Management of postmenopausal women: Collège National des Gynécologues et Obstétriciens Français (CNGOF) and Groupe d'Etude sur la Ménopause et le Vieillissement (GEMVi) Clinical Practice Guidelines

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Practice Guidelines

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ABSTRACT

Aim: The aim of these recommendations is to set forth an individualized approach to the management of early postmenopausal women (i.e., within the first 10 years after natural menopause) covering all aspects of lifestyle and therapeutic management, with or without menopause hormone therapy (MHT).

Materials and methods: Literature review and consensus of French expert opinion. Recommendations were graded according to the HAS methodology and levels of evidence derived from the international literature, except when there was no good-quality evidence.

Summary recommendations: The beginning of menopause is an ideal time for each woman to evaluate her health status by assessing her bone, cardiovascular, and cancer-related risk factors that may be amplified by postmenopausal estrogen deficiency and by reviewing her lifestyle habits. Improving lifestyle, including nutrition and physical activity, and avoiding risk factors (notably smoking), should be recommended to all women. MHT remains the most effective treatment for vasomotor symptoms but it could be also recommended as first-line treatment for the prevention of osteoporosis in early postmenopausal women at low to moderate risk for fracture. The risks of MHT differ depending on its type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. There is reasonable evidence that using transdermal estradiol in association with micronized progesterone or dydrogesterone may limit both the venous thromboembolic risk associated with oral estrogens and the risk of breast cancer associated with synthetic progestins. Treatment should be individualized to each woman, by using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of its benefit–risk balance. For bothersome genitourinary syndrome of menopause (GSM) symptoms, vaginal treatment with lubricants and moisturizers is recommended as first-line treatment together with low-dose vaginal estrogen therapy, depending on the clinical course. No recommendation of an optimal duration of MHT can be made, but it must take into consideration the initial indication for MHT as well as each woman's benefit–risk balance. Management of gynecological side-effects of MHT is also examined. These recommendations are endorsed by the Groupe d'Etude sur la Ménopause et le Vieillissement hormonal (GEMVI) and the Collège National des Gynécologues-Obstétriciens Français (CNGOF).

1. Introduction

Menopause is a physiologic event defined by the loss of ovarian follicular function and the final menstruation period. The average age of menopause has been remarkably stable over time and varies little between ethnic groups. In France, it is 51 years of age. Menopause is considered natural (or physiologic) when it occurs spontaneously after the age of 45 years. It is surgical when the ovarian insufficiency results from bilateral oophorectomy or iatrogenic (e.g., by chemotherapy or pelvic radiation) when it occurs in a woman of childbearing age.

Menopause is described as early when it occurs in women aged 40 to 45 years. It must be differentiated from premature ovarian failure, which occurs before the age of 40. The terms early menopause and premature menopause are no longer used in this situation, and premature ovarian failure implies the need to seek its etiology.

Menopause is said to be late when it occurs after the age of 55. Perimenopause is defined as the onset of abnormal cycles and the occurrence of climacteric signs until ovarian activity stops completely. It begins on average at 47 years of age and lasts on average 4 years [1].

2. Objectives

The objectives of this work were to establish recommendations for the management of early postmenopausal women, i.e., within the first 10 years after the onset of physiologic postmenopausal amenorrhea. These recommendations do not concern the field of premature ovarian failure.

The questions were chosen to help healthcare providers involved in these women's care in all aspects of menopause, including lifestyle issues and therapeutic management (including vasomotor symptoms (VMS),

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genitourinary syndrome of menopause (GSM) and osteoporosis prevention), especially with menopause hormone treatment (MHT). Recommendations for the management of climacteric syndrome were limited to vasomotor symptoms, in the absence of sufficient data for other types of symptoms.

3. Methodology and organization

These guidelines were developed according to the method described in the HAS (Haute Autorité de Santé, national authority for health) methodological guide, available on its website: https://www.hassante.fr/upload/docs/application/pdf/201802/good_practice_guidelines_cpg_method.pdf.

This is a rigorous method based on:

- Transparency with regard to the critical analysis of the literature, the essential debates and decisions made by the members of the working group, the opinions of the members of the reading group, and all the participants in the different groups;
- Independence in the development of recommendations;
- The management of the financial interest disclosure declared by the experts of the working group.

The literature search was systematic, prioritized, and structured. Each scientific article selected was analyzed according to the principles of critical reading of the literature, focusing first on evaluating the study method used, then the results, and finally the benefits or risks for the patient. The drafting of the scientific argument was based both on the critical analysis and synthesis of the literature performed by the editors and the opinions of the working group.

In accordance with the HAS recommendations, and depending on their level of evidence, their expected benefit for patients, and their feasibility in clinical practice, recommendations were rated from A to C such as:

Grade A was based on studies with a high level of evidence (LE1): high powered randomized controlled trials without major bias, meta-analyses of randomized trials, decision analysis on well-conducted studies;
Grade B was based on a scientific presumption derived from studies of intermediate level of evidence (LE2), such as low-powered randomized controlled trials, well-conducted non-randomized studies or cohort studies;
Grade C was based on studies with a lower level of evidence, such as case-control studies (LE3), retrospective studies, case series or comparative studies with significant bias (LE4);

Expert opinion: in the absence of (conclusive) studies, the recommendations resulted from an agreement between experts of the working group and after consultation with the reading group.

The project and the working group were coordinated by Nathalie Chabbert, Xavier Fritel, Olivier Graesslin, Patrice Lopès, Geneviève Plu-Bureau and Florence Trémollieres. This organizing committee, which was appointed by the Collège National des Gynécologues-Obstétriciens Français (CNGOF) and the Groupe d'Etudes sur la Ménopause et le Vieillissement hormonal (GEMVI), defined the scope of the recommendations and the list of topics to be covered.

A working group was set up with experts in women's midlife health from a wide range of specialties. They devoted significant time and effort to ensuring the accuracy and relevance of each key point and clinical recommendation (see the list of authors). Authors of every section were selected from this working group. They met several times to develop the initial version of the recommendations [2–17] based on the rationale provided by the writers, which was then submitted to the reading group (see list of reviewers at the end of the text). The members of the working group and the Scientific Bureau of the CNGOF and GEMVi validated the final version of these guidelines. Funding was provided by the CNGOF and GEMVI.

4. Clinical practice guidelines

4.1. The menopause diagnosis

In physiologic situations, when there are no or minimal climacteric complaints, it is not necessarily useful to know the woman's menopausal status. However, some situations may require a diagnosis [2].

4.1.1. In the physiological situation

The diagnosis of menopause is clinical and is made retrospectively after 12 months of amenorrhea without any other obvious cause [1,18]. It occurs at an average age of 51 but can vary widely from 45 to 55 years. The associated climacteric signs (e.g., hot flushes, night sweats, and vaginal dryness) are variable, and they are not essential to establish this diagnosis [19,20].

No study has evaluated the predictive value of the progestin test for the diagnosis of menopause. It consists of giving a progestin (typically, 20 mg/day of dydrogesterone) for 10 days to a woman with an amenorrhea period of less than 12 months. The test is considered positive if withdrawal bleeding occurs when the progestin is stopped, indicating that the endometrium is still under estrogen influence. On the other hand, a negative test (no withdrawal bleeding) suggests the absence of ovarian activity but does not necessarily define menopause. The number of negative tests to be repeated to diagnose menopause is not clearly defined.

In the perimenopausal period, phases of transient hypoestrogenism are frequent and resolve spontaneously.

Although fertility decreases with age, especially in the last stages before menopause, the risk of pregnancy is not null, but rather in the order of 1 to 5/1000 woman-years, in women over the age of 50 years [21,22].

> In physiological situations, no additional evaluation is required to diagnose menopause (grade A). The progestin test is not recommended for this diagnosis (expert opinion).

4.1.2. In women using hormonal contraception

> Neither hormone assays [22–24] nor pelvic ultrasound has been shown to be useful for the diagnosis of menopause in women using hormonal contraception (level of evidence [LE3]).
>
> Their use cannot be recommended in routine practice to decide whether or not hormonal contraception may be stopped (grade C).

When needed, the strategy that could be proposed is to discontinue hormonal contraception and set up a clinical follow-up (onset of amenorrhea) (expert opinion); during this period, non-hormonal contraception (most often a barrier method) may be used until one year of amenorrhea, when it may be discontinued (expert opinion).

4.1.3. In women with a history of hysterectomy (without bilateral oophorectomy) or endometrectomy, followed by amenorrhea

When necessary and in the absence of evaluable clinical symptoms (amenorrhea), repeated FSH assays (≥30 IU/L) associated with low estradiol (<20 pg/mL) for at least 3 months after surgery could be

helpful for the diagnosis of menopause [25–27] (expert opinion). Nevertheless, in symptomatic women, use of MHT may be discussed even if the diagnosis of menopause is not fully confirmed.

4.1.4. In women treated for cancer (excluding breast cancer)

The ovarian toxicity of chemotherapy varies with the type of cytotoxic agent, cumulative dose, and the patient's ovarian reserve at the time of treatment (which is age-dependent) [28–32]. Radiation therapy also increases primordial follicle atresia; its toxicity is modulated by age, dose, and the radiation field [33].

Amenorrhea is common during chemotherapy; the time to resumption of cycles is variable and sometimes very late after chemotherapy ended. Even after a prolonged period of amenorrhea, ovarian activity may resume, especially in women who were treated before the age of 40 years [34,35]. Again, in symptomatic women, use of MHT can be discussed even if there is no confirmation of the premature ovarian failure diagnosis. In the youngest, the need for contraception has to be considered.

> The clinical criterion of 12 months of amenorrhea cannot be used for the diagnosis of menopause in women who have received gonadotoxic treatment for cancer (expert opinion). No additional evaluation can be recommended to confirm a diagnosis of menopause after gonadotoxic chemotherapy (expert opinion).

4.1.5. In women treated for breast cancer

Antiestrogenic hormone therapies used in the management of breast cancer are not gonadotoxic [36]. They can nonetheless cause amenorrhea, although not necessarily related to ovarian failure.

The hormonal status to be considered for the choice of antiestrogen therapy is that observed at the time of breast cancer diagnosis; a woman may be considered menopausal if she had an amenorrhea period of more than 12 months before the start of treatment and an age compatible with physiological menopause (>45 years). Hormonal assessments may be made in women who have undergone hysterectomy, and the decision will be based on a set of clinical data including age and climacteric symptoms (expert opinion).

If at the time of breast cancer diagnosis, the menopausal status is not known because of hormonal contraception, it is preferable to consider that the woman is not menopausal [37] (expert opinion).

In women treated with GnRH agonists or tamoxifen, no additional evaluation (hormone assays or ultrasound) [38,39] can be recommended to make a diagnosis of menopause (expert opinion).

4.2. The first menopause consultation

The focus of this first consultation is to address and provide answers to women's questions about menopause. It is also the ideal time to screen for clinical risk factors for the different disorders that may be worsened by the estrogen deficiency of menopause. Finally, this consultation gives healthcare providers the opportunity to promote healthy lifestyle changes [3,4] and advise the avoidance of toxic substances (e.g., tobacco and alcohol).

Among the pathologies whose incidence significantly increases after menopause, postmenopausal osteoporosis and cardiovascular disease (CVD) are the most emblematic. For a 50-year-old woman, the lifetime risk of having an osteoporotic fracture is about 40%, with an estimated risk of a hip fracture around 17% [40]. At the age of 50, the lifetime risk of dying from CVD is about 45% [41].

Various clinical risk factors have been associated with the risks of CVD and osteoporosis. Some of these factors, especially aging, are common to both, but most will be accentuated by postmenopausal estrogen deficiency. Screening for these different risk factors at the beginning of menopause enables the implementation of preventive measures whenever necessary.

Table 1
Clinical risk factors for fracture.

Nonmodifiable risk factors	Modifiable risk factors
▪ Age ▪ Personal history of fracture ▪ Family history of vertebral or hip fracture ▪ History of early hypogonadism (before 40 years) ▪ History of demineralizing endocrinopathies or pathologies	▪ Low BMI (<19 kg/m^2) ▪ Tobacco ▪ Systemic corticosteroid treatment (more than 7.5 mg prednisone equivalent for more than 3 months) ▪ Demineralizing treatments (e.g., aromatase inhibitors)

4.2.1. Evaluation of the risk of osteoporosis

This consultation should include the identification of clinical risk factors that contribute to bone loss and increased fracture risk (Table 1) and measurement of bone mineral density (BMD) at the spine and femur by DXA. The risk of osteoporotic fracture increases exponentially with the number of risk factors [42–45] and the decrease in BMD [46,47] [LE1]. Moreover, they act synergistically on the gradient of risk [LE2].

- The clinical risk factors, taken alone or in combination in different clinical scores or fracture-probability algorithms (the only one currently used in France is the FRAX), perform poorly in predicting fractures among early postmenopausal women [48–50] [LE2]. Their value is limited, as is that of the clinical FRAX score in predicting low BMD (T-score < -2.5) in these women, given its low specificity (around 50%) for a sensitivity of around 50–60% [LE1] [49,51,52].
- Dual X-ray absorptiometry (DXA) is the gold standard for measuring BMD [46]. The two reference bone measurement sites are the lumbar spine and the upper femur (femoral neck or total hip). The BMD result in g/cm^2 is converted to the difference in standard deviations from the mean of the young adult, i.e., the T-score. The WHO definition of osteoporosis is a T-score ≤ 2.5 at, at least one of the bone sites measured [42,53].

BMD is strongly correlated with both in vitro and in vivo bone strength. More than 20 prospective epidemiologic studies have established a strong relation between decreased BMD and increased fracture incidence [46,47]. BMD measurement by DXA in early postmenopausal women is predictive of the 10-year—and even up to 20-year—risk of osteoporotic fractures [53–58] [LE2]. Its sensitivity is about of 60% and its specificity of 70% [57].

To date, no data formally demonstrate the impact of BMD testing at the beginning of menopause on the subsequent fracture and mortality rates [LE2]. The majority of international guidelines recommend BMD testing by DXA in postmenopausal women less than 65 years old who have clinical risk factors for fracture [46,59–61]. Accordingly, systematic testing of the risk of osteoporosis by DXA at menopause cannot thus be recommended in the general population (grade B). Nevertheless, in some women, knowledge of BMD value may contribute to the management of menopause, especially with MHT. BMD may also be considered an important determinant of the benefit-risk balance of MHT, given the positive associations between high BMD and increased risk of breast cancer or on the other hand, osteoporosis and increase risk of cardiovascular disease.

At the time of menopause, screening for clinical risk factors for fracture is recommended (grade A).

Measurement of bone mineral density by dual X-ray absorptiometry is recommended in early postmenopausal women with one or more clinical risk factors for fracture (grade A).

It could also be proposed on a case-by-case basis when knowledge of the level of bone mineral density is likely to affect a woman's management at menopause, in particular, the individual benefit-risk balance of menopause hormone treatment (expert opinion).

Table 2
Clinical risk factors for cardiovascular disease.

CVD risk level	Risk factors
High to very high	- Coronary or neurovascular disease - Obliterative arterial disease of the lower limbs or abdominal aortic aneurysm - Moderate or severe renal impairment; or microalbuminuria (>30 mg/g) - Diabetes
Moderate ≥2 major risk factors	Standard risk factors - Current smoking or cessation < 3 years - Uncontrolled treated hypertension - Treated and untreated dyslipidemia - 1st degree family history of CVD <55 years in men and <65 years in women - Abdominal obesity waist circumference (≥88 cm) Emerging risk factors or conditions - History of pregnancy hypertension (preeclampsia, HELLP syndrome) or gestational diabetes - Sedentariness - Metabolic syndrome - Systemic autoimmune disease or chronic inflammatory disease - Atrial fibrillation - Subclinical atherosclerosis - Poor cardiovascular adaptation to exercise
Low to moderate	- Treated, uncomplicated hypertension with no other associated risk factors - Optimal lifestyle

(Adapted from the French society for arterial hypertension [65].)

4.2.2. Evaluation of the cardiovascular risk

Major risk factors for CVDs in both sexes are listed in Table 2. In postmenopausal women, the other risk factors include time since menopause and an age over 60 years [LE1], as well as a history of preeclampsia or gestational diabetes [6,62–64] [LE2].

It is recommended that women be asked about symptoms that could point to coronary artery disease (chest pain that is often atypical at rest or with exercise; worsening fatigue or dyspnea with exercise; digestive signs such as epigastralgia or nausea; palpitations at rest or with exercise).

The level of cardiovascular risk is classified as high, intermediate, or low (Table 2).

At menopause, individual assessment of the cardiovascular risk is recommended (grade A).

4.3. Lifestyle and menopause

At menopause, improving lifestyle which includes healthy nutrition [3] and the promotion of physical activity [4] and avoiding risk factors (smoking) could help limit the long-term impact of estrogen deficiency as well as that of aging on the development of several pathologies.

4.3.1. Nutrition

4.3.1.1. Weight gain. Longitudinal studies have shown that weight gain begins well before the onset of menopause and continues thereafter with great interindividual variability [66]. The role of energy expenditure is primordial and excess intake may be both relative and absolute. Only a chronically positive balance likely promotes weight gain, which means that only repeated excesses and/or a chronic quantitative and qualitative dietary imbalance are usually the cause of weight gain [67,68].

The causes of these excesses and/or imbalance include sleep deprivation and, more broadly, disturbances in the rhythm of life, stress and its consequences on eating, physical inactivity and sedentariness, socio-economic conditions, and psychological factors [3].

In overweight postmenopausal women, a moderate reduction in energy intake together with increased physical activity is recommended to limit lean body mass loss (grade C).

4.3.1.2. Cardiometabolic risk. Nutrition plays a role in preventing cardiovascular risk in postmenopausal women in the same way as in the general population.

In the case of excess abdominal weight, priority should be given to moderate weight loss (5 to 10% of body weight) through moderate overall energy reduction (of lipids and carbohydrates), associated with an increase in physical activity [69,70].

4.3.1.3. Osteoporosis risk. Given the hormonal determinism of early postmenopausal bone loss, the preventive impact of nutritional measures is relatively weak, although some deficits are likely to amplify postmenopausal bone loss; its beneficial impact on the risk of fracture later in life could justify the implementation of nutritional measures together with an increase in physical activity [71,72].

Postmenopausal women should have a sufficiently diversified intake of proteins and of calcium, preferably dietary calcium (dairy products), as well as sufficient intake of vitamin D, 80% of which is provided by skin synthesis of vitamin D through the effect of ultraviolet light (grade C).

4.3.2. Physical activity

It must be adapted to the risk profile of each patient, bearing in mind that the benefits of physical activity of moderate intensity will be the greatest in women at risk for CVD [73,74] [LE1]. The benefit is less for the prevention of osteoporosis and fractures, particularly at the beginning of the menopause, given the strong estrogen dependence of bone loss [LE1], or when the risk of fracture is already increased [72,74] [LE2]. Its benefit is clearer later in life, particularly if the risk of fracture is low to moderate [LE2], which justifies promoting physical activity from the beginning of menopause. It is also likely to increase the beneficial effect of MHT on bone density [75] [LE1].

4.3.2.1. Impact on mortality and cardiovascular risk. Regular moderate physical activity significantly decreases overall and cardiovascular mortality in postmenopausal women [LE1]; most studies also show the protective role of low-intensity physical activity and decreased sedentary behavior [73] [LE2].

After menopause, regular low to moderate physical activity and reduction of sedentary lifestyle is recommended to decrease mortality and cardiovascular risk (grade A).

4.3.2.2. Impact on osteoporosis risk. Combined exercises associating weight-bearing exercises with impact and muscle strengthening are the most effective in decreasing postmenopausal bone loss and fracture incidence (around 10%, particularly later in life) [LE2]. This benefit is less than that of preventing overall and cardiovascular mortality and significantly less than any pharmacological intervention for osteoporosis prevention. It also raises the question of long-term adherence [76].

At menopause, in women at risk for osteoporosis, physical activity combining weight-bearing and muscle-strengthening exercises and reducing sedentariness are recommended (grade B).

4.3.2.3. Impact on body composition. All intervention studies in postmenopausal women have shown that regular endurance/aerobic type physical activity without dietary restriction significantly but only moderately decreases total body fat (on average −3%) [LE2]. Only muscle strengthening or combined training (aerobic/endurance + muscle strengthening) with high loads have been shown to be effective in slowing down muscle mass loss (or even increasing muscle mass). However, there is evidence to suggest that even short-term compliance with such intense exercise is low and that many women drop out of training after only a few weeks. In addition, some women may have a physical disability that prevents them from following such a training program [77] [LE1].

4.4. Management of symptomatic postmenopausal women

Climacteric disorders include hot flushes and night sweats, sleep disturbances, mood disorders, arthralgia, and genitourinary syndrome of menopause (GSM). Vasomotor symptoms are very common, affecting approximately 80% of Western postmenopausal women, 25% of whom experience severe disability [20,78–80]. They last on average 5 to 7 years but can persist more than 15 years [20,81].

4.4.1. Menopause hormone treatment (MHT): general principles

Prescription of MHT (specific substance, route of administration, regimen) [7] is underpinned, on one hand, by the benefit-risk balance (see Section 4.6) and the risk of adverse effects (see Section 4.8), and on the other hand by its clinical tolerance, which is a key factor for adherence and continuation.

Because of the possibility of persistent ovarian activity or transient resumption of ovarian activity during the menopausal transition, which would contribute to hyperestrogenism-related side effects such as breast tenderness/pain or abnormal uterine bleeding in a treated woman, it is recommended that MHT not be prescribed until the diagnosis of menopause is confirmed. On the other hand, given the increase in the cardiovascular risk associated with MHT when it is started 10 years or more after menopause (see Section 4.6.2), it is recommended that MHT be used within the first 10 years after menopause.

In women with a uterus, MHT requires the combination of estrogens with progesterone/dydrogesterone or a synthetic progestin, the duration of which partly determines the benefit-risk balance (see Section 4.6), as does the occurrence of withdrawal bleeding. In France, only estradiol and estradiol valerate are available estrogen compounds.

In hysterectomized women, it is not necessary to combine a progestin with estrogen. In some cases, particularly in women with a history of endometriosis, the combination of progestin and estrogen may be preferred even in the case of hysterectomy [82].

Given the risk of hyperestrogenism related to the persistence (or transient resumption) of ovarian activity, it is recommended that menopause hormone treatment be started only after clinical confirmation of menopause (grade B).

It is recommended that menopause hormone treatment not be started more than 10 years after the beginning of menopause (grade B).

17Beta-estradiol or estradiol valerate with micronized progesterone or dydrogesterone at least 12 days per month is recommended as menopause hormone treatment (grade B); in women who have had hysterectomies, estradiol or estradiol valerate alone without progesterone or progestin is recommended (grade B).

The choice between sequential or combined regimens should consider the patient's desire to have or not have withdrawal bleeding. The combined regimen is the most commonly used because of its endometrial protection benefit [LE1] and most patients' desire to avoid withdrawal bleeding [LE3] [83–91].

A continuous combined regimen should be preferred if hot flushes recur upon discontinuation of treatment or in the case of symptoms related to hormonal variations (migraines) or difficulties in complying with a sequential regimen (expert opinion).

4.4.2. Effectiveness of MHT on vasomotor symptoms (VMS)

All molecules with estrogenic activity are effective in reducing the frequency and intensity of VMS, regardless of the route of administration (whether cutaneous or oral) [LE1]. The efficacy is dose-dependent as in most tissues with a hierarchy of estrogen sensitivity; breast, endometrium, and bone are the most estrogen-dependent tissues [92,93] [LE1].

All doses of estrogen, including low doses, and all types of treatment regimens (combined or sequential, continuous or discontinuous) are effective in reducing the frequency and intensity of VMS [NP1].

In women with moderate to severe vasomotor symptoms and in the absence of contraindications, it is recommended to prescribe menopause hormone therapy as first-line treatment (grade A).

4.4.3. Nonhormonal alternatives to MHT

Nonhormonal alternatives have been evaluated mainly in the management of VMS [8]. Their efficacy (when documented) is lower than that of MHT; in randomized trials, the difference with placebo is small (on the order of 10 to 40% depending on the substance and dose). There is a placebo effect with a reduction in the frequency of VMS averaging 25 to 58% [94–96] (LE1).

4.4.3.1. Pharmacological interventions. Apart from beta-alanine, none of the interventions listed below have a marketing authorization in France for treatment of VMS. There have been no head-to-head trials evaluating the effectiveness against VMS of the different nonhormonal alternatives. Their use is generally limited by their adverse effects.

- Beta-alanine: data are insufficient to evaluate its efficacy in the treatment of VMS and therefore it cannot be recommended [97].
- Among selective serotonin reuptake inhibitors (SSRIs), paroxetine, citalopram, and escitalopram are effective in reducing the frequency and severity of VMS [LE2]. Studies of fluoxetine and sertraline are inconclusive [98–100] [LE2]. It should be noted that fluoxetine, paroxetine, and to a lesser degree, sertraline, citalopram, and escitalopram are competitive inhibitors of CYP 450 2D6, which is involved in tamoxifen metabolism [101,102].
- Among serotonin norepinephrine reuptake inhibitors (SNRIs), venlafaxine at low doses is effective in decreasing the frequency and severity of VMS [103] [LE1]. Desvenlafaxine, the active metabolite of venlafaxine, is effective in decreasing the frequency and severity of hot flushes [104] [LE1].
- Gabapentin [105], pregabalin [106], oxybutinin [107,108] and clonidine [109,110] are effective in decreasing the frequency and severity of VMS [LE2].
- Homeopathy (tested mainly in women with a history of breast cancer) [111], vitamin E [112,113], and omega 3 [114] have not been shown to be effective in managing VMS.

4.4.3.1.1. Phytoestrogens. Phytoestrogens are plant compounds with estrogen-like properties. They have 2 major classes: isoflavones and lignans. Though much research has been devoted to determining whether phytoestrogens are well tolerated and effective in the treatment of VMS, study results have been inconclusive, and no consensus has been reached about their utility. Multiple factors may be responsible for the conflicting data, including variations in studies' inclusion criteria, types and dosages of phytoestrogens, a lack of appropriate study controls, control for the consumption of phytoestrogens from other sources, and differences in the outcome measures used. At high doses, genistein was shown to significantly reduce the frequency of hot flushes [115,116] [LE2].

Given their mechanism of action through the estrogen receptor and even though this can be discussed, the French Food Safety Agency (AFSSA) has formally recommended that phytoestrogens not be used in women with estrogen-dependent disease [117].

Placebo-controlled studies show no significant difference in the frequency and severity of VMS in women taking red clover [116], black cohosh (or *Cimicifuga racemosa*) [118], or Chinese herbs [119] [LE2].

> Use of phytoestrogens cannot to be recommended for the management of vasomotor symptoms although benefits derived from concentrates of genistein should be possible (grade B).

4.4.3.1.2. Other compounds. Only one small randomized trial has evaluated the efficacy of purified pollen extracts combining pollen, pistil extracts from a plant of the Poaceae family, and vitamin E. It showed significant decrease in VMS compared with placebo [120] [LE3].

Neither primrose oil [121] nor ginseng appears to be effective in reducing the frequency of VMS or improving the quality of life score in postmenopausal women [122] [LE2].

4.4.3.2. Nonpharmacological interventions. Evaluation of the effectiveness of acupuncture on VMS is made difficult by the lack of a control group. Some uncontrolled trials have reported that it is effective in reducing the frequency and severity of VMS [123,124] (LE3).

Cognitive-behavioral therapy (CBT) [125,126] [LE2], hypnosis [116–118] [LE2] and yoga [119] [LE3] appear to reduce the frequency and severity of VMS compared to placebo. Mindfulness therapies also appear to relieve the severity of hot flushes, but affect their frequency less [127] [LE2].

Neither physical exercise nor relaxation had any significant effect on the frequency of VMS [128–130] [LE2].

The small number of published studies on aromatherapy/essential oils and reflexology does not justify any conclusion about their efficacy in decreasing VMS [LE3].

> Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, oxybutynin, clonidine, genistein, cognitive-behavioral therapy (CBT), hypnosis and yoga have been shown to have some efficacy and can be discussed for the management of menopausal vasomotor symptoms (grade B).

In women with postmenopausal breast cancer and VMS

> When tamoxifen is used, it is recommended that fluoxetine, paroxetine, and sertraline not be used to treat vasomotor symptoms due to their interaction with cytochrome P450 2D6 (grade B).
>
> In women with postmenopausal breast cancer, it is recommended that phytoestrogens not be used to treat vasomotor symptoms (grade A).

4.5. *Management of genitourinary syndrome of menopause [10]*

The term genitourinary syndrome of menopause (GSM) has replaced the term vulvovaginal atrophy [131]. Its prevalence varies according to studies from 27% to 70% [132–134].

GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder [131,135,136]. The syndrome may include but is not limited to:

- vulvovaginal symptoms: dryness, pain, burning, irritation, pruritus;
- sexual symptoms: essentially dyspareunia of intromission, due to lack of lubrication and sometimes orifice stenosis.
- urinary symptoms, which may include polyuria, urinary urgency, or recurrent urinary infections (urinary burning).

The clinical symptoms of GSM impair women's quality of life and worsen with age and duration of menopause, but decrease with the frequency of sexual intercourse [137]. Complementary examinations (pH, mucosal biopsy, microbiota assessment, etc.) are not useful in the diagnosis of GSM (LE2).

> The genitourinary syndrome of menopause is a clinical diagnosis. Women may present with some or all of the signs and symptoms which is sufficient to support the genitourinary syndrome of menopause. It is thus recommended that no additional tests be performed to confirm this diagnosis (grade B).

Maintaining regular sexual activity provided that it remains painless increases vaginal vascularization, provides prostaglandins and fatty acids, and helps maintain vaginal flexibility (expert opinion).

4.5.1. Local nonhormonal and nonphysical treatments for GSM

Moisturizers and/or lubricants can be used in all women with GSM. Vaginal hyaluronic acid has been associated with significant improvement in GSM symptoms [LE3], but remains less effective than vaginal estrogen therapy [135] [LE3].

4.5.2. Hormonal treatments

Systemic MHT, regardless of its route of administration and type of estrogen, and including tibolone, has a partial and inconsistent effect on GSM [LE2]. Low-dose vaginal estrogens are significantly superior to systemic MHT, particularly for urinary symptoms [138,139] [LE1]. All low-dose vaginal estrogens, including estradiol and estriol, have been shown to improve GSM symptoms [140] [LE2].

The combination of estriol and lactobacilli appears to have synergistic effects [141] [LE2]. Pharmacological data are not available for promestriene. Prasterone (DHEA) is effective against GSM symptoms [142] [LE2]. Herbal therapy has not been shown to be effective in managing this syndrome [143] [LE3].

Low-dose vaginal estrogens for durations of treatment of less than 2 years have not shown any effect on the endometrium [144] [LE1]. Current data do not show an increased risk of breast cancer in women without a history of breast cancer [144,145], but the safety of using this type of local treatment in women with a history of breast cancer is uncertain [146] [LE2].

There is no predefined duration of treatment. Discontinuation of treatment is associated with a rapid recurrence of GSM symptoms [LE2].

4.5.3. Physical methods for the treatment of GUSM [11]

These are of more recent use, particularly lasers. Numerous studies have evaluated the efficacy of lasers (CO2 and Erb-Yag) on GSM symptoms. They are effective in reducing these symptoms compared with placebo [147–149] [LE2]. However, there are still a lack of data confirming long term safety and efficacy.

In cases of vulvar or vaginal stenosis, the use of vaginal dilators of progressively increasing size with lubricants is possible.

> For the management of genitourinary syndrome of menopause, vaginal treatment is recommended in first line (grade A). Lubricants and moisturizers should be recommended as first line treatment with low-dose vaginal hormonal treatment in second line depending on the clinical course (expert opinion).
>
> Pending confirmation of long-term safety and efficacy, lasers should not still be used as first-line treatment for the management of symptoms of genitourinary syndrome of menopause (grade C).

4.6. The benefit-risk balance of menopausal hormone treatment

The initial prescription of MHT and its renewal must be based on a prior assessment of its benefit-risk balance and a regular reassessment, particularly when the prescription is renewed.

4.6.1. Bone beneficial effects [5]

Estrogens are effective in preventing postmenopausal bone loss and microarchitectural degradations. After 12 to 18 months of treatment, bone remodeling stabilizes at a premenopausal level and BMD is maintained as long as estrogen treatment is continued [150,151] [LE1].

Estrogens have a dose-effect relation [LE1], but with great interindividual variability in the densitometric response to MHT [152–154]. Neither the route of estrogen administration [155,156] nor the type of treatment regimen (with or without progesterone or a synthetic progestin) [157,158] influences the bone response to MHT [LE1].

MHT significantly decreases the risk of fracture at all bone sites in postmenopausal women, including women at low risk of fracture [159–163] [LE1].

Given the fact that to date, osteoporosis is a chronic disease that cannot be cured, the choice of the 1st treatment option should be made as part of a comprehensive long-term strategy. MHT represents a genuine preventive treatment option in early postmenopausal women found to be at low to moderate risk of fragility fracture over the next 10 years but who may have a much greater lifetime risk. In the absence of contraindication, MHT is a valuable option for the maintenance of bone health in those women where specific bone active medications are not warranted. It must be considered as a true primary preventive therapy to maintain bone mass and quality as well as decrease the risk of fracture at an age when this risk is not yet as high as later in life [164,165].

> In women at low to moderate risk of fracture, it is recommended that menopause hormone treatment be proposed as first-line treatment to prevent osteoporosis (grade A).
>
> This decision should consider other clinical risk factors for fracture and the individualized benefit-risk balance of menopause hormone treatment (grade C).
>
> In this situation, it is not possible to recommend a standard estrogen dose (Grade B).

4.6.2. Cardiovascular impact [6]

Although the incidence of ischemic arterial diseases (including myocardial infarction (MI) and ischemic stroke) is lower than that of men before menopause, its incidence quickly rises after menopause to reach that of men resulting in the leading cause of death among postmenopausal women in France.

Randomized trials in postmenopausal women with a history of one or more coronary events (the HERS study in secondary prevention) and in healthy postmenopausal women (primary prevention) [166], in particular the Women's Health Initiative (WHI) [167], have largely called into question the expected benefit of MHT on the CVD risk [168]. It should be noted that almost all these trials have evaluated the combination of oral conjugated equine estrogens (CEE) with or without medroxyprogesterone acetate (MPA).

4.6.2.1. Myocardial infarction (MI). Overall, no increase in the risk of MI with the use of CEE associated with MPA has been observed for any duration of use [168] [LE1]. Nevertheless, the risk of a first coronary event has been reported to rise the first year of use [166,167] [LE2].

The risk of MI was not increased [LE1] and indeed appeared significantly reduced when MHT is used within the first 10 years after menopause [LE2] or before the age of 60 years [LE3]. It is therefore important to consider the timing hypothesis in the evaluation of the benefit-risk balance of MHT.

In older women who reached menopause more than 15 years earlier, the risk of MI rises with the initiation of MHT [168,169] [LE1].

The risk of MI does not differ by type of estrogen [LE2], route of estrogen administration (LE3), or type of progestin [170] [LE3].

No randomized trial has analyzed the impact of progesterone or progestins given alone.

> Given the current state of knowledge, menopause hormone treatment is not recommended for the prevention of myocardial infarction (grade B).

4.6.2.2. Ischemic stroke. The risk of ischemic stroke rises significantly with oral estrogens, whether taken alone or in combination with a progestin [LE1]; risk increases with the estrogen dose [167,171] [LE2]. An excess risk of ischemic stroke is associated with MHT regardless of age and years since menopause [LE1]. The absolute risk of ischemic stroke nonetheless remains low in early postmenopausal women [LE1].

Transdermal estrogen therapy in low or moderate doses combined with oral natural progesterone does not seem to be associated with the risk of ischemic stroke [172,173] [LE3].

To limit the risk of ischemic stroke associated with oral menopause hormone therapy, it is recommended that a combination of transdermal estradiol and oral progesterone be preferred (grade B).

4.6.2.3. Venous thromboembolic risk [11]. Venous thromboembolic disease (VTE) includes deep vein thrombosis and pulmonary embolism. The incidence of VTE increases with age [174].

Oral estrogens (CEE and estradiol) multiply the risk of VTE in the general population by a factor of 1.7 compared with placebo [175] [LE1]. The risk appears to be greater with CEE than with estradiol [LE2] and to be modulated by the type of progestin [176] [LE2].

Transdermal estradiol does not appear to increase the risk of VTE in the general population [LE2]. This risk appears to be neutral with the combination of transdermal estradiol and oral micronized progesterone, dydrogesterone, chlormadinone acetate, medrogestone, cyproterone acetate, and medroxyprogesterone acetate, but increases with nomegestrol acetate and promegestone in the general population [171,175–178] [LE3].

In women with a personal history of VTE (deep vein thrombosis or pulmonary embolism), oral estrogen therapy increases the risk of VTE recurrence [179] [LE1]. Transdermal estradiol does not further increase the risk of VTE recurrence [180] [LE2], but women with a history of VTE have an increased risk of further VTE given their history.

Obesity increases the risk of VTE. The use of oral estrogens in obese women is associated with an increased risk of VTE [181–183] [LE1]. Transdermal estradiol does not appear to be associated with an increased risk of VTE regardless of BMI [176,184] [LE2].

In women with a factor V Leiden mutation or a G20210A prothrombin mutation, oral estrogens increase the risk of VTE [185] [LE1]. Transdermal estradiol does not appear to increase this risk [186] [LE3]. Current published data do not permit any definitive conclusion about the MHT-associated risk of VTE in women with a family history of VTE.

To limit the venous thromboembolic risk attributable to oral estrogens, it is recommended that transdermal estradiol be preferred (grade B).

In cases of a personal history of venous thromboembolic disease, obesity, or biological thrombophilia (factor V Leiden mutation, prothrombin G20210A mutation), it is recommended that oral estrogens not be used (grade A).

In these situations, the use of transdermal estradiol may be proposed in combination with oral progesterone according to the individualized benefit-risk balance of menopause hormone therapy (grade C).

4.6.3. Gynecological cancers [12]

4.6.3.1. Breast cancer. The lifetime risk of breast cancer for a woman aged 50 years is estimated at 9%. In France, the incidence of breast cancer increased from 2010 to 2018 (+0.6% per year on average), after having stabilized between 2003 and 2010, particularly in women aged 55 to 69 years. In contrast, mortality has fallen steadily between 1990 and 2018 (−1.3% per year) [187].

The meta-analysis of the Collaborative Group on Hormonal Factors in Breast Cancer published in 1997 [188] had quantified the absolute excess risk of breast cancer associated with MHT as about 2 additional cases per 1000 women treated for 5 years and 6 additional cases per 1000 women treated for 10 years.

The WHI trial was the first randomized trial to confirm the increased risk of breast cancer with the combination of CEE and MPA after 5 years of treatment [LE1] [189]. On the other hand, CEE alone was associated with a decreased risk of breast cancer after almost 7 years of treatment [LE1] [190]. The relative risk of breast cancer attributable to CEE and MPA was 1.26 (IC 95% 1.01–1.59) and that of CEE alone was 0.77 (IC 95% 0.59–1.01).

European and French observational studies (E3N, EPIC, CECILE, Finnish and British studies) show that the risk of breast cancer attributable to MHT is higher with estrogen-progestogen combinations than with estrogens alone [LE1] and depends on the specific progestins used [145,191–194] [LE2]. Combinations of estradiol with micronized progesterone or dydrogesterone do not significantly increase the risk of breast cancer for treatment durations less than 5 years [180–184] [LE2]. However, for longer durations, there is a slight increase in the relative risk of breast cancer [LE3].

There are no data about the excess risk of breast cancer and the dose of estrogens, nor does the risk appear to differ by the route of their administration—oral or transdermal [LE2]. Combined regimens are associated with a higher risk of breast cancer than sequential regimens [83–85] [LE2].

In most studies, the excess risk of breast cancer disappears when MHT is stopped [LE1] after 5 to 10 years, depending in part on the duration of prior use [195–197] [LE2].

Breast cancer mortality is not higher in MHT-treated women in either randomized trials or observational studies, regardless of the MHT type [83,195,198] [LE1].

To limit the excess risk of breast cancer associated with menopause hormone therapy, it is recommended in France that estradiol be combined with progesterone or dydrogesterone (grade B).

In women who have had a hysterectomy, there is no breast benefit to combining progesterone or a progestin with estradiol (grade A).

4.6.3.2. Endometrial cancer. The risk of endometrial hyperplasia and cancer increases with the duration of estrogen therapy used alone [199] [LE1]. This increased risk is no longer observed when estrogens are combined with a progestin [LE1] and is reduced for continuous combined regimens for treatment durations of less than 10 years [167,200] [LE1].

For sequential regimens, the short term risk of endometrial cancer does not increase as long as the progestin is taken for a minimum of 12 days per month [201,202] [LE2]. For longer durations of treatment, some data suggest a slight increase in the risk of endometrial cancer associated with sequential regimens compared to continuous combined regimens [87,88].

In combination of estrogen + progestogen, the type of progestin could influence endometrial risk, with synthetic progestins having a greater preventive effect on estrogen-induced endometrial risk than progesterone or dydrogesterone [87,203] [LE3].

A combination of progestin with estrogens is recommended for the prevention of estrogen-induced endometrial cancer (grade A); for optimal prevention, the recommended duration of progestin use should be at least 12 days per month for sequential regimens (grade B) or even better, a continuous combined regimen (grade A).

4.6.3.3. Ovarian cancer. Most observational studies report a higher risk of serous cancers associated with MHT (LE2), and the risk increases with the treatment's duration [204–206] [LE2].

A meta-analysis of retrospective and prospective observational studies and randomized trials published in 2015 reported an increase by a factor around 1.5 in the relative risk of ovarian cancer associated with MHT, both with estrogen alone and estrogen-progestin combinations, and regardless of treatment duration [LE2]. The attributable excess risk was estimated as 1 additional case per 8000 treated women [LE2]. The excess risk of cancer mainly concerns serous and endometrioid cancers but not mucinous or clear cell cancers [207] [LE1].

In the WHI randomized trial, the combination of CEE and MPA was not associated with an increased risk of ovarian cancer for a treatment duration of 5 years [208].

4.6.4. Digestive cancers [12]

4.6.4.1. Colorectal cancer. The oldest meta-analyses of observational studies reported a reduced risk of colorectal cancer associated with MHT [209] [LE2]. Similarly, cohort studies in northern Europe, using mainly estradiol, found a significant reduction in risk [210,211] (RR = 0.8 to 0.9). The benefit was greater for transdermal than for oral estradiol (LE2) and did not seem to be influenced by the addition or type of progestin [LE3].

In the WHI randomized trial, the combination of CEE and MPA was associated with a decreased risk of colon cancer [208] [LE2].

4.6.4.2. Pancreatic cancer. Two large cohort studies have reported a decreased risk of pancreatic cancer in MHT-treated women [212,213] [LE2]. The benefit increases with the duration of MHT use [LE3] and appears to be greater with estrogens alone than with estrogen-progestin combinations [LE3].

4.6.4.3. Esophageal and gastric cancer. All observational studies report a reduced risk of esophageal cancer in women taking estrogen alone or combined estrogen-progestin therapy, regardless of histological type (squamous cell carcinoma, adenocarcinoma) [214,215] [LE2].

4.6.4.4. Liver cancer. Only a few studies have evaluated the relation between MHT and liver cancer. A single large cohort study from northern Europe reports a nearly 20% decrease in the risk of liver cancer in women using MHT [216] [LE2]. This decreased risk was reported both with estradiol alone and in combination with any type of progestin. Combined regimens were associated with a greater decrease in risk than sequential regimens [LE3].

4.6.5. Lung cancer

The relationships between MHT and lung cancer are still discussed and remain inconclusive [217]. In a post-hoc analysis of the WHI observational study, the hazard ratio for lung cancer in MHT users was 1.71 (95% CI 1.16–2.52) after 8 years of follow up but became non-significant when the follow up period was extended to 14 years [218]. On the other hand, a protective role of MHT was reported in smokers in a recent cohort study [219].

Menopause hormone treatment appears to be associated with a slight increased risk of breast [LE1] and serous and endometrioid ovarian cancers [LE2] and with a slight decreased risk of colorectal [LE2], pancreatic [LE2], esophageal, gastric [LE2] and liver [LE3] cancers. It is recommended that these findings be considered in the assessment of the individualized benefit-risk balance and in the shared treatment decision (grade B).

4.6.6. Cognitive impairment and dementia [14]

There is an epidemiological link between the risk of dementia and duration of estrogen exposure [220]. Oophorectomy before menopause significantly increases the risk of dementia and a threefold increase in the risk of Alzheimer's disease (AD) was reported in women who had experienced oophorectomy before the age of 38–40 years [221,222]. Estrogen replacement therapy, at least until the age 50, appears to limit or even eliminate this excess risk [221] [LE2].

Knowledge of the relation between MHT and cognitive functions is limited by the paucity of randomized controlled trials available and the lack of comparative studies between different estrogens and progestins.

4.6.6.1. MHT and risk of Alzheimer disease. In women with AD, MHT has been associated with worsened cognitive impairment [223,224] [LE1].

It is recommended that menopause hormone treatment not be prescribed for women with Alzheimer disease (grade A).

Observational studies performed before the WHI reported an association between MHT and a 29–44% reduction in AD risk [225,226] [LE2]. As in their assessment of cardiovascular risk, the limitation of these studies is the so-called “good health” bias, as treated women are likely to be in better health, particularly cardiovascular health, and have a higher level of education; all these factors being recognized as protectors against AD.

An ancillary study of the WHI trial in women over 65 years of age reported an increase in cognitive decline associated with both CEE + MPA and CEE alone [227,228] [LE1]. Several observational studies suggest that when MHT is started early in menopause, there is no deleterious effect on cognitive functions [LE2]; it may even limit the risk of AD [LE3]. On the other hand, when MHT is started long after menopause began, the risk is aggravated [229–231] [LE2].

It is recommended that menopause hormone treatment not be started for the sole purpose of preventing Alzheimer disease (grade C).

4.6.6.2. MHT and cognitive impairment. Randomized trials conducted among young early postmenopausal women, or even later on, regardless of how long they had been menopausal, showed mostly neither any benefit nor any deterioration of cognitive functions associated with MHT (CEE or estradiol combined with progesterone) [232,233] [LE1].

It is recommended that menopause hormone treatment not be started for the sole purpose of preventing cognitive impairment (grade B).

4.6.7. Mortality [13]

The WHI trial showed a reduction in mortality associated with MHT (CEE + MPA and CEE alone) in women aged 50–59 years [LE2].

Mortality did not differ significantly in the other age groups (60–69 and 70–79) [234] [LE2].

All meta-analyses of observational studies and randomized trials have confirmed a decrease in overall mortality associated with MHT for women younger than 60 years [LE2]. This reduction appears to be related to lower cardiovascular mortality when MHT is initiated within the first 10 years after menopause [235] [LE2] which again, emphasizes the importance of the timing hypothesis.

4.7. Practical management of MHT

The practical management of MHT depends on the evaluation of its effectiveness on its two main indications (climacteric syndrome and prevention of osteoporosis) as well as the duration of treatment.

4.7.1. Evaluating the effectiveness of MHT

4.7.1.1. On vasomotor symptoms. In randomized trials, MHT significantly decreases the frequency and intensity of VMS within 2 to 6 weeks by 75% and 87%, respectively [236] [LE1].

> It is recommended that the efficacy of menopause hormone treatment on vasomotor symptoms be evaluated clinically (grade B).

The failure of VMS to decrease with MHT should lead to a re-evaluation of the treatment modalities, both in terms of compliance and adaptation of estrogen dosages.

In case of persistent failure, this may question a lack of absorption of transdermal estrogens or raises the issue of non-menopausal causes of hot flushes (expert opinion) [14].

Such causes should be particularly investigated when hot flushes appear or reappear far from the onset of menopause, when there are changes in the usual VMS or when they are associated with other functional signs, such as headaches, palpitations, malaise, diarrhea, or hypertensive episodes.

4.7.1.2. In the prevention of postmenopausal osteoporosis [5]. Given the multifactorial and random nature of osteoporotic fractures over time, the absence of a fracture at a given time cannot be considered proof of MHT's effectiveness.

4.7.1.2.1. Clinical markers of MHT effectiveness on bone. Neither the improvement of climacteric symptoms nor the presence of withdrawal bleeding (for sequential regimens) is correlated with the bone effectiveness of MHT [237,238] [LE2].

4.7.1.2.2. Plasma estradiol assays. Studies that have assessed the predictive value of plasma estradiol are too methodologically insufficient to be conclusive [239,240].

> It is not recommended that estradiol levels be used to monitor the bone efficacy of menopause hormone treatment (grade B).

4.7.1.2.3. Biochemical markers of bone remodeling. The most relevant marker for bone formation is the N-terminal propeptide of type I collagen (P1NP). For bone resorption, both the C-terminal (CTX) and N-terminal (NTX) telopeptides are relevant [241] [LE1].

Several clinical studies have shown a significant decrease in both bone resorption and formation markers from the beginning of MHT. Their decrease after 3 to 6 months of treatment has been significantly correlated with BMD changes measured at 1 or 2 years [242–244] [LE2].

There is no definition of a bone response to MHT based on bone remodeling markers. However, these assays may be useful for the management of the bone efficacy of MHT (expert opinion).

4.7.1.2.4. Densitometric follow-up. The two reference bone sites for BMD measurements are the lumbar spine and the hip (femoral neck or total hip); BMD measured at the radius (proximal or ultra-distal sites) is not recommended for monitoring bone changes in early postmenopausal women [42] [LE1].

Changes between two BMD values should be expressed in g/cm^2 (not as a percentage); it requires direct comparison of BMD values (not T-scores or Z-scores) [245].

Because of the expected variation in BMD, a delay of at least 2 years between repeated BMD measurements is necessary to identify the majority of non-responders to MHT [246] [LE1].

The parameter used as a criterion for MHT bone effectiveness is thus the absence of bone loss during individual BMD follow-up [247] [LE1].

> When a woman is given menopause hormone treatment in order to prevent osteoporosis, lumbar and femoral BMD measurements should be repeated (on the same DXA device) after 2 years of treatment (expert opinion); the absence of bone loss at 2 years being the goal of treatment [LE1].
>
> Evaluation of the bone remodeling markers (especially, plasma C-terminal telopeptides) may be suggested (expert opinion) when there are difficulties in interpreting the densitometric variation between two measurements 2 years apart or when an earlier confirmation of the bone impact of menopause hormone treatment may be necessary (women at high risk of fracture, doubts about adherence to the treatment, or possible insufficient dosages).

4.7.2. Duration of MHT

There is currently no consensus on either the minimum or maximum duration of MHT. The French health authorities (HAS) recommend the shortest possible duration of MHT but for as long as climacteric symptoms persist, with regular reassessment of the benefit-risk balance of MHT to determine whether it should be continued or stopped.

For prevention of osteoporosis, it has been shown that a treatment duration of at least 5 years is associated with a significant reduction of fracture risk [161] [LE1]. Moreover, all studies show that the anti-fracture benefit is maintained for the duration of treatment [162,163] [LE1]. MHT should be considered as the first option of a long-term strategy of osteoporosis prevention in early postmenopausal women with a low-to-moderate risk of fracture, for whom specific bone-active medications are not warranted. Clearly the approach chosen should be tailored to each woman's benefit-risk balance; subsequent reassessment is thereafter recommended, with the possibility of switching to another osteoporosis treatment if the balance is not considered as favorable as at the beginning of the menopause for women still at high risk of fracture (see below, section on MHT discontinuation) [248].

> The minimum effective estrogen dose may vary over time [LE2] and it is necessary to re-evaluate annually not only the dose but also the appropriateness of the prescription (expert opinion).

It is the risk of breast cancer, which increases with the duration of MHT [196], that requires reassessment of the individual benefit-risk balance of the treatment, together with its underlying indications

(climacteric symptoms and/or prevention of fracture risk) [8].

The modalities of discontinuation (immediate or gradual by decreasing estrogen doses) do not appear to determine the resumption of VMS [249,250] [LE2].

Current data do not allow the recommendation of an optimal duration of menopause hormone treatment, which must take into account its initial indication and its benefit-risk balance (expert opinion).

It is recommended that each woman be provided with complete information and that the benefit-risk balance of menopause hormone treatment be reassessed annually, considering the woman's individual characteristics and the type of hormone treatment she has been taking (grade A).

The available data do not support a recommendation for tapering off menopausal hormone therapy versus immediate discontinuation (grade B).

4.7.2.1. Discontinuation of MHT and climacteric symptoms [8]. Most studies have reported the reappearance of climacteric symptoms after MHT discontinuation [LE1], as well as a deterioration in quality of life [251,252] [LE3].

For women who have no contraindication to MHT, it is possible to resume it at the minimum effective dose to correct climacteric symptoms after full and complete information about each woman's individual benefit-risk balance (expert opinion).

4.7.2.2. Discontinuation of MHT and fracture risk [5]. All controlled longitudinal studies have reported that MHT discontinuation is associated with resumption of bone loss [253–255] [LE1] at a rate similar to that observed at the beginning of menopause [LE2]. After an average 5 years of cessation of MHT, BMD usually does not differ between former users and non-users [256] [LE2].

There is no rebound phenomenon after stopping MHT [257], and the subsequent risk of fracture does not exceed the physiological age-related risk [LE1]. The risk of fracture in former MHT users becomes similar to that of never-treated women within 1 to 5 years of treatment cessation in observational studies, depending on the previous duration of MHT [LE2]; in the WHI trial, risks became similar after 5 years [160,258] [LE1].

The subsequent fracture risk depends on the T-score value measured at the end of MHT as well as on age and other risk factors for fracture [LE2]. In women at risk, treatment with a bisphosphonate (alendronate) as a replacement for MHT can block the resumption of bone loss associated with the cessation of treatment [LE2].

When menopause hormone treatment is prescribed for the prevention of osteoporosis in a woman at risk of fracture, it is recommended that bone mineral density be measured by DXA upon discontinuation of therapy to enable further appropriate management of fracture risk (expert opinion).

4.7.2.3. Discontinuation of MHT and cardiovascular risk. Data on the evolution of cardiovascular risk after cessation of MHT are very limited [259,260] [LE3].

After discontinuation of menopausal hormone treatment, medical follow-up of postmenopausal women should continue, including screening and active management of vascular and metabolic risk factors (expert opinion).

4.7.2.4. Discontinuation of MHT and cancer risk. Among women stopping MHT, the incidence of breast cancer would fall within 2 years to that of women never treated, according to the WHI trial [195] [LE1], and within 10 years, according to the most recent meta-analysis [196] [LE2].

The excess risk of ovarian cancer disappears 5 years after discontinuing MHT in women treated for less than 5 years [LE2], but appears to persist beyond 5 years among women who took it longer than 5 years [207] [LE3].

No current literature has considered the effect of stopping MHT on the incidence of other cancers.

4.8. Management of gynecological side effects of MHT

4.8.1. Abnormal uterine bleeding [16]

Abnormal uterine bleeding in a woman taking MHT (FIGO 2011) is defined as that which occurs before the progestin discontinuation period in sequential regimens. Inversely, the incidence of amenorrhea when taking combined MHT increases significantly after 6 months of treatment [261–263] (LE2).

Abnormal bleeding is uncommon during MHT (less than 15%) and is observed more often at the beginning of MHT; thereafter, it is linked to poor treatment adherence. It should be investigated to rule out organic causes, endometrial cancer in particular. The main functional causes of bleeding in MHT-treated woman are resumption of ovarian activity, poor adherence, and trophic disorders of the endometrium [LE3]. They depend on the type of MHT used [264] [LE2].

In woman receiving MHT with abnormal uterine bleeding, measurement of endometrial thickness by pelvic ultrasound is useful in screening for endometrial cancer [LE1], with a thickness of 4 mm the upper limit of normal for combined MHT [265–267] [LE1].

For the diagnosis of intracavitary uterine lesions, the sensitivity and specificity of hysteroscopy are superior to those of both hysterosonography and endovaginal pelvic ultrasound [268,269] [LE1].

If abnormal uterine bleeding occurs in a postmenopausal woman taking menopause hormone treatment, it is recommended to rule out any organic cause (grade A); pelvic ultrasound should be performed (grade A) at the end of the progestogen sequence in sequential regimens, or any time in combined treatment (expert opinion); in case of a single episode of abnormal uterine bleeding and if endometrial thickness is less than or equal to 4 mm, no further uterine exploration is recommended (expert opinion).

In case of recurrent abnormal uterine bleeding or when the endometrial thickness exceeds 4 mm in a treated postmenopausal woman, additional uterine explorations (hysteroscopy and histology) are recommended (grade B).

4.8.2. Breast pain [16]

In postmenopausal women, the frequency of breast pain decreases significantly less with aging in women taking MHT [LE1] than in

untreated women. It increases significantly in women treated with CEE and progestin [LE1] but not in early postmenopausal women taking low doses of estradiol in combination with micronized progesterone [270–273] [LE2].

Given the relationship between breast pain and the risk of breast cancer, prescription for MHT should be accompanied by information about breast pain (grade B).

Women reporting moderate to severe breast pain/tenderness, either before or related to MHT use, have a significantly higher risk of breast cancer than women with no breast pain [270,274] [LE2].

Breast imaging is not contributory for the exploration of diffuse breast pain that is not associated with clinical abnormalities [275].

When women report bilateral breast pain (without any clinical abnormality), the usual indications for breast cancer screening and its modalities should not be changed (expert opinion).

In MHT-treated women, breast pain most often indicates increased breast sensitivity to estrogen. At the beginning of treatment, it may be related to the resumption of ovarian activity.

In case of bilateral breast pain in early postmenopausal women, the modalities of MHT should be reviewed with the possible need to reduce estrogen dosages or even to stop treatment (expert opinion).

4.8.3. Clinical or radiological breast tumor [17]

Discontinuation of menopausal hormone treatment is recommended for the diagnostic management of a breast mass (grade A).

Mammography and breast ultrasound are recommended for the exploration of a clinical breast mass [276] (grade B).

Management of breast cysts is not modified by the use of MHT and has been described in the CNGOF guidelines [277].

Nothing in the international literature contraindicates the continuation of MHT after surgical removal of benign breast lesions [278,279].

Definitive cessation of menopausal hormone treatment is recommended for malignant breast lesions, regardless of hormone receptor status and tumor type (in situ or invasive) (grade A).

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