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Menopause and

Postmenopausal Hormone Therapy Menopause is the permanent cessation of menstruation due to loss of ovarian follicular function. It is diagnosed retrospectively after 12 months of amenorrhea. The average age at menopause is 51 years among U.S. women. Perimenopause refers to the time period preced ing menopause, when fertility wanes and menstrual cycle irregularity increases, until the first year after cessation of menses. The onset of perimenopause precedes the final menses by 2–8 years, with a mean duration of 4 years. Smoking accelerates the menopausal transition by 2 years. PART 12 Endocrinology and Metabolism Although the peri- and postmenopausal transitions share many symptoms, the physiology and clinical management of the two differ. Low-dose oral contraceptives have become a therapeutic mainstay in perimenopause, whereas postmenopausal hormone therapy (HT) has been a common method of symptom alleviation after menstruation ceases. PERIMENOPAUSE ■ ■PHYSIOLOGY Ovarian mass and fertility decline sharply after age 35 and even more precipitously during perimenopause; depletion of primary follicles, a process that begins before birth, occurs steadily until menopause (Chap. 404). In perimenopause, intermenstrual intervals shorten sig nificantly (typically by 3 days) as a result of an accelerated follicular phase. Follicle-stimulating hormone (FSH) levels rise because of altered folliculogenesis and reduced inhibin secretion. In contrast to the con sistently high FSH and low estradiol levels seen in menopause, peri menopause is characterized by “irregularly irregular” hormone levels. The propensity for anovulatory cycles can produce a hyperestrogenic, hypoprogestagenic environment that may account for the increased incidence of endometrial hyperplasia or carcinoma, uterine polyps, and leiomyoma observed among women of perimenopausal age. Mean serum levels of selected ovarian and pituitary hormones during the menopausal transition are shown in Fig. 407-1. With transition into menopause, estradiol levels fall markedly, whereas estrone levels are relatively preserved, a pattern reflecting peripheral aromatization of adrenal and ovarian androgens. Levels

of FSH increase more than those of luteinizing hormone, presumably because of the loss of inhibin as well as estrogen feedback.

FSH (IU/L)

LH or FSH, IU/L LH (IU/L)

Estrone (pg/mL)

Estradiol (pg/mL)

–2 –4 –6

Menopause, years FIGURE 407-1 Mean serum levels of ovarian and pituitary hormones during the menopausal transition. FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Data from G Rannevik et al: A longitudinal study of the perimenopausal transition: Altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas 21:103, 1995.)

■ ■DIAGNOSTIC TESTS The Stages of Reproductive Aging Workshop +10 (STRAW+10) classification provides a comprehensive framework for the clini cal assessment of ovarian aging. As shown in Fig. 407-2, menstrual cycle characteristics are the principal criteria for characterizing the menopausal transition, with biomarker measures as supportive cri teria. Because of their extreme intraindividual variability, FSH and estradiol levels are imperfect diagnostic indicators of perimenopause in menstruating women. However, a consistently low FSH level in the early follicular phase (days 2–5) of the menstrual cycle does not sup port a diagnosis of perimenopause, while levels >25 IU/L in a random blood sample are characteristic of the late menopause transition. FSH measurement can also aid in assessing fertility; levels of <20 IU/L, 20 to <30 IU/L, and ≥30 IU/L measured on day 3 of the cycle indicate a good, fair, and poor likelihood of achieving pregnancy, respectively. Anti-müllerian hormone and inhibin B may also be useful for assessing reproductive aging. ■ ■SYMPTOMS Determining whether symptoms that develop in midlife are due to ovarian senescence or to other age-related changes is difficult. There is strong evidence that the menopausal transition can cause hot flashes, night sweats, irregular bleeding, and vaginal dryness, and there is moderate evidence that it can cause sleep disturbances in some women. There is inconclusive or insufficient evidence that ovarian aging is a major cause of mood swings, depression, impaired memory or con centration, somatic symptoms, urinary incontinence, or sexual dys function. In one U.S. study, nearly 60% of women reported hot flashes in the 2 years before their final menses. Symptom intensity, duration, frequency, and effects on quality of life are highly variable. TREATMENT Perimenopause PERIMENOPAUSAL THERAPY For women with irregular or heavy menses or hormone-related symptoms that impair quality of life, low-dose combined oral contraceptives are a staple of therapy. Static doses of estrogen and progestin (e.g., 20 µg of ethinyl estradiol and 1 mg of norethindrone acetate daily for 21 days each month) can eliminate vasomotor symptoms and restore regular cyclicity. Oral contraceptives provide other benefits, including protection against ovarian and endome trial cancers and increased bone density, although it is not clear whether use during perimenopause decreases fracture risk later in life. Moreover, the contraceptive benefit is important, given that the unintentional pregnancy rate among women in their forties rivals that of adolescents. Contraindications to oral contraceptive use

include cigarette smoking, liver disease, a history of thrombo embolism or cardiovascular disease, breast cancer, or unexplained vaginal bleeding. Progestin-only formulations (e.g., 0.35 mg of nor ethindrone daily) or medroxyprogesterone (Depo-Provera) injec tions (e.g., 150 mg IM every 3 months) may provide an alternative for the treatment of perimenopausal menorrhagia in women who smoke or have cardiovascular risk factors. Although progestins nei ther regularize cycles nor reduce the number of bleeding days, they reduce the volume of menstrual flow. Estradiol or estrone, pg/mL Nonhormonal strategies to reduce menstrual flow include the use of nonsteroidal anti-inflammatory agents such as mefenamic acid (an initial dose of 500 mg at the start of menses, then 250 mg qid for 2–3 days) or, when medical approaches fail, endometrial ablation. It should be noted that menorrhagia requires an evalu ation to rule out uterine disorders. Transvaginal ultrasound with saline enhancement is useful for detecting leiomyomata or polyps, and endometrial aspiration can identify hyperplastic changes. TRANSITION TO MENOPAUSE For sexually active women using contraceptive hormones to alle viate perimenopausal symptoms, the question of when and if to

Menarche FMP (0) –3a –2 –1 +2 +1a +1b +1c Terminology Stage –5 –4 –3b Reproductive Early Early Early Peak Late Late Late Perimenopause Variable Duration Principal criteria Subtle changes in flow/ length Menstrual cycle Variable to regular Regular Regular Supportive criteria Endocrine FSH AMH Inhibin B Antral follicle count Variable* Variable* Variable Stabilizes Low Low Low Low Low Low Low Low Descriptive characteristics Symptoms *Blood draw on cycle days 2–5 = elevated. **Approximate expected level based on assays using current international pituitary standard. FIGURE 407-2 The Stages of Reproductive Aging Workshop +10 (STRAW +10) staging system for reproductive aging in women. AMH, anti-müllerian hormone; FSH, folliclestimulating hormone. (Reproduced with permission from SD Harlow et al: Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause 19:387, 2012.) switch to HT must be individualized. Doses of estrogen and proges togen (either synthetic progestins or natural forms of progesterone) in HT are lower than those in oral contraceptives and have not been documented to prevent pregnancy. Although a 1-year absence of spontaneous menses reliably indicates ovulation cessation, it is not possible to assess the natural menstrual pattern while a woman is taking an oral contraceptive. Women willing to switch to a barrier method of contraception should do so; if menses occur spontane ously, oral contraceptive use can be resumed. The average age of final menses among relatives can serve as a guide for when to initi ate this process, which can be repeated yearly until menopause has occurred. MENOPAUSE AND POSTMENOPAUSAL HT One of the most complex health care decisions facing women is whether to use postmenopausal HT. Once prescribed primarily to relieve vasomotor symptoms, HT has been promoted as a strategy to forestall various disorders that accelerate after menopause, including osteoporosis and cardiovascular disease. In 2000, nearly 40% of post menopausal women aged 50–74 in the United States had used HT. This widespread use occurred despite the paucity of conclusive data, until recently, on the health consequences of such therapy. Although many women rely on their health care providers for a definitive answer to the question of whether to use postmenopausal hormones, balancing the benefits and risks for an individual patient is challenging. Although observational studies suggest that HT prevents cardio vascular and other chronic diseases, the apparent benefits may result at least in part from differences between women who opt to take postmenopausal hormones and women who do not. Those choos ing HT tend to be healthier, have greater access to medical care, are more compliant with prescribed treatments, and maintain a more

Postmenopause Menopausal transition Variable Remaining lifespan 1–3 years 3–6 years 2 years (1+1) Menopause and Postmenopausal Hormone Therapy CHAPTER 407 Interval of amenorrhea of ≥60 days Variable Length Persistent ≥7-day difference in length of consecutive cycles

> 25 IU/L** Low Low Low Low Very low Very low Very low Low Low Very low Increasing symptoms of urogenital atrophy Vasomotor symptoms Most likely Vasomotor symptoms Likely health-promoting lifestyle. Randomized trials, which eliminate these confounding factors, have not consistently confirmed the benefits found in observational studies. Indeed, the largest HT trial to date, the Women's Health Initiative (WHI), which examined >27,000 post menopausal women aged 50–79 (mean age, 63) for an average of 5–7 years, was stopped early because of an overall unfavorable benefitrisk ratio in the estrogen-progestin arm and an excess risk of stroke that was not offset by a reduced risk of coronary heart disease (CHD) in the estrogen-only arm. The following summary offers a decision-making guide based on a synthesis of currently available evidence. Prevention of cardiovascular disease is eliminated from the equation due to lack of evidence for such benefits in randomized clinical trials. ■ ■BENEFITS AND RISKS OF POSTMENOPAUSAL HT See Table 407-1. Definite Benefits • SYMPTOMS OF MENOPAUSE Compelling evidence, including data from randomized clinical trials, indicates that estrogen therapy is highly effective for controlling vasomotor and genitourinary symptoms. Alternative approaches, including the use of antidepressants (such as paroxetine mesylate, 7.5 mg/d; venlafaxine, 37.5–75 mg/d; desvenlafaxine, 100 mg/d; fluoxetine, 20–30 mg/d; sertraline, 50–100 mg/d; citalopram, 10–30 mg/d; and escitalopram, 10–20 mg/d); the neurokinin-3 receptor antagonist fezolinetant (45 mg/d); the γ-aminobutyric acid analogue gabapentin (300 mg nightly, up to 900 mg in divided doses); and the antispasmodic anticholinergic oxy butynin (2.5–5 mg twice per day) may also alleviate vasomotor symp toms, although they are less effective than HT. Evidence is inconsistent on the efficacy of pregabalin (75–150 mg/d twice per day) and cloni dine (oral, 0.1–1 mg/d, or transdermal, 0.1–0.3 mg weekly). Paroxetine mesylate and fezolinetant are the only nonhormonal drugs approved

TABLE 407-1 Benefits and Risks of Postmenopausal Hormone Therapy in the Overall Study Population of Women aged 50–79 Years in the Intervention Phase of the Women's Health Initiative (WHI) Estrogen-Progestin and Estrogen-Alone Trialsa RELATIVE BENEFIT OR RISK OUTCOME EFFECT Definite Benefits Symptoms of menopause Definite improvement ↓65–90% decreased riskc Osteoporosis Definite increase in bone mineral density and decrease in fracture risk ↓33% decreased risk for hip fracture PART 12 Endocrinology and Metabolism Definite Risksh Endometrial cancer Definite increase in risk with estrogen alone

(see below for estrogen-progestin) See below See below 4.6 excess cases (observational studies) Pulmonary embolism Definite increase in risk ↑98% increased risk 9 excess cases

(18 vs 9) Deep-vein thrombosis Definite increase in risk ↑87% increased risk 11.5 excess cases (25 vs 14) Breast cancer Definite increase in risk with long-term use

(≥5 years) of estrogen-progestin ↑24% increased risk 8.5 excess cases

(43 vs 35) Gallbladder disease Definite increase in risk ↑57% increased risk 47 excess cases

(131 vs 84) Probable or Uncertain Risks and Benefitsh Coronary heart diseased Probable increase in risk among older women and women many years past menopause; possible decrease in risk or no effect in younger or recently menopausal womene ↑18% increased risk (n.s.) Myocardial infarction Significant interaction by age group for estrogen alone, with reduced risk in younger—but not older—women (p for trend by age = .02) ↑24% increased risk (n.s.) Stroke Probable increase in risk ↑37% increased risk 9 excess cases

(33 vs 24) Ovarian cancer Probable increase in risk with long-term use

(≥5 years) ↑41% increased risk (n.s.) Endometrial cancer Probable decrease in risk with estrogenprogestin during long-term follow-up (see above for estrogen alone) ↓33% decreased riskf 3 fewer cases

(7 vs 10) Urinary incontinence Probable increase in risk ↑49% increased risk 549 excess cases (1661 vs 1112) Colorectal cancer Probable decrease in risk with estrogenprogestin; possible increase in risk in older women with estrogen alone (p for trend by age = .02 for estrogen alone) ↓38% decreased risk 6.5 fewer cases

(10 vs 17) Type 2 diabetes Probable decrease in risk ↓19% decreased risk 16 fewer cases

(72 vs 88) Dementia (age ≥65) Increase in risk in older women (but inconsistent data from observational studies and randomized trials) ↑101% increased risk 23 excess cases

(46 vs 23) Total mortality Possible increase in risk among older women and women many years past menopause; possible decrease in risk or no effect in younger or recently menopausal women (p for trend by age <.05 for both trials combined) No increase in risk No difference in risk No increase in riske No difference in riske Global indexg Probable increase in risk or no effect among older women and women many years past menopause; possible decrease in risk or no effect in younger or recently menopausal women (p for trend by age = .02 for estrogen alone) ↑12% increased risk 20.5 excess cases (189 vs 168) aThe estrogen-progestin arm of the WHI assessed 5.6 years of conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) versus placebo. The estrogen-alone arm of the WHI assessed 7.1 years of conjugated equine estrogens (0.625 mg/d) versus placebo. bNumber of cases per 10,000 women per year. cThe WHI was not designed to assess the effect of hormone therapy (HT) on menopausal symptoms. Data from other randomized trials suggest that HT reduces risk for menopausal symptoms by 65–90%. dCoronary heart disease is defined as nonfatal myocardial infarction or coronary death. eThere was a significant interaction by age; that is, the association between HT and the specified outcome was different in younger women and older women. fThis is the risk reduction that was observed during a cumulative 13-year follow-up period (5.6 years of treatment plus 8.2 years of postintervention observation). gThe global index is a composite outcome representing the first event for each

participant from among the following: coronary heart disease, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (estrogen-progestin arm only), hip fracture, and death. Because participants can experience more than one type of event, the global index cannot be derived by a simple summing of the component events. hIncludes some outcomes where results were divergent between the estrogen-progestin arm and the estrogen-alone arm. Abbreviation: n.s., not statistically significant. Source: Data from JE Manson et al: Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310:1353, 2013.

ESTROGEN-PROGESTIN ESTROGEN ALONE ABSOLUTE BENEFIT OR RISKb RELATIVE BENEFIT OR RISK ABSOLUTE BENEFIT OR RISKb ↓65–90% decreased riskc 6 fewer cases

(11 vs 17) of hip fracture 6 fewer cases

(13 vs 19) of hip fracture ↓33% decreased risk for hip fracture 4 excess cases

(14 vs 10) ↑35% increased risk (n.s.) ↑48% increased risk 7.5 excess cases

(23 vs 15) 7 fewer cases

(28 vs 35) ↓21% decreased risk (n.s.) ↑55% increased risk 58 excess cases

(164 vs 106) 6 excess cases

(41 vs 35) No increase in risk No difference in risk 6 excess cases

(35 vs 29) No increase in riske No difference in riske ↑35% increased risk 11 excess cases

(45 vs 34) 1 excess case

(5 vs 4) Not available Not available See above See above ↑61% increased risk 852 excess cases (2255 vs 1403) No increase or decrease in riske No difference in riske 21 fewer cases

(134 vs 155) ↓14% decreased risk 15 excess cases

(44 vs 29) ↑47% increased risk (n.s.) No increase in riske No difference in riske

by the U.S. Food and Drug Administration for treatment of vasomotor symptoms. Bazedoxifene, an estrogen agonist/antagonist, in combina tion with conjugated estrogens has also received approval for this use. Cognitive behavioral therapy and clinical hypnosis have been shown in randomized trials to help with vasomotor symptom management. The consumption of phytoestrogens, including soy isoflavones, may be effective in women who are able to metabolize the isoflavone daidzein to the biologically active metabolite equol. Weight loss, mindfulnessbased stress reduction, and stellate ganglion block are also promis ing strategies, although more trials are needed. For genitourinary syndrome of menopause, the efficacy of low-dose vaginal estrogen is similar to that of oral or transdermal estrogen; oral ospemifene and vaginal prasterone are additional options. OSTEOPOROSIS (See also Chap. 423) Bone density By reducing bone turnover

and resorption rates, estrogen slows the aging-related bone loss experienced by most postmenopausal women. More than 50 randomized trials have demonstrated that post menopausal estrogen therapy, with or without a progestogen, rapidly increases bone mineral density at the spine by 4–6% and at the hip by 2–3% and that those increases are maintained during treatment. Fractures Data from observational studies indicate a 50–80% lower risk of vertebral fracture and a 25–30% lower risk of hip, wrist, and other peripheral fractures among current estrogen users; addition of a progestogen does not appear to modify this benefit. In the WHI, 5–7 years of either combined estrogen-progestin or estrogen-only therapy was associated with a 33% reduction in hip fractures and 25–30% fewer total fractures among a population unselected for osteoporosis. Bisphos phonates (such as alendronate, 10 mg/d or 70 mg once per week; risedro nate, 5 mg/d or 35 mg once per week; ibandronate, 2.5 mg/d or 150 mg once per month or 3 mg every 3 months IV; or zoledronic acid, 5 mg once per year IV) and denosumab (60 mg twice per year SC) increase bone mass density by reducing bone resorption and have been shown in randomized trials to decrease fracture rates. Other treatment options include bazedoxifene in combination with conjugated estrogens; the selective estrogen receptor modulator (SERM) raloxifene (60 mg/d); and parathyroid hormone (teriparatide, 20 µg/d SC). Unlike estrogen, these alternative therapies do not appear to have adverse effects on the endometrium or breast. Increased weight-bearing and resistance exer cise; adequate calcium intake (1000–1200 mg/d through diet or supple ments in two or three divided doses); and adequate vitamin D intake (600–1000 IU/d) may also reduce the risk of osteoporosis-related frac tures. According to a 2011 report by the Institute of Medicine (now the National Academy of Medicine), 25-hydroxyvitamin D blood levels of ≥50 nmol/L are sufficient for bone-density maintenance and fracture prevention. The Fracture Risk Assessment (FRAX®) score, an algorithm that combines an individual's bone-density score with age and other risk factors to predict her 10-year risk of hip and major osteoporotic fracture, may be of use in guiding decisions about pharmacologic treat ment (see www.sheffield.ac.uk/FRAX/). Definite Risks • ENDOMETRIAL CANCER (WITH ESTROGEN ALONE) A combined analysis of 30 observational studies found a tripling of endometrial cancer risk among short-term users (1–5 years) of unopposed estrogen and a nearly 10-fold increased risk among longterm users (≥10 years). These findings are supported by results from the randomized Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, in which 24% of women assigned to unopposed estrogen for 3 years developed atypical endometrial hyperplasia—a premalignant lesion—as opposed to only 1% of women assigned to placebo. Use of a progestogen, which opposes the effects of estrogen on the endome trium, eliminates these risks and may even reduce risk (see later). VENOUS THROMBOEMBOLISM A meta-analysis of observational stud ies found that current oral estrogen use was associated with a 2.5-fold increase in risk of venous thromboembolism in postmenopausal women. A meta-analysis of randomized trials, including the WHI, found a 2.1-fold increase in risk. Results from the WHI indicate a nearly twofold increase in risk of pulmonary embolism and deep-vein thrombosis with estrogen-progestin and a 35–50% increase in these

risks with estrogen-only therapy. Transdermal estrogen, taken alone or with certain progestogens (micronized progesterone or pregnane derivatives), appears to be a safer alternative with respect to thrombotic risk.

BREAST CANCER (WITH ESTROGEN-PROGESTIN) An increased risk of breast cancer has been found among current or recent estrogen users in observational studies; this risk is directly related to duration of use. In contrast to findings for endometrial cancer, combined estrogenprogestin

regimens appear to increase breast cancer risk more than estrogen alone. In a 2019 meta-analysis of 58 observational studies (108,647 breast cancer cases) published between 1992 and 2017, the relative risks (RRs) for incident breast cancer with current use of estro gen-progestin for 1–4, 5–9, 10–14, and ≥15 years were 1.60 (95% confi dence interval [CI], 1.52–1.69), 1.97 (95% CI, 1.90–2.04), 2.26 (95% CI, 2.16–2.36), and 2.51 (95% CI, 2.35–2.68), respectively, compared with never use. The corresponding statistics for incident breast cancer with current use of estrogen alone were 1.17 (1.10–1.26), 1.22 (1.17–1.28), 1.43 (1.37–1.50), and 1.58 (1.51–1.66), respectively. Data from ran domized trials also indicate that estrogen-progestin raises breast cancer risk. In the WHI, women assigned to receive combination hormones for an average of 5.6 years were 24% more likely to develop breast cancer than women assigned to placebo, but 7.1 years of estrogenonly therapy did not increase risk. Indeed, the WHI showed a trend toward a reduction in breast cancer risk with estrogen alone, although it is unclear whether this finding would pertain to formulations of estrogen other than conjugated equine estrogens or to treatment dura tions of >7 years. In the Heart and Estrogen/Progestin Replacement Study (HERS), combination therapy for 4 years was associated with a 27% increase in breast cancer risk. Although the latter finding was not statistically significant, the totality of evidence strongly implicates estrogen-progestin therapy in breast carcinogenesis. Menopause and Postmenopausal Hormone Therapy CHAPTER 407 Some observational data suggest that the length of the interval between menopause onset and HT initiation may influence the asso ciation between such therapy and breast cancer risk, with a “gap time” of <3–5 years conferring a higher HT-associated breast cancer risk. (This pattern of findings contrasts with that for CHD, as discussed later in this chapter.) However, this association remains inconclusive and may be a spurious finding attributable to higher rates of screen ing mammography and thus earlier cancer detection in HT users than in nonusers, especially in early menopause. Indeed, in the WHI trial, relative risk (RRs) for HT and breast cancer risk did not differ among women 50–59, those 60–69, and those 70–79 years of age at trial entry. (There was insufficient power to examine finer age categories.) Addi tional research is needed to clarify the issue. GALLBLADDER DISEASE Large observational studies report a two- to threefold increased risk of gallstones or cholecystectomy among postmenopausal women taking oral estrogen. In the WHI, women randomized to estrogen-progestin or estrogen alone were ~55% more likely to develop gallbladder disease than those assigned to placebo. Risks were also increased in HERS. Transdermal HT might be a safer alternative, but further research is needed. Probable or Uncertain Risks and Benefits • CORONARY HEART DISEASE/STROKE Until recently, HT had been enthusiasti cally recommended as a possible cardioprotective agent. In the past three decades, multiple observational studies suggested, in the aggre gate, that estrogen use leads to a 35–50% reduction in CHD incidence among postmenopausal women. The biologic plausibility of such an association is supported by data from randomized trials demonstrating that exogenous estrogen lowers plasma low-density lipoprotein (LDL) cholesterol levels and raises high-density lipoprotein (HDL) cholesterol levels by 10–15%. Administration of estrogen also favorably affects lipoprotein(a) levels, LDL oxidation, endothelial vascular function, fibrinogen, and plasminogen activator inhibitor 1. However, estrogen therapy has unfavorable effects on other biomarkers of cardiovascular risk: it boosts triglyceride levels; promotes coagulation via factor VII, prothrombin fragments 1 and 2, and fibrinopeptide A elevations; and raises levels of the inflammatory marker C-reactive protein.

Randomized trials of estrogen or combined estrogen-progestin in women with preexisting cardiovascular disease have not confirmed the benefits reported in observational studies. In HERS (a secondaryprevention trial designed to test the efficacy and safety of estrogenprogestin therapy

with regard to clinical cardiovascular outcomes), the 4-year incidence of coronary death and nonfatal myocardial infarction was similar in the active-treatment and placebo groups, and a 50% increase in risk of coronary events was noted during the first year among participants assigned to the active-treatment group. Although it is possible that progestin may mitigate estrogen's benefits, the Estrogen Replacement and Atherosclerosis (ERA) trial indicated that angio graphically determined progression of coronary atherosclerosis was unaffected by either opposed or unopposed estrogen treatment. More over, no cardiovascular benefit was found in the Papworth Hormone Replacement Therapy Atherosclerosis Study, a trial of transdermal estradiol with and without norethindrone; the Women's Estrogen for Stroke Trial (WEST), a trial of oral 17β-estradiol; or the Estrogen in the Prevention of Reinfarction Trial (ESPRIT), a trial of oral estradiol valerate. Thus, in clinical trials, HT has not proved effective for the sec ondary prevention of cardiovascular disease in postmenopausal women.

PART 12 Endocrinology and Metabolism Primary-prevention trials also suggest an early increase in cardio vascular risk and an absence of cardioprotection with postmenopausal HT. In the WHI, women assigned to 5.6 years of estrogen-progestin therapy were 18% more likely to develop CHD (defined in primary analyses as nonfatal myocardial infarction or coronary death) than those assigned to placebo, although this risk elevation was not sta tistically significant. However, during the trial's first year, there was a significant 80% increase in risk, which diminished in subsequent years (p for trend by time = .03). In the estrogen-only arm of the WHI, no overall effect on CHD was observed during the 7.1 years of the trial or in any specific year of follow-up. This pattern of results was similar to that for the outcome of total myocardial infarction. However, a closer look at available data suggests that timing of initiation of HT may critically influence the association between such therapy and CHD. Estrogen may slow early stages of atherosclerosis but have adverse effects on advanced atherosclerotic lesions. It has been hypothesized that the prothrombotic and proinflammatory effects of estrogen manifest themselves predominantly among women with subclinical lesions who initiate HT well after the menopausal transi tion, whereas women with less arterial damage who start HT early in menopause may derive cardiovascular benefit because they have not yet developed advanced lesions. Data from experiments in nonhu man primates and from some randomized trials in humans support this concept. Conjugated estrogens had no effect on the extent of coronary artery plaque in cynomolgus monkeys assigned to receive estrogen alone or combined with progestin starting 2 years (~6 years in human terms) after oophorectomy and well after the establishment of atherosclerosis. However, administration of exogenous hormones immediately after oophorectomy, during the early stages of athero sclerosis, reduced the extent of plaque by 70%. In the Early versus Late Intervention Trial with Estradiol (ELITE), a 6-year trial among 643 healthy postmenopausal women that was designed to test whether effects of estrogen on the development and progression of atheroscle rosis depend on age at initiation of therapy, oral 17β-estradiol admin istered with or without vaginal micronized progesterone significantly slowed carotid atherosclerotic progression in women within 6 years of menopause onset (mean age, 55.4 years) but not in women >10 years past menopause onset (mean age, 65.4 years) (p for interaction = .007). On the other hand, in the Kronos Early Estrogen Prevention Study (KEEPS), a 4-year trial among 729 healthy postmenopausal women within 3 years of menopause onset at trial entry (mean age, 53 years), neither oral conjugated estrogens nor transdermal estradiol, admin istered with oral micronized progesterone, affected carotid athero sclerotic progression. However, the low prevalence of this endpoint in the overall study population may have curtailed power to detect a treatment difference. Lending further credence to the timing

hypothesis are results of subgroup analyses of data from observational studies and large clini cal trials. For example, among women who entered the WHI trial with

a relatively favorable cholesterol profile, estrogen with or without pro gestin led to a 40% lower risk of incident CHD. Among women who entered with a worse cholesterol profile, therapy resulted in a 73% higher risk (p for interaction = .02). The presence or absence of the metabolic syndrome (Chap. 420) also strongly influenced the relation between HT and incident CHD. Among women with the metabolic syndrome, HT more than doubled CHD risk, whereas no associa tion was observed among women without the syndrome. Moreover, although there was no association between estrogen-only therapy and CHD in the WHI trial cohort as a whole, such therapy was associated with a CHD risk reduction of 40% among participants aged 50–59; in contrast, a risk reduction of only 5% was observed among those aged 60–69, and a risk increase of 9% was found among those aged 70–79 (p for trend by age = .08). For the outcome of total myocardial infarction, estrogen alone was associated with a borderline-significant 45% reduction and a nonsignificant 24% increase in risk among the youngest and oldest women, respectively (p for trend by age = .02). Estrogen was also associated with lower levels of coronary artery calcified plaque in the younger age group. Although age did not have a similar effect in the estrogen-progestin arm of the WHI, CHD risks increased with years since menopause (p for trend = .08), with a significantly elevated risk among women who were ≥20 years past menopause. For the outcome of total myocardial infarction, estrogenprogestin was associated with a 9% risk reduction among women <10 years past menopause as opposed to a 16% increase in risk among women 10–19 years past menopause and a twofold increase in risk among women >20 years past menopause (p for trend = .01). In the large observational Nurses' Health Study, women who chose to start HT within 4 years of menopause experienced a lower risk of CHD than did nonusers, whereas those who began therapy ≥10 years after menopause appeared to receive little coronary benefit. Observational studies include a high proportion of women who begin HT within 3–4 years of menopause, whereas clinical trials include a high pro portion of women ≥12 years past menopause; this difference helps to reconcile some of the apparent discrepancies between the two types of studies. For the outcome of stroke, WHI participants assigned to estrogenprogestin or estrogen alone were ~35% more likely to suffer a stroke than those assigned to placebo. Whether or not age at initiation of HT influences stroke risk is not well understood. In the WHI and the Nurses' Health Study, HT was associated with an excess risk of stroke in all age groups. Further research is needed on age, time since meno pause, and other individual characteristics (including biomarkers) that predict increases or decreases in cardiovascular risk associated with exogenous HT. Furthermore, it remains uncertain whether different doses, formulations, or routes of administration of HT will produce different cardiovascular effects. COLORECTAL CANCER Observational studies have suggested that HT reduces risks of colon and rectal cancer, although the estimated magnitudes of the relative benefits have ranged from 8 to 34% in various meta-analyses. In the WHI (the sole trial to examine the issue), estrogen-progestin was associated with a significant 38% reduction in colorectal cancer over a 5.6-year period, although no benefit was seen with 7 years of estrogen-only therapy. However, a modifying effect of age was observed, with a doubling of risk with HT in women aged 70–79 but no risk elevation in younger women (p for trend by age = .02). COGNITIVE DECLINE AND DEMENTIA A meta-analysis of 10 casecontrol and two cohort studies suggested that postmenopausal HT is associated with a 34% decreased risk of dementia. Subsequent random ized trials (including the WHI), however, have failed to demonstrate any benefit of estrogen or estrogen-progestin therapy on the progres sion of mild to moderate Alzheimer's disease and/or have

indicated a potential adverse effect of HT on the incidence of dementia, at least in women ≥65 years of age. Among women randomized to HT (as opposed to placebo) at age 50–55 in the WHI, no effect on cognition was observed during the postintervention phase. Determining whether timing of initiation of HT influences cognitive outcomes will require further study.

OVARIAN CANCER AND OTHER DISORDERS On the basis of limited observational and randomized data, it has been hypothesized that HT increases the risk of ovarian cancer and reduces the risk of type 2 diabetes mellitus. Results from the WHI support these hypotheses. The WHI also found that HT use was associated with an increased risk of urinary incontinence and that estrogen-progestin was associated with increased rates of lung cancer mortality. ENDOMETRIAL CANCER (WITH ESTROGEN-PROGESTIN) In the WHI, use of estrogen-progestin was associated with a nonsignificant 17% reduction in risk of endometrial cancer. A significant reduction in risk emerged during the postintervention period (see later). ALL-CAUSE MORTALITY In the overall WHI cohort, estrogen with or without progestin was not associated with all-cause mortality. How ever, there was a trend toward reduced mortality in younger women, particularly with estrogen alone. For women aged 50–59, 60–69, and 70–79 years, RRs associated with estrogen-only therapy were 0.70, 1.01, and 1.21, respectively (p for trend = .04). OVERALL BENEFIT-RISK PROFILE Estrogen-progestin was associ ated with an unfavorable benefit-risk profile (excluding relief from menopausal symptoms) as measured by a “global index”—a composite outcome including CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and death (Table 407-1)—in the WHI cohort as a whole, and this association did not A CEE+MPA Trial

Intergroup difference in no. of events per 1000 women over 5 yr

Risks

2.5 5.0

2.5

–5 Benefits –10 –15 –20 Stroke Deep-vein thrombosis Breast cancer Colorectal cancer All cancers All fractures Death from any cause Diabetes Coronary heart disease B CEE+Alone Trial

Intergroup difference in no. of events per 1000 women over 5 yr

Risks

2.5

–0.5 –5 –5.5 Benefits –10 –15 –20 Stroke Deep-vein thrombosis Breast cancer Colorectal cancer All cancers All fractures Death from any cause Diabetes Coronary heart disease FIGURE 407-3 Benefits and risks of the two hormone therapy (HT) formulations evaluated in the Women’s Health Initiative, in women aged 50–59 years. Results are shown for the two formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA). Risks and benefits are expressed as the difference in number of events (number in the HT group minus the number in the placebo group) per 1000 women over 5 years. (Reproduced with permission from JE Manson, AM Kaunitz: Menopause Management–Getting Clinical Care Back on Track. N Engl J Med

374:803, 2016.)

vary by 10-year age group. Estrogen-only therapy was associated with a neutral benefit-risk profile in the WHI cohort as a whole. However, there was a significant trend toward a more favorable benefit-risk pro file among younger women and a less favorable profile among older women, with RRs of 0.84, 0.99, and 1.17 for women aged 50–59, 60–69, and 70–79 years, respectively (p for trend by age = .02). The balance of benefits and risks of estrogen with and without progestin among women aged 50–59 is shown in Fig. 407-3.

CHANGES IN HEALTH STATUS AFTER DISCONTINUATION OF HT In the WHI, many but not all risks and benefits associated with active use of HT dissipated within 5–7 years after discontinuation of therapy. For estrogen-progestin, an elevated risk of breast cancer persisted (RR = 1.28; 95% CI, 1.11–1.48) during a median cumulative 13-year followup period (5.6 years of treatment plus 8.2 years of postintervention observation), but most cardiovascular disease risks became neutral. A reduction in hip fracture risk persisted (RR = 0.81; 95% CI, 0.68–0.97), and a significant reduction in endometrial cancer risk emerged (RR = 0.67; 95% CI, 0.49–0.91). For estrogen alone, the reduction in breast cancer risk became statistically significant (RR = 0.79; 95% CI, 0.65– 0.97) during a median cumulative 13-year follow-up period (6.8 years of treatment plus 6.6 years of postintervention observation), and signif icant differences by age group persisted for total myocardial infarction and the global index, with more favorable results for younger women. During a median cumulative 18-year follow-up, estrogen alone was Menopause and Postmenopausal Hormone Therapy CHAPTER 407 3.0 –0.5 –0.5 –5.0 –5.5 –12.0 –2.5 –1.5 –4.0 –8.0 –5.5 –13.0

associated with a significant reduction in all-cause mortality in women aged 50–59 years (RR = 0.79; 95% CI, 0.64–0.96); the protective effect was seen primarily in those with bilateral oophorectomy (RR = 0.68; 95% CI, 0.48–0.96). During a median cumulative 20-year follow-up, estrogen-progestin was associated with a significant elevation in breast cancer risk (RR = 1.28; 95% CI, 1.13–1.45) and a suggestive elevation in breast cancer mortality (RR =1.35; 95% CI, 0.94–1.95; p = .11), whereas estrogen alone was associated with a significant reduction in breast cancer risk (RR = 0.78; 95% CI, 0.65–0.93) and breast cancer mortality (RR = 0.60; 95% CI, 0.37–0.97).

APPROACH TO THE PATIENT Postmenopausal HT PART 12 Endocrinology and Metabolism The rational use of postmenopausal HT requires balancing the potential benefits and risks. Table 407-2 provides one approach to decision-making. This approach applies to women with meno pausal symptoms who are age 45 years and older or to women who have had removal of both ovaries, regardless of age. Women below age 45 years or those with uncertain menopausal status may need additional clinical evaluation before determining a management plan. The clinician should first assess whether the patient has moderate to severe hot flashes and/or night sweats—the primary indication for initiation of systemic HT—that do not subside in response to behavioral/lifestyle modifications, such as lowering the thermostat, dressing in layers, avoiding warm beverages, and not smoking. Systemic HT may also be used to prevent osteoporo sis in women at high risk of fracture who cannot tolerate alterna tive osteoporosis therapies. (Vaginal estrogen or other medications may be used to treat genitourinary syndrome of menopause in the absence of vasomotor symptoms [see later].) The benefits and risks of such therapy should be reviewed with the patient, giving more emphasis to absolute than to relative measures of effect

and TABLE 407-2 Approach to Initiating Menopausal Hormone Therapy for Vasomotor Symptom Management

1. Vasomotor symptom assessment Confirm that hot flashes and/or night sweats are adversely affecting sleep, daytime functioning, or quality of life.
2. Risk factor assessment Confirm that there are no absolute contraindications to menopausal hormone therapy Breast, endometrial, or other estrogen-dependent cancer Cardiovascular disease (heart disease, stroke, transient ischemic attack) Active liver disease Undiagnosed vaginal bleeding
3. Menopausal hormone therapy initiation CONSIDER WITH CAUTION AVOID RECOMMEND Age <60 years and Menopause onset within 10 years and Low risk of breast cancera and cardiovascular diseaseb Age ≥60 years • • • • • • • OR • • • • • • • Menopause onset

> 10 years prior • • • • • • • OR • • • • • • • Moderate risk of breast cancera High risk of breast cancera or cardiovascular diseaseb • • • • • • • • • OR • • • • • • • • • Age ≥60 years or menopause onset >10 years prior and Moderate risk of breast cancera or cardiovascular diseaseb or cardiovascular diseasea aFor online tools to assess breast cancer risk, see AH McClintock et al: Breast cancer risk assessment: A step-wise approach for primary care providers on the front lines of shared decision making. Mayo Clin Proc 95:126, 2020. bFor online tools to assess cardiovascular disease risk, see D Lloyd-Jones et al: Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: A special report from the American Heart Association and American College of Cardiology. Circulation 139:e1162, 2019. Source: Adapted from JL Shifren et al: JAMA 2019; 321:2458-2459.

pointing out uncertainties in clinical knowledge where relevant. Because chronic disease rates generally increase with age, absolute risks tend to be greater in older women, even when RRs remain similar. Potential side effects—especially vaginal bleeding that may result from use of the combined estrogen-progestogen formula tions recommended for women with an intact uterus—should be noted. The patient's own preference regarding therapy should be elicited and factored into the decision. Contraindications should be assessed routinely and include unexplained vaginal bleeding; liver dysfunction or disease; venous thromboembolism; known blood clotting disorder or thrombophilia (transdermal estrogen may be an option); untreated hypertension; history of endometrial cancer (except stage 1 without deep invasion), breast cancer, or other estrogen-dependent cancer; and history of CHD, stroke, or transient ischemic attack. Relative contraindications to sys temic HT include an elevated risk of breast cancer (e.g., women who have one or more first-degree relatives with breast cancer, susceptibility genes such as BRCA1 or BRCA2, or a personal history of cellular atypia detected by breast biopsy); hypertriglyc eridemia (>400 mg/dL); an elevated risk of cardiovascular disease; and active gallbladder disease (transdermal estrogen may be an option in the latter three cases because it has a less adverse effect on triglyceride levels, clotting factors, and inflammation factors than oral HT). Primary prevention of heart disease should not be viewed as an expected benefit of HT, and an increase in the risk of stroke as well as a small early increase in the risk of coronary artery disease should be considered. Nevertheless, such therapy may be appropriate if the noncoronary benefits of

treatment clearly outweigh the risks. Reassess benefits and risks at least once every 6–12 months, assuming the patient’s continued preference for HT, or if the patient’s health status changes. A woman who suffers an acute coronary event or stroke while taking HT should discontinue therapy immediately. Many options for systemic HT are available. Estrogen alone is recommended for women with hysterectomy, whereas estrogen plus progestogen is recommended for women with a uterus. In the United States, the most commonly prescribed oral estrogens for systemic treatment of vasomotor symptoms are 17β-estradiol (1.0 or 0.5 mg/d or other doses) and conjugated equine estrogens (CEE; 0.625, 0.45, or 0.3 mg/d or other doses). The most commonly prescribed transdermal estrogen products are 17β-estradiol skin patches (0.035 or 0.05 mg/d or other doses). The most commonly prescribed progestogens are medroxyprogesterone acetate (MPA; 2.5, 5, or 10 mg/d) and micronized progesterone (100 or 200 mg/d). Also available are oral estrogen-progestin combinations, such as oral CEE and MPA, oral 17β-estradiol or ethinyl estradiol with norethindrone acetate, oral estradiol with progesterone, and other options. CEE/bazedoxifene may be an option for women with a uterus, especially those with concerns about breast tenderness, breast density, or uterine bleeding. Contraindications to CEE/baze doxifene are similar to those for systemic HT. Short-term use (<5 years for estrogen-progestogen and <7 years for estrogen alone) is appropriate for relief of menopausal symp toms among women without contraindications to such use. How ever, such therapy should be avoided by women with an elevated baseline risk of future cardiovascular events. Women who have contraindications for or are opposed to HT may derive benefit from the use of certain antidepressants (including paroxetine, mesylate, venlafaxine, fluoxetine, and others), fezolinetant, gabapentin, or oxybutynin. Long-term use (≥5 years for estrogen-progestogen and ≥7 years for estrogen alone) is more problematic because a heightened risk of breast cancer must be factored into the decision, especially for estrogen-progestogen. Reasonable candidates for such use include postmenopausal women who have persistent severe vasomotor symptoms along with an increased risk of osteoporosis (e.g., those with osteopenia, a personal or family history of nontraumatic fracture, or a weight <125 lb), who also have no personal or

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