Menopause

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Epidemiology

The Stages of Reproductive Aging Workshop (STRAW), in 2001, proposed a staging system, including menstrual and hormonal criteria, to define each stage of the process of reproductive senescence, constituting the gold standard to characterize all steps of the period [1].

Although the average age at menopause is 51 years, in 5% of women it occurs after 55 years of age, which is considered late menopause and in 5% between 40 and 45 years, which defines premature menopause. The cessation of cycles that occurs before the age of 40 is considered premature ovarian failure [2].

Various factors are considered as determinants of age at menopause. Thirteen common genetic variants located on chromosomes 5, 6, 19, and 20 related to age at menopause were identified [3]. Genetic variation in the estrogen receptor gene may be another determining factor, as well as permutations in the FMR1 gene that defines fragile X syndrome and causes premature ovarian failure [4].

Women with a family history of early menopause are at increased risk of developing amenorrhea earlier on. Women whose mothers started the phase of menopause at a young age have a sixfold greater likelihood of early menopause [5]. Race and ethnicity may also affect age at menopause. In two prospective, multiethnic studies, natural menopause occurred earlier among Hispanic women and later on in Americans and Japanese, when compared with a Caucasian population [6].

Smoking reduces age at menopause by about 2 years [7]. A study of 10,606 middle-aged women showed that 31% of female smokers developed natural menopause earlier than nonsmokers [8]. Other factors also seem to be involved, such as the consumption of galactose, a history of type 1 diabetes, intrauterine exposure to diethylstilbestrol, and nulliparity [3, 9].

Hormonal changes begin years before the menopause. In the final years of reproductive life, menstrual cycles are ovulatory, but gradually, the duration of the follicular phase begins to decrease. In the initial transition to menopause, women experience some menstrual irregularity, and in this phase inhibin B concentrations begin to fall due to a decline in the number of ovarian follicles, whereas FSH levels begin to rise with a relative maintenance of estradiol levels, but with low concentrations of progesterone [10].

In late transition there is an increase in the variability of the cycle, with fluctuations in serum levels of FSH and estradiol. Following menopause, when there is a total loss of ovarian follicles, the ovary can no longer synthesize estradiol but keep producing and secreting the androgenic hormones under the stimulus of luteinizing hormone (LH) [11].

Other endocrine changes present in the menopausal transition include the reduction of the anti-Müllerian hormone (AMH), a product of the granulosa cell, and the reduction in antral follicle count (AFC) of the ovary, defined as follicles of 2–10 mm in diameter on the transvaginal ultrasound [1].

After 12 months of amenorrhea in a woman aged over 45 years and in the absence of other physiological or pathological causes, we identify the presence of menopause.[4, 6]

Clinical Manifestations

Clinically women experience drastic changes in the body (Table 13.1). Chronic anovulation and progesterone deficiency can lead to long periods of uterine exposure to estrogen, thereby generating anovulatory bleeding and endometrial hyperplasia. Hot flashes, which are manifested in 75% of women, are the most common acute change during menopause. They are self-limited, with an average duration of 5 years, begin suddenly, and are characterized by a feeling of warmth in the face and chest that spreads rapidly. The heat sensation lasts about 2–4 min and is associated with intense

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Table 13.1 Prevalence of menopausal symptoms

Symptoms	Prevalence
Hot flashes	41–79%
Sleep disturbance	38–43%
Depression	33%
Dementia	Uncertain
Vaginal dryness	20–47%
Sexual function	Uncertain
Cognitive changes	Uncertain
Joint pain	Uncertain
Fat mass gain	Uncertain
Skin changes	Uncertain
Breast pain	Uncertain

sweating, palpitations, and anxiety. It occurs predominantly at night, causing severe sleep disturbances [6].

Sleep disorders may be present in postmenopausal women, even in the absence of hot flashes at night. Anxiety and depression also influence, reducing patients' quality of life. Sexual dysfunction may be associated with impaired sleep [12].

As the epithelia of the vagina and urethra are sensitive to the action of estrogen, its thinning occurs during menopause, resulting in vaginal atrophy and related symptoms, a genitourinary syndrome of menopause (GSM) such as vaginal dryness, vaginitis, itching and pain during intercourse, and urethral atrophy, causing greater susceptibility to infections, overactive bladder, and urinary incontinence [13].

Sexual dysfunctions are highly prevalent in this period. Estradiol deficiency significantly reduces blood flow to the vagina and vulva, resulting in decreased vaginal lubrication and pudendal nerve neuropathy [14]. Vaginal dryness and dyspareunia, as previously mentioned, may contribute to decreased sexual function in this period [15].

Studies investigating the relationship between menopause and depression present conflicting findings. Some longitudinal studies have found no association. However, several others have shown a significant association between the menopausal transition and depression [16]. The largest prospective study to date, the Study of Women's Health Across the Nation (SWAN) trial, reported that perimenopausal women showed a higher rate of depressive symptoms (14.9–18.4%) than premenopausal women (8–12%), the most common symptoms being irritability, nervousness, and emotional lability [17].

Other, less common, symptoms are breast tenderness, headache, skin aging, and joint pain [18].

Diagnosis

Menopause is clinically defined as a period of 12 months of amenorrhea in a woman over 45 years of age in the absence of other biological or physiological causes. The best approach to the diagnosis of perimenopause is a longitudinal evaluation of the history of the menstrual cycle and menopausal symptoms (vasomotor waves, mood swings, sleep disturbances). There is no need for measurement of serum FSH, estradiol, or inhibin levels for diagnostic purposes.

Some medical conditions can mimic conditions of menopause, such as hyperthyroidism, which should always be considered in the differential diagnosis, and occur together with irregular menstruation, sweats (although different from typical hot flushes), and mood changes. Other causes for menstrual cycle changes should be considered, including pregnancy, hyperprolactinemia, and other thyroid diseases. Atypical hot flashes and night sweats may be present in other disorders, such as drug use, pheochromocytoma, carcinoid tumors, or other malignancies [19].

Hormone Therapy

Hormone therapy (HT) in postmenopausal women is currently recommended for use in short-term treatment of moderate to severe vasomotor symptoms. Long-term use for primary or secondary prevention of cardiovascular disease and osteoporosis is no longer recommended [20].

According to the recommendations of the American Association of Clinical Endocrinologists (AACE) 2017, the use of hormone therapy in postmenopausal symptomatic women should take into account all risk factors for cardiovascular disease, age, and time of menopause [21].

Vasomotor Symptoms

Hormone therapy, estrogen with or without progesterone, remains the gold standard treatment for the relief of menopausal vasomotor symptoms and their consequences. In a systematic review involving 24 trials and 3329 women, estrogen therapy was able to reduce 75% of frequency and 87% of the intensity of vasomotor symptoms when used at a standard dose. However, lower doses are also capable of minimizing 65% of the heat waves [22, 23]. It is therefore a reasonable option for most postmenopausal women, except those with a history of breast cancer and coronary heart disease, previous thromboembolic event or stroke, or at high risk for these complications. In healthy women, the absolute risk of an adverse event is extremely low [20]. The exclusive use of progesterone also reduces vasomotor symptoms, but less efficiently than estrogen therapy [24].

Genitourinary Tract

Both vaginal and urethral epithelia are sensitive to estrogen, and estrogen deficiency leads to their thinning, resulting in vaginal atrophy, which may generate symptoms of vaginal dryness, itching, and often dyspareunia. Both systemic and

local estrogen therapy are effective for symptoms of genitourinary atrophy. Vaginal administration (available as creams, tablets, or rings) is an extremely effective therapy, making it an excellent choice for nearly all postmenopausal women (with the exception of patients with breast cancer) and can be administered in the long term, since systemic absorption is minimal [20].

Local estrogen therapy may benefit some women with an overactive bladder. A clinical study demonstrated that using an estradiol ring showed clinical efficacy similar to the use of oxybutynin in women suffering from an overactive bladder [25]. The use of low-dose transdermal estradiol, however, did not affect the development of urinary incontinence [26]. A recent clinical trial reported an increased risk of nephrolithiasis in healthy women on hormone therapy, but the mechanisms involved have not been elucidated [27]. Two studies have shown a reduced risk of recurrent urinary tract infection in women using vaginal estrogen therapy [28, 29].

Sexual Function

Hormone therapy is not recommended for the treatment of sexual dysfunction, including decreased libido [20]. There is no evidence that estrogen therapy acts independently in sexual interest, arousal, and orgasmic response. Low doses of local estrogen can improve sexual function merely by increasing local blood flow and vaginal lubrication [30].

Quality of Life

Although there is no approval for the use of hormone therapy for the sole purpose of improving the quality of life of women, data shows that symptomatic women show an improvement in some areas of quality of life through relief of vasomotor symptoms. There is no evidence to support this improvement in asymptomatic women [20].

Osteoporosis

Some randomized controlled trials and those controlled with placebo support the use of estrogen therapy for the prevention of osteoporosis and fractures, including hip fractures and treatment of proven osteoporosis [20]. However, to date, there has been no approval for their use in the treatment of osteoporosis in postmenopausal women without vasomotor symptoms. When prescribed for the prevention of postmenopausal osteoporosis, hormone therapy should only be considered for women with a significant risk of osteoporosis and fractures and for whom non-estrogenic drugs are considered inappropriate.

The results of the WHI trials indicated some benefits with hormone therapy. Women randomly assigned to estrogen and progesterone had a 34% reduction in the risk of vertebral and hip fractures (hip, 6 fewer per 10,000 woman-years; vertebral, 6 fewer per 10,000 woman-years; and total, 46 fewer per 10,000 woman years) [31].

Women randomly assigned to estrogen alone had fewer fractures (hip, 7 fewer per 10,000 woman-years; vertebral, 6 fewer per 10,000 woman-years; and total, 56 fewer per 10,000 woman-years). However, fractures were a major predefined secondary outcome and were determined by clinical criteria [31].

In a cross-sectional study, Papadakis and colleagues evaluated data from the OsteoLaus cohort involving 1279 menopausal women in 2016, investigating the positive impact of hormone therapy on the preservation of bone mineral density (BMD) and, for the first time, on the trabecular index (TBS), persistent effects for up to 2 years after withdrawal of hormone therapy [32].

When there are failures or adverse effects of standard therapy for osteoporosis, prolonged use of hormone therapy is an option for women at high risk of osteoporotic fractures. However, its beneficial effects on bone mass and fracture reduction are minimized quickly after its administration has been discontinued [33].

In women who experience premature menopause, unless there are contraindications, hormone therapy should be used for the purpose of bone loss prevention, rather than the standard therapy for osteoporosis, until they reach the age of menopause, when the treatment should be reevaluated [20].

Cardiovascular Effect

Based on extensive observational data, it was believed that estrogen exerted a cardioprotective effect, and as a result, estrogen therapy was routinely prescribed for primary and secondary prevention of cardiovascular disease (CVD).

In 1995, the PEPI Trial evaluated cardiovascular risk in healthy postmenopausal women. A total of 875 women between the ages of 45 and 64 years were evaluated. Participants were randomized into five groups: the placebo group; those who used conjugated equine estrogen at a dose of 0.625 mg/day alone; associated with cyclic medroxyprogesterone acetate, 10 mg daily for 12 days per month; conjugated equine estrogen associated with medroxyprogesterone of continuous use at the dose of 2.5 mg/day; and estrogen at the dose of 0.625 mg/day associated with cyclic micronized progesterone 200 mg/day for 12 days in the month. It was concluded that the use of estrogen alone or in combination with progesterone improved lipoproteins and reduced levels of fibrinogen, without significant effects on insulin or blood pressure. When estrogen alone was evaluated, it was ideal for

the elevation of HDL, but restricted for hysterectomized women. In women with uterus, estrogen with the cyclic micronized progesterone had a more favorable effect on HDL [34].

Data from the Heart and Estrogen/Progestin Replacement Study (HERS I and II), other small controlled trials and two meta-analyses have not confirmed this protective effect on the heart [35–37]. The HERS I study demonstrated a twofold to threefold increase in the risk of venous thrombosis and pulmonary embolism with hormone therapy. However, the absolute risk was low, ranging from one case to two or three cases per 100,000 women. The data is related to the oral use of the hormone. The HERS II study found a 2.89 times risk of thromboembolism in users of combined hormone therapy, estrogen/progesterone, compared with the placebo and a trend toward an increased risk of pulmonary embolism.

In 2002, the subgroup of women in the WHI who used the estrogen-progestin combination showed an increased risk of coronary heart disease and breast cancer, and the study was discontinued prematurely. The results of the subgroup that used only estrogen therapy, published in 2004, showed a tendency to a decreased risk of breast cancer, but an increased risk of stroke and thromboembolic disease, and no benefits on coronary heart disease [20, 31].

Some, but not all, observational studies suggest that long-term hormonal therapy is associated with a smaller accumulation of calcium in the coronary arteries, data which is strongly correlated with the presence of atheromatous plaques and the risk of future coronary events [38].

The WHI trial found a risk twice higher of pulmonary embolism in users of combined hormone therapy, representing eight more cases of pulmonary embolism in 10,000 women/year. This risk was attributed to the combination of estrogen and progestin [20, 31]. There is no data for other, non-oral forms of administration of hormonal therapy.

The WHI showed an increase in the risk of stroke, but no effect on hemorrhaging. When all women in that trial were analyzed, there were 8 additional cases of stroke per 10,000 women/year in combined therapy and 11 cases per 10,000 women/year in estrogen-alone therapy, and in both, the risk was eliminated after discontinuation of treatment [31]. In a recent data analysis from the WHI trial involving only women aged 50–59 years, there was no significant effect on the risk of stroke [39]. The risk of stroke did not significantly increase in the HERS I and II studies [40, 41]. The data from observational studies on the association between hormone therapy and stroke have been inconsistent. Various studies have indicated a positive association, but others showed no effect on the risk of stroke [20].

One difference between observational studies and the WHI study is the fact that the women enrolled in the latter presented an average age of 63 years at the start of the use of hormone therapy, about 12 years after menopause had begun [20, 31]. Participants in the observational studies began therapy immediately after the beginning of menopause, with a mean age of 51 years, that is, women from the WHI were older and began using the hormone later, which is unusual in clinical practice. As the atherosclerotic lesions develop early, it is likely that the WHI participants already presented subclinical coronary disease and therefore would not be candidates for hormonal regime, since hormonal therapy appears to be more effective in primary prevention than in secondary prevention. The idea that differences in age or time since menopause at the start of hormone therapy are responsible for differences in cardiovascular outcomes has become known as the "window of opportunity" [42].

In the observational studies and in animal models that suggested beneficial cardiovascular effects of hormone therapy, the subjects generally initiated therapy at the time of menopause (often for management of vasomotor symptoms), or in animal studies, treatment began immediately after ovariectomy. This contrast with the WHI, which treatment was initiated more than a decade after menopause in most study participants, led to the development of the "window of opportunity." This theory proposed that initiation of HT at or shortly after menopause is cardioprotective, whereas starting treatment at a time remote from menopause may be harmful. Indeed, in the WHI, the trend toward lower rates of CVD events was noted in women who were within 10 years of menopause or who were aged 50–59 years at the time of entry into the trial. In the estrogen and progestin arm, women within 10 years of the menopausal transition had a hazard ratio (HR) of coronary heart disease (CHD) events of 0.89, compared with 1.71 in those more than 20 years from menopausal transition. In the conjugated equine estrogen (CEE) alone arm, those aged 50–59 years had an HR of 0.56, compared with older women, whose HR was almost 1.0 [42].

In addition, women enrolled in the CEE arm and aged 50–59 at baseline had coronary calcium measured by computed tomography; women who received CEE had significantly lower scores at trial completion than those who received placebo [38]. In this young population, the incidence of coronary events was low, and the absolute risk of clinical CHD events was small. In a more recent analysis, the results were examined after pooling the data from the WHI estrogen-alone and estrogen and progestin trials [42]. Women enrolled within 10 years of the onset of menopause had a HR for CHD of 0.76 (CI, 0.50–1.16). The HR continued to rise years after the menopause. Initiating therapy from 10 to 19 years after menopause gave a HR of 1.10 (CI, 0.84–1.45), and when initiated after 20 or more years, the HR was 1.28 (CI, 1.03–1.58). The P value for the trend was 0.02, supporting the timing hypothesis, which predicts that protection from atherosclerosis is evident only when hormone therapy is initiated shortly prior to the onset of menopause and before the development of advanced atherosclerotic plaques.

The timing hypothesis is further supported by several recent studies. A Bayesian meta-analysis of hormone therapy mortality in younger postmenopausal women (mean age, 55 years) presented the combined results of 19 randomized clinical trials that enrolled 16,000 women at a mean age of 55 years, totaling 83,000 patient-years. This study showed a relative risk of mortality of 0.73 [20]. The analysis also demonstrated a cardiovascular benefit when HT was initiated early, supporting the timing hypothesis. Current ongoing prospective randomized trials will formally test this hypothesis.

Despite this reassuring data, HT in postmenopausal women is still indicated only for the management of vasomotor symptoms, since there is no data to support its use in primary or secondary prevention of coronary disease.

The Kronos Early Estrogen Prevention Study (KEEPS) evaluated cardiovascular risk in 728 women aged 42 to 58 years who started hormone therapy in the first months of menopause (6–36 months postmenopausal). HT consisted of oral conjugated estrogens (Premarin®, 0.45 mg), transdermal estradiol (Climara®, 50 μg), or placebo with micronized progesterone (Prometrium®, 200 mg) for 12 days per month or placebo for women with an intact uterus. The endpoints were the coronary artery calcification score measured by computed tomography and the intima carotid thickness (IMT). Preliminary results showed no difference in the rate of progression of intima carotid thickness in the three groups. No estrogenic formulation raised blood pressure. Conjugated oral estrogens increased HDL and reduced LDL and increased triglycerides and C-reactive protein. Transdermal estradiol improved glucose levels and insulin sensitivity. In this study there were no significant differences in rates of clinical events including breast and endometrial cancer and cardiovascular disease among the three groups. It should be noted that the population studied consisted of a small group of healthy and relatively young women. In the group treated with hormones, symptoms such as heat waves were reduced; BMD and sexual function improved when compared to controls [21, 43].

The Early versus Late Intervention Trial with Estradiol (ELITE) [44] evaluated a total of 643 healthy postmenopausal women using estradiol 1 mg daily and progesterone 45 mg during 10 days of each 30-day cycle with women with preserved uterus for 5 years, comparing them with distinct times of the beginning of HT (<6 years, early onset, or >10 years, late onset). Women treated with estradiol in both age groups/timing had lower LDL and higher levels of HDL and triglycerides compared to untreated women in both groups. The rate of progression of coronary artery calcification measured by CT was lower in the postmenopausal group treated with estrogen than in its placebo group or the group treated with estrogen later on in the menopause. The group treated later in menopause did not differ from the cohort taken with placebo. The study concluded that oral estradiol therapy was associated with a lower progression of subclinical atherosclerosis (measured as IMT) than placebo when therapy was initiated within 6 years after menopause but not when 10 or more [21, 44].

A subgroup analysis of the Danish Osteoporosis Prevention Study, involving 1006 women aged 45 to 58 years, randomized to the use of three-phase estradiol and norethisterone acetate in those with uterus and estradiol 2 mg day in those hysterectomized versus placebo demonstrated, after 10-year and 16-year follow-up, that 16 women in the treatment group had the primary composite outcome (death, hospital admission for heart failure, and myocardial infarction) compared to 33 in the control group (hazard ratio 0.48, confidence interval 95%, 0.26 to 0.87, $P = 0.015$), and 15 died compared to 26 (0.57, 0.30 to 1.08, $P = 0.084$). Reduction in cardiovascular events was not associated with increased cancer (36 in the treated group, 39 in the control group, 0.92, 0.58 to 1.45, $P = 0.71$) or with breast cancer (10 in the treated group, 17 in the control group, 0.58, 0.27 to 1.27, $P = 0.17$). The risk ratio for deep vein thrombosis (2 in treated group, 1 in the control group) was 2.01 (0.18 to 22.16) and for stroke (11 in treated group, 14 in the control group) was 0.77 (0.35 to 1.70). After 16 years, the reduction in the primary outcome result was still present and not associated with an increase in cancer. After 10 years of treatment, women who received HT early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction without any apparent increase in the risk of cancer, venous thromboembolism, or stroke [21].

Another topic of constant debate is the role of the mode of administration of the hormone in relation to the adverse effects observed in large studies. The oral route is associated with an increase in thrombotic effects and decreased synthesis of thrombolytic factors in the liver, induced by the hepatic first pass of estradiol, which could justify a two- to threefold increase in the risk of thromboembolism observed with the use of oral, but not transdermal, estrogen [20, 45]. Low-dose, cyclic, and transdermal formulations have been suggested as potentially favorable alternatives. Unfortunately, no large, prospective, randomized trials exist that carefully compare these alternative regimens.

Diabetes Mellitus

Large clinical trials have shown that hormone therapy reduces the appearance of type 2 diabetes mellitus (T2DM), despite not having been approved as a prevention measure in this disease. Women in the WHI and HERS studies who received estrogen/progesterone showed an average reduction of 21% in the incidence of T2DM [46].

Endometrial Cancer

Women constantly exposed to endogenous or exogenous estrogens not neutralized by progesterone are at increased risk of developing hyperplasia and endometrial cancer. The risk of endometrial cancer is six to eight times higher in women using estrogen compared with women who do not use it [47].

Breast Cancer

The relationship between breast cancer and hormone therapy is complex. There are dozens of observational, case-control, and cohort studies, with results which are not very consistent. A meta-analysis of observational studies, carried out in 1997, summed up 90% of the literature (53,705 women with breast cancer, compared with 108,411 controls) and showed that each year of hormone therapy confers a relative risk for breast cancer of 2.3%, attributable to the use of progesterone [48].

Despite demonstrating an increased incidence, the present study, like others, showed no increase in mortality from the disease. The use of estrogen/progestin for the group of women in the WHI study was discontinued because of the 26% increase in the risk of breast cancer, that is, for every 10,000 women, 38 developed breast cancer, while among nonusers of hormone therapy, 30 cases of breast cancer in 10,000 women were found [31].

Studies have not clarified whether the risk of breast cancer differs between continuous and intermittent use of progesterone, with observational studies suggesting that the risk may be greater with the continuous use of this drug. It is also unclear whether there is a class effect of progesterone or if a specific agent influences a higher risk of breast cancer. Data from a large observational study suggests that hormone therapy with micronized progesterone carries a low risk of breast cancer with short-term use but generates an increased risk if used for long periods [49].

It is known that combination therapy and, to a lesser extent, estrogen-alone therapy promote increased proliferation of breast cells, breast tenderness, and increased mammographic density, complicating the interpretation of mammography and delaying the diagnosis of breast cancer [20].

In The Million Women Study (MWS), researchers reported an increased risk of breast cancer in women who start hormone therapy soon after menopause [50]. Women in the WHI study who used estrogen alone had no increased risk of developing breast cancer after an average of 7.1 years of use, and there was even a decrease in the risk in this arm of the study, despite having shown an increase in risk early in treatment. It is claimed that the hypothesis that justifies this reduction in risk is the probable apoptotic effect exerted by estrogen on neoplastic mammary cells in an environment with low levels of estrogen [20]. This finding was not demonstrated in the MWS [50].

Ovarian Cancer

The association between hormone therapy and ovarian cancer is unclear. A cohort study of 44,241 postmenopausal women concluded that women who used estrogen alone as hormone therapy for more than 10 years had a significant risk of developing ovarian cancer, while those who used combined therapy for a short period showed no increased risk [51]. According to data from the MWS, women using hormone therapy are at increased risk for ovarian cancer [52]. Another observational study found a strong association between estrogen and death due to ovarian cancer. Moreover, the risk is increased in women who used estrogen for 10 years or more [20].

In a post hoc analysis of the arm of WHI using combination therapy for an average of 7.1 years, the incidence of non-small cell lung cancer did not increase significantly; there was, however, a significant increase in the number of deaths from this cancer, as well as the presence of metastatic and poorly differentiated tumors. This association was found exclusively in women over 60 years who were smokers or who had a history of smoking. The arm that used only estrogen therapy exhibited no increase in incidence or mortality from lung cancer [53].

Cognition and Dementia

Randomized controlled studies of short duration, comparing estrogen with placebo, show inconsistent results. The methodology, the type of estrogen, age, the type of menopause (natural or surgical), and, in particular, the tests performed are different. Some studies show benefits in some tests, focused mainly on memory and verbal fluency in patients using estrogen [20]. A meta-analysis concluded that the evidence is still scanty and inconsistent and does not explain the improvement in symptoms and relief from depression, indicating the need to evaluate the various types of hormone therapy used [54].

WHIMS reported hormone therapy (HT), conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA), increased the risk for dementia [HR 1.76 (95% CI, 1.19–2.60); $P = 0.005$] and global cognitive decline, with a mean decrement relative to placebo of 0.21 points on the Modified Mini-Mental State Examination in women aged 65 and older. A subset of WHIMS participants joined the ancillary WHI Study of Cognitive Aging

(WHISCA) trials, in which domain-specific cognitive tests and mood were measured annually. Compared with placebo, CEE + MPA had a negative impact on verbal memory over time and CEE-alone was associated with lower spatial rotational ability at the initial assessment, but the difference diminished over time. The ancillary WHIMS-MRI study measured subclinical cerebrovascular disease to possibly explain the negative cognitive findings reported by WHIMS and the increased clinical stroke in older women reported by the WHI. WHIMS-MRI reported that while CEE + MPA and CEE-alone were not associated with increased ischemic brain lesion volume relative to placebo, both CEE + MPA and CEE-alone were associated with lower mean brain volumes in the hippocampus, frontal lobe, and total brain [55].

The evidence linking estrogen use with the prevention of Alzheimer's disease is still inconsistent. Some observational, case-control, and cohort studies have shown reduced incidence of Alzheimer's disease in women using estrogen compared with nonusers. Not all studies have shown favorable results [20].

Principles of Treatment

Patient Selection

In view of the results of the new clinical trials and the legacy brought by WHI, a risk stratification for the use of hormone therapy was developed, suggesting that a certain group of women would have a lower risk of adverse cardiovascular outcome. An age less than 60 years, onset of HT in the first 10 years postmenopausal, LDL less than 130 mg/dl or LDL/HDL ratio <2.5, absence of metabolic syndrome, and absence of genotype for Leiden factor V confer less risk. When analyzing the clinical impact of the KEEPS, WHI, and ELITE studies, we found that the results are reassuring for patients who require HT to treat menopausal symptoms at a young age [21, 44].

Although there are alternative therapies for the treatment of vasomotor symptoms, none appear to be as effective in the short term as hormone therapy, which is the gold standard treatment for most women with postmenopausal symptoms, except for those with a history of breast cancer and coronary heart disease, with a previous thromboembolic event or CHD, or at high risk for these complications. In the past, short-term therapy was defined as less than 5 years. This definition is somewhat arbitrary, since there is no consensus on the duration of treatment.

To date, postmenopausal HT, either using estrogen alone or in combination, should not be initiated for the prevention of cardiovascular diseases. Furthermore, postmenopausal HT is no longer considered a first-line option for the prevention and treatment of osteoporosis [20].

Preparations

Both estrogen and progesterone present common features typical of the class of drug, but also with potentially different properties (Table 13.2). In the absence of clinical trials designed to compare different hormonal formulations, it is necessary to generalize the results to all drugs belonging to this class. It is possible, however, to find differences within each family, such as potency, androgenicity, glucocorticoid effect, bioavailability, and route of administration.

Progesterone is recommended for all postmenopausal women with an indication for hormone therapy to prevent the risk of endometrial cancer in those women with an intact uterus [20].

Dose and Route of Administration

Although it is not known whether lower doses of estrogen and progesterone have less effect on the cardiovascular system and the risk of breast cancer, it is recommended to use low hormone doses, when possible (e.g., 0.3–0.45 mg of oral conjugated estrogens, 0.5 mg of oral estradiol, or 0.014–0.0375 mg of transdermal estradiol). In some studies, these doses have proved to be suitable for the treatment of symptoms. Many studies on the efficacy and safety of use of estrogen have used conjugated estrogen at a dose of 0.625 mg, considered to be the standard dose. Low-dosage preparations generally contain half this dose [56].

Low-dose estrogen formulations are also available in the form of gel, cream, ova pill, and spray. The use of low hormonal doses sometimes requires a longer period of treatment to achieve maximum effectiveness in reducing vasomotor symptoms. Individualization of doses according to the woman's needs presents a good therapeutic strategy. Lower doses are associated with a lower incidence of side effects such as uterine bleeding and breast tenderness and may have a more favorable risk-benefit ratio [20].

In a case-control study, the risk of CHD was not increased with the use of low-dose transdermal estrogen (0.05 mg) but showed an increase with the use of oral and transdermal formulation with a higher dosage [57]. All routes of administration can effectively treat vasomotor symptoms. Non-oral routes of administration, including vaginal and intrauterine ones, and transdermal patches, may offer both advantages and disadvantages compared to the oral route, but the long-term risk-benefit ratio has still not been demonstrated in clinical trials [20].

There are differences regarding the role of the hepatic first-pass effect, the hormone concentrations in the blood, and the biological activity of preparations. With transdermal therapy there is no significant increase in triglyceride levels, C-reactive protein, hormone-binding globulin, and the effect

Table 13.2 Types of hormonal therapy for vasomotor symptoms

Drug	Route	Dose
17β-Estradiol	Oral	1–2 mg/day
Ethinyl estradiol	Oral	0.02–0.05 mg 1–3 times daily
Conjugated equine estrogens	Oral	0.3–1.25 mg/day
17β-Estradiol patch	Transdermal	0.014 mg/d–0.0375 mg/day 1 patch twice/week
17β-Estradiol gel	Transdermal	0.25 mg/d or 0.75 mg/d 0.25 g gel daily 1.25 g gel daily
Estradiol 1 mg + norethindrone acetate 0,5 mg	Oral	1 tab daily
Ethinyl estradiol 5mcg + norethindrone acetate 1 mg	Oral	1 tab daily
17β-Estradiol 1 mg + norgestimate 0.09 mg	Oral	First 3 tablets contain estrogen, next 3 contain both hormones, alternate pills every 3 days
CEE 0.625 mg + medroxyprogesterone acetate 5 mg	Oral	First 14 tablets contain estrogen only and remaining 14 tablets contain both hormones
CEE 0.625 mg + medroxyprogesterone acetate 2.5 mg or 5 mg	Oral	1 tab daily
17β-Estradiol + norethindrone acetate	Transdermal	0.05 mg/0.14 mg daily; 1 patch twice/week
17β-Estradiol + levonorgestrel	Transdermal	0.45 mg/0.015 mg daily; 1 patch weekly
CEE 0.45 mg + Bazedoxifene 20 mg	Oral	1 tablet daily
Medroxyprogesterone acetate	Oral	1.5–2.5 mg daily
Norethindrone acetate	Oral	0.1 mg daily in combination preparations or 14 days/month
Drospirenone	Oral	0.25 mg daily
Micronized progesterone	Oral	100 mg/d continuously or 200 mg/d for 12 days/month
Norethindrone acetate	Transdermal	0.14 mg/d 1 patch twice/week
Levonorgestrel	Transdermal	0.015 mg/d 1 patch/week

on arterial pressure. It is suggested by the AACE 2017 recommendations that the transdermal route may be advantageous for diabetic women and other cardiovascular risk factors as well as for women in old age [21]. There is a growing observational evidence that the transdermal route may be associated with a lower risk of deep vein thrombosis, CHD, and myocardial infarction [20].

There are various dosage options of progesterone with no harm to the endometrium. The dose varies according to the progestin chosen and the estrogen system used, starting with the lowest effective doses, such as 1.5 mg of medroxyprogesterone acetate, 0.1 mg of norethindrone acetate, 0.5 mg of drospirenone, or 100 mg micronized progesterone. Oral progestogens, oral estrogen combinations, and combinations in the form of a patch have demonstrated endometrial protection and have been approved for use in postmenopausal hormone therapy.

Duration of Treatment

For postmenopausal women with moderate to severe vasomotor symptoms, and no contraindication for the use of estrogen, hormonal therapy is suggested as the treatment of choice. The lowest effective dose of estrogen should be used, with the shortest possible duration. Short-term therapy is considered for 2–3 years and generally not more than 5 years. Only a minority of women unable to successfully discontinue treatment without the persistence of symptoms may be considered for a longer period of use, under close medical supervision [20]. Hormone therapy does not need to be routinely discontinued in women over 60 or 65 years old, and maintenance of its use may be considered beyond 65 years for persistent vasomotor symptoms, severe impairment of quality of life, or prevention of osteoporosis after adequate evaluation and advice on benefits and risks. Annual reassessment including review of comorbidities and periodic HT reduction or discontinuation testing or change to low-dose transdermal patch routes should be considered [58].

Discontinuation of Treatment

Many women do not have problems at the time of discontinuation of treatment. Observational studies suggest that 40–50% of women discontinue hormone therapy 1 year after starting treatment, and 65–75% stop in the second year, most often without medical follow-up. For other women the abrupt discontinuation of medication provokes the return of vasomotor symptoms and requires the resumption of treatment [20].

The North American Menopause Society suggests that after a failed attempt to stop the therapy, prolonged use of postmenopausal hormone therapy may be reasonable for women who find that the benefits of symptom relief outweigh the risks. In this context, additional attempts are required at a later date for the discontinuation of postmenopausal hormone therapy [58].

Complementary and Alternative Therapies

Nonhormonal Therapy for Vasomotor Symptoms

α-Adrenergic agonists such as clonidine have been used with variable success, although scientific data is contradictory [59]. A randomized clinical trial using oral clonidine showed no reduction in vasomotor symptoms. Normally, doses of 0.1 mg a day are required. Sometimes it can cause postural hypotension and have side effects in 50% of users, including insomnia. Beta-blockers have been used for the control of anxiety and palpitation but are not useful for hot flashes [60].

Serotonin selective reuptake inhibitors such as fluoxetine, paroxetine, and citalopram have been used in some studies. The most favorable finding indicates paroxetine at a dose of 10 mg per day, as higher doses were not associated with better symptom control. It may have adverse effects on the libido and should not be prescribed in patients with breast cancer using tamoxifen because it may modify the action of that drug [61].

Selective noradrenaline reuptake inhibitors, such as venlafaxine, have been reported as effective in some small studies, especially in women with breast cancer unable to use hormone therapy. Usually venlafaxine is initiated at a dose of 37.5 mg and adjusted to a dose of 75 mg a day if necessary [61].

Gabapentin has also been used to relieve vasomotor symptoms in women with breast cancer. The dose used is usually 300 mg three times a day, but in order to reduce side effects, the dose may be gradually titrated, in other words, 300 mg per day for 2 weeks, 300 mg twice a day for 2 weeks, and finally, 300 mg three times a day after the first month (Table 13.3) [61].

Table 13.3 Nonhormonal pharmacological therapy for vasomotor symptoms

Class	Drug	Dose
α-Adrenergic agonists	Clonidine	0.1 mg a day
Serotonin selective reuptake inhibitors	Fluoxetine	20 mg a day
Anticholinergic	Oxybutynin	5–10 mg a day
Serotonin selective reuptake inhibitors	Paroxetine	7.5–10 mg a day
Serotonin selective reuptake inhibitors	Citalopram	20 mg a day
Selective noradrenaline reuptake inhibitors	Venlafaxine	75 mg a day
Selective noradrenaline reuptake inhibitors	Desvenlafaxine	100 mg a day
Structural analogue gamma aminobutyric acid	Gabapentin	900 mg a day

Other Hormone Therapies

In the USA dehydroepiandrosterone (DHEA) has been used to relieve vasomotor symptoms but has not been widely used in other countries such as the UK. Some studies have shown beneficial effects on libido, bone metabolism, cognition, well-being, and vaginal lubrication. An uncontrolled pilot study showed a slight decrease in hot flashes using DHEA. The treatment of GSM in estrogen-sensitive cancer survivors is challenging, since vaginal estrogen may be contraindicated. In a randomized study comparing two doses of vaginal DHEA with a nonhormonal vaginal moisturizer in postmenopausal cancer survivors, especially breast cancer, all three groups reported similar improvement in dyspareunia and vaginal dryness symptoms after 12 weeks of treatment, but only the group that used DHEA at the highest dose reported significant improvement in sexual function. Although it is a promising treatment for this specific subgroup of women, safety data are required [62]. Evidence on the use of natural progesterone cream is limited, with studies showing no symptom relief compared with placebo [63].

Phytohormones

Phytoestrogens, nonsteroidal compounds that are naturally present in many plants, fruits, and vegetables, present both estrogenic and antiestrogen activities. They are usually found in soybeans, lentils, flaxseed, grains, fruits, and vegetables. Data suggests that the lower risk of heart disease among Asian women compared with Western populations is due to the high consumption of soy products. This observation has led to an increasing interest in the potential use of phytoestrogens as an alternative to hormone therapy in postmenopausal women. In fact, an increasing percentage of women (including women with a history of breast cancer) use soy products in their diet to help control the symptoms of menopause. Moreover, many women believe that phytoestrogens, because they are "natural," are safer than hormone therapy, although this has never been proven [64].

A review of the Cochrane Database of 30 randomized trials evaluated the efficacy, safety, and acceptability of foods and supplements, including all phytoestrogens. The reviewers concluded that there was no evidence that phytoestrogens help relieve menopausal symptoms [64].

Botanicals

There is a wide range of natural products that have been used as a complementary therapy in menopause, without scientific evidence, such as St. John's wort, *Cimicifuga racemosa*, ginseng, dong quai, agnus castus, and *Gingko biloba* [65].

Tibolone

Tibolone, a drug that has been widely used in Europe and other countries for almost 20 years, is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties. It reduces vasomotor symptoms when compared to placebo and has a beneficial effect on bone mineral density. Limited data suggests that it may also have a modest effect on symptoms of sexual dysfunction. However, tibolone has been associated with an increased risk of stroke recurrence and possibly breast cancer, based on data from the LIFT and LIBERATE studies, respectively, and is therefore not recommended for routine use in the management of menopausal symptoms [66]. The LIFT trial, designed to examine the effect of tibolone on vertebral fractures in postmenopausal women, reported a reduction in the absolute risk of vertebral and non-vertebral fractures (8.6 and 6.9 per 1000 person-years, respectively, relative hazards of 0.55, 95% CI 0.41–0.74 and 0.74, 95% CI 0.58–0.93, respectively). However, this trial was discontinued early, owing to an increased risk of stroke [67].

Ospemifene

Ospemifene is a SERM with agonist action of estrogen in the vaginal epithelium and without estrogenic effect clinically significant in the endometrium or in the breast. Ospemifene was approved by the US Food and Drug Administration (FDA) in 2013 for the treatment of moderate to severe dyspareunia caused by vulvovaginal atrophy in menopausal women. Its use is indicated for women with symptomatic vulvovaginal atrophy refractory to non-pharmacological therapy, with contraindication to the use of vaginal estrogen or in those with difficulty of application, as in patients with severe obesity. Its disadvantages in relation to the use of vaginal estrogen are the need for daily use, the appearance of heat waves, and the potential risk of thromboembolism [68].

Bazedoxifene, a selective estrogen receptor modulator (SERM) with breast and endometrial safety, combined with conjugated estrogens, is available in the USA and Europe for the treatment of vasomotor symptoms and prevention of osteoporosis. The combination of conjugated estrogen at the dose of 0.45 mg and bazedoxifene 20 mg in women with moderate to severe heat waves decreases their frequency by approximately 75% versus 50% for placebo. To date no serious adverse events have been reported [69, 70].

Others

A neurokinin 3 receptor antagonist (NK3R) is a potential non-hormonal therapy for the control of heat waves. In a randomized, placebo-controlled clinical trial of an oral NK3R antagonist administered for 4 weeks in symptomatic postmenopausal women, the average weekly number of heat waves decreased from approximately 85 at the baseline to 20 and 50 in the treatment and placebo, respectively. The residual heat waves in the treatment group were also less severe. While the results of this assay are encouraging, long-term trials are required to determine the efficacy and safety of this drug [71].

Vitamin E has been associated with decreased vasomotor symptoms in an isolated clinical trial [72]. Herbs of traditional Chinese medicine, reflexology, and magnetic devices have been studied but have no beneficial effects [73]. Acupuncture has been studied as a potential therapy for hot flashes, but results so far are not promising [74].

The Future

Although there is a real need to treat vasomotor symptoms and sleep disturbance in the menopausal transition, the long-term risks of hormone therapy preclude extended duration of use for the prevention of chronic disease. Although studies are currently under way to determine whether CHD risk will be impacted by the timing of initiation, the cancer risks are present at all ages, and some seem to persist after cessation of hormone therapy. The reduction in hip and vertebral fracture dissipates after stopping hormone therapy, whereas the long-term risk of breast cancer and possibly lung and ovarian cancers continues. Alternative therapies for menopausal symptoms that would not increase the risk of cancer are sorely needed. Because breast cancer seems significantly impacted by the use of progestin, ways to oppose estrogen's effect on the uterus without the use of a progestin are currently being developed.

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