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REVIEW

Menopause hormone therapy: latest developments and clinical practice

Tomas Fait MD, PhD

Department of Obstetrics and Gynecology, Faculty Hospital Motol, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic

Abstract

Menopause hormone therapy (MHT) is the most efficient treatment for symptoms of acute climacteric syndrome and for efficient prevention of long-term estrogen deficiency. Vaginal administration of low doses of estrogen is a therapy of choice for treatment and prevention of urogenital atrophy and its consequences. Systemic treatment may include estrogen, but an equally efficient alternative is tibolone. Nonhormonal therapy relies on phytoestrogens, black cohosh extract, and serotonin reuptake inhibitors.

Keywords: atrophic vaginitis, bazedoxifene, climacteric syndrome, menopause hormone therapy, phytoestrogens, tibolone.

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Introduction

The extensive climacteric symptomatology falls into somatic (vegetative) symptoms (vasomotor disorders, psychic disorders), organic symptoms (skin changes, urogenital changes, weight changes), and metabolic symptoms (lipid spectrum changes, atherosclerosis, osteoporosis).

Pharmacotherapy can be divided into hormonal and nonhormonal therapy. Menopause hormone therapy (MHT), or hormone replacement therapy (HRT), consists of a group of preparations with sex hormones administered in cases of low level of estrogen. Estrogen-only therapy is labeled as estrogen replacement therapy (ET, ERT). For combination of estrogens and progestogens, the term is estrogen–progestogen therapy (EPT). It is advisable to distinguish between them because of significant differences in their benefit–risk ratio.

Therapeutic administration of estrogens results in removing almost all climacteric symptoms. Their administration is an effective strategy for the long-term prevention of estrogen deficiency as well as some other diseases where a direct connection is not obvious.[1]

The hormone therapy of choice for women in early menopausal transition is gestagen substitution, levonorgestrel intrauterine system (LNG-IUS), or low-dose monophasic contraception. In late menopausal transition, there should be an initial switch to gestagen-dominated combined sequential EPT. Start with low doses and, if not effective, increase the dose. In an effort to maintain the cycle, the patient's wishes, the duration of administration of the replacement therapy, and the patient's age should be considered. Sometimes, the age of 52 is said to be a threshold for administering sequential EPT. Later, in postmenopausal cases, a switch to combined continuous EPT is recommended. This is also a therapy of choice in postmenopausal women who have not used MHT so far (Table 1).[2]

Menopause hormone therapy

Estrogens can be administered orally, transdermally, percutaneously, intramuscularly, intranasally, subcutaneously, or locally (vaginally) with doses and timing tailored to each patient.

The transdermal administration is preferred in case of oral treatment intolerance, alteration of liver function, hypertriglyceridemia, diabetes mellitus, and in case of a risk of thromboembolic disease. This administration route bypasses the first-pass effect seen with the oral route of administration and the resulting load of the liver cell, provides better bioavailability, and facilitates a long-term balance of estrogen levels and the physiological ratio of the levels of estradiol and estrone.

The newest application method is the metered-dose transdermal spray (EMDTS). In one recent study, the serum levels of estradiol, estrone, and estrone sulfate increased

Table 1. Key to starting MHT.

Point		Go to point
1 = start	A woman without contraindications to MHT	3
	A woman with contraindications to MHT	2
2	Alternative therapy	
3	A woman with intact uterus	5
	A woman after hysterectomy	4, 9
4	Estrogen therapy	
5	A postmenopausal woman	8, 9
	A perimenopausal woman	6
6	A woman with LNG-IUS	4
	A woman who wishes to menstruate	7
	A woman who does not wish to menstruate	8
7	Combined sequential estrogen–gestagen therapy	
8	Combined continuous estrogen–gestagen therapy	
9	Tibolone	

LNG-IUS, levonorgestrel intrauterine system; MHT, menopause hormone therapy.

with the number of EMDTS 1.53 mg doses in symptomatic menopausal women.[3] Maximum levels were 36 pg/mL estradiol and 50 pg/mL estrone after one puff, and 54 pg/mL and 71 pg/mL after three puffs. The maximum estradiol concentration was achieved 18–20 hours after application. A stable level was reached on the 7th–8th day of application. Transdermal estrogen spray combines the advantages of safety of transdermal application with the possibility of precise dosing.[3]

ET is for women without a uterus. For women with intact uterus, estrogen–progestogen blends are administered, and their application regimen consists of continual administration or cyclic administration for 21 days with a 7-day pause. Standard and low doses of estrogens have mitogenic activity for endometrium cells; therefore, they must be administered in combination with progestins to women with an intact uterus. Progestins administered continuously or sequentially for 10–14 days in the second half of the cycle cause endometrium growth and thus also pseudomenstrual bleeding. The progestin used affects clinical and metabolic effects of the preparation. In practice, micronized progesterone and dydrogesterone appear to have the most favorable safety profile from all progestogens. IUS-LNG has a local effect on the endometrium with minimal systemic effects.[4]

Benefits of menopause hormone therapy

Vasomotor symptoms

Vasomotor symptoms (VMS) in menopause are associated with sleeping disorders, concentration disorders, and lowered quality of life and overall health condition (cardiovascular risk, cognitive functions, bone loss). They last on average for 7.4 years. Estrogens reduce the frequency of symptoms by 75% and their intensity by 87%. Low doses (conjugated equine estrogen [CEE] 0.3 mg, estradiol 0.5 mg, estradiol patch 0.025 mg) need 6–8 weeks to reach their maximum effect.[5] Gestagen therapy (medroxyprogesterone acetate 10 mg per day, megestrol acetate 20 mg per day, micronized progesterone 300 mg) is effective, but it does not have long-term safety data. After discontinuing treatment, the problems return in about 50% of women. It has not been proved whether it is better to quit 'cold turkey' or step by step.[6]

Sleeping disorders

MHT improves chronic insomnia in menopausal women. Some progestogens (especially oral micronized progesterone) have a slight sedative effect probably due to their agonistic action on gamma-aminobutyric acid (GABA) receptors.[7]

Sexuality

The positive effect of estrogens on sexuality is caused by resolving vulvovaginal atrophy (VVA) and reducing VMS. Other mechanisms have not been proved. Transdermal estrogens are preferred to oral estrogens in women with lowered libido because they do not increase the level of sex hormone-binding globulin (SHBG) and thus do not reduce bioavailability of testosterone.[8] Continuous testosterone therapy has benefits for women diagnosed with hypoactive sexual desire disorders.[9]

Premature ovarian insufficiency

Premature ovarian insufficiency (POI), or premature ovarian failure or premature menopause, is defined as a primary hypogonadism before the age of 40 years. Premature onset of estrogen deficiency is associated with a risk of persistent VMS, bone loss, VVA, mood swings, ischemic cardiac disease, dementia, cerebrovascular accidents, Parkinsonism, eye disorders, and increased overall mortality. POI management includes, besides suitable MHT, calcium supplements, vitamin D, and exercise. Hormonal contraception without a hormone-free interval is also suitable.[10] POI is a mandatory indication for hormone therapy.

Quality of life

MHT increases quality of life by eliminating VMS symptoms.[11] Estrogens modify the course of inflammation and regeneration

of the epithelium. They improve the quality of skin.[12] MHT increases the risk of dry eye syndrome but reduces the risk of cataract and glaucoma.[13]

Musculoskeletal system

A standard dose of estrogen prevents bone loss by inhibition of osteoclast activity and reducing bone turnover, and reduces the number of osteoporosis fractures in all locations – even in women without osteoporosis. However, MHT is not first-line therapy position for osteoporosis, but is best for prevention of osteoporosis. Studies about the effect on joints have inconsistent results but the positive effect prevails. The effect of MHT on frailty syndrome and sarcopenia is positive especially in combination with exercise.[14]

Diabetes mellitus

MHT users have a significantly lower risk of the onset of type 2 diabetes mellitus. Its protective effect disappears when discontinued.[15] Estrogens may help to prevent fat accumulation by stimulating estrogen receptor alpha.[16]

Depression and memory

MHT improves mood and has a positive effect on menopause-associated depression.[17] Cognitive functions are improved by MHT only in case of an early start (critical window hypothesis, healthy cell bias hypothesis).[18] On the contrary, at the age over 65, it increases the risk of dementia. The same dependence applies to Alzheimer's disease.[19]

Cardiovascular diseases

The positive effect of MHT on ischemic cardiac disease prevails in healthy women within 10 years of their menopause or, more precisely, until the age of 60 years the number of cerebrovascular accidents does not increase.[20] According to the Cochrane database, the risk ratio (RR) of ischemic cardiac disease is 0.52 and RR for overall mortality is 0.7 when MHT is started within 10 years from the menopause.[21,22]

Risks of menopause hormone therapy

As with every therapeutic agent, MHT brings certain risks and undesirable side effects that should be taken into account.

Mastodynia, fluid retention, nausea, lower extremities cramps, and headache may occur during usage of estrogens. Depression, anxiety, flatulence, and increased appetite are associated with the gestagen components. When using MHT, unwanted bleeding caused by a decrease in hormone levels, may be detected.[23–25]

Relative contraindications of MHT such as hypertension, ischemic cardiac disease, diabetes mellitus, migraine, benign breast disease, uterus myomatosus, and endometriosis have nowadays been abandoned as unjustified. There are only several instances where MHT is contraindicated (Box 1).[26]

Long-term use of MHT (more than 10 years) increases the risk of breast cancer by 10–30%. Estrogens do not induce breast cancer as oncogenes but may become a promoter of its growth. In 1997, the Collaborative Group on Hormonal Factors in Breast Cancer published a reanalysis of 51 epidemiologic studies (52,705 women with carcinoma, 108,411 healthy women) and found a relative risk (RR) when used for less than 5 years of 1.023 per year of use, and an RR of 1.35 when used for more than 5 years.[27] At 5 years after discontinuing MHT, the RR was 1.0 independent on the length of use. The influence of MHT decreases with increasing body mass index (BMI).

Box 1. Contraindications of MHT.

- Breast carcinoma – current, in personal anamnesis, suspected
  - invasive breast carcinoma, premalignant changes of breast (atypical ductal hyperplasia, lobular neoplasia) and a ductal carcinoma *in situ* (intraductal carcinoma)
- Estrogen-dependent malignant carcinoma – known or suspected
  - e.g. unfounded bleeding from genitals as a sign of endometrial carcinoma
- Untreated estrogen-dependent carcinomas
  - endometrial carcinoma, breast carcinoma, endometrial stromal sarcoma
- Active hepatopathy
- Anamnestic or current idiopathic thromboembolic disease
  - pulmonary embolism, phlebothrombosis
- Active or recent arterial thromboembolism
  - e.g. coronary thrombosis, angina pectoris
- Known intolerance to a certain constituent of the preparation.

MHT, menopause hormone therapy.

Beral and colleagues summarized the results of the following studies: HERS, WHI, WEST, and EVTET.[28] These were placebo-controlled, prospective studies with more than 20,000 women observed for 4–9 years. In summary, they stated that MHT significantly increases the risk of thromboembolic disease (TEN) with an RR of 2.16.

The ESTHER study comprised 155 TEN cases and 381 controls. The results showed, not only a significant RR of thromboembolic disease for users of oral estrogen replacement therapy (RR 3.5 [CI: 1.8–6.8]) compared with women without treatment, but also with women undergoing transdermal treatment (RR 4 [CI: 1.9–8.3]).[29]

There is an RR of 2.3–9.5 that endometrial carcinoma may arise in women with intact uterus when using unopposed estrogens. Adding progestin reduces the risk to a value lower than the value in nonusers. That has been proved even by the EPT arm of the WHI study (RR 0.81 [0.46–1.36]).[30]

Tibolone

Tibolone is a progestogen with selective tissue estrogenic activity. It exhibits weak estrogenic, progestogenic, and androgenic activity. It suppresses vasomotor problems and improves mood and libido at the recommended dose of 2.5 mg/day. It improves vaginal atrophy but it does not affect the endometrium. It has a protective effect on bone mass, even in a dose of 1.25 mg/day. It reduces proliferation of breast epithelial cells, does not increase mammographic density, and reduces cyst diameter of fibrocystic mastopathy.[31,32]

Tibolone is a therapy of choice for women with a history of endometriosis and unwanted side effects with conventional MHT (Box 2).[33] However, prolonged use of tibolone in older women has been associated with an increased risk of stroke.[34] There is also evidence that tibolone could slightly increase the risk of recurrence in breast cancer patients.[35]

Estetrol

In the 1960s, estetrol E_4 joined the hitherto known natural estrogens – estrone E_1, estradiol E_2, and estriol E_3. It is a steroid with an estrogen structure and four hydroxyl groups: estra-1, 3, 5(10)-trien-3, 15α,16α,17β-tetrol. It can be also called 15α-hydroxyestriol. It is produced exclusively by cell microsomes of fetal liver.[36]

Esterol has a very good oral bioavailability: 70% in comparison with subcutaneous application. It binds to estrogen receptor (ER) alpha 4–5 times stronger than to ER beta. Unlike the other estrogens, it does not induce production of SHBG and does not bind to it. Initial studies showed efficacy at tested doses of 2 and 10 mg E_4 per day.[37]

The potential of E_4 when used as hormone replacement in women after breast cancer surgery, in women treated by aromatase inhibitors or tamoxifen, has been indicated by initial observation within a clinical study.[38]

Box 2. Guidelines on tibolone administration: when to prefer tibolone to MHT.

Postmenopausal women with acute climacteric syndrome
• Lower sexual appetite or sexual dysfunction
• Mood swings
• Accelerated bone loss (osteoporosis prevention during the early postmenopausal period
• Anamnesis of premenopausal mastalgia and breast tension
• High breast density
• Myomas
• Urogenital problems
Transfer from MHT to tibolone
• Mastalgia or breast tension
• Increased breast density with need to repeat mammography or when the mammogram is unreadable
• Mood swings
• Sexual appetence disorders
• Irregular bleeding without a histopathological finding
Women without acute climacteric syndrome
• Lowered sexual appetence
• Mood swings
• Osteopenia
Younger women – possible use
• Premature ovarian failure – with sexual dysfunction and mood swings
• Long-term add-back therapy of agonists GnRH

GnRH, gonadotropin-releasing hormone; MHT, menopause hormone therapy.

Selective estrogen receptor modulators

The clinically oldest selective estrogen receptor modulator (SERM), tamoxifen, acts in breast tissue as an estrogen antagonist and therefore it is used in treatment and chemoprevention of breast carcinoma while its agonistic effect causes endometrial hyperplasia.[39]

Bazedoxifene (BZA) is a new SERM that verifiably reduces bone mass loss in postmenopausal women and reduces the risk of vertebral and nonvertebral (in the high-risk group) fractures without stimulating breast tissue or endometrium.[40]

It can be used for treatment or prevention of osteoporosis in postmenopausal women. It does not stimulate the mammary gland or the endometrium. When used at a dose of 20 or 40 mg per day, it protects the endometrium during systematic estrogen treatment (tissue selective estrogen complexes [TSECs]).[41]

Nonhormonal therapy

The climacteric syndrome can also be treated nonhormonally. The preparations used may improve symptoms of acute estrogen shortage to a certain extent but their effect on long-term changes caused by estrogen deficiency has never been proved.

Reflexive electro-analgesia, spa treatment, and physical exercise are possible therapeutic elements that can remedy regimen flaws and lifestyles that do not include adequate physical activity.

Antidepressants

The selective serotonin reuptake inhibitors (SSRI), paroxetine[42] and venlafaxine, may reduce hot flushes. It has been examined in more than 4200 women in total. Venlafaxine (100 mg) produced a significant reduction of number and intensity of hot flushes and episodes of night awakenings after 4 and 12 weeks of use ($p < 0.001$).[43]

Some small studies show usefulness of gabapentin[44] and clonidine.[45]

Phytoestrogens

Phytoestrogens improve symptoms of acute climacteric syndrome.[46] However, the studies proving their efficiency are considerably nonhomogenous. Phytoestrogens are nonsteroid plant-derived compounds able to produce an estrogenic effect. They are usually divided into three groups:

- isoflavones (daidzein, genistein, biochanin A, formononetin, glycitein)
- lignans (secoisolariciresinol-diglucosid, matairesinol)
- coumestans.

Epidemiologic observations of Asian women whose lifelong diet contains large quantity of phytoestrogens have shown significantly lower occurrence of acute climacteric syndrome and osteoporosis but also of lifestyle diseases including breast carcinoma than in European and North American women populations. There is a clear link between the consumption of soy rich in isoflavones and lower risk of the breast cancer; however, it is strongly dependent on the age when the intake of soya started.[47,48]

The main source of phytoestrogens is soya. In our natural environment, most phytoestrogens are found in red clover and alfalfa in bloom and their germinated seeds. The important sources of phytoestrogens are varieties of cohosh, red grapevine, cereals, rice, strawberries, garlic, liquorice, and dates.

CRE

An extract made of root of the Black cohosh (*Cimicifuga racemose*), CRE, contains 43 triterpene glycosides and more than 20 polyphenols. They are able to inhibit α-amylase, carboxypeptidase, and collagenase, and have anti-inflammatory and natural antioxidizing effect. An important component is n(omega)-methylserotonin that reduces serotonin reuptake. That could explain its effect on the climacteric syndrome.[49]

The efficacy of CRE in the treatment of the vegetative climacteric syndrome has been proved by a meta-analysis of nine clinical randomized double-blind studies with the reduction of problems by 26% against placebo.[50]

There are no changes in the plasma profile of sex hormones, which confirms the theory of an effect on the central nervous system. Almost zero stimulation of estrogen receptors enables, for example, women with the case history of breast carcinoma to use CRE for the treatment of the climacteric syndrome.[51]

Pollen extracts

Pollen extracts have been used as an alternative therapy of the climacteric syndrome. While some widely used bee products contain whole pollen grain, and they are a variable blend of different plants' pollen, the patented purified cytoplasm of pollen extract PI82/GC Fem is extracted from exactly defined monocultures.[52]

The extract does not have any estrogenic activity. It inhibits reuptake of serotonin in the hypothalamus similarly to SSRI, which influences sleep and thermoregulation. However, unlike SSRI, it does not in any way influence enzymes involved in the metabolism of tamoxifen.

In a prospective, open, multicenter study, 160 mg (twice daily) of pollen extract was able to reduce significantly menopausal symptoms such as vasomotor symptoms, fatigue, irritability, depression, or vaginal dryness.[53]

Genitourinary syndrome of menopause

Skin atrophy caused by estrogen deficiency including adnexas of vulva and vaginal mucosa is an example of VVA – vulvovaginal atrophy combined with dyspareunia, pruritus, and chronic vaginitis.

Estrogen replacement is a dominant form of treatment and the only causal therapy of vaginal atrophy. Estriol (E3) is administered in a starting dose of 0.5 mg/24 hours for 2–3 weeks in the beginning of the therapy and later in a maintenance dose of 0.5 mg 1–2 times per week. Estradiol (E2) may be administered in the form of vaginal tablets in a dose of 0.01 mg daily for 10–14 days in the beginning, then twice per week.

Long-term administration of higher doses of estrogens could have undesirable trophic effects on the endometrium but at prescribed doses this danger is eliminated – with a total dose of 1.14 mg of estradiol per year, it is possible to treat the symptoms of vaginal atrophy safely and effectively.[54]

Ospemifene in a daily dose of 60 mg is also approved for VVA treatment in postmenopausal women. It reduces the percentage of parabasal cells in vaginal cytology by 30–40%, increases the number of superficial cells by 5–10%, and lowers the vaginal pH. It reduces dyspareunia and vaginal dryness. It improves sexual functions in postmenopausal women. Ospemifene does not affect hematologic, biochemical, and renal indicators. Its effect on the lipid profile is positive. The most frequent undesirable side effects are hot flushes (7.5% against 2.6 using placebo), vaginal discharge (3.8% against 0.3%), and muscle spasms (3.2% against 0.9). A higher frequency of cardiovascular accidents, proliferative effects on the endometrium, or a negative effect on breast tissue have not been proved.[55]

Women who are wary of hormone therapy may be administered preparations with hyaluronic acid or prasteron to improve the vaginal trophic condition.[56] Some uncontrolled studies exist for usage of fractional CO_2 laser or erbium laser.[57]

Vaginal moisturizers and lubricants are commonly used as symptomatic help for sexual intercourse in elderly age.

The trophic effect of estrogens administered vaginally is irreplaceable in the treatment of vaginal atrophy. It can be used as an individual therapy or in combination in women for whom the overall administration of systemic MHT or tibolone would not be sufficient.

Conclusion

Menopause hormone therapy still remains a dominant therapeutic modality in climacteric medicine. The core medical skill is the ability to choose the optimal MHT preparation for the given patient. Such choice is based on an understanding of various clinical and metabolic effects of MHT depending on the composition, dosage, and the method of application (Box 3).

The general trends are individualization, dose minimization, and early start of therapy. When those rules are observed, the benefits of therapy will prevail over its risks.

There are nonhormonal and nonpharmacological alternatives for the treatment of acute climacteric syndrome – while they may have a better safety profile, they are less effective. Pharmacotherapy should be regarded as only one of the pillars of the comprehensive care for aging menopausal woman.

Box 3. Indications of MHT.

- Climacteric syndrome
  - vasomotor problems
  - psychic problems
- Estrogen-deficiency syndrome
  - organic – urogenital atrophy
  - metabolic – osteoporosis

  primary prevention of the ischemic cardiac disease; with early start only
- Expected effects of long-term administration of estrogens – contrary to the risks of the long-term use
  - Prevention of Alzheimer's disease and Parkinson's disease and strengthening their treatment
  - Prevention of senile macular degeneration and geriatric blindness
  - Prevention of geriatric tooth loss and oral health
  - Prevention of colorectal cancer

MHT, menopause hormone therapy.

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Correspondence: Tomas Fait, Department of Obstetrics and Gynecology, Faculty Hospital Motol, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic. tfait@seznam.cz

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