MENOPAUSAL HORMONE THERAPY: BENEFITS AND DIFFERENT FORMS

HORMONSKA TERAPIJA U MENOPAUZI: KORISNI EFEKTI I RAZLIČITI OBLICI

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Summary

Introduction. Declining of ovarian hormone production can seriously disturb the quality of woman’s life, with physical and emotional consequences and to potentiate the development of additional health risks such as cardiovascular diseases and osteoporosis which are already present in women of older age. Benefits of Menopausal Hormone Therapy. Menopausal hormone therapy ameliorates the quality of life by resolving the atrophic symptoms and vasomotor problems, protecting from the osteoporosis, maintaining the skin and connective tissue turgor, as well as by improving libido, mood and depression during the menopausal transition. Forms of Menopausal Hormone Therapy. There are several possibilities to treat menopausal problems: estrogen, combination of estrogen and progestogen, androgens, selective estrogen receptor modulators, tissue selective estrogen complex, tibolon and alternatives.

Initiating, Monitoring and Discontinuing Menopausal Hormone Therapy. Menopausal hormone therapy should be started when the problems due to menopausal symptoms appear. It is important to have on mind that the effects of hormones depend on age and actual condition of the woman’s organism. The goal is effective treatment at the lowest dose and during the shortest interval needed for symptom control. The therapy must be reevaluated every year and potential risks must be discussed as well. Conclusion. Menopausal hormone therapy ameliorates the quality of woman’s life in perimenopause. Type, doses and duration of the menopausal hormone therapy should be individualized.

Key words: Hormone Replacement Therapy; Menopause; Treatment Outcome; Quality of Life; Symptoms and Signs; Risk Factors; Bone Density; Estrogen Replacement Therapy; Progestins; Androgens; Drug Compounding

Introduction

Menopause is not a pathological, but quite a normal life event. Still, declining hormone production can essentially disturb the quality of woman’s life, with physical and emotional consequences, and, which is more important, it may potentiate the development of additional health risks, such as cardiovascular diseases and osteoporosis already present in women of older age.

The aim of this article is to present current treatment of perimenopausal problems.

Benefits of Menopausal Hormone Therapy

The benefits of menopausal hormone therapy (MHT) are obvious - it efficiently solves the menopausal problems, such as vasomotor symptoms (hot flushes), atrophic changes (superficial dyspareunia and vaginal dryness), urinary problems (frequent urination and urgency), etc. [1–6].
Menopausal hormone therapy (MHT) is recommended not only to control vasomotor problems and atrophic changes in the patients with premature ovarian failure, but also to slow down atherosclerosis, to decrease the risk from cardiovascular diseases, osteoporosis and, possibly, Alzheimer’s disease [11, 12].

Most women tolerate MHT well, but side effects of standard doses are possible, such as breast tenderness, vaginal bleeding, the sense of swelling (due to water retention) and headaches [6]. The use of MHT could be also associated with depression and mood changes.

### Forms of Menopausal Hormone Therapy

Different treatment options for menopausal symptoms are listed in Table 1.

#### Estrogen

The use of estrogen is the oldest way to treat menopausal problems. Estrogen is successful in solving vasomotor symptoms, atrophic changes and their consequences (dyspareunia, vaginal dryness and urinary problems). Daily doses of estrogen are shown in Table 2.

There are two routes of estrogen administration: oral and transdermal (using patches or subcutaneous implants).

Orally administered estrogen follows the effect of first liver pass, which could disturb coagulation cascade (hypercoagulability as an end effect) and could also make changes in markers of inflammation including C-reactive protein [13]. Oral estradiol is converted into estrone in the liver and intestinum, which is not a case with transdermal estradiol. Oral estrogens increase hepatic synthesis of sex-hormone binding globulin (SHBG), decreasing the levels of free testosterone, which could result in lower libido [14].

Local (vaginal) estrogen administration is approved when there are only atrophic changes. Locally administered estrogen regenerates the atrophic vaginal epithelium and resolves dyspareunia successfully. The treatment effect could be monitored by measuring the vaginal pH – it should be less than 4.5. Although local absorption is small, it does exist; it is even increased through atrophic vaginal mucosa [15]. This is clinically important: in cases of topical estrogen treatment longer than 6 months, the thickness of the endometrium should be measured by transvaginal ultrasound and biopsy should be performed if indicated. Bearing in mind estrogen effects on breast tissue, breast control is also mandatory during the treatment. The current recommendation is to use the lowest estrogen dose which could control symptoms since the safety of using vaginal estrogen preparations for the period longer than one year has not been proved [1]. Transdermal or local use of estrogen is more adequate for patients over 60 years of age [11].

#### Combination of Estrogen and Progestogen

An endometrial response to unopposed estrogen is hyperplasia, so progestogen is added to protect the endometrium against the uncontrolled proliferation (progestogen induces endometrial secretory transformation). There are two ways to administer the combination of estrogen and progestogen: the sequential and continuous regimen.
The sequential regimen means that estrogen (Es) is administered every day and progestogen (Pr) is used for 14 days (minimum 10 days). The patient has cyclic progestin withdrawal bleeding and this regimen is suitable for patients in the beginning of perimenopause.

The continuous regimen means the administration of Es+Pr combination every day, and there is no withdrawal bleeding. This regimen is more suitable for postmenopausal patient who does not want to have cyclic bleedings.

Daily doses used in Es+Pr combination are shown in Table 2. It is better to add progestogen in the evening; metabolites pregnenolon and alopregnenolone improve sleeping [15]. Micronized oral progestogen seems to be a better option in comparison with synthetic progestogens because it has no metabolites with androgenic and glucocorticoid activities. On the contrary, it has slightly hypotensive effects due to its anti-mineralocorticoid effects as well as the overall favorable cardiovascular impact (decreasing the risk of venous thromboembolism, probably the stroke). Micronized oral progestogen has lower mitogenic activity on the breast tissue than medroxyprogesteron acetate – levonorgestrel [16]. Micronized oral progesterone seems to be a better option in comparison with synthetic progestogens because it has no metabolites with androgenic and glucocorticoid activities. On the contrary, it has slightly hypotensive effects due to its anti-mineralocorticoid effects as well as the overall favorable cardiovascular impact (decreasing the risk of venous thromboembolism, probably the stroke). Micronized oral progestogen has lower mitogenic activity on the breast tissue than medroxyprogesteron acetate – levonorgestrel [16].

There are alternatives to oral Es+Pr combination, such as adding of progestogen in the form of vaginal gel [17], combination of transdermal estradiol and micronized oral progesterone [18] and combination of oral estrogen and intrauterine device with progestogen – levonorgestrel [19]. Intrauterine administration of progestogen, especially levonorgestrel, as a part of MHT, is considered safe and efficient in the endometrial protection [19]. This is also true for progesterone administered in the form of vaginal gel or pessaries. However, the effects of progestogen administered in such a way on the bone and breast as well as other systemic effects have not been completely tested.

The use of combined (Es+Pr) MHT could cause the occurrence of progestogenic side effects, including breast tenderness, swelling due to body water retention, headaches, mood changes and depression. Progestogen administration in the forms of vaginal gel, pessaries or levonorgestrel releasing intrauterine system reduces systemic side effects; however, they could not be completely eliminated. Continuous combined regimens are associated with continuous low-grade side effects of progestogen [1].

Complications of sequential combined regimen in form of irregular bleedings do not practically exist, so every irregular bleeding must arouse the suspicion of possible organic causes and require the prompt evaluation.

A relatively frequent complication of continuous (Es+Pr) combined regimen is breakthrough bleeding, with the same pathogenesis with oral contraceptive use, usually disappearing after 6 – 12 months of administration. If the breakthrough bleedings are persistent, it is possible to start with the sequential regimen or to apply intrauterine device with progestogen. Alternatives are endometrial ablation or even vaginal hysterectomy [15]. The main question is when to perform endometrial biopsy. Endometrial biopsy is needed before the treatment with Es+Pr combination in the patients at risk factors for endometrial proliferation or in patients who have used unopposed estrogen as MHT at any time. In case of the solicitude of the patient or her gynecologist during the treatment, biopsy is justifiable, which is mandatory in cases of irregular bleeding during the treatment with unopposed estrogen, persistence of bleeding after 6 months of continuous combined (Es+Pr) therapy or if endometrial thickness is more than 4 mm on transvaginal ultrasound examination in a postmenopausal patient. Standard combined regimens (Es every day + Pr 14 days or Es+Pr every day) protect the endometrium, but every irregular bleeding must arouse the suspicion of possible organic causes and require the prompt evaluation.

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**Androgens**

Androgens are added as short-term MHT because of their favorable psychological effects and to improve the libido, but only high doses have such effects. Methyltestosterone (synthetic androgen) could be used at a dose of 1.25 to 2.5 mg a day [15]. Androgens could be administered orally, intramuscularly or in...
the form of gel, patches or implants [1]. On the other side, androgens have no influence on hot flushes and breakthrough bleedings (they do not protect the endometrium) [15], and density of the bones can be improved only by their high doses or in combination with estrogen. Other treatment options include transdermal testosterone administration or dehydroepiandrosterone treatment [20].

Unwanted effects of androgen use are hirsutism, acne and alopecia, as well as the unfavorable effect on the lipid profile, i.e. decreasing the levels of high density lipoproteins (HDL), the latter one is lost with parenteral administration. Most guidelines do not recommend androgens for hormone replacement in women [21], and if used, it is mandatory to monitor the patient’s lipid status and the occurrence of symptoms and signs of androgen excess along with measuring the serum testosterone, which should be in physiological levels between 0.7 and 2.8 nmol/l for women [15].

Selective Modulators of Estrogen Receptors
New agents for the control of menopausal symptoms are introduced in order to avoid steroid action on the endometrial and breast tissue proliferation: selective estrogen agonists/antagonists or selective estrogen receptor modulators (SERM). The second generation of SERM has no proliferative action on the endometrium as was the case with previously used tamoxifen. The second SERM generation includes raloxifene, and newer SERM molecules are bazedoxifene, lasofixene, teremifene, ospemifene and arzoxifene [22, 23]. Raloxifene administered at an oral dose of 60 mg a day is the one most frequently used.

Raloxifene is the only SERM internationally approved for prevention and treatment of osteoporosis and vertebral fractures. Raloxifene improves the bone density and lipid profile. Extensive MORE (Multiple Outcome of Raloxifene Evaluation) study has revealed that raloxifene reduces the risk of vertebral fractures, acts as antiestrogen on the breast tissue (according to STAR – Study of Tamoxifen and Raloxifene), but has no significant action on vasomotor symptoms and atrophic changes [24, 25]. RUTH (Raloxifene Use for The Heart) study has shown that raloxifene does not affect cardiovascular diseases [26]. Raloxifene should be used in the patients who need the protection from osteoporosis, but who do not want or should not take hormone replacement therapy containing steroids.

Ospemifene at an oral dose of 60 mg/day (30 – 90 mg/day) is most effective in the control of atrophic changes, it successfully reduces moderate and severe dyspareunia. Side effects of ospemifene are hot flushes, excessive sweating, increased vaginal secretion and muscular spasms. Ospemifene does not influence the endometrial thickness [6, 27].

The main concerns with SERMs are thrombotic events: raloxifene increases the risk from thrombosis [26], but this is not a case with ospemifene [27]. Selective estrogen receptor modulators (SERMs) are a good treatment option for younger patients at an increased risk for fractures, who have to take the long-term therapy, and for the patients without a risk for thrombosis, but who have contraindications for other treatments [28]. Nowadays, studies are being performed to find an “ideal” SERM which would have the estrogen-like effect on the bones and lipids while being neutral on the level of endometrium and having antiestrogenic action on the breast, without side effects, especially on coagulation profile [22].

Table 2. Estrogen and progestagen daily dose in MHT

<table>
<thead>
<tr>
<th>Standard dose/Standardna doza</th>
<th>Low dose/Niska doza</th>
</tr>
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<tbody>
<tr>
<td>conjugated equine estrogen 0.625 mg</td>
<td>conjugated estrogen 0.3 – 0.45 mg</td>
</tr>
<tr>
<td>konjugovani ekvini estrogen 0.625 mg</td>
<td>konjugovani estrogen 0.3–0.45 mg</td>
</tr>
<tr>
<td>micronized estradiol 1 – 2 mg</td>
<td>micronized estradiol 0.5 mg</td>
</tr>
<tr>
<td>mikronizovani estradiol 1–2 mg</td>
<td>mikronizovani estradiol 0.5 mg</td>
</tr>
<tr>
<td>ethinyl estradiol 5 μg/etinil estradiol 5 μg</td>
<td>ethinyl estradiol 2.5 μg</td>
</tr>
<tr>
<td>estradiol valerate 2 mg/estradiol valerat 2 mg</td>
<td>etinil estradiol 2.5 μg</td>
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</tbody>
</table>

Progestogen dose/Doze progestagena

<table>
<thead>
<tr>
<th>Standard dose/Standardna doza (sequential regimen/sekvencijalni režim)</th>
<th>Low dose/Niska doza (continued regimen/kontinuirani režim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>medroxyprogesterone acetate 5 mg</td>
<td>medroksiprogesteron acetat 1,5 – 2,5 mg</td>
</tr>
<tr>
<td>medroksiprogesteron acetat 5 mg</td>
<td>medroksiprogesteron acetat 1,5–2,5 mg</td>
</tr>
<tr>
<td>norethindrone 0.7 mg/noretindron 0,7 mg</td>
<td>norethindron acetate 0,35 mg/noretindron 0,35 mg</td>
</tr>
<tr>
<td>norethindrone acetate 1 mg/noretindron acetat 1 mg</td>
<td>norethindron acetate 0,5 or 1 mg</td>
</tr>
<tr>
<td>micronized progesterone 200 mg</td>
<td>micronized progesterone 100 mg</td>
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<tr>
<td>mikronizovani progesteron 200 mg</td>
<td>mikronizovani progesteron 100 mg</td>
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breast. TSEC is a combination of one or more estrogens and selective estrogen receptor modulator [29]. In practice this is the combination of conjugated estrogen (at a daily dose of 0.625 mg or 0.3 mg or 0.45 mg) and bazedoxifene (20 mg/day) [30]. Bazedoxifene is chosen because it can inhibit the action of conjugated estrogen on the endometrium [31]. Clinical studies have revealed that the combination of conjugated estrogen (0.45 mg or 0.625 mg) and bazedoxifene (20 mg) is a good alternative to the traditional Es+Pr MHT in the control of vasomotor symptoms, vulvovaginal atrophy and dyspareunia, as well as in the prevention of osteoporosis in postmenopausal women with uterus [32].

With TSEC as MHT, the use of progestogen and its side effects are also avoided, thus contributing to further individualization of therapy for menopausal symptoms [33]. Additional studies are needed to determine the long-term safety of TSEC on the cardiovascular system and breast [34].

**Tibolon**

Tibolon molecule is structurally similar to 19-nortestosterone, binding to the estrogen receptor. Its 3-OH metabolites have 100 times higher affinity for α-estrogen receptor (ER) comparing to β-ER, and Δ4-ketoisomer metabolite has androgenic and progestogenic effects. It is administered at a daily dose of 2.5 mg (1.5 mg). Clinical studies have revealed that tibolone successfully improves the bone mineral density and symptoms of urogenital atrophy [35]. The impact of tibolone on the libido is very impressive (androgen metabolites), especially on mood, which we have also seen in our clinical practice.

Tibolon can stimulate the endometrium very rarely: tibolone metabolite Δ4-ketoisomer, which is dominant on the level of endometrium, binds to progestosterone receptors and protects the endometrium from metabolites with estrogenic activity. Nevertheless, close monitoring of endometrial thickness is needed in patients on tibolone and biopsy is mandatory in cases with uterine bleeding [15].

In the beginning of tibolon use, it was considered that tibolone could absolutely protect the breast tissue from proliferation, due to inhibitory action of its metabolites on sulphatase, the consequence is inhibited conversion of estrone sulfate to estradiol. Nevertheless, tibolone could increase the breast tissue density on mammography [35]. In fact, tibolone acts as an androgen and progestogen on the breast. Regular control of the breast is mandatory on patient on tibolone, as during any MHT.

Due to its androgenic effects, tibolone influences the lipid profile, decreasing the level of HDL, but it has a neutral effect on low density lipoproteins (LDL) [36].

**Bioidentical Hormone Therapy**

Menopausal hormone therapy is available not only in the form of commercial preparations, but there is also a possibility to compose components depending on individual needs of the patient. “Bioidentical hormone” preparations are often used to such purpose. It has become very popular in the United States due to the fear resulting from the findings of Women Health Initiative (WHI) study and a widespread opinion that the natural therapy is the best therapy [37]. The term “bioidentical hormone therapy” is a commercial term, and it is not based on scientific evidence. “Bioidentical hormone therapy” means the use of bioidentical hormones, derived from plants (e.g. soya) and chemically modified to be similar or structurally identical to human endogenous hormones. Different doses and routes of administration are used. These preparations could be efficient in the control of menopausal symptoms [38, 39]. The issue of their safety as compared with traditional forms of hormones is very important. Theoretically, the risk should be the same as for conventional forms of MHT, but there is still the question of their bioavailability, problems with sub- or overdosing and effect of different combinations. There are no adequate studies about pharmacokynetics, effectiveness and possible risks from these preparations. The current opinion is that their use is less favorable than of conventional MHT [40]. Moreover, there are guidelines that do not recommend the use of custom-compounded bioidentical hormone therapy [4], and others that allow the use of that therapy only in cases of allergies to ingredients contained in conventional MHT [5].

**Introduction, Monitoring and Discontinuation of MHT**

Menopausal hormone therapy should be initiated when menopausal problems appear. MHT is not obligatory for every woman, but it would be ideal if every woman were informed about benefits and risks associated with MHT. It must be kept in mind that the effects of hormones are determined by the age and current health condition, so the concepts of “window of opportunity” and “timing hypothesis” have been developed [11, 41]. It is generally accepted that the benefits from MHT overcome the risks for symptomatic women who are under 60 years of age or within 10 years of menopause, especially if other, non-hormonal treatments have had no effects. In older women and women having been in postmenopause for more than ten years, the risk/benefit ratio is less favorable [4, 11]. Current recommendations for patients with premature ovarian failure are that MHT should be used at least to the age when natural menopause occurs [1–6, 42, 43]. The preventive effect of MHT on the development of osteoporosis is the only one proved up to now [44], but it is not always the case with the prevention of cardiovascular diseases [45]. MHT should not be used either for primary or secondary prevention of stroke [1] or dementia [12]. To be more specific, the standard-dose of estrogen-alone MHT may decrease the progression of atherosclerosis and incidence of coronary heart disease (and all-cause mortality as well) in wo-
men younger than 60 years of age or within 10 years of menopause [4]. The combination of estrogen and progestogen MHT in this population has no significant effects on coronary heart disease [4]. If MHT is initiated at an older age, it could destabilize atherosclerotic plaques and increase the risk from myocardial infarction and stroke [41].

When estimating the risk for thromboembolic complication associated with MHT, it is necessary to take into account the presence of the individual risk factors for every patient [46]. TREATS study (The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening) has shown that genetic affinity to thrombophilia has also an important role in the occurrence of increased risk for venous thromboembolism (VTE) in MHT users who are carriers of factor V Leiden mutation [47].

The choice of route, form and dose of MHT depends on the age and health status of the individual patient, time interval from menopause, the treatment goals and presence of specified contraindications, along with identification of individual risk factors (taken from family medical history as well). The target is to control the symptoms and achieve the wanted effect at the lowest possible dose and in the shortest time interval [5, 11]. Introduction of MHT in women using transdermal estradiol in combination with micronized progesterone in their early and mid 50s is now believed to be associated with a lower risk [2].

**Monitoring During Administration of MHT**

The first control should be taken after few months of using MHT to establish the effects and adjust the dose, if necessary. Reevaluation is mandatory after one year, with consideration of possible risks. It is recommended to take once a year the clinical breast examination (and mammography for older than 40) as well as pelvic examination, to assess the symptom control and possible occurrence of new health risks, to discuss the possibilities of new or alternative treatments, as well as to evaluate woman’s individual needs [11].

**Discontinuing MHT**

It is generally recommended to limit MHT use to the shortest interval and lowest dose needed to achieve treatment goals. Duration of the MHT should be limited to 3 to 5 years in women having reached menopause around the average age due to breast risks [5, 11, 48]. Studies have shown that estrogen only therapy has no such risk even after 7 years of use [5, 11, 49]. For some patients, e.g. those at high risk from osteoporotic fractures, in whom alternative treatments are not appropriate or tolerated, MHT use could be extended for longer intervals if the patients are provided with the information about benefits and risks and undergo appropriate clinical supervision [5, 11].

After MHT has been discontinued, recurrence of vasomotor symptoms is possible in 50%; independent of age, duration of use and the way of discontinuing MHT (gradually or not) [5, 11].

In everyday clinical practice with patients requiring MHT, numerous guidelines could be very helpful, but the most useful is the advice of L. Speroff: “let the patient be your guide” [15].

**Conclusion**

Menopause is not a pathological, but normal life event. Hormone therapy is not the standard for every perimenopausal women, but it would be ideal if every woman could be informed on the benefits and risks of menopausal hormone therapy.

Menopausal hormone therapy improves the quality of life in perimenopause by solving the symptoms of urogenital atrophy and controlling vasomotor problems, protecting from osteoporosis, maintaining the skin and connective tissue turgor and improving the libido and mood.

Every individual patient having menopausal problems should have the therapy determined and individual risk/benefit ratio estimated. The treatment goal is the effective treatment at the lowest dose and the shortest duration of the treatment possible.

The decision about the form, dose and duration of menopausal hormone therapy should be individual for every patient. It should be reevaluated once a year, with risk reassessment. It must be taken into account that the effects of hormones on woman’s organism depend on age and the current health status. It is generally accepted that the benefit from menopausal hormone therapy surpass the risk in patients under 60 years of age or if started within 10 years of natural menopause, especially if other, non-hormonal treatments have failed. In women older than 60 or after 10 years from menopause, lower doses are needed (transdermal or locally), and risk/benefit ratio from menopausal hormone therapy is less favorable. Patients with premature ovarian failure should use menopausal hormone therapy at least until the age of average menopause.

**References**


