

Benefits and risks of hormonal replacement therapy

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ABSTRACT

Menopause, defined as the permanent cessation of menstruation resulting from the loss of the ovarian function, has gradually become a fundamental health concern. Menopause hormonal replacement therapies (HRT) were initially developed with the purpose to alleviate the estrogen deficiency induced symptoms. Currently, HRT is approved by the FDA (Food and Drug Association) for four indications: bothersome vasomotor symptoms (VMS); prevention of bone loss; hypogonadism caused by hypogonadism, castration, or premature ovarian failure and genitourinary symptoms. For patients younger than 60 years or within the first 10 years from menopause onset and without contraindications, the benefit-risk ratio should be favorable for treatment of VMS and for preventing bone loss and related fractures. For women who initiate HRT more than 10 / 20 years from menopause onset (or aged 60 years or older), the benefit-risk balance seems to be less favorable than for younger patients because of greater absolute risks of cardiovascular disease, stroke and VTE. Even though the management of menopausal symptoms through pharmacological and cognitive-behavioral therapy improves quality of life of affected women in the short term, there is a need for the development of strategies to modify menopausal health risks, in the long term.

Keywords: menopause, hormone replacement therapy, progestins, vasomotor symptoms, genitourinary syndrome

INTRODUCTION

Menopause, defined as the permanent cessation of menstruation resulting from the loss of the ovarian function, has gradually become a fundamental health concern through the last decades [1-3]. Women longevity is increasing worldwide, by 2050, the world's female population aged 50 years and older being believed that will total 1.6 billion [4] and with a life expectancy greater than 80 years, women can live around 30 years after menopause [5].

As ovarian function declines, estradiol production falls to a small fraction of premenopausal levels and in his place the predominant estrogen becomes estrone, which has approximately one tenth the potency of estradiol. Cessation of ovarian function also implies a marked reduction of progesterone secretion [3].

Menopause hormonal replacement therapies (HRT) were initially developed with the purpose to

alleviate the estrogen deficiency induced symptoms [5]. According to current practices, the use of HRT has extended, and it is taken into consideration even for different cultural or minority populations of women, including women with hypogonadism, early menopause, primary ovarian insufficiency, surgical menopause, for prevention of bone loss, cognition and mood issues, for women older than 65 years of age, and in observational studies for heart disease prevention [6-9].

Unfortunately, HRT along with benefits has proven to have risks as well, so, the initiation and the choosing of a regimen (chemical compound/-s and doses) should be carefully weighted and be also dictated by tolerance in the attempt to ensure compliance [1,5].

The optimal duration of HRT remains an unsolved issue and must be decided after taking into account the initial indication and the benefit-risk

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balance, which is specific to each patient. Continuation of HRT is also conditioned by the benefit-risk balance, which must be assessed regularly, and also by the evolution of symptoms when HRT is interrupted [5].

After stopping HRT, medical follow-up is necessary and should be adapted to the clinical situation of each woman in regard to her gynecological and cardiovascular risk factors [1,7,10].

BENEFITS OF HORMONAL REPLACEMENT THERAPIES (HRT)

The most frequent reason for prescribing HRT – usually involving estrogen (E) with / without a progestin (P) – is to treat the plethora of vasomotor, somatic and psychologic symptoms related to estrogen deficiency that represents the menopausal syndrome [7,11].

Currently, HRT is approved by FDA (Food and Drug Association) for the following four indications: bothersome vasomotor symptoms (VMS); prevention of bone loss; hypoestrogenism caused by hypogonadism, castration, or premature ovarian failure and genitourinary symptoms [6,7,12].

Central nervous system related symptoms appear as a consequence of the neurobiochemical changes occurring after ovarian failure, and include VMS, anxiety, migraine, sleep disturbances, depression and changes in cognitive performance [13]. Fatigue, insomnia, loss of concentration, anxiety, irritability and depression appear in 30 to 40% of patients, the menopausal transition being a very favorable period for the onset of depressive symptoms [13]. Some reports state that sleep disturbances (particularly nocturnal awakenings) are major complaints in the case of up to 60% of menopausal women [13-15].

Vasomotor instability, manifests through hot flashes / flushes, this being the most common symptom, that can start years before the actual menopause. When ovarian endocrine function declines, about 75% of women begin to experience episodes of extreme heat sensation that starts unexpectedly and can last from 30 seconds to 5 minutes [13]. They are many times accompanied by other vasomotor manifestations like palpitations, headaches, dizziness, diaphoresis, nausea and night sweats [2].

In the absence of HRT, VMS will manifest for more than a year in 85% of affected women, whereas in 25% to 50% may continue for more than 5 years [3]. In most cases, hot flushes are infrequent and mild, but some women report symptoms so disturbing that they result in severe insomnia or nervousness that interfere with their social / professional functioning [3].

Women who undergo surgical menopause may experience even more frequent and intense hot

flashes than the ones going through natural menopause, especially in the first 6 months after surgery [2].

HRT has been shown in double-blind RCTs to relieve hot flashes and is approved as first-line therapy for relief of menopause symptoms in appropriate candidates. [6,16]. Research has shown also marked improvements in affective symptoms or general well-being and quality of life with HRT [3].

Urogenital atrophy usually translates into genitourinary syndrome of menopause (GSM) the affection that includes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract. GSM is highly prevalent, and it affects according to various studies 27 to 84% of postmenopausal women [17,18].

The most apparent changes affect the vaginal mucosa, which's thickness and rugae decrease. Also, the glycogen production falls leading to a more alkaline vaginal pH with a more friable mucosa. Blood flow and vaginal lubrication also diminish. Women are also less likely to have a Lactobacillus-dominant vaginal flora, this also affecting the vaginal pH [17]. All these changes will usually lead to vaginal dryness, pruritus, dyspareunia, sometimes bleeding, increased risk of infection and intercourse discomfort with loss of sexual interest [2]. Low estrogen levels also lead to atrophy of the urethra and trigone of the bladder and the pubococcygeal muscle, changes that may cause symptoms of urethritis, cystitis, and urge / stress incontinence [3].

HRT has been shown in RCTs to effectively restore genitourinary tract anatomy, reduce vaginal pH, increase vaginal mucosa thickness, and successfully treat symptoms of GSM [6].

Commonly used regimens include low-dose vaginal estrogens, vaginal DHEA inserts and oral ospemifene [6]. Transdermal and oral HRT are effective options in the case of women with moderate to severe dyspareunia and concurrent VMS. Symptom alleviation may take 1 to 3 months, and continued therapy is generally necessary because symptoms usually recur on cessation of therapy [17].

Osteoporosis is a serious condition, often debilitating, consisting of a reduction in bone mass that compromises the biomechanical integrity of the skeleton leading to an increased risk for fractures. Current statistics sustain that 40% of women worldwide will experience an osteoporosis-related fracture by age 70, while, by age 80, 15% will have sustained a hip fracture [3,12].

The rapid loss of bone mass that occurs in response to estrogen depletion may start a year before menopause, so it is not necessary for a patient to be postmenopausal to receive estrogen. She only needs to present irregular periods and menopausal

symptoms. One way to establish the onset of menopause is to measure serum follicle-stimulating hormone level annually, starting at age 50, and when its value becomes greater than 40 IU/ml, it is time to begin HRT [3,12].

HRT was proven in double-blind RCTs to prevent bone loss and, when administered for a period of minimum 5 years early in the climacteric, to reduce osteoporosis related hip and wrist fractures by 50% and vertebral crush fractures by 80% [3]. Also, in the Women's Health Initiative (WHI) landmark study (16,000 postmenopausal women; mean age 64; daily conjugated equine estrogens / CEE 0.625 mg plus medroxyprogesterone acetate / MDPA 2.5 mg) HRT was found to reduce fractures in postmenopausal women [6,12,19].

Cardiovascular disease prevention used to be an indication for HRT, but over time studies showed contradictory information and, even though a clear consensus has not been reached, this is not an FDA approved indication for HRT. The WHI study (16,000 postmenopausal women; mean age 64) assessed CEE 0.625 mg daily with MDPA 2.5 mg daily and found that EP HRT increased the risk for cardiovascular events [10,19].

RISKS ASSOCIATED TO HRT

Endometrial adenocarcinoma

Available data show that the use of unopposed estrogen therapy invariably leads to adenomatous endometrial hyperplasia, a presumed neoplasia precursor, and that it associates a fourfold to tenfold increased risk of endometrial adenocarcinoma in postmenopausal women, this increase being related to dosage and duration of treatment [5,6,19].

It has been demonstrated that adding a P to E-HRT markedly reduces the development of endometrial hyperplasia, being able to even cause regression of preexisting hyperplasia at higher doses [3]. Limited data suggest that the risk of endometrial cancer depends also on the type of P used, indicating that natural progesterone offers a diminished protection compare to dydrogesterone and other synthetic progestatives [5].

Given the above, it is now standard practice to add a P whenever E-HRT is given to a woman with an intact uterus [2,3,5,19].

Breast cancer

There appears to be a growing consensus that short-term E-HRT does not associate an increased breast cancer risk. However, giving that a few studies with small numbers of long-term E users have showed a modest increase in risk, the long-term use (>15 years) is still open to debate [3,20,21].

The risk of breast cancer seems to be greater when opting for EP than for E alone [5,21,22], although the preferential use of progesterone / dihydrogesterone may limit the additional risk for HRT related breast cancer, at least when the duration of treatment doesn't exceed 5 to 7 years [5]. Available data seem to suggest that there is even a slight diminution of risk with the use of CEE compared to placebo [22].

In addition, the type of P appears to influence the risk of EP-HRT related breast cancer, as there are 4 European cohort studies that report a lower risk for women using progesterone or dydrogesterone compared to combinations including other synthetic progestatives when treated for 5 years or less [5,20,23-25]. It is noteworthy that the WHI study, found that EP-HRT increased the risk for breast cancer [19].

Venous thromboembolism (VTE)

Clinical data shows no increase in the risk of VTE for postmenopausal women using oral E-HRP [3]. On the other hand, women using EP-HRT have two-to-five-fold higher risk for the development of VTE than nonusers [19,26-28].

The Heart and Estrogen/progestin Replacement Study (HERS) which assessed the administration of daily oral CEE 0.625 mg combined with MDPA 2.5 mg in 2,763 women with coronary artery disease (mean age 67 years) found that HRT users had a twofold increased risk of developing VTE (OR 2.08; 95% CI: 1.28-3.40) and pulmonary embolism (OR 2.86; 95% CI: 1.13-7.26). HERS does not contain data about estrogen-only and transdermal HRT preparations [19,27].

The WHI study also found that EP-HRT associates a twofold increased risk of VTE in users (OR 2.11; 95% CI: 1.58-2.82) [19].

Great caution should be exercised in recommending HRT to women who are at risk for vascular thrombosis or embolism. In the presence of these disorders, HRT should be interrupted. Transdermal E, however, may be used by patients with history of thromboembolic disease giving that it associates less hepatic production of clotting factors and theoretically implies less risk of thromboembolic disease [2,26].

Hypertension

Hypertension doesn't seem to be caused by postmenopausal HRT according to most available data, and it has been suggested that the therapy may even have a beneficial effect. But, given the occasional reports of marked, idiosyncratic hypertension attributed to E-HRT, blood pressure should be monitored shortly after initiation of therapy and periodically after [3,26].

Glucose tolerance

Estrogen improves carbohydrate metabolism, and this may be why many women with diabetes tolerate glucose better with E-HRT than without it. On the other hand, P seem to counteract this effect and decrease glucose tolerance. However, the doses used in HRT are lower than with combined oral contraceptives, and glucose tolerance deterioration rarely occurs as a result of EP-HRT [3,26].

EVALUATING THE INDIVIDUAL RISKS AND BENEFITS OF HRT

One way to evaluate HRT risks and benefits balance is to consider the change in life expectancy / mortality among patients. Available data suggest that EP-HRT decreases by 211 per 100,000 women, the total annual mortality among patients aged 65 to 74 years [3].

HRT must be individualized, by taking into account evidence-based treatment goals, patient's age, time since menopause, personal health risks and preferences in order to decide therapy initiation / continuation, and the balance of potential benefits and risks of HRT versus nonhormonal therapies [6].

For patients younger than 60 years or who are within the first 10 years from menopause onset and are without contraindications, the benefit-risk ratio should be favorable for treatment of VMS and for preventing bone loss and related fractures. Longer duration treatment may be more beneficial for E-HRT than for EP-HRT, based on the WHI RCTs. For women who initiate HRT more than 10 / 20 years from menopause onset (or when aged 60 years or older), the benefit-risk balance seems to be less favorable than for younger patients because of greater absolute risks of cardiovascular disease, stroke and VTE [6,26].

AVAILABLE HRT REGIMENS

Various treatment regimens are used to provide HRT (Table 1).

For patients that do not need endometrial protection, current recommendation is to use unopposed estrogen, so daily E-HRT is the most common method for hysterectomized women [3]. In non-hysterectomized women, HRT include both estrogens and progesterone, the latter having the purpose to counteract the negative impact the estrogen has on endometrial proliferation [1,5,7].

The estrogens most commonly used are micronized 17 β -estradiol, CEE (synthetic conjugated estrogens) and ethinylestradiol. CEE are isolated from the urine of pregnant mares and consist of estrone sulfate (less potent than estradiol) and a mixture of more than 10 minor components of different

active forms of estrogens (weak E agonists). CEE and estradiol are rapidly metabolized into less potent estrogens like estrone [6].

Some patients who use EP-HRT complain of severe side effects, like migraines, headaches or dysphoria, that persist even when changing the P or the dosage. Unopposed E with careful monitoring including annual endometrial biopsy may be an option in their case [2,29].

TABLE 1. HRT regimens [1,6,29]

Class	Substance (Route)
Estrogens	17- β estradiol (oral / transdermic / vaginal)
	Estradiol valerate (oral)
	Estriol (oral)
	Estradiol hemihydrate (vaginal)
Progestins	Natural progesterone (oral)
	Dydrogesterone (oral)
	Norethisterone acetate (oral)
	Drospirenone (oral)
	MDPA (oral)
	Norgestrel (oral)
	Chlormadinone acetate (oral)
	Medrogestone (oral)
	Cyproterone acetate (oral)
	Levonorgestrel IUD
Estro-progestins	CEE + MDPA
	Estradiol + Cyproterone acetate (oral)
	17- β estradiol + Drospirenone (oral)
	17- β estradiol + Dydrogesterone (oral)
	Estradiol valerate + MDPA (oral)
	17- β estradiol + Norethisterone acetate (oral)
17- β estradiol + Levonorgestrel (transdermic)	
Others	Tibolone (oral)
	Ospemifene (oral)
	Prasterone (DHEA) (vaginal)
<i>CEE – conjugated equine estrogens, MDPA – medroxyprogesterone acetate</i>	

HRT may be given on a cyclic schedule: an E for 25 days and a P added on days 1-12 / 14-25. Another option is to give E daily, and a P added for the first 12 days of the month. The progestin supplementation has a (considered by some) major disadvantage represented by the vaginal bleeding occurring after P withdrawal in as many as 97% of patients until age 60, and 60% of patients older than 65 years. Many women are reluctant to the returning of the menses, considering them “unnatural” after menopause and this can make them hesitant to start / continue HRT. Thus, it is important to inform them about the protective effect of P against endometrial adenocarcinoma and also to underline the fact that withdrawal menses are usually light, free of dysmenorrhea, of short duration (3-4 days) and predictable, regular withdrawal bleeding generally oc-

curing shortly after the P is stopped. A bleeding occurring before P is withdrawn usually indicates that the dosage should be increased, while a bleeding starting more than 4 days after P withdrawal must be investigated. For women taking EP-HRT, an endometrial biopsy is warranted only if unexpected, prolonged or excessive bleeding occurs [3,29].

Continuous daily administration of both E and P in another quite popular alternative with the advantage of achieving amenorrhea in approximately 60% of patients within 4 to 6 months. Most women using this regimen eventually achieve endometrial atrophy. Patients must be informed that frequent and unpredictable bleeding is not unusual during the first months of this therapy. Because of this bleeding, an endometrial biopsy should be obtained (to rule out hyperplasia) prior to initiating HRT [2].

Usually, it is recommended to opt for 17 β -estradiol or estradiol valerate in association with progesterone or dydrogesterone [5]. The combination of low-dose CEE / bazedoxifene may be an option for menopausal women intolerant or having contraindications to P [1].

Practitioners should use an appropriate HRT regimen (pharmacologic substance type, dose, combination, administration route and treatment duration to achieve clinical objectives, and also make

periodic reassessment of the eventual changes in a woman health status, and anticipated risks, benefits [6].

CONCLUSIONS

HRT can prevent some estrogen deprivation related health issues and should be recommended to most menopausal women in order to preserve their vitality and good health giving that, in most cases, more than one third of their lives is postmenopausal. HRT has proven very effective in the treatment of VMS and GSM and also to prevent bone loss and related fractures.

HRT implies risks that should be carefully weighted and individualized for each woman as these risks differ depending on type, dose, route of administration, duration of treatment, initiation moment and the need for a progestative, and periodic reevaluation of risk-benefits balance is mandatory.

Even though the management of menopausal symptoms through pharmacological and cognitive-behavioral therapy improves quality of life of affected women in the short term, there is a need for the development of strategies to modify menopausal health risks, in the long term.

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REFERENCES

- Akter N, Kulinskaya E, Steel N, Bakbergenuly I. The effect of hormone replacement therapy on the survival of UK women: a retrospective cohort study 1984-2017. *BJOG*. 2021 Nov 12.
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2002;288:321-333.
- McKeon VA. Hormone replacement therapy: evaluating the risks and benefits. *J Obstet Gynecol Neonatal Nurs*. 1994 Oct;23(8):647-57.
- Zhang GQ, Chen JL, Luo Y, Mathur MB, Anagnostis P, Nurmatov U, et al. Menopausal hormone therapy and women's health: An umbrella review. *PLoS Med*. 2021 Aug 2;18(8):e1003731.
- Gosset A, Robin G, Letombe B, Pouillès JM, Trémollières F. Menopause hormone treatment in practice. Postmenopausal women management: CNGOF and GEMVi clinical practice guidelines. *Gynecol Obstet Fertil Senol*. 2021 May;49(5):358-372.
- The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause*. 2017;24(7):728-53.
- Natari RB, Hollingworth SA, Clavarino AM, Dingle KD, McGuire TM. Long term impact of the WHI studies on information-seeking and decision-making in menopause symptoms management: a longitudinal analysis of questions to a medicines call centre. *BMC Womens Health*. 2021 Oct 4;21(1):348.
- Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril*. 2016 Dec;106(7):1588-1599.
- Sarrel PM, Sullivan SD, Nelson LM. Hormone replacement therapy in young women with surgical primary ovarian insufficiency. *Fertil Steril*. 2016 Dec;106(7):1580-1587.
- Kim JE, Chang JH, Jeong MJ, Choi J, Park J, et al. A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. *Sci Rep*. 2020 Nov 26;10(1):20631.
- Velentzis LS, Egger S, Banks E, Canfell K. Menopausal hormone therapy: Characterising users in an Australian national cross-sectional study. *PLoS One*. 2021 Aug 11;16(8):e0253725.
- Cauley JA, Robbins J, Chen Z, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290:1729-1738.
- Monteleone P, Mascagni G, Giannini A, Genazzani AR, Simoncini T. Symptoms of menopause – global prevalence, physiology and implications. *Nat Rev Endocrinol*. 2018;14(4):199-215.
- Polo-Kantola P. Sleep problems in midlife and beyond. *Maturitas*. 2011 Mar;68(3):224-32.
- Kravitz HM, Joffe H. Sleep during the perimenopause: a SWAN story. *Obstet Gynecol Clin North Am*. 2011 Sep;38(3):567-86.
- MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flashes. *Cochrane Database Syst Rev*. 2004;4:CD002978.
- The 2020 genitourinary syndrome of menopause position statement of the North American Menopause Society. *Menopause*. 2020; 27(9):976-92.
- Palma F, Volpe A, Villa P, Cagnacci A; Writing group of AGATA study. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: The AGATA study. *Maturitas*. 2016;83:40-44.
- Douketis J. Hormone replacement therapy and risk for venous thromboembolism: what's new and how do these findings influence clinical practice? *Curr Opin Hematol*. 2005 Sep;12(5):395-400.
- Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat*. 2008; 107:103-11.

21. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet*. 2019; 394(10204):1159-68.
22. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of Menopausal Hormone Therapy with Breast Cancer Incidence and Mortality During Longterm Follow-up of the Women's Health Initiative Randomized Clinical Trials. *JAMA*. 2020;324:369-80.
23. Cordina-Duverger E, Truong T, Anger A, Sanchez M, Arveux P, Kerbrat P, Guénel P. Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. *PLoS One*. 2013 Nov 1;8(11):e78016.
24. Bakken K, Fournier A, Lund E, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2011;128:144-56.
25. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2020; 371:m3873.
26. L'Hermite M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. *Climacteric*. 2013 Aug;16 Suppl 1:44-53.
27. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone replacement therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/Progestin Replacement Study. *Ann Intern Med*. 2000;132:689-696.
28. de Oliveira ALML, Paschôa AF, Marques MA. Venous thromboembolism in women: new challenges for an old disease. *J Vasc Bras*. 2020 Jul 6;19:e20190148.
29. Armeni E, Paschou SA, Goulis DG, Lambrinoudaki I. Hormone therapy regimens for managing the menopause and premature ovarian insufficiency. *Best Pract Res Clin Endocrinol Metab*. 2021 Dec;35(6):101561.