.

Low-Dose Hormone Therapy

3 Increasingly, it has become recognized that use of hormone therapy at doses lower than prescribed historically is effective in the management of menopausal symptoms (see Table 85–2). The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial demonstrated equivalent symptom relief and bone density preservation without an increase in endometrial hyperplasia using lower doses of hormone therapy (CEE 0.45 mg/day and medroxyprogesterone acetate 1.5 mg/day).[27–31] Whether lower doses of estrogen will be safer (lower incidence of venous thromboembolism and breast cancer) remains to be proven. Nonetheless, evidence of harm associated with a standard dose of hormone therapy[2,3] has prompted many patients to either discontinue such therapy or taper to lower doses.

ANDROGENS

Pathophysiologic states affecting ovarian and adrenal function, along with aging, have been associated with androgen deficiency in women.[39] Therapeutic use of testosterone in women, although controversial, is becoming more widespread despite the lack of accurate clinical or biochemical findings of androgen deficiency.[39] Androgens have important biologic effects in women, acting both directly via androgen receptors in tissues, such as bone, skin fibroblasts, hair follicles, and sebaceous glands, and indirectly via the aromatization of testosterone to estrogen in the ovaries, bone, brain, adipose tissue, and other tissues.

A cluster of symptoms that characterizes androgen insufficiency in women, manifested as diminished sense of well-being, persistent or unexplained fatigue, and sexual function changes such as decreased libido, decreased sexual receptivity, and decreased pleasure, has been reported.[39] However, studies designed to evaluate this have shown no relationships between serum total and free testosterone levels and either sexual function[40] or well-being[41] in women. Thus, as data supporting an androgen deficiency syndrome are lacking, in 2006 the American Endocrine Society recommended against making a diagnosis of androgen deficiency in women at the present time.[40] Evidence of short-term efficacy of testosterone is seen in selected populations, such as surgically menopausal women.[42] Studies with adequate followup are necessary to assess long-term safety and efficacy of androgen therapy in women.

Absolute contraindications to androgen therapy include pregnancy or lactation and known or suspected androgen-dependent neoplasia. Relative contraindications include concurrent use of CEEs (for parenteral testosterone therapy), low sex hormone–binding globulin level, moderate–to-severe acne, clinical hirsutism, and androgenic alopecia.

Adverse effects from excessive dosage include virilization, fluid retention, and potentially adverse lipoprotein lipid effects, which are more likely with oral administration.

Testosterone is available as oral methyltestosterone in the United States and as testosterone implants in the United Kingdom. Of the available oral preparations, methyltestosterone in combination with esterified estrogen (either 0.625 mg esterified estrogen plus 1.25 mg methyltestosterone or 1.25 mg esterified estrogen plus 2.5 mg methyltestosterone) is the most widely studied.

Testosterone replacement for women is available in a variety of formulations (Table 85–5). Most of the earlier studies showing clinical improvement with testosterone therapy reported supraphysiologic levels. More recent studies using transdermal patch therapy have shown efficacy with free testosterone levels in the upper normal range for young women. The availability of testosterone regimens specifically designed for women has the potential to maintain testosterone levels within the normal range and help to clarify whether the apparent beneficial effects of testosterone therapy are physiologic or pharmacologic.[42,43] In general, testosterone treatment should not be administered to postmenopausal women who are not receiving concurrent estrogen therapy until completion of studies on the use of testosterone without estrogen. At present, generalized use of testosterone is not recommended because the indications are inadequate, and evidence from long-term studies evaluating safety is lacking.[44]

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) are a group of nonsteroidal compounds that are chemically distinct from estradiol. They act as estrogen agonists in some tissues, such as bone, and as estrogen antagonists in other tissues, such as breast, through specific, high-affinity binding to the estrogen receptor.

The ideal SERM would protect against osteoporosis and decrease the incidence of breast, endometrial, and colorectal cancer and coronary heart disease without exacerbating menopausal symptoms or increasing the risk of venous thromboembolism or gallbladder disease. To date, no SERM meets these ideals. Tamoxifen, the first-generation SERM (a nonsteroidal triphenylethylene derivative), has estrogen antagonist activity on the breast and estrogen-like agonist activity on bone and endometrium. The second generation of SERMs, most notably raloxifene (a nonsteroidal benzothiophene derivative), has become available for prevention of osteoporosis. Raloxifene does not alleviate, and may even exacerbate, vasomotor symptoms.

Raloxifene decreases bone loss in recently menopausal women without affecting the endometrium and has estrogen-like actions on lipid metabolism.[45] Raloxifene generally is well tolerated. Its adverse effects include leg cramps and hot flushes.

The Multiple Outcomes of Raloxifene Evaluation (MORE), a multicenter randomized, blinded, placebo-controlled trial, showed that raloxifene increases bone mineral density in the spine and femoral neck and reduces the risk of vertebral fractures.[45] More important, the same study[46] and the Continuing Outcomes Relevant to Evista (CORE) trial[47] suggest that raloxifene use is associated with a significantly lower incidence of breast cancer compared with placebo. This benefit is primarily due to a reduced risk of estrogen receptor–positive invasive breast cancers.[47,48] A prospective randomized study (Raloxifene Use for the Heart [RUTH]) of 10,101 postmenopausal women (mean age 67.5 years) with coronary heart disease or multiple risk factors for coronary heart disease showed that raloxifene did not significantly affect the risk of coronary heart disease.[48] Nonetheless, raloxifene use increases the risk of venous thromboembolism[45–48] and stroke[48] to a degree similar to that of oral estrogen.

TABLE 85-5 Androgen Regimens Used for Women

Regimen	Dose	Frequency	Route
Methyltestosterone in combination with esterified estrogen	1.25–2.5 mg	Daily	Oral
Mixed testosterone esters	50–100 mg	Every 4–6 weeks	Intramuscular
Testosterone pellets	50 mg	Every 6 months	Subcutaneous (implanted)
Transdermal testosterone system[a]	150–300 mcg/day	Every 3–4 days	Transdermal patch
Nandrolone decanoate	50 mg	Every 8–12 weeks	Intramuscular

[a]Undergoing clinical trials in the United States.

TIBOLONE

Tibolone is a gonadomimetic synthetic steroid in the norpregnane family with combined estrogenic, progestogenic, and androgenic activity.[49] Tibolone has been used for almost 2 decades in Europe for treatment of menopausal symptoms and prevention of osteoporosis. The hormonal effects of this synthetic steroid depend on its metabolism and activation in peripheral tissues. The parent compound has been described as a prodrug that is metabolized quickly in the gastrointestinal tract. It has several active metabolites, including a $\Delta 4$-isomer and 3α-OH and 3β-OH compounds.[49] The $\Delta 4$-isomer metabolite confers significant progestogenic and androgenic properties. Tibolone has beneficial effects on mood and libido and improves menopausal symptoms and vaginal atrophy. Tibolone protects against bone loss and reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.[50] Tibolone use in elderly women has been reported to be associated with an increased risk of stroke.[50]

Tibolone reduces concentrations of total cholesterol, triglycerides, and lipoprotein (a) but significantly decreases HDL cholesterol and thus may increase overall cardiovascular risk.[22] Long-term safety data are lacking. The Million Women Study, a cohort study, suggested that current users of tibolone may be at increased risk for breast cancer (adjusted relative risk 1.45, 95% CI 1.25–1.68).[21] This study had multiple limitations, including biased prescribing of tibolone in the community to women at greater risk for breast cancer. The Million Women Study also indicated a greater risk of endometrial cancer (adjusted relative risk 1.79, 95% CI 1.43–2.25).[51] However, other controlled studies contradict this finding and suggest that tibolone has an endometrial safety profile similar to continuous-combined CEE and medroxyprogesterone acetate.[52]

The major adverse effects of tibolone include weight gain and bloating. Additional studies are necessary to identify the true risk-to-benefit ratio of tibolone with respect to its overall effect on coronary artery disease and breast cancer.

TREATMENT CONSIDERATIONS

In the absence of contraindications, hormone therapy is appropriate mainly for women with hot flashes and vulvar or vaginal atrophy.[53] It is contraindicated in women with endometrial cancer, breast cancer, undiagnosed vaginal bleeding, coronary heart disease, thromboembolism (including recent spontaneous thrombosis or in the presence of a thrombophilia), stroke or transient ischemic attack, and active liver disease.[53] Relative contraindications include uterine leiomyoma, migraine headaches, and seizure disorder. In addition, oral estrogen should be avoided in women with hypertriglyceridemia, liver disease, and gallbladder disease. For these women, transdermal administration is a safer approach. The main reasons for discontinuing hormone therapy are side effects such as bleeding, breast tenderness, bloating, and "premenstrual-like symptoms." Reducing the dose or changing the regimen or the route of administration can minimize these effects.

Pretreatment Assessment

The initial visit of a perimenopausal or postmenopausal woman is the most appropriate time to obtain a complete medical history, perform a physical examination, and educate the patient. Medical history should include a personal or family history of coronary heart disease and thrombotic problems. The physical examination should include a complete cardiovascular examination, clinical assessment of thyroid status, and breast and pelvic examinations. Papanicolaou cervical cytologic examination and screening mammography negative for malignancy are required before initiating hormone therapy. Thyroid function tests and lipoprotein lipid profile also are performed at the discretion of the clinician.

Each patient should be evaluated for the presence of indications (i.e., menopausal symptoms such as hot flushes or vaginal dryness) and possible contraindications. The risks and benefits of hormone therapy should be discussed with the patient so that she can weigh the risks and benefits versus alternatives and make a rational decision about whether to use hormone therapy.

BENEFITS OF HORMONE THERAPY

Relief of Menopausal Symptoms

Vasomotor Symptoms 4 The major indication for postmenopausal hormone therapy is management of vasomotor symptoms. Most women with vasomotor symptoms require hormone treatment for fewer than 5 years, so the risk appears to be small.

Fewer than 25% of women experience a menopausal transition without symptoms, whereas more than 25% suffer severe menopausal symptoms, most commonly hot flushes and night sweats.[54]

Without treatment, hot flushes in most women typically disappear within 1 to 2 years, but in some untreated women hot flashes continue for more than 20 years.[32] Women with mild vasomotor symptoms often experience relief by lifestyle modification (e.g., wearing layered clothing that can be removed or added as necessary); reduction in intake of hot spicy foods, caffeine, and hot beverages; exercise; and other good general health practices. At least 25% of women in clinical trials reported significant improvement of vasomotor symptoms when taking placebo. However, no therapy has been shown to be as effective as estrogen therapy in alleviating significant vasomotor symptoms. Estrogens diminish hot flushes in most women, and all types and routes of administration of estrogen are equally effective.[55] A dose-dependent relationship between estrogen administration and suppression of hot flushes is well established. Some women, especially younger women, may require a higher than average dose of estrogen to suppress symptoms. On the other hand, many women with hot flushes at the time of menopause require lower dose of estrogen.[55] Hormone therapy for menopausal symptoms can be stopped about 2 or 3 years after starting. If treatment can be tapered and stopped within 5 years, no evidence of increased risk of breast cancer is seen.[2]

Alternatives to estrogen for treatment of hot flushes include tibolone, selective serotonin reuptake inhibitors (e.g., paroxetine, fluoxetine), dual serotonin and noradrenaline reuptake inhibitors (e.g., venlafaxine), medroxyprogesterone acetate, megestrol acetate, clonidine, and gabapentin (Table 85–6).[56] Progestogens alone may be an option for some women (e.g., those with a history of breast cancer or venous thrombosis), but weight gain, vaginal bleeding, and other adverse effects often limit their use. Tibolone and progestogens cannot be considered nonhormonal agents for treatment of hot flushes in women for whom hormone therapy is contraindicated. For this group of patients, selective serotonin reuptake inhibitors and venlafaxine are considered by some to be a first-line therapy.[56,57] However, the efficacy of venlafaxine for treatment of hot flushes has not been shown to extend beyond 12 weeks.[58] Furthermore, in breast cancer patients, evidence suggests that selective serotonin reuptake inhibitors could interfere with metabolism of endocrine therapies, such as tamoxifen.[59] Clonidine often is effective for symptom control but is not always well tolerated by women.

Randomized, placebo-controlled trials of nonhormonal therapies have been equivocal and have not established the safety and efficacy of herbal remedies, homeopathic treatments, or acupuncture for prevention or treatment of hot flushes.

Vaginal Atrophy Estrogen receptors have been demonstrated in the lower genitourinary tract, and at least 50% of postmenopausal women suffer symptoms of urogenital atrophy caused by estrogen deficiency.[60] Atrophy of the vaginal mucosa results in vaginal dryness

TABLE 85-6 Alternatives to Estrogen for Treatment of Hot Flushes

Drug	Dose (Oral)	Interval	Comments
Tibolone	2.5–5 mg	Once daily	Tibolone is not recommended during the perimenopause because it may cause irregular bleeding
Venlafaxine	37.5–150 mg	Once daily	Side effects include dry mouth, decreased appetite, nausea, and constipation
Paroxetine	12.5–25 mg	Once daily	12.5 mg is an adequate, well-tolerated starting dose for most women; adverse effects include headache, nausea, and insomnia
Fluoxetine	20 mg	Once daily	Modest improvement seen in hot flushes
Megestrol acetate	20–40 mg	Once daily	Progesterone may be linked to breast cancer etiology; also, there is concern regarding the safety of progestational agents in women with preexisting breast cancer
Clonidine	0.1 mg	Once daily	Can be administered orally or transdermally; drowsiness and dry mouth can occur, especially with higher doses
Gabapentin	900 mg	Divided in three daily doses	Adverse effects include somnolence and dizziness; these symptoms often can be obviated with a gradual increase in dosing

and dyspareunia. Lower urinary tract symptoms include urethritis, recurrent urinary tract infection, urinary urgency, and frequency. Most women with significant vaginal dryness because of vaginal atrophy require local or systemic estrogen therapy for symptom relief. Such treatment also reduces the risk of recurrent urinary tract infections, possibly by modifying the vaginal flora.[61] Vaginal dryness and dyspareunia can be treated with a topical estrogen cream, tablet, or vaginal ring. In clinical trials, topical estrogen appears to be better than systemic estrogen for relieving these symptoms and avoids high levels of circulating estrogen. Concomitant progestogen therapy generally is unnecessary if women are using low-dose micronized 17β-estradiol. However, regular use of CEE vaginal creams and other products that potentially promote endometrial proliferation in women with an intact uterus requires intermittent progestogen challenges (i.e., for 10 days every 12 weeks). This is an important caveat because vaginal atrophy requires long-term estrogen treatment.[61]

Urinary incontinence, which becomes more prevalent with increasing age, usually is not improved by estrogen therapy. In one large clinical trial, estrogen–progestogen therapy actually increased incontinence.[62]

Osteoporosis Prevention

5 Postmenopausal osteoporosis is a serious age-related disease that affects millions of women throughout the world. The WHI randomized trial was the first study to demonstrate that hormone therapy reduces the risk of fractures at the hip, spine, and wrist.[2,63] Hip and clinical vertebral fractures are reduced by 34%, and total osteoporotic fractures are reduced by 24%.[63] These findings are in agreement with observational data and several meta-analyses of the efficacy of hormone therapy for reducing fractures in postmenopausal women.[64]

Menopause is accompanied by accelerated bone loss, and the central role of estrogen deficiency in postmenopausal osteoporosis is well established. Osteoporosis is characterized by reduced bone mass associated with architectural deterioration of the skeleton and increased risk for fracture.[65] Estrogen deficiency results in bone loss through its actions in accelerating bone turnover and uncoupling bone formation from resorption. Annual decrements in bone mass of 3% to 5% are common in the years soon after the menopause, and decrements of 0.5% to 1% are seen after age 65 years.[66] Estrogen therapy reduces bone turnover and increases bone density in postmenopausal women of all ages. Nonetheless, the protective effect persists as long as the treatment is maintained. With cessation of therapy, postmenopausal bone loss resumes at the same rate as in untreated women. The standard bone-sparing daily estrogen dose is equivalent to 0.625 mg CEE[26] (see Table 85–2). Even low doses of estrogen may increase bone mass when they are supplemented with adequate calcium intake.[26]

Osteoporosis prevention remains an indicated use of estrogen products; however, nonestrogen products, such as raloxifene and bisphosphonates, are as effective as hormone therapy for preventing osteoporosis (Table 85–7). The FDA has withdrawn the "osteoporosis treatment" indication from estrogen products.

Raloxifene decreases the risk of vertebral fracture by 30% to 50%, although it has not been shown to decrease the risk of hip fracture.[46] The bisphosphonates reduce the risk of both hip and vertebral fractures by 30% to 50%.[65] Bisphosphonates are analogs of pyrophosphate that inhibit bone resorption. Drugs in this class include alendronate, etidronate, pamidronate, risedronate, tiludronate, and zoledronate. Bisphosphonates have no known impact on the incidence of cardiovascular disease or breast or endometrial cancer. Adverse effects include upper gastrointestinal side effects, especially if not taken properly. A few trials have shown improved bone density over single therapy when a bisphosphonate is combined with estrogen or raloxifene, but no fracture data are available.[67]

Tibolone can prevent bone loss and vertebral fractures in postmenopausal women with osteoporosis.[50]

TABLE 85-7 Alternatives to Hormone Therapy for Osteoporosis Prevention

Drug	Dose	Comments
Raloxifene	60 mg/day	Raloxifene reduces the risk of vertebral fractures. Adverse effects include hot flushes and leg cramps. Slowly increasing the dose of raloxifene may help reduce the incidence and severity of hot flushes.
Tibolone	1.25 mg or 2.5 mg/day	Tibolone prevents bone loss. No data regarding fracture rates are available.
Alendronate	5 mg/day or 35 mg/wk	A 50% reduction in the risk of fractures is observed in women with osteoporosis. In younger postmenopausal women without osteoporosis, therapy with alendronate protected all women from bone loss for up to 4 years. Side effects include upper gastrointestinal symptoms, especially if the drug is not taken as directed.
Risedronate	5 mg/day or 35 mg/wk	A 40% reduction in vertebral and nonvertebral fractures is observed in women with osteoporosis. In postmenopausal women without osteoporosis, risedronate increases bone mineral density over 2 years. Significant side effects were not observed.
Etidronate	Intermittent administration of 400 mg/day (in 2-wk cycles); dose repeated every 3 months	Calcium is taken between the cycles of etidronate. Continuous daily use may cause abnormalities in bone mineralization. A 37% reduction is observed in the risk of vertebral fractures (but not nonvertebral fractures) in women with osteoporosis. Therapy in women without osteoporosis prevents bone loss over 2 years. Side effects include diarrhea and nausea.
Zoledronic acid	4 mg as a single intravenous infusion once yearly	Effects on bone turnover and bone density were similar to those with daily oral bisphosphonates. Adverse effects include myalgia and pyrexia.

General protective measures, such as adequate calcium intake (1,200 mg/day),[68] regular weight-bearing exercise, and avoidance of detrimental lifestyle habits such as smoking and alcohol abuse, are appropriate for all women. Most women require calcium supplementation to their dietary intake. Adequate exposure to sunlight is believed to protect against vitamin D deficiency, but many western women are deficient in this vitamin. The current recommended dietary intake for vitamin D is 400 international units/day for women aged 51 to 70 years and 600 international units/day for women older than 70 years.[68]

Low bone density is the most important risk factor for osteoporosis. According to the World Health Organization, a woman with a bone mineral density >2.5 SD below the mean peak density has osteoporosis.[65] The rates of osteoporosis vary with ethnicity; it is more common in whites and those of Asian descent and less common in blacks.[65] In the United States, approximately 20% of white women 50 years and older have osteoporosis.[65]

Bone mass measurement accurately determines the bone density in the spine and hip. The current "gold standard" method of bone density testing is dual-energy x-ray absorptiometry (DEXA).[65] In the United States, bone density testing is recommended for all women with medical causes of bone loss and for all women 65 years or older. Bone density testing should be assessed in conjunction with clinical risk profile evaluation. For women at high risk for fracture (i.e., T-score <2, previous nonspine fracture, family history of hip or spine fracture, and low body weight), bisphosphonates are the treatment of choice because of demonstrated fracture protection.[65] There are no clear indications for treating women at low risk for fracture (T-score >2), but raloxifene, tibolone, and bisphosphonates can be used. Long-term hormone therapy is no longer an appropriate first-choice option for osteoporosis prevention because of the risks associated with its long-term use. Therefore, hormone therapy should be considered for osteoporosis prevention only in women at significant risk for osteoporosis who cannot take nonestrogen regimens.

Colon Cancer Risk Reduction

Colorectal cancer is the fourth most common cancer and the second leading cause of cancer death in the United States (see Chapter 133). The estrogen-progestogen arm of the WHI study was the first randomized, controlled trial to confirm that combined estrogen–progestogen therapy reduces colon cancer risk. Compared with placebo, six fewer colorectal cancers are reported per year in every 10,000 women taking hormone therapy.[2]

Other

Diabetes In healthy postmenopausal women, hormone therapy appears to have a beneficial effect on fasting glucose levels in women with elevated fasting insulin concentrations.[69] Also, in women with coronary artery disease, hormone therapy reduces the incidence of diabetes by 35%.[70] These findings provide important insights into the metabolic effects of hormone therapy but are insufficient to recommend the long-term use of hormone therapy in women with diabetes.

Body Weight A meta-analysis of randomized controlled trials showed that unopposed estrogen or estrogen combined with a progestogen has no effect on body weight, suggesting that hormone therapy does not cause weight gain in excess of that normally observed at the time of menopause.[71]

■ RISKS OF HORMONE THERAPY

Cardiovascular Disease

6 Cardiovascular disease, including coronary artery disease, stroke, and peripheral vascular disease, is the leading cause of death among women. The American Heart Association recommends that postmenopausal hormone therapy should not be used for reducing the risk of coronary heart disease.[72]

In the last decade, an expectation of coronary benefit had been a major reason for use of postmenopausal hormone because observational studies indicated that women who use hormone therapy have a 35% to 50% lower risk of coronary heart disease than do nonusers.[73] In addition, previous studies have shown that estrogen exerts protective effects on the cardiovascular system, including lipid-lowering,[74] antioxidant,[75] and vasodilating effects.[76] Nevertheless, recent randomized clinical trials have provided no evidence of cardiovascular disease protection and even some evidence of harm with hormone therapy.[2,77–80]

The primary findings of the estrogen-progestogen arm of the WHI trial showed an overall increase in the risk of coronary heart disease (HR 1.24, 95% CI 1–1.54) among healthy postmenopausal women 50 to 79 years old receiving combined estrogen–progestogen hormone therapy compared with those receiving placebo.[2,80] The primary findings of the estrogen-only arm of the WHI trial show no effect (either increase or decrease) on the risk of coronary heart disease in women taking estrogen alone.[3] However, recent analysis revealed that women in this cohort who initiated hormone therapy closer to the time of menopause tended to have decreased coronary heart disease risk compared to the increased risk noted among women who were more distant from menopause when estrogen therapy was initiated.[81,82]

In the estrogen–progestogen arm of the WHI trial, the elevation in coronary heart disease risk was most apparent at 1 year (HR 1.81, 95% CI 1.09–3.01). The increased risk for stroke and venous thromboembolism continued throughout the 5 years of therapy.[2] Increased risk was observed only for ischemic stroke and not for hemorrhagic stroke.[83] In the estrogen-alone arm of the study, a similar increased risk for stroke was observed.[3] Recent evidence suggests that hormone therapy has different effects on coronary heart disease risk in women when initiated in the early menopausal years (50–59 years of age) versus long after the menopause (i.e., menopausal for more than a decade), emphasizing the importance of timing of hormone therapy initiation.[81,82,84]

Raloxifene therapy does not significantly affect the risk for coronary heart disease.[48]

In the WHI trial, it is unclear whether the cardiovascular effects of hormone therapy during the perimenopause/early menopause and late menopause differ. There is a need for a long-term randomized controlled study of low-dose hormone therapy started around the time of menopause.[85] Hormone therapy should not be initiated or continued for the prevention of cardiovascular disease. Adherence to a healthful lifestyle (cessation of smoking, regular exercise, healthy diet, and body mass index <25) may prevent the onset of cardiovascular disease in postmenopausal women.[86,87]

Breast Cancer

The WHI trial found that combined estrogen–progestogen therapy has an increased risk of invasive breast cancer (HR 1.26, 95% CI 1.0–1.59) and a trend toward increasing risk with increasing duration of therapy.[2] The estrogen-only arm of the WHI trial found no increased risk for breast cancer during the 7-year followup period. [3] In the estrogen–progestogen arm, the increased breast cancer risk did not appear until after 3 years of study participation.[2] The breast cancers diagnosed in women in the hormone therapy group had similar histology and grade but were more likely to be in an advanced stage compared with women in the placebo group.[88] In an unselected postmenopausal population, the Million Women Study found that current use of hormone therapy increased breast cancer risk and breast cancer mortality (relative risk 1.66 and 1.22, respectively). Increased incidence was observed for estrogen-only use (relative risk 1.30), for estrogen–progestogen (relative risk 2), and for tibolone (relative risk 1.45).[21]

The lifetime risk of developing breast cancer in the United States is approximately one in eight women,[89] and the greatest incidence occurs in women older than 60 years (see Chapter 131). In a collaborative reanalysis of data from 51 studies evaluating more than 52,000 women with breast cancer and 108,000 controls, less than 5 years of therapy with estrogen combined with progestogen was associated with a 15% increase in the risk of breast cancer, and the increase was greater with longer duration (relative risk 1.53 after ≥5 of use).[90] However, 5 years after discontinuation of hormone replacement therapy, the risk of breast cancer was no longer increased.[90]

Addition of progestogens to estrogen may increase breast cancer risk beyond that observed with estrogen alone.[91] The Iowa Women's Health Study showed that exposure to hormone therapy is associated with an increased risk of breast cancer that has a favorable prognosis.[92] These findings have been attributed to an increased breast cancer screening in women taking hormone therapy. A study of the effects of hormone therapy in women with a family history of breast cancer found that those who currently were receiving hormone therapy had approximately the same increased relative risk compared with those who did not have a family history.[93] The overall mortality for women with a family history of breast cancer from all causes was reduced significantly among hormone therapy users.[93] These data suggest that hormone therapy use in women with a family history of breast cancer is not associated with a significantly increased incidence of the disease.

Sex steroid deficiency during menopause results in lipomatous involution of the breast, which is seen as decreased mammographic breast density and markedly improved radiotransparency of breast tissue. Thus, mammographic changes indicating breast cancer can be recognized more easily and earlier after the menopause. Conversely, combination hormone therapy results in increased mammographic breast density, and increased density on mammography has been associated with higher breast cancer risk.[94] Of note, increased mammographic density is not observed with estrogen-only therapy.[95]

Although raloxifene is not approved for prevention or treatment of breast cancer, a 4-year trial of raloxifene in women with osteoporosis (who were not at increased risk for breast cancer) showed a 76% risk reduction for estrogen receptor–positive breast cancer[46] (relative risk 0.24, 95% CI 0.13–0.44). Furthermore, the CORE trial, a study evaluating the efficacy of an additional 4 years of raloxifene therapy in women with osteoporosis, showed that the reduction in incidence of estrogen receptor–positive breast cancer continues for up to 8 years (HR 0.24, 95% CI 0.15–0.40).[47] Importantly, a prospective randomized double-blinded trial of 19,747 women at high risk for breast cancer (Study of Tamoxifen and Raloxifene [STAR]) showed that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of thromboembolic events.[96]

Endometrial Cancer

The WHI trial suggests that combined hormone therapy does not increase endometrial cancer risk compared with placebo (HR 0.81, 95% CI 0.48–1.36).[97] Estrogen alone given to women with an intact uterus significantly increases uterine cancer risk.[35] With unopposed estrogen therapy, the risk of endometrial cancer increases within 2 years.[35] The excess risk increases with dose and duration of estrogen (10 years of unopposed estrogen increases the risk 10-fold), is apparent within 2 years of the start of treatment, and persists for many years after estrogen replacement is discontinued. Estrogen-induced endometrial cancer usually is of a low stage and grade at the time of diagnosis,[32] and it can be prevented almost entirely by progestogen coadministration. The sequential addition of progestogen to estrogen for at least 10 days of the treatment cycle or continuous combined estrogen–progestogen does not increase the risk of endometrial cancer.[98]

Lower doses of estrogen may be associated with a lower risk of endometrial hyperplasia.[99] Raloxifene does not result in endometrial hyperplasia, has no effect on endometrial thickness, is not associated with polyp formation, and has virtually no proliferative effect on the endometrium.[100] A 4-year trial of raloxifene in women with osteoporosis showed no increased risk of endometrial cancer.[48]

Ovarian Cancer

Lifetime risk of ovarian cancer is low (1.7%). The WHI trial suggests that combined hormone therapy may increase the risk of ovarian cancer (HR 1.58, 95% CI 0.77–3.24).[97] However, a study reported an increased risk of ovarian cancer in women taking postmenopausal estrogen therapy for more than 10 years (relative risk 1.8, 95% CI 1.1–3.0) but no increased risk of ovarian cancer among women receiving combination estrogen–progestogen therapy.[101] Additional large, controlled studies are needed to confirm these findings.

Venous Thromboembolism

Venous thromboembolism, including thrombosis of the deep veins of the legs and embolism to the pulmonary arteries, is uncommon in the general population. The absolute risk of venous thromboembolism in nonhormone therapy users is approximately 1 in 10,000 women.[102] Women taking combined estrogen–progestogen hormone therapy have a twofold increased risk for thromboembolic events, with the highest risk occurring in the first year of use.[103] The absolute increase in risk is small, with 1.5 venous thromboembolic events per 10,000 women in 1 year.[103] Lower doses of estrogen are associated with a decreased risk for thromboembolism as compared with higher doses.[102] Oral administration of estrogen increases the risk of venous thromboembolism compared to the transdermal route.[104] Also, the norpregnane progestogens, unlike micronized progesterone and pregnane derivatives (e.g., medroxyprogesterone acetate), appear to be thrombogenic.

Currently, there is no indication for thrombophilia screening before initiating hormone therapy. However, hormone therapy should be avoided in women at high risk for thromboembolic events.

Gallbladder Disease

Gallbladder disease is a commonly cited complication of oral estrogen use. A randomized trial showed an increased risk for cholecystitis, cholelithiasis, and cholecystectomy among women taking oral estrogen or estrogen–progestogen therapy.[105] Transdermal estrogen is an alternative to oral therapy for women at high risk for cholelithiasis.

CLINICAL CONTROVERSY

Some clinicians believe that hormone therapy improves well-being and quality of life of postmenopausal women, whereas others believe that hormone therapy, at best, has no effect. Hormone therapy improves mood and well-being mainly in women with vasomotor symptoms and sleep disturbance.

■ OTHER EFFECTS OF HORMONE THERAPY

Quality of Life, Mood, Cognition, and Dementia

7 Hormone therapy improves depressive symptoms in symptomatic menopausal women, most probably by relieving flushing and improving sleep.[106] Women with vasomotor symptoms receiving hormone therapy have improved mental health and fewer depressive symptoms compared with women receiving placebo; however, hormone therapy may worsen quality of life in women without flushes.[107]

There is no evidence that hormone therapy improves quality of life or cognition in older, asymptomatic women.[106–110]

More than 33% of women 65 years and older will develop dementia during their lifetime.[111] Several observational studies have suggested that estrogen therapy may be protective against Alzheimer's disease (see Chapter 67). The WHI Memory Study (an ancillary study of WHI trial) evaluated the effect of combined hormone therapy on dementia and cognition in 4,532 women 65 years and older.[110] The study found that postmenopausal women 65 years and older taking estrogen plus progestogen therapy had twice the rate of dementia, including Alzheimer's disease, than women taking placebo (HR 2.05, 95% CI 1.21–3.48).[110] In addition, estrogen plus progestogen therapy in these women did not prevent mild cognitive impairment, a cognitive and functional state between normal aging and dementia that frequently progresses to dementia.[110] The estrogen-alone arm of the WHI trial showed similar findings.[112,113]

Raloxifene does not have a significant effect on cognitive function; however, there is a trend toward a smaller decline in verbal memory and attention scores among women receiving raloxifene.[114]

Hormone therapy does not improve quality of life in postmenopausal women who do not have vasomotor symptoms. Hormone therapy does not improve cognitive function compared with placebo and, more importantly, produces an increased risk (albeit small) of clinically meaningful cognitive decline among women 65 years and older taking hormone therapy.[107–110,112,113]

INDIVIDUALIZING HORMONE THERAPY

8 Menopause is a natural life event, not a disease. The decision to take hormone therapy must be individualized and based on several parameters, including menopausal symptoms, osteoporosis risk, coronary artery disease risk, breast cancer risk, and thromboembolism risk. Recommendations should be specific to each woman and her background (Table 85–8). Thus, menopausal treatment should be based on each woman's clinical profile and concerns. Approved indications of hormone therapy include treatment of vasomotor symptoms and urogenital atrophy and prevention of osteoporosis. Weighing risks and benefits, the FDA determined that the indication for vasomotor symptoms (hot flushes and night sweats) should remain unchanged, but the other two indications for hormone therapy should be revised. For treatment of vasomotor symptoms, systemic hormone therapy remains the most effective pharmacologic intervention (Fig. 85–1). For symptoms of urogenital atrophy, such as vaginal dryness, topical products should be considered. In addition, although prevention of postmenopausal osteoporosis remains an indicated use of hormone therapy, consideration should be given to approved nonestrogen products, such as raloxifene and bisphosphonates (Fig. 85–1). Clinicians should prescribe the lowest effective dose of hormone therapy for the shortest duration, weighing the potential benefits and risks for the individual woman. Measures to reduce the risks of cardiovascular disease (e.g., treating hypertension and avoiding smoking) and osteoporosis (e.g., taking calcium supplements and vitamin D, changing diet, and performing weight-bearing exercise) should be addressed.

TABLE 85-8 Evidence-Based Hormone Therapy Guidelines for Menopausal Symptom Management

Recommendation	Recommendation Grade[a]
In the absence of contraindications, estrogen-based postmenopausal hormone therapy should be used for treatment of moderate-to-severe vasomotor symptoms	A1
Systemic or vaginal estrogen therapy should be used for treatment of urogenital symptoms and vaginal atrophy	A1
Hormone therapy should be prescribed at the lowest effective dose and for the shortest duration	B2
Postmenopausal women taking estrogen-based therapy should be followed-up every year, taking into account findings from new clinical trials	A1
Postmenopausal women taking estrogen-based therapy for longer than 5 years should be informed about potential risks	A1
Safety and tolerability may vary substantially with the type and regimen of hormone therapy	B2
Breast cancer risk increases after use of continuous combined hormone therapy for longer than 5 years	A1
Breast cancer risk does not increase after long-term estrogen-only therapy (6.8 years) in postmenopausal women with hysterectomy	A1
Hormone therapy should not be used for primary or secondary prevention of coronary heart disease	A1
Oral hormone therapy increases risk of venous thromboembolism	A1
Parenteral hormone therapy may be safer for postmenopausal women at risk for venous thromboembolism who choose to take hormone therapy	B2
Oral hormone therapy increases risk of ischemic stroke	A1
Although hormone therapy decreases risk of osteoporotic fractures, it cannot be recommended as a first-line therapy for the treatment of osteoporosis	A1
Potential harm (cardiovascular disease, breast cancer, and thromboembolism) from long-term hormone therapy (use greater than 5 years) outweighs potential benefits	A1
Young women with premature ovarian failure have severe menopausal symptoms and increased risk for osteoporosis and cardiovascular disease. Decisions on whether and how these young women must be treated should not be based on studies of hormone therapy in women older than 50 years	B3

Quality of evidence: 1 = evidence from more than one properly randomized, controlled trial; 2 = evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series; or dramatic results from uncontrolled experiments; 3 = evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

[a]Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively.

EVALUATION OF THERAPEUTIC OUTCOMES

After the menopausal woman begins hormone therapy, a brief followup visit 6 weeks later may be useful to discuss patient concerns about hormone therapy and to evaluate the patient for symptom relief, adverse effects, and patterns of withdrawal bleeding. The FDA recommends that women who choose estrogen-based therapy should have yearly breast examinations, perform monthly breast self-examinations, and receive periodic mammograms (scheduled based on their age and risk factors). Also, women receiving hormone therapy should undergo annual monitoring, including a medical history, physical examination, pelvic examination, blood pressure measurement, and routine endometrial cancer surveillance, as indicated. Additional followup is determined based on the patient's initial response to therapy and the need for any modification of the regimen. Endometrial biopsy should be considered in women taking cyclic hormone therapy if vaginal bleeding occurs at any time other than the expected time of withdrawal bleeding or when heavier or more prolonged withdrawal bleeding occurs. In women taking continuous combined hormone therapy, endometrial evaluation should be considered when irregular bleeding persists for more than 6 months after initiating therapy. Endovaginal ultrasonography also has been used for evaluation of abnormal uterine bleeding in women receiving hormone therapy. However, there is no universal agreement that endovaginal ultrasonography is adequate for excluding endometrial pathology.

The main indication for hormone therapy is relief of menopausal symptoms, and hormone therapy should be used only as long as symptom control is necessary (typically 2–3 years). When hormone

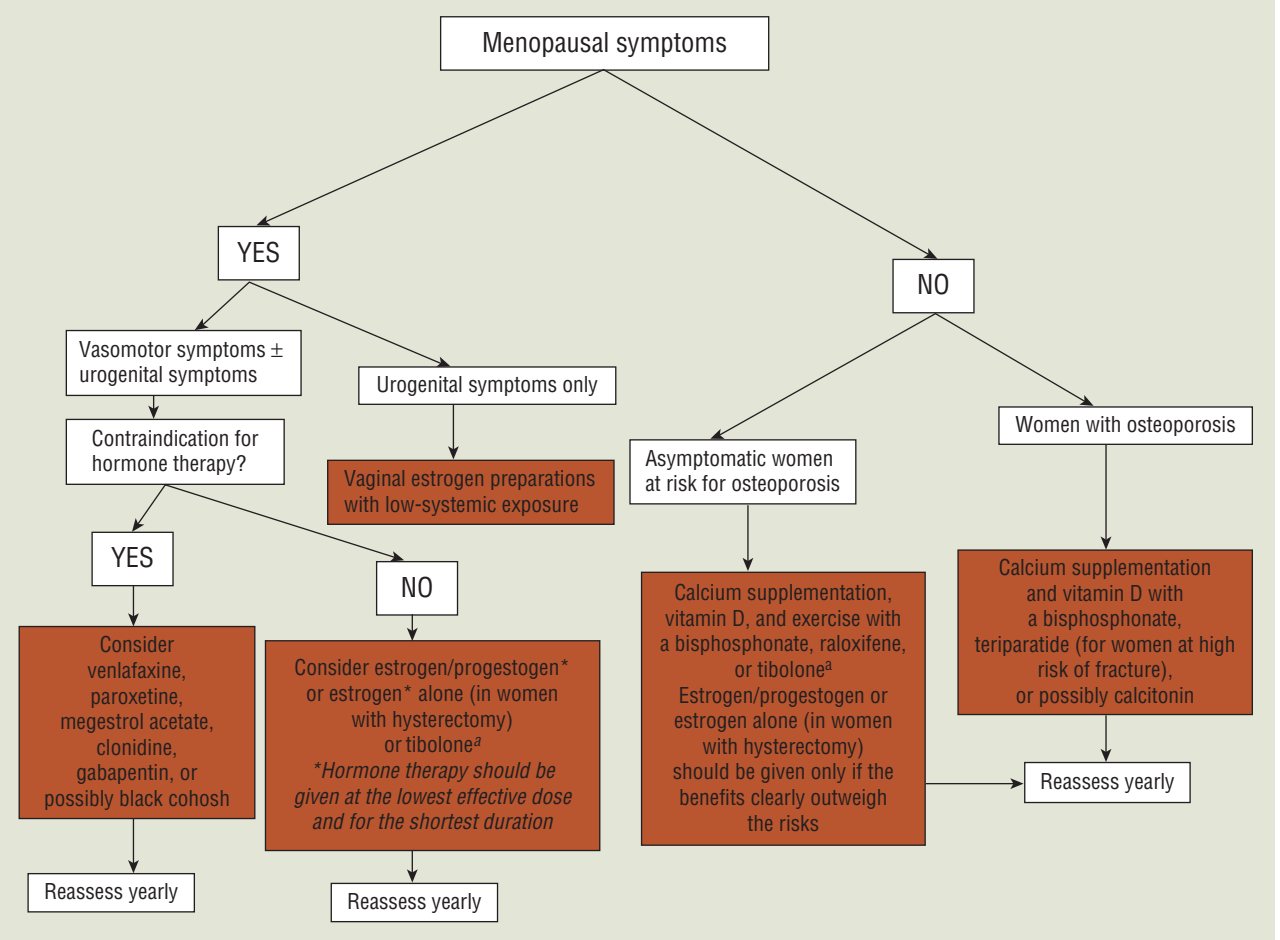

FIGURE 85-1. Algorithm for management of postmenopausal women. [a]Tibolone is currently not approved for use in the United States.

therapy is used under such conditions, the absolute risk of harm to an individual woman is very small.[2]

Many women have no difficulty abruptly stopping hormone therapy; others develop vasomotor symptoms after discontinuation. Although these symptoms usually are mild and resolve over a few months, in some women the symptoms are severe and intolerable. Few studies have addressed the appropriate method for discontinuing use of hormone therapy. There is no evidence that gradual discontinuation of hormone therapy reduces the recurrence of hot flushes compared with sudden discontinuation. Studies determining effective ways to reduce symptoms of estrogen withdrawal are needed.

Bone mineral density should be measured in women older than 65 years and in women younger than 65 years with risk factors for osteoporosis. Although bone densitometry has been shown to predict fractures, at present there are no guidelines for followup bone mineral density testing. However, in women with significant bone loss, repeat testing should be performed as clinically indicated.

PHARMACOECONOMIC CONSIDERATIONS

Estrogens and progestogens used for postmenopausal hormone therapy still are prescribed commonly in the United States, especially for the management of menopausal vasomotor symptoms. Even before publication of the WHI trial findings, only a fraction of women filled their hormone therapy prescriptions, and only 25% to 40% continued to take postmenopausal hormone therapy for more than 1 year.[115] This may be due to women's attitudes toward hormone therapy or a result of fear about adverse effects and associated risks. Hormone therapy use in the United States declined substantially after dissemination of the WHI trial results.[116]

Use of hormone therapy for the management of vasomotor symptoms is cost effective, and data supporting the use of nonhormonal alternatives are limited. The cost of hormone therapy varies depending on the route and method of delivery. Transdermal preparations are about twice as expensive as their equivalent oral preparations.[117] Women who have undergone hysterectomy use hormone therapy more frequently than do women with an intact uterus (58.7% vs 19.6%).[5]

Raloxifene adversely affects hot flushes, but it is likely to be used for osteoporosis prevention. For women with a history of breast cancer or thromboembolic disease, alternative means of reducing the risk of osteoporosis, such as bisphosphonates, should be considered.

The results of randomized trials suggest that hormone therapy should not be used for cardiovascular disease prevention. Women with coronary disease risk factors (e.g., hypertension, lipid abnormalities) can benefit from reduction of these risk factors through interventions such as weight loss, lipid-lowering therapy, use of aspirin, use of antioxidants, and physical activity.

CONCLUSIONS

During the past decade, postmenopausal hormone therapy became one of the most frequently prescribed therapies in the United States. Menopause is a natural life event, not a disease. Therefore, the decision to use hormone therapy must be individualized based on the severity of menopausal symptoms, risk of osteoporosis, and

consideration of factors such as coronary artery disease, breast cancer, and thromboembolism.

Large prospective, randomized trials have shown that postmenopausal hormone therapy prescribed for disease prevention may cause more harm than good.[2,77] The WHI trial reported increased risk of cardiovascular disease, breast cancer, stroke, and thromboembolic disease among women using continuous-combined therapy with CEE plus medroxyprogesterone acetate compared with placebo.[2] In the estrogen-alone arm of the study, CEE had no effect on cardiovascular disease or breast cancer risk compared to placebo, but an increased risk of stroke and thromboembolic disease was noted in those who received estrogen.[3] The WHI trial also demonstrated that quality of life[109] and cognition[110,112,113] were no better in the group receiving hormone therapy than in the placebo group.

Postmenopausal symptoms, such as hot flushes and vaginal dryness, remain a valid indication for hormone therapy in the absence of contraindications. For short-term use of hormone therapy for the relief of menopausal symptoms, the benefits for many women generally outweigh the risks. For symptoms of genital atrophy alone, local estrogen and/or nonhormonal lubricants should be considered.

Long-term use of hormone therapy cannot be recommended routinely for osteoporosis prevention given the availability of alternative therapies, such as raloxifene and the bisphosphonates. For long-term hormone therapy use, the potential harm (cardiovascular disease, breast cancer, and thromboembolism) outweighs the potential benefits.

PREMATURE OVARIAN FAILURE AND PREMENOPAUSAL HORMONE REPLACEMENT

PATHOPHYSIOLOGY

Premature ovarian failure is a condition characterized by sex-steroid deficiency, amenorrhea, and infertility in women younger than 40 years.[118] It affects 1% of women by age 40 years.[119] Premature ovarian failure once was considered irreversible and was described as "premature menopause." Premature ovarian failure is not an early natural menopause. Normal menopause results from ovarian follicle depletion, whereas premature ovarian failure is characterized by intermittent ovarian function in half of affected women.[118] For this reason, the term "primary ovarian insufficiency" may be a more accurate term to describe this condition. These women produce estrogen intermittently and may ovulate despite the presence of high gonadotropin concentrations. Pregnancies have occurred in 5% to 10% of women after the diagnosis of premature ovarian failure, even in women with no follicles observed on ovarian biopsy.

Premature ovarian failure may occur as a result of ovarian follicle dysfunction or ovarian follicle depletion and may present as either primary amenorrhea (absence of menses in a girl who has reached age 16 years) or secondary amenorrhea (cessation of menses in a woman previously menstruating for at least 6 months).

In most cases, the etiology cannot be identified (Table 85–9). In the majority of patients, ovarian failure develops after the establishment of regular menses. Young women with premature ovarian failure who develop ovarian dysfunction before they achieve peak adult bone mass sustain sex steroid deficiency for more years than do naturally menopausal women. This deficiency can result in a significantly higher risk for osteoporosis[120] and cardiovascular disease.[121,122] Importantly, a survey of more than 19,000 women between the ages of 25 and 100 years suggests that ovarian failure occurring before age 40 years is associated with significantly increased mortality, with an age-adjusted odds ratio for all-cause mortality of 2.14 (95% CI 1.15–3.99).[123]

CLINICAL PRESENTATION OF PREMATURE OVARIAN FAILURE

Symptoms

- *Primary amenorrhea*: No symptoms of estrogen deficiency
- *Secondary amenorrhea*: Vasomotor symptoms (hot flushes and night sweats), sleep disturbances, mood changes, sexual dysfunction, problems with concentration and memory, vaginal dryness, dyspareunia

Signs

- *Primary amenorrhea*: Incomplete development of secondary sex characteristics
- *Secondary amenorrhea*: Normal development of secondary sex characteristics, signs of urogenital atrophy

Laboratory Tests

- FSH >40 international units/L
- Other relevant diagnostic tests (e.g., bone mineral density, ultrasound of the ovaries)
- Thyroid function tests, fasting glucose level, and adrenocorticotropic hormone stimulation test

CLINICAL PRESENTATION

No characteristic menstrual pattern or history precedes premature ovarian failure. Approximately 50% of patients with this condition have a history of oligomenorrhea or dysfunctional uterine bleeding (prodromal premature ovarian failure), and approximately 25% develop amenorrhea acutely. Some patients develop amenorrhea postpartum, whereas others experience amenorrhea after discontinuing oral contraceptives. Primary amenorrhea is not associated with symptoms of estrogen deficiency. In cases of secondary amenorrhea, symptoms may include hot flushes, night sweats, fatigue, and mood changes. Prodromal premature ovarian failure may present with hot flushes even in women who menstruate regularly. Incomplete development of secondary sex characteristics may occur in women with primary amenorrhea, whereas these characteristics typically are normal in women with secondary amenorrhea. In general, women with premature ovarian failure have normal fertility before the disorder develops.

Approximately 50% of women with premature ovarian failure have documented ovarian follicle function.[118]

Premature ovarian failure is defined by the presence of at least 4 months of amenorrhea and at least two serum FSH concentrations measuring >40 international units/L (obtained at least 1 month apart) in women younger than 40 years. A complete history should be taken, considering other factors that can affect ovarian function such as prior ovarian surgery, chemotherapy, radiation, and autoimmune disorders. In patients with primary amenorrhea, particular

TABLE 85-9 Etiology of Premature Ovarian Failure

Idiopathic: *Karyotypically normal spontaneous premature ovarian failure*
Autoimmunity: (A) isolated autoimmune premature ovarian failure or (B) as a component of an autoimmune polyglandular syndrome in association with Addison's disease, hypothyroidism, hypoparathyroidism, or mucocutaneous candidiasis
Iatrogenic: *Chemotherapy, radiation, extensive ovarian surgery*
X-chromosome abnormalities
Gonadotropin and gonadotropin-receptor abnormalities: Signal defects
Enzyme deficiencies: Cholesterol desmolase, 17α-hydroxylase, 17, 20-desmolase
Galactosemia
Blepharophimosis, ptosis, and epicanthus inversus syndrome type 1: Rare autosomal dominant syndrome in which premature ovarian failure is the predominant syndrome
Perrault's syndrome: Familial autosomal recessive premature ovarian failure in association with deafness

attention should be paid to breast and pubic hair development according to Tanner stages. Short stature, stigmata of Turner's syndrome, and other dysmorphic features of gonadal dysgenesis should be considered. Ideally, a pelvic examination is performed but is not always clinically appropriate. Alternatively, transabdominal ultrasonography can be performed in patients with primary amenorrhea to confirm the presence of normal anatomic structures. In the majority of cases, physical examination is completely normal. A karyotype should be performed in all patients experiencing premature ovarian failure. Women with ovarian failure and a karyotype containing a Y chromosome should undergo bilateral gonadectomy because of substantial risk for gonadal germ cell neoplasia.[124] Ovarian biopsy and antiovarian antibody testing are investigational procedures with no proven clinical benefit in premature ovarian failure. As clinically indicated, the workup should include tests for the diagnosis of other possible associated autoimmune disorders, such as hypothyroidism, diabetes mellitus, and Addison disease.

Young women find the diagnosis of premature ovarian failure particularly traumatic and frequently need extensive emotional and psychological support. Although most of these women will, in fact, be infertile, it is important to emphasize that premature ovarian failure can be transient and that spontaneous pregnancies have occurred even years after diagnosis.

TREATMENT

Premature Ovarian Failure

9 Postmenopausal women who take hormone therapy prolong their exposure to estrogen beyond the average age of completion of their reproductive phase. In contrast, women with premature ovarian failure need exogenous sex steroids to compensate for the decreased production by their ovaries. Importantly, 47% of young women with premature ovarian failure have significantly reduced bone mineral density within 1.5 years of their diagnosis despite taking standard hormone therapy.[120]

The goal of therapy in young women with premature ovarian failure is to provide a hormone replacement regimen that maintains sex steroid status as effectively as the normal, functioning ovary.

PHARMACOLOGIC THERAPY: HORMONAL REGIMENS

Optimal hormone therapy depends on whether the patient has primary or secondary amenorrhea. Young women with primary amenorrhea in whom secondary sex characteristics have failed to develop initially should be given very low doses of estrogen in an attempt to mimic the gradual pubertal maturation process. A typical regimen is 0.3 mg CEE unopposed (i.e., no progestogen) daily for 6 months, with incremental dose increases at 6-month intervals until the required maintenance dose is achieved. Gradual dose escalation often results in optimal breast development and allows time for the young woman to adjust psychologically to her physical maturation. Cyclic progestogen therapy, given 12 to 14 days per month, should be instituted toward the end of the second year of treatment.

Women with secondary amenorrhea who have been estrogen deficient for 12 months or longer also should be given low-dose estrogen replacement initially to avoid adverse effects such as mastalgia and nausea. However, the dose can be titrated up to maintenance levels over a 6-month period, and progestogen therapy can be instituted with the initiation of estrogen therapy. Women with a brief history of secondary amenorrhea are less likely to experience undesired effects from hormone therapy if they are given a reduced dose for the first month of therapy, followed by a full dose from the second month onward.

TABLE 85-10 Premenopausal Hormone Replacement Therapy for Young Women with Premature Ovarian Failure

Regimen	Dose	Frequency	Route
Estrogen therapy			
Conjugated equine estrogen	1.25 mg	Daily	Oral
Piperazine estrone sulfate	2.5 mg	Daily	Oral
Micronized 17β-estradiol	4 mg	Daily	Oral
Transdermal estrogen system	100 mcg/24 h	Once or twice weekly	Transdermal patch
Progestogen therapy			
Medroxyprogesterone acetate	10 mg	12–14 days[a]	Oral
Dydrogesterone[b]	20 mg	12–14 days[a]	Oral
Norethindrone acetate	10 mg	12–14 days[a]	Oral
Norethisterone[b]	1 mg	12–14 days[a]	Oral
Micronized progesterone	200 mg	12–14 days[a]	Oral
Transdermal norethindrone[c]	250 mcg/24 h	Twice weekly for 14 days per calendar month	Transdermal patch

[a]Per calendar month.
[b]Not available in a progestogen-only oral dosage form in the United States.
[c]Available only in combination with estradiol.

An estrogen dose equivalent to at least 1.25 mg CEE (or 100 mcg transdermal estradiol) is needed to achieve adequate estrogen replacement in young women. A progestogen should be given for 12 to 14 days per calendar month to prevent endometrial hyperplasia (Table 85–10). Estrogens given in usual replacement doses do not suppress spontaneous follicular activity or ovulation. Because women with premature ovarian failure can have spontaneous pregnancies, hormone therapy should produce regular, predictable menstrual flow patterns (i.e., only cyclic regimens should be used). Patients who miss an expected menses should be tested for pregnancy and should discontinue hormone therapy. Because most young women negatively associate hormone therapy with menopause in older women, some clinicians prefer to prescribe oral contraceptives for hormone replacement in premenopausal women with hypogonadism. However, oral contraceptives may not inhibit ovulation or effectively prevent pregnancy in young women with elevated gonadotropin levels.

Women with premature ovarian failure have testosterone deficiency.[125] In these young women, testosterone replacement, in addition to estrogen, may be important.[43] However, preliminary analysis of a prospective study at the National Institutes of Health suggests that long-term "physiologic" testosterone supplementation (150 mcg/day), in addition to standard hormone replacement, did not significantly improve bone density and sexual function in these young women.[126,127]

Importantly, all women with premature ovarian failure should understand that hormone therapy generally should be continued until the average age of natural menopause and that long-term follow up is necessary.

EVALUATION OF THERAPEUTIC OUTCOMES

Young women with premature ovarian failure should be monitored annually for their response to treatment, and their compliance with hormone therapy should be assessed regularly. Patients should be evaluated continuously for the presence of signs and symptoms of associated autoimmune endocrine disorders, such as hypothyroidism, adrenal insufficiency, and diabetes mellitus. Baseline bone mineral density testing should be performed in all women with premature ovarian failure. Mammography should be performed annually after age 40 years in accordance with accepted guidelines. Additional mammography screening in premenopausal women younger than 40 years who are receiving physiologic hormone therapy is not warranted. Other tests should be performed as clinically indicated.

CONCLUSIONS

Approximately 1% of women spontaneously develop ovarian failure before age 40 years.[5] Premature ovarian failure is not an early natural menopause. Most affected women produce estrogen intermittently and may ovulate despite the presence of high gonadotropin concentrations. However, these women sustain sex steroid deficiency for more years than do naturally menopausal women, resulting in a significantly higher risk for osteoporosis[120] and cardiovascular disease.[121,122]

Women with premature ovarian failure need exogenous sex steroids to compensate for the decreased production by their ovaries. Thus, premenopausal hormone therapy is required at least until these women reach the age of "natural menopause."

The goal of therapy is to provide a hormone replacement regimen that maintains sex steroid status as effectively as the normal, functioning ovary. This usually requires the administration of estrogen at a dose greater than the standard dose given to older women experiencing natural menopause.

Because women with premature ovarian failure can have spontaneous pregnancies, hormone therapy should produce regular, predictable menstrual flow patterns. Patients who miss an expected menses should be tested for pregnancy and promptly discontinue the hormone treatment.

Annual followup should include assessment of adherence with the prescribed hormone therapy regimen and evaluation for signs and symptoms of associated endocrine disorders.[118]

ABBREVIATIONS

CEE: conjugated equine estrogens

CORE: Continuing Outcomes Relevant to Evista

FDA: Food and Drug Administration

FSH: follicle-stimulating hormone

GnRH: gonadotropin-releasing hormone

HDL: high-density lipoprotein

LDL: low-density lipoprotein

LH: luteinizing hormone

MORE: Multiple Outcomes of Raloxifene Evaluation

NETA: norethindrone acetate

SERM: selective estrogen receptor modulator

WHI: Women's Health Initiative

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