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Menopausal hormone therapy in questions and answers – a manual for physicians of various specialties

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Abstract

This manual has been prepared by the Expert Team of the Polish Menopause and Andropause Society for physicians representing various medical specialties who see patients with menopausal symptoms in their daily practice. In order to make the manual as practical as possible, the current state of knowledge on menopausal hormone therapy (MHT) is presented in the form of questions and answers. They address issues which are essential for initiating and managing MHT based on the most up-to-date treatment algorithms and, at the same time, in line with the old maxim "*primum non nocere*".

Key words: menopause, menopausal hormone therapy.

Introduction

The manual has been prepared by the Expert Team of the Polish Menopause and Andropause Society (PTMA) for physicians representing various medical specialties who see patients with menopausal symptoms in their daily practice. The manual is based on the most up-to-date recommendations and consensus statements of different expert groups representing a number of highly reputable institutions including National Institute for Health and Care Excellence (NICE), North American Menopause Society (NAMS), International Menopause Society (IMS), American College of Endocrinology (ACE), Polish Society of Gynecologists and Obstetricians (PTGiP), Polish Cardiac Society (PTK) or PTMA. In order to make the manual as practical as possible, we have decided to present the current state of knowledge on menopausal hormone therapy (MHT) in the form of questions and answers. They address issues which are essential for initiating and managing MHT based on the most up-to-date treatment algorithms and, at the same time, in line with the old maxim "*primum non nocere*".

What is the aim of menopausal hormone therapy?

The primary aim of menopausal hormone therapy (MHT) is to improve women's quality of life by relieving or eliminating menopausal symptoms [1-4].

Menopausal hormone therapy is an individual choice motivated by improvement in the quality of life and health priorities, and involving multiple additional factors such as age, time since the last menstruation, risk of venous thromboembolism (VTE), stroke, ischemic heart disease and breast cancer. The decision to start therapy and the selection of treatment modality should be individualized, taking into account the woman's quality of life and priorities as well as specific risk factors and potential threats [1-5].

What are the indications for menopausal hormone therapy?

The indications to initiate MHT are listed below.

1. Menopausal symptoms, primarily moderate and severe vasomotor symptoms.

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2. Symptoms of genitourinary syndrome of menopause (GSM) – typically vaginal dryness, pollakiuria, nocturia, urinary urgency, recurrent vaginitis and cystitis. Both systemic and topical estrogen treatments are effective. In some cases, the concurrent use of both routes of estrogen administration is justified. If symptoms of urogenital atrophy are the only reason for starting MHT, or if systemic hormone treatment is contraindicated, topical estrogen therapy is recommended.
3. Primary ovarian insufficiency: premature and early menopause – treatment should be continued until at least 51 years of age.
4. Osteoporosis – prevention and treatment, particularly until the age of 60 years. The therapeutic management is effective in preventing bone mass loss (also at ultra-low doses) and reducing the incidence of fractures – including vertebral and hip fractures (at a standard dose). The effect is sustained only for the duration of estrogen administration. After the discontinuation of treatment, accelerated bone mass loss typical of the menopause is observed.
5. Prevention of systemic disorders associated with estrogen deficiency which increase in the postmenopausal period. Reduced risk of cardiovascular diseases, diabetes, metabolic syndrome, Alzheimer's disease and Parkinson's disease, provided that therapy is initiated in the perimenopausal period or during the first few years after the last menstruation.

What is the effect of menopausal hormone therapy on the brain?

All brain structures and functions are estrogen-sensitive. Estrogens have a protective effect on the neurons. The latter activity of estrogens is based on reducing oxidative stress, promoting the formation of new neurons and synapses, and enhancing the ability to remodel and repair brain structures or brain damage. Estrogens regulate the bioenergetic system of the brain: estradiol increases glucose uptake and sustains the process of energy use from glucose in the brain. Estrogen deficiency induces the so-called hypometabolic state of the brain associated with inadequate supply of glucose and the need to derive energy from lipid metabolism, promoting the development of Alzheimer's disease [6].

What is the effect of menopausal hormone therapy on metabolism?

Estradiol increases the uptake of glucose by various tissues. The administration of the hormone increases insulin sensitivity. The concentrations of glucose, insulin and lipids in diabetic women receiving hormone therapy during the menopause are closer to the norm than in women who do not take hormones [6, 7].

Estrogens play a major role in the body's energy metabolism also by affecting the hypothalamic neurons. They stimulate the appetite suppressing center and suppress the appetite center. They affect the distribution of body fat. Women with estrogen deficiency are more susceptible to gain weight and an increase in abdominal fat accumulation. Estrogen deficiency leads to post-menopausal weight gain [8].

Do estrogens have a cardioprotective effect?

Estrogen therapy initiated during the so-called optimum therapeutic window (i.e. < 60 years of age or < 10 years after the last menstruation) produces a beneficial effect on vascular function, cholesterol concentration and carbohydrate metabolism, which lowers the incidence of coronary episodes and myocardial infarctions, and reduces total mortality. However, the initiation of MHT in women older than 60 years of age or > 10 years after the last menstruation may lead to an increased incidence of coronary episodes, particularly during the first two years of treatment [1, 9-11].

What is the role of menopausal hormone therapy in the prevention and treatment of osteoporosis?

Menopausal hormone therapy is an effective and appropriate modality for preventing osteoporotic fractures in women under the age of 60 years or within 10 years after the last menstruation.

Menopausal hormone therapy is the first-line management for the prevention and treatment of osteoporosis in women with premature menopause, and until 60 years of age. Standard-dose estrogen therapy reduces the risk of vertebral and hip fractures and other extravertebral fractures. Low and ultra-low doses of estrogens, regardless of the route of administration, show a positive effect on bone mass density. The effect is sustained during the entire period of supplementation, and it subsides after the discontinuation of therapy [4].

What are the absolute contraindications to systemic menopausal hormone therapy?

Based on the most up-to-date recommendations the absolute contraindications to MHT include:

- pregnancy,
- undiagnosed abnormal uterine bleeding,
- high risk of venous thromboembolism,
- inadequately controlled arterial hypertension,
- past history of myocardial infarction, stroke or unstable coronary disease,

- active liver disease, liver failure,
- active or past history of estrogen-related cancer.

A contraindication to progestogen therapy is meningioma [1, 2, 4].

Is menopausal hormone therapy associated with an increased risk of breast cancer?

The potential increase in breast cancer risk associated with estrogen/progestogen therapy is small (< 1 case/1,000 women/year), comparable to the risk induced by a post-menopausal weight gain of 5 kg or regular consumption of strong alcoholic beverages. A very important role seems to be played by progestogen and its administration regimen. The most favorable safety profile has been demonstrated for progesterone and dydrogesterone, and sequential therapy has been shown as superior to the continuous regimen [1, 4].

Based on the current state of knowledge, MHT is not indicated in women after breast cancer treatment.

What is the effect of menopausal hormone therapy on the risk of venous thromboembolism and ischemic stroke?

Venous thromboembolism is one of the two major complications potentially occurring during MHT. The risk increases with women's age, BMI (> 30 kg/m^2 – a nearly threefold increase) and estrogen dose, and it is the highest during the first year of therapy. A WHI trial has shown additional 11 cases/10,000 women for the estrogen/progestogen therapy, and 4 additional cases/10,000 women in the age range of 50-59 years taking estrogens alone [4, 12, 13].

The risk of VTE and ischemic stroke increases in patients using oral MHT, but the absolute risk in women under 60 years of age is low. A lower risk, or likely absence of risk increase, has been shown for transdermal therapy.

Blood coagulation tests for thrombophilia may be recommended in patients with a positive personal and family history.

What are the most common reasons for menopausal hormone therapy discontinuation?

Only 1 in 5 women starting MHT continue the treatment for more than 2 years. The most common adverse reaction and, at the same time, the most frequent reason for early discontinuation of MHT is abnormal uterine bleeding occurring particularly during continuous combined therapy. Although the symptom is usually transient and carries no risks, it is responsible for the discontinuation of hormone therapy in almost one in every two cases. There are many reasons for abnormal uterine bleeding during MHT, the most common of which are:

- patient's incorrect use of MHT,
- lack of synchronization with endogenous ovarian function,
- suboptimal E + P combination (e.g. excessive dose of estrogen, continuous regimen in a premenopausal patient or shortly after the menopause),
- endometrial atrophy,
- previously undiagnosed organic abnormalities such as endometrial polyp, endometrial hyperplasia/cancer, uterine fibroids or *vaginitis atrophica*.

What is the recommended duration of menopausal hormone therapy?

The duration and dose of MHT should be individualized depending on the goals of therapy and safety concerns [4].

The lowest effective estrogen dose should be prescribed. Most up-to-date recommendations do not impose any arbitrary restrictions on the duration of MHT. The continuation of treatment depends on the patients' health status and individual risk profile, and the decisions made by informed patients. According to PTMA experts longer MHT is possible depending on the woman's symptoms and/or preferences, when individual long-term benefits associated with improved quality of life and reduced risk of chronic diseases outweigh potential risks [1, 2].

The discontinuation of treatment may be considered in cases of contraindications to MHT, lack of patient acceptance or inability to perform follow-up examinations which are essential for safe continuation of treatment.

If the patient's sole motivation to start MHT is the elimination of climacteric symptoms, the only way to determine whether the therapy should be continued is temporary discontinuation of hormonal supplementation followed by the patient's self-assessment of the severity of menopausal complaints or objectivized evaluation using a validated scale (e.g. Greene Climacteric Scale). A recurrence of menopausal symptoms causing impaired quality of life represents an indication to resume MHT.

What is the recommended starting dose of estradiol in menopausal hormone therapy?

Menopausal hormone therapy can be used at standard, low or ultra-low doses. In consideration of the risk of adverse reactions the goal should be to use the lowest individually adjusted effective hormone doses. Based on the current state of knowledge, the standard dose is 2 mg of estradiol (E_2) for oral administration

and 50 µg of E_2 for transdermal administration. The low dose is 1 mg of E_2 for oral administration or 25-37.5 µg of E_2 for transdermal administration. The ultra-low dose is 0.5 mg of E_2 for oral administration or 14 µg of E_2 for transdermal administration. The simplest method of evaluating the efficacy of treatment is the woman's response and the degree of elimination of existing menopausal symptoms depending on the dose during the first 2-3 months. A clear correlation is observed between the dose of estrogens and the degree of elimination/relief of menopausal symptoms. The lowest dose causing a statistically significant reduction in the frequency of hot flushes is the ultra-low estradiol dose of 0.5 mg. Further dose reductions result in the loss of therapeutic effect [2].

The therapeutic dose can also depend on the patient's age and type of menopause (natural vs. surgical). Younger women more commonly need higher doses, whereas postmenopausal patients usually note an improvement after using low or ultra-low doses of estrogens.

An appendix to this manual contains a list of drugs for estrogen-progestogen MHT which are available in Poland. The drugs are sorted by the dose of estrogens in their composition.

What is the role of the route of hormone administration in menopausal hormone therapy?

Hormone substitution can be administered orally, transdermally, intramuscularly and intravaginally. However, subcutaneous estradiol implants and estradiol-releasing vaginal rings are currently unavailable in Poland. Progestogen can also be administered directly into the uterine cavity via levonorgestrel intrauterine systems (LNG-IUS). Hormones are most commonly taken via the oral route. Oral administration is associated with a more prominent beneficial effect on the parameters of lipid metabolism, but at the same time it is a more common trigger of thromboembolic complications.

Transdermal MHT can be administered in the form of skin patches, gels or sprays. Transdermal patches available in Poland contain estradiol alone or in combination with norethisterone acetate, and can be used in sequential or continuous treatment regimens. Gels and sprays available in Poland contain estradiol alone.

On the Polish market, there is also one product containing estradiol and prasterone sulfate (precursor for dehydroepiandrosterone synthesis) intended for intramuscular administration every 4-6 weeks. As in the case of oral products containing estradiol alone, the product should be supplemented with progestogen in women with preserved uterus.

There are a number of medical conditions justifying the use of transdermal or intramuscular dosage forms, including diseases of the liver, biliary and digestive systems, thyroid disorders, hypertension, hypertriglyceridemia, and polypragmasia. Transdermal therapy has not been found to increase the risk of thromboembolic complications or mammographic density [1, 2, 14].

What is the role of progestogen selection in combined menopausal hormone therapy?

Progestogens are used in MHT solely to prevent endometrial hyperplasia. Hysterectomized women should receive estrogens alone. Combined estrogen-progestin therapy involves a slightly higher risk of breast cancer and has a reduced cardioprotective effect. The choice of progestogen type and route of administration depends on the metabolic safety profile and the patient's personal preferences. Progesterone- or dydrogesterone-based MHT is the most metabolically beneficial treatment modality. In addition, it is associated with the lowest risk of breast cancer. Testosterone-derived progestogens have a positive effect on bone mass density. There are reports suggesting that progestogens belonging to this group may enhance the quality of sexual life. Progestogens with antiandrogenic activity are prescribed in the treatment of hirsutism in women [1-4].

What aspects should be considered for the selection of menopausal hormone therapy regimen?

Women with preserved uterus can use MHT consisting of estrogen and progestogen administered in a sequential or continuous regimen. The selection of delivery regimen is independent of the route of hormone administration.

The sequential regimen may involve drug administration for 21 days: initially estrogens alone, followed by estrogens combined with progestogen for the remaining 10-12 days. The 7-day break in hormone use causes a withdrawal bleed. This therapeutic regimen is beneficial only during the early perimenopause. Because of a marked decrease in estrogen concentration and climacteric symptoms occurring occasionally towards the end of the 7-day break, the regimen commonly used from the late menopause is based on continuous administration of estrogens combined with a 12-14 day progestogen course. As soon as one pack of the drug is used, the next pack should be started. Progestogen withdrawal bleeding usually occurs during the first days after starting a new pack of the drug. Also, it may be acceptable to extend the period of treatment with estrogens alone and induce bleeding on a two- or three-monthly basis.

Sequential regimens are most typically prescribed to women with premature loss of ovarian function and to patients during the perimenopausal period.

The continuous regimen involves the concurrent administration of estrogen and progestogen, usually at lower single doses. Consequently, continuous administration of progestogens causes endometrial atrophy, which stops withdrawal bleeding. However, the risk of uncontrolled uterine spotting must be considered. Even though the frequency of spotting episodes decreases with therapy, it must be noted that the elimination of bleeding in continuous therapy is difficult to achieve in women during the perimenopausal period, with uterine fibroids or history of profuse menstrual bleeding, and treated with drugs affecting the coagulation system (anti-coagulation and anti-aggregation agents).

The continuous regimen is prescribed to patients who no longer want uterine bleeding, in the postmenopausal period, preferably at least a year after the last menstruation. Women who want to maintain uterine bleeding and patients who do not accept spotting associated with continuous therapy can be prescribed sequential MHT in the postmenopausal period.

The essential factor in MHT selection should be individualization – adjustment of therapy to the woman's needs, risk factors and personal preferences [1, 2].

What examinations should be performed before the start of menopausal hormone therapy?

1. Personal medical history (diseases, surgical procedures, medications, obstetric history including gestational hypertension, preeclampsia, gestational diabetes) and patient's family history (cancer, arterial and venous vascular diseases).
2. Physical examination with measurements of body weight and BMI, arterial blood pressure and waist-hip ratio (if required).
3. Gynecological examination with cytological smear for cancer screening and transvaginal ultrasound scan.
4. Palpatory breast examination and verification of most recent results of imaging examinations (mammography and/or ultrasonography). Recent mammography or breast ultrasound results do not absolve the physician from the obligation to perform a palpatory examination.
5. Determination of fasting glucose and total cholesterol concentrations, and in patients with risk factors or abnormalities – oral glucose tolerance test (OGTT), preferably with lipid profile.
6. In uncertain cases, an assessment (even repeated) of the follicle-stimulating hormone (FSH) and estradiol concentrations, and in selected cases also the anti-Müllerian hormone (AMH) concentration (in hysterectomized women or in patients using hormonal contraception or other hormonal therapies).
7. In selected clinical situations, the spectrum of examinations may be extended to include the assessment of TSH, transaminases, bilirubin or coagulation system parameters, abdominal ultrasound imaging, evaluation of the venous system of the lower extremities, examination of carotid arteries, densitometry or assessment of genetic predisposition to breast and ovarian cancer. In the majority of patients there is no need to perform the examinations listed above before initiating MHT [2].

What follow-up examinations should be performed during menopausal hormone therapy and at what frequency?

The first follow-up examination should be scheduled after 3 to 4 months of therapy. The aim is to review the efficacy of treatment and discuss side effects, adjust treatment components, doses or route of administration, and address any concerns the patient may have. Every woman receiving MHT should undergo follow-up examinations once a year as a minimum. After taking the patient's history and a general physical examination followed by blood pressure and body weight measurements, the patient should undergo a gynecological examination. Cytological tests for cancer screening should be repeated on a three-yearly basis in low-risk groups, and once a year in patients with increased risk. Transvaginal ultrasound scan is not necessary in patients with normal pattern and severity of bleeding in sequential therapy or no bleeding in continuous therapy. Every patient should undergo a palpatory breast examination on a yearly basis, and should be referred for breast imaging examinations. The basic examination recommended for diagnostic breast cancer screening is mammography, however if mammographic findings suggest higher sensitivity of ultrasonographic diagnostic techniques, mammography can be substituted by or combined with sonographic examination.

The frequency of follow-up laboratory tests depends on the results of preliminary examinations. It should be noted that glucose and cholesterol tests in women over 45 years of age should be performed every 5 years as a minimum. If any abnormalities are found, a 75 g OGTT and a full lipid profile test should be performed. Women with diabetes, impaired glucose tolerance, obesity, hypertension, and other risk factors for atherosclerosis should have the tests performed at an appropriately higher frequency [2].

What is the recommended menopausal hormone therapy approach in hysterectomised women?

Menopausal hormone therapy in women after total/subtotal hysterectomy is based on the continuous

administration of a fixed dose of estrogen alone. In these women, there are no factors justifying the concurrent administration of progestogen or breaks in hormone therapy [1, 2, 4].

What is the recommended menopausal hormone therapy approach in patients with premature ovarian insufficiency?

In women with premature ovarian insufficiency, systemic MHT is recommended at least until the average age of the menopause in the general population.

Premature menopause affects 1% of women < 40 years of age, and early menopause occurs in 5% of women < 45 years of age. The standard dose (equivalent to 2 mg of E_2 orally) is usually effective in eliminating menopausal symptoms and reducing the risk of cardiovascular diseases and osteoporosis. The benefits of therapy are vast, and the safety profile is generally favorable [1, 4].

What strategy should be used in patients with topical symptoms (e.g. vaginal dryness, dyspareunia, etc.) persisting despite systemic menopausal hormone therapy?

Symptoms of genitourinary syndrome of menopause (GSM) include vaginal dryness, irritation, dysuria, dyspareunia and recurrent infections. Low-dose local estrogen therapy is more effective (80-90%) than general systemic therapy (75%). However, it must be noted that such therapy fails to eliminate symptoms of GSM in approximately 30-40% of patients with indications for systemic MHT. In such cases, topical treatment (i.e. intravaginal administration of estriol or estradiol) should be considered an adjunct to systemic treatment. Topical therapy requires no supplementation with progestogen. Also, it is not subject to any time constraints regarding the initiation and duration of treatment [4, 15].

Intravaginal products available in Poland act topically and have a negligible or no systemic effect (estradiol). It can be assumed that there are no absolute contraindications to local therapy of GSM [2]. Concurrent administration of probiotics and/or topical hyaluronic acid products is recommended in patients with recurrent vaginitis secondary to atrophy.

Are there any effective alternatives to menopausal hormone therapy, such as plant-based therapies?

Menopausal hormone therapy is the most effective treatment modality for vasomotor symptoms in patients of any age, but the benefit-to-risk ratio is the greatest in patients in whom MHT was initiated under the age of 60 years or within 10 years after the last menstruation. Only with respect to the initiation of therapy.

The latest meta-analyses show that studies investigating the application of phytotherapy in menopausal medicine published to date have limited strength of evidence. This is due not only to the imperfect design of these studies, but also to the placebo effect which is particularly strongly marked in this therapeutic area. The conclusions of these meta-analyses should be interpreted as the absence of unambiguous evidence for the efficacy of phytoestrogens but, at the same time, the absence of clear evidence for their inefficacy. The level of data reliability is slightly higher with respect to the tolerance and safety profile of phytoestrogen products. Most of the available studies addressing this topic provide evidence that long-term therapy with these drugs is both well-tolerated and safe. However, the thesis on the complete oncological safety of phytoestrogens, especially soya, remains to be proven [16].

The Expert Team of the Polish Menopause and Andropause Society has issued the following statement: "Phytoestrogens should be considered in women whose quality of life has been significantly impaired by menopausal symptoms and who cannot or do not want to use menopausal hormone therapy involving systemic treatment with estrogens and/or progestogens".

Who is authorized to issue prescriptions for menopausal hormone therapy drugs?

All doctors, including primary care physicians, are authorized to prescribe drugs for MHT. Since the availability of this therapy is still limited, it is important to ensure that as many physicians of different medical specialties as possible engage in the initiation/management of MHT in low-risk patients.

Disclosure

The authors report no conflict of interest.

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Appendix

Menopausal hormone therapy (estrogen-progestogen therapy) – drugs available in Poland

Ultra-low doses:
0.5 mg E_2 orally or 0.014 mg E_2 transdermally

Oral therapy

Product	Dosage form	Composition and dose	Type of therapy
Femoston mini®	Tablets	28 tablets: 0.5 mg E_2 + 2.5 mg DYD	Continuous

Low doses:
1 mg E_2 orally or 0.025-0.0375 mg E_2 transdermally

Oral therapy

Product	Dosage form	Composition and dose	Type of therapy
Novofem®	Tablets	16 tablets: 1 mg E_2 + 12 tablets: 1 mg E_2 + 1 mg NETA	Sequential
Femoston mite®	Tablets	14 tablets: 1 mg E_2 + 14 tablets: 1 mg E_2 + 10 mg DYD	Sequential
Activelle®	Tablets	28 tablets 1 mg E_2 + 0.5 mg NETA	Continuous
Cliovelle®	Tablets	28 tablets 1 mg E_2 + 0.5 mg NETA	Continuous
Angeliq®	Tablets	28 tablets 1 mg E_2 + 2 mg DRSP	Continuous
Vielbiene Mini®	Tablets	28 tablets 1 mg E_2V + 2 mg DNG*	Continuous
Femoston conti®	Tablets	28 tablets 1 mg E_2 + 5 mg DYD	Continuous

Standard doses:
2 mg E_2 orally or 0.05 mg E_2 transdermally

Oral therapy

Product	Dosage form	Doses	Type of therapy
Klimonorm®	Tablets	9 tablets: 2 mg E_2V + 12 tablets: 2 mg E_2V + 0.15 mg LNG	Sequential with 7-day break
Cyclo-Progynova®	Tablets	11 tablets: 2 mg E_2V + 10 tablets: 2 mg E_2V + 0.5 mg NOR	Sequential with 7-day break
Divina®	Tablets	11 tablets 2 mg E_2V + 10 tablets: 2 mg E_2V + 10 mg MPA	Sequential with 7-day break
Trisequens®	Tablets	12 tablets: 2 mg E_2 + 10 tablets: 2 mg E_2 + 1 mg NETA	Sequential
Femoston®	Tablets	14 tablets 2 mg E_2 + 14 tablets: 2 mg E_2 + 10 mg DYD	Sequential

Transdermal therapy

Product	Dosage form	Doses	Type of therapy
Systen Sequi®	Transdermal system – skin patches	4 patches releasing 50 µg E_2/24 h + 4 patches releasing 50 µg E_2 + 170 µg NETA/24 h	Sequential
Fem7 combi®	Transdermal system – skin patches	2 patches releasing 50 µg/24 h + 2 patches releasing 50 µg E_2 + 10 µg LNG/24 h	Sequential
Systen Conti®	Transdermal system – skin patches	8 patches releasing 50 µg E_2 + 170 µg NETA/24 h	Continuous
Estalis®	Transdermal system – skin patches	8 patches releasing 50 µg E_2 + 140 g NETA/24 h	Continuous

E_2 – estradiol, DYD – dydrogesterone, E_2V – estradiol valerate, DRSP – drospirenone, LNG – levonorgestrel, NOR – norgestrel, MPA – medroxyprogesterone acetate, *2 mg of estradiol valerate (E_2V) is equivalent to 1.53 of estradiol (E_2)