

Chapter 27

Hormonal Therapy after Menopause

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Introduction

Menopause is characterized by the exhaustion of the ovarian production of oocytes, estrogens and progesterone, with consequent permanent amenorrhea, anovulation and sterility. The ovarian production of testosterone is gradually reduced from the twenties onwards, but is maintained across natural menopause [1,2]. It is completely lost in surgical menopause (bilateral oophorectomy) [Tab.1].

The loss of sexual hormones has a widespread effect on all systems and organs, as virtually all cells of the female body have receptors for sexual hormones [3]. This loss accelerates the negative multi-systemic effects of ageing, with a further detrimental effect. Menopause is characterized by symptoms and signs of sexual hormone loss, with a spectrum of variability and severity, according to: age at menopause (the younger the women the higher the vulnerability) [4,5]; its etiology (spontaneous or iatrogenic, from benign or malignant conditions) [4-5]; the genetic inheritance of the organ vulnerability to this loss, the woman's general health status and life style [2,5] and the quality of medical care [5]. Predisposing, precipitating and maintaining factors, biological and psychosocial, specifically contribute to the pathophysiology of female sexual disorders during the menopausal transition [6]. Symptoms and signs of menopause can be attenuated by the possibility, availability and feasibility of Hormone Replacement Therapy (HRT) [6-10], now under further study [10-14].

Even the wording of HRT has been questioned [11,13,14]. Following the Women's Health Initiative (WHI) report [9], the National Institute of Health (NIH) suggested that a combination of estrogen and progestogen is not a physiological replacement. The US Food and Drug Administration (FDA) has recommended the use of the term HT (Hormone Therapy) as the more correct description of this treatment, an indication completely accepted by the North American Menopause Society position statement (October 2004) [11]. The ongoing international debate has now accepted HT as a comprehensive term, while maintaining HRT for the symptomatic woman [10,12,14], up to five years after the menopause. The acronyms currently used in the literature to describe different hormonal treatments are summarized in Tab.2. However, for ease of reading, the comprehensive word HT will be used, unless specific words are needed.

Current Controversy on HT

Epidemiological studies indicate that current key predictors of HT use are: *age at menopause* (the younger the women the higher the probability she will require and be prescribed HT); *type of*

menopause (surgical menopause is three times more likely to be hormonally treated) and *education and socioeconomic level* (women better educated and with higher socioeconomic background are more likely to require and use HT) (reviewed in [5]).

Up to 75% of women with a premature, early or natural menopause may complain of one or more impairing menopausal symptoms, affecting their quality of life, which may be alleviated or cured with appropriate HT [10-14,18-24].

Unfortunately, the Women's Health Initiative (WHI) publication [9] and the following data analysis [15,16] led to concerns, fear and distrust toward HRT, in women and in physicians [5]. WHI data exacerbated the worries previously raised by the Heart and Estrogen/Progestin Replacement Study (HERS I) [7] and HERS II [8]. The Million Women Study (MWS) [17], in spite of its lower level of evidence (II-2) compared to the WHI (I) and HERS I and HRS II (I), further increased concerns by the extensive negative media coverage it generated. Weaknesses and strength of the WHI have been discussed in previous papers [5,11-12,14,18,24,37]. Critical data emerging from the WHI are discussed under the paragraphs: "Indications for HT" and "Risks of HT."

Fear was triggered by the inappropriate media reading of odd ratios. A key practical recommendation, when discussing risk and benefit with patients, is to distinguish absolute risk/benefit from relative risk/benefit, which is expressed as a percentage increase or decrease in absolute risk. This means, for example, that the reported 26% increase in the relative risk of breast cancer in the WHI is actually an absolute excess of four breast cancers for 1000 women treated for 5 years or *less than one excess case per 1000 women per year of treatment*. [14]. The latter simple figure should be used. In recognition of this communication and risk perception problem, the Council for International Organizations of Medical Sciences (CIOMS) task force released its report in 1998, providing a risk categorization to assist health care professionals and the public when interpreting risks [discussed in 11]. In this context, risks are considered as follows:

- $< 1/1,000$ = rare
- $< 1/10,000$ =very rare

The meanings of absolute risks of HT are reviewed in detail in recent position papers [10-12].

Reactions to the findings of the Randomized Controlled Trials (RCT) on impact of HT on women's health have caused a significant drop in medical prescriptions. They have dramatically illustrated the uncertainty and the emotional vulnerability of the medical profession regarding the usefulness and even the safety of HT [5]. Authoritative position statements [10-12] and practical recommendations and guidelines [14,18-20] aimed at helping clinicians in clarifying the contradictory evidence emerging from the previous observational data vs the most recent RCT, HERS I, HERS II and WHI, have been published. Their conclusions and the most relevant published data will be the base of the present chapter, aimed at helping the clinician in his/her daily practice with the increasing population of postmenopausal women. Indeed, the negative domino effect of a symptomatic menopause may negatively affect the sexual well being of the woman and the couple, unless appropriately treated (see the review of RCT on HT and sexuality of Alexander et al. [21]; the review of observational studies on menopause and sexuality of Dennerstein et al [22], the comprehensive clinical approach to FSD and HT discussed by Graziottin and Basson [4], focused on premature menopause and sexuality, and by Graziottin [23] focused on natural menopause and senium.

Clinical approach to HT

HT consists of an estrogen (estradiol or equine conjugated estrogens) combined with a progestogen, in non-hysterectomized women. Progestogens are given either cyclically or continuously with the estrogen, to protect the endometrium from hyperplasia. They are not indicated in hysterectomized women. Different routes of administration are used: oral, transdermal, subcutaneous, intranasal and vaginal. Because of the lack of the first-pass effect on the liver, the non-oral route of administration may be preferable in women with hypertriglyceridemia, migraine headache or even increased risk of venous thrombosis [14]. Progestogens can be administered through an intrauterine device (IUD). Over 50 types and combinations of HT are available [24].

Initiation of treatment

As a general principle, HT should be initiated when menopausal symptoms occur [10-12,14,18]. In the perimenopause, treatment will be tailored according to the type of symptoms. HT includes:

- progestogens during the second half of the cycle, if menstrual disturbances are the main symptom;
- HT, if vasomotor symptoms have begun even in presence of sporadic menstrual periods, or if cycle regulation is needed;
- hormonal contraceptives (oral, preferably low-dose, patches or vaginal ring), if contraception is required.

The majority of metabolic changes, including bone resorption, start during the perimenopause.

Dose recommendation and hormone choice

a) **Estrogens.** The dose of estrogen should be the lowest needed to relieve symptoms effectively. Recommended starting dose include:

- 0.5-1mg 17 β -estradiol
- 0.3-0.45 mg conjugated equine estrogens
- 25-37.5 μ g transdermal (patch) estradiol
- 0.5mg estradiol gel
- 150 μ g intranasal estradiol

Symptoms should be reassessed after 8-12 weeks of treatment and the dose adjusted if necessary [14]. In about 10% of patients, especially women with Premature Ovarian Failure (POF) or early iatrogenic menopause, a higher dose may be required [10-12,14,18].

b) **Progestogens.** Three major classes of progestogens are currently available, according to their origin from 17-OH-progesterone, 19-nor-testosterone, 17 alpha-spirolactone (reviewed in [6]). They may interact with five different receptors: progestinic, estrogenic, androgenic, glucocorticoid and mineralcorticoid, with agonist, antagonist or neutral effect [6]. Their metabolic, endocrine and sexual action can therefore be very different from one progestogen to another. This is the major reason why some negative data emerging from RCT, such as WHI, using the specific progestogen Medroxyprogesterone Acetate (MPA) with a high mineralcorticoid affinity and therefore a negative vascular profile, *should not* be generalized to the whole class of progestogens [6, 14,18]. The choice of progestogens (progesterone or synthetic progestins) should be tailored according to the patient's therapeutic needs (androgenic, antiandrogenic, neutral) and metabolic risk profile [6]. The dose and schedule should be adjusted to: the dose of estrogens, to guarantee the endometrial protection; to the

regimen preferred (continuous combined versus sequential) and to the route of administration (oral, transdermal, subcutaneous, vaginal or intrauterine (Progestogen Releasing Intrauterine Device)).

Other hormonal options for the treatment of menopausal symptoms:

* **Androgens.** RCT indicate the positive effect of androgens, namely testosterone, on different domains of female sexual function [reviewed in 21 and 22]. The use of androgens locally for vulvar dystrophy and clitoral insensitivity is often overlooked, but is a very efficacious treatment for genital sexual dysfunction [14]. Dehydroepiandrosterone (DHEA) administration is able to improve the quality of life in elderly patients. It also determines an estrogen-like restoration of β -endorphin basal and stimulated level, indicating a modulation of the neuroendocrine function. In addition, the positive effect on Kuppermann score (which quantifies menopausal symptoms' severity) with no changes on endometrial thickness, suggests that DHEA administration in the postmenopause may be considered as a possible real replacement treatment [20]. However, no androgenic treatment for the menopause has yet been approved at the time this paper was written (November 2005).

* **Tibolone.** This molecule is a derivative of norethynodrel, a progestogen with androgenic activity. It has been defined as a selective tissue estrogenic activity regulator (STEAR). Tibolone is a prodrug that rapidly converts after intake in the intestinal tract and liver to various metabolites that are systemically active as progestogen, androgen or estrogen. It has different actions on different target organs, which provide an overall favorable risk-benefit profile [14, 19, 23, 26]. Clinically, tibolone treats menopausal symptoms, including hot flushes and vaginal dryness, as effectively as estrogen therapy, and, most importantly, improves sexual response, while having a positive effect on the bone [14,19]. Widely used across the world, it is not approved in the USA, at the time this paper was written (November 2005).

Duration of treatment

The duration of treatment is based on the indication and the persistence of symptoms. Guidelines and position statement [10-12, 14,18] recommend that:

- the appropriate indication, dose and type of HT should be re-evaluated annually;
- the need for continuing treatment to relieve menopausal symptoms can be determined only by temporarily discontinuing the therapy. In general, this can be considered after 2-3 years. If symptoms do not recur, HT does not need to be reinstated;
- long-term therapy, usually topical, i.e. vaginal, may be required for ongoing relief from the symptom of urogenital atrophy (see also the sub-chapters on arousal and sexual pain disorders).

Monitoring treatment

* **Pretreatment clinical assessment** should include history and physical examination, with measurement of weight and blood pressure. The history should be directed, in particular, to potential indications and contraindications (see below). Menopausal symptoms, menstrual and *sexual* history, co-morbidity between urogenital and sexual disorders [4, 23], personal and or family history of osteoporotic fracture, venous thromboembolism, breast cancer, cardiovascular disease and Alzheimer disease should be evaluated and reported in the medical record [12,14,18]. The clinical examination should include a complete breast and gynecological examination [12]. It should pay special attention to the vulvovaginal trophism, including the measurement of vaginal pH, the pelvic floor tonus, which may indicate specific non-hormonal –besides topical hormonal -

treatment to address urogenital and sexual co-morbidities [25,26] and the presence of painful vulvar, mid-vaginal and deep painful points (see also the sub-chapter on sexual pain disorders) [4,23,25]. Patients should be re-evaluated annually. Additional investigations should be guided by this evaluation [14].

Additional instrumental assessments:

- *Mammography*: frequency according to local national guidelines. When mammographic density is present, to avoid diagnostic difficulties, discontinuation of HT for 2-4 weeks before mammography can be considered;
- *Vaginal ultrasound and/or endometrial biopsy*: if indicated by abnormal vaginal bleeding;
- *Bone mineral density measurement* based on national guidelines [10-12,14,18];

Indications for HT and benefits

Menopausal symptoms and quality of life

Menopause related decline in estradiol has been linked to a decline in sexual interest, enjoyment, arousal and orgasm in observational studies [23] and has been found in RCT to have positive effects on a number of domains of sexual function (see the review of RCTs by Alexander et al [22]). The direction of causality is that decline in estradiol increases vasomotor symptoms, which affect mood, which then affects sexual response.

Autonomic disturbances such as hot flushes, sweating, insomnia and palpitations can be relieved by HT [2,4-6,10-12,14,18,26]. Other symptoms such as fatigue, irritability, nervousness and depressed mood may be improved [2,4-6,10-12,14,18]. Sexual symptoms, when caused by a domino negative effect consensual to the menopausal autonomic disruption, and loss of genital trophism, may be improved as well. In this way, the quality of life can be maintained. Progestogens, according to their structure, metabolic and endocrine profile [6,14,18], can potentiate or oppose the action of estrogens. Every systemic ET/EPT product is government-approved for this indication [11].

Premature menopause

Women undergoing premature menopause (PM) (either premature ovarian failure (POF) or iatrogenic) are exposed to the dramatic long term consequences of sexual hormones deprivation, the earlier the menopause, the worse the impact on general health and sexual well-being [4]. This neglected group of patients is increasing. Table 3 outlines the various etiologies underlying PM, including genetic, autoimmune, associated with chronic disease, as well as iatrogenic in the context of benign or malignant disease (reviewed in [4]). Spontaneous ovarian failure affects on average 1% of women under 40 years of age [27], although percentages as high as 7.1% have been recently reported [28]. The Study of Women Across the Nation (SWAN) [27], indicates that POF was reported by 1.1% of women. By ethnicity, 1.0% of Caucasian, 1.4% of African American, 1.4% of Hispanic, 0.5% of Chinese and 0.1% of Japanese women experienced POF. The differences in frequency across ethnic groups were statistically significant ($p=0.01$). Lifestyle related sociocultural factors may be important contributors to age at menopause, as well as modulators of its impact on sexual well being.

Iatrogenic menopause, for benign and malignant conditions, affects 3.4-4.5% of women under 40 [4,29,30], and up to 15% between 40 and 45 years of age. The 5-year survival for all malignancies in childhood and adolescence is 72% (up to 90% for some cancers) [31,32,33], with an increasing number of survivors facing the challenges of adulthood deprived of their gonadal hormones, unless an appropriate HT for dosage, type and *length of treatment* is prescribed. Premature menopause is associated with an accelerated risk of osteoporosis, and probably coronary heart disease [12,14,18] and Alzheimer disease. Distressing sexual disorders are more frequently reported in women with PM [4,34], particularly after bilateral oophorectomy. A recently published randomised placebo controlled trial was conducted in surgically menopausal women (aged 24-70) who developed stressful hypoactive sexual desire disorder [35]. Treatment with 300-µg/d testosterone patches on estrogen repleted women increased sexual desire and frequency of satisfying sexual activity and were well tolerated [35]. However, this treatment has not been approved at this time.

In PM women, the risk of breast cancer after HT corresponds to the risk found in premenopausal women of similar age who have not suffered an iatrogenic or premature menopause. Consensus therefore exists on the recommendation that women who have undergone premature menopause (unless associated with hormone-dependent cancer, such as breast cancer or genital adenocarcinomata) should be offered HT, *at least until the average age of menopause* (51 years) [10-12,14,18].

Urogenital and sexual symptoms

Atrophic changes in the urogenital tract and their consequences (e.g vaginal dryness, dyspareunia, urinary frequency and urgency, post-coital cystitis) are improved by estrogen therapy (ET). When prescribed *solely* for the treatment of such symptoms, topical low dose vaginal products are the treatment of choice [4-6, 10,12,14,18]. ET may well address the urogenital comorbidity [35] that increases with increasing age, unless appropriate ET is prescribed. Long-term treatment is often required as symptoms can recur on cessation of therapy. Every systemic and local ET/EPT product is government-approved for this indication [11].

Osteoporosis

Necessary but not sufficient measures in the prevention and treatment of postmenopausal osteoporosis include regular weight-bearing exercise, cessation of smoking, adequate calcium intake and insuring normal levels of vitamin D. Estrogens prevent postmenopausal bone loss and reduce fracture risk (as shown both in observational studies and in RCT) [8, 9], reviewed in [19]. Some progestogens (19-nor-testosterone derivatives) potentiate the action of estrogens. Low dose HT prevents the loss of spinal and hip bone mass both in recently post-menopausal women and in elderly patients. Standard dose HT lowers the risk of spine, hip and forearm fractures [10-12,14,18,19]. HT may be an initial option for osteoporosis prevention and for fracture risk reduction in the asymptomatic woman at significantly increased fracture risk. Such treatment could be the first step of a long term program, which may subsequently involve the use of selective estrogen receptor modulators (SERM), and/or bisphosphonates and tetiparatide, when indicated [10-12,14,18,19].

Colon cancer

EPT reduces the risk of colorectal cancer. Both previous observational data and the EPT part of the WHI trial show a significant reduced risk. It is unknown how long the effect of combined HT

persists after treatment is stopped or how HT affects mortality from colorectal cancer. The reduction of risk has not been shown with ET [12].

Diabetes

HT may decrease the risk of developing type 2 diabetes by increasing insulin sensitivity. The EPT part of the WHI study [9] as well as HERS [7,8] demonstrated a significant decreased risk of developing diabetes in hormonal treated women [12].

Other benefits

HT can slow the typical thinning of the skin and the mucosal atrophy that occurs after menopause. Lacrimal and salivary secretion are modulated by sexual hormones. Eye dryness and mouth dryness, increasingly complained of after the menopause, can be attenuated by HT. The positive impact of skin appearance and trophism can greatly improve personal confidence and feeling of well-being [4,14,23].

Tab.5 summarizes the latest recommendations of the European Menopause and Andropause Society, EMAS.[12]

Risks of Hormonal Therapy

Breast cancer

Breast cancer risk probably increases with EPT use beyond 5 years [11]. In absolute terms, this increased risk is small in the WHI, being 4 to 6 additional invasive cancers per 10,000 women who use it for 5 or more years and of possible statistical significance [11]. *There is no mortality difference between users and non users.* Women in the estrogen-only (CEE) arm of the WHI demonstrated no increased risk of breast cancer after an average of 6.8 years of use. There was a non significant trend toward *reduction* of breast cancer in women overall, with this trend strongest in women under age 60 (7 fewer breast cancers per 10,000 women) [11,12]. Specific subgroups may be affected in different ways [11,12]. To place the above in perspective, the increased risk of diagnosis of breast cancer with HT is similar to the increased risk of it with such factors as an early menarche (before age 11 years), a late first pregnancy (over 35), nulliparity and moderate alcohol consumption (>20g/day). *The increased risk attributed to HT is much less than that associated with obesity* [36]. Due to the risk of recurrence, HT should not be prescribed to women with previous breast cancer (Grade B recommendation) [12].

Endometrial cancer

In women with an intact uterus, unopposed ET causes a dose and duration dependent increase in the risk of endometrial hyperplasia and cancer. *Estrogen should therefore be combined with progestogen therapy* (Grade A recommendation). Endometrial protection is currently the only menopause related indication for progestogen use [10,-12,14,18,36]. No increased risk of endometrial cancer has been found with continuous combined regimens.

Ovarian cancer

Observational studies and the WHI indicate that EPT may be associated with a slightly, albeit significant, risk of epithelial ovarian cancer after long term use (>10 years) [12]. However, with continuous combined therapy this risk does not seem apparent.

Venous thromboembolism

HT should not be prescribed to women with a previous episode of deep venous thromboembolism (DVT) (Grade A recommendation). HT increases risk of DVT three fold with the highest risk occurring in the first year of use. The overall risk in menopausal women age 50-59 is of the order of 3-4 in 10,000 per year. The absolute rate increase is impacted by Body Mass Index (BMI) and genetic predisposition.

The absolute risk of pulmonary embolism (PE) based on data from all trials implies that in 1000 women 50-59 years of age, taking HT for 5 years there would be an additional 2 cases [12]. According to CIOMS criteria, this is a rare event [11]. Transdermal estradiol could be different in that the metabolic impact on thrombophilia is different according to the route of administration, being higher with oral CC.

Stroke

HT should not be prescribed to women with previous stroke (Grade A recommendation) [12]. The WHI trial evidence that both ET and ERT increase the risk of stroke, with an excess risk of 8 more strokes per year for every 10,000 women on HT. When separating by stroke subtypes, ERT was associated with an increased risk of ischemic stroke only. In women 50-59 years of age, five years use of HT would yield 1 additional case of stroke per 1000 women [12], a rare event according to CIOMS criteria [11].

Gallbladder

The WHI confirmed the observation of HERS that HT increases the risk of gallbladder disease. As gallbladder disease increases with ageing and with obesity, HT users may have a silent pre-existing disease [24].

Controversial risk/benefit issues and “window of opportunity”

Based on observational studies [38, 39], prevention of coronary heart disease and of Alzheimer disease were considered an indication for HT. The recent RCT (WHI and HERS I and HERS II) questioned this indication. Accurate revision of data per cohort of age suggest that *HT* prescribed *soon after the menopause may have a favourable protective effect on all vessels*, when treated women are still relatively healthy. HT may precipitate adverse vascular events when prescribed later in life, when vascular atherosclerotic damage has already been established. Similar mechanisms seem to be valid for the brain.

The concept of “*window of opportunity*” [14] suggests therefore that *timing of HT* may be critical in modulating positive or adverse effects. In particular:

- **HT may have a positive cardiovascular effect when prescribed during and after the menopausal transition [14];**
- **HT should *not* be used as prevention against CHD (Grade A clinical recommendation).** Results from both the secondary prevention HERS and the EPT of the WHI study show that EPT does not confer cardiac protection and may increase the early risk of CHD. However, the information from the ET WHI study indicates no harmful effect of ET on the CHD rate. The concept of either “window of opportunity” or of “therapeutic window” may help to understand the contradictory data between early observational data and the HERS and WHI trial [14];
- **HT should *not* be used as a prevention against Alzheimer disease (Grade A clinical recommendation).** HT does not improve *established* brain damage. The WHI found a two-fold risk of dementia (possibly of thrombotic origin), significant in women only over the age of 75. Deterioration of cognitive functions in the WHI was found in women over age 65, especially in those with lower cognitive function at the initiation of treatment. However, the cohort analysis, indicating a cognitive benefit for women on HRT soon after the menopause, suggests that the concept of “therapeutic window” may apply to brain health as well.

Contraindications

According to regulatory authorities, contraindications can be summarized as follows [36]:

- Current, past or suspected breast cancer
- Known or suspected estrogen-dependent genital malignant tumors (e.g. adenocarcinoma of the endometrium, ovary and cervix)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary thromboembolism)
- Active or recent arterial disease (eg. angina, myocardial infarction)
- Untreated hypertension
- Active liver disease (hepatitis)
- Porphyria cutanea tarda (an absolute contraindication)
- Known hypersensitivity to the active substances or to any of the excipients

Therapeutic options and alternatives

When HT is not tolerated, or is contraindicated, a number of alternative therapies can be considered [14,37,40,41];

- Phytoestrogens-rich herbal extracts, may improve menopausal symptoms, although such improvement may be similar to that seen with placebo. The plausibility of this effect is based on the affinity of phytoestrogens for the estrogen beta receptors. The total picture produced by conscientious review of the studies is bleak overall, but there seems to be good reason to pursue the possibilities inherent in soy protein with phytoestrogens in populations of women who endogenously produce equol [40]. However, the phytoestrogen’s action is currently being investigated with contradictory findings. No conclusions on their specific role, efficacy dose,

side effects and contraindications can be determined at the moment of this writing (November 2005) [14,37,40,41];

- Phyoestrogens may slow the rate of bone loss, but fracture risk reduction has not been demonstrated [14, 19,37];
- α -Adrenergic agonists, such as clonidine, are moderately effective in relieving hot flushes;
- High doses of progestogens (5-10 mg Norethisterone acetate, (NETA), 20-40 mg MPA or megestrol acetate/day) effectively reduce hot flushes. Long term safety on the breast has not been demonstrated [14,19];
- Neuroactive drugs, eg. selective serotonin receptor inhibitors (SSRI), are able to relieve vasomotor symptoms with moderate efficacy and may be tried for short periods when HT is contraindicated or not desired [42];
- Recent reports, including a RCT in 420 breast cancer patients [43], suggest that gabapentin, an antiseizure medication, reduces hot flushes;
- Bisphosphonates can be used to treat osteoporosis, especially in older post-menopausal women with a history of osteoporotic fracture [14,19,37];
- Selective Estrogen Receptor Modulators (SERMs), such as raloxifene, are licensed for the prevention and treatment of spinal osteoporosis in postmenopausal women. They have not been shown to reduce hip fracture risk. In early postmenopausal women, SERMs are not able to reduce the vasomotor symptoms and may make them worse [14,44]. Preliminary evidence suggests that they may reduce breast cancer risk.

Conclusions

Healthy life styles, with emphasis on exercise, dietary intake and cessation of smoking is recommended, to increase the quality of life and reduce the risk of cardiovascular disease, osteoporotic fractures and also breast cancer, before and after menopause.

With the current level of evidence, HT should only be prescribed when it is clearly indicated, primarily *for symptom relief*. In this context, there is no effective alternative to estrogen or estrogen/progestogen treatment. HT has a specific role in women with premature menopause, and should be considered until the age of natural menopause (51 years). It has numerous beneficial effects, if prescribed soon after the menopause, when the “window of opportunity” potentiates its beneficial impact on likely healthy organs and tissue. HT involves some additional risks of venous thromboembolic disease, stroke and breast cancer after long term therapy. The incidence of these risks is evaluated as rare or very rare, according to CIOMS’ criteria. The need to continue with treatment and the indications for HT should be reviewed regularly when used in the long term. Constant updating is required in the rapidly evolving field of menopausal management.

References

1. Burger HG, Dudley EC, Hopper JL, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. *J Clin Endocrinol Metab* 1999;84:4025–30.

2. Lobo RA. Treatment of the Postmenopausal Woman: Basic and Clinical Aspects. Lippincott Williams & Wilkins: Philadelphia, 1999.
3. Gronemeyer H, Gustafsson JA, Laudet V. Principles for modulation of the nuclear receptor superfamily. *Nature* 2004; 3:950-964.
4. Graziottin A, Basson R. Sexual dysfunction in women with premature menopause. *Menopause*. Nov-Dec 2004;11(6 Pt 2):766-777.
5. Graziottin A. The woman patient after WHI. *Maturitas* 2005;51(1):29-37
6. Graziottin A, Leiblum SR. Biological and psychosocial pathophysiology of female sexual dysfunction during the menopausal transition *J Sex Med* 2005; Supp.3; 133-145
7. Hsia J, Simon JA, Lin F, et al. Peripheral arterial disease in randomized trial of estrogen with progestin in women with coronary heart disease: the Heart and Estrogen/progestin Replacement Study (HERS I) *Circulation* 2000;102:2228-2232
8. Grady D, Herrington D, Bittner V, et al. for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II) *JAMA* 2002;288:49-57
9. Writing Group for the Women's Health Initiative Investigators. Risk and benefits of estrogens plus progestins in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321:333
10. Writing Group of the International Menopause Society Executive Committee. Guidelines for the hormone treatment of women in the menopausal transition and beyond *Climacteric* 2004;7:8-11
11. The North American Menopause Society Position statement. Recommendations for estrogen and progestogen use in peri and postmenopausal women: october 2004 *Menopause* 2004; 11 (6): 589-600
12. Skouby SO and the EMAS Writing Group (*David Barlow, Martina Dören, Göran Samsioe, Anne Gompel, Amos Pines, Farook Al-Azzawi, Alessandra Graziottin, Decebal Hudita, Erdogan Ertüngealp, Joaquin Calaf-Alsina, Serge Rozenberg and John C. Stevenson*) Climacteric medicine: European Menopause and Andropause Society (EMAS) Position statements on postmenopausal hormonal therapy *Maturitas* 2004; 48:19-25
13. Sturdee DW, MacLennan A. HT or HRT, that is the question? (editorial). *Climacteric* 2003; 6:1
14. Burger H. and the IMS Writing group: Practical recommendations for hormone replacement therapy in the peri and post menopause *Climacteric* 2004; 7:1-7
15. Chlebowsky RT, Hendrix SL, Langer RD, et al, for the Women's Health Initiative Investigators. Influence of estrogens plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003; 289:3243-3253
16. Manson JE, Hsia J, Johnson KC, et Al. for the Women's Health Initiative Investigators. Estrogens plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534
17. Million Women Study Collaborators. Breast cancer and hormone replacement study. *Lancet* 2003;362:419-27

18. Naftolin F, Schneider HPG, Sturdee DW. and The Writing Group of the IMS Executive Committee –Guidelines for the hormone treatment of women in the menopausal transition and beyond- Position statement by the Executive Committee of the International Menopause Society, *Maturitas*, 2004; 48:27-31
19. Genazzani AR, Gambacciani M, Schneider HPG, Christiansen C. Controversial issues in climacteric medicine IV. Postmenopausal osteoporosis: therapeutic options *Climacteric* 2005;8-99-109
20. Genazzani AR, Gambacciani M, Simoncini, Schneider HPG, Controversial issues in climacteric medicine. Series 3rd Pisa workshops "HRT in Climacteric and aging brain" *Maturitas* 2003; 46:7-26
21. Leventhal Alexander J, Kotz K, Dennerstein L, Kutner SJ, Whallen K, Notelovitz M. The effects of menopausal hormone therapies on female sexual functioning: Review of double-blind randomized controlled trials. *Menopause* 2004; 11 (4):749-765
22. Dennerstein L, Alexander JL, Kotz K. The menopause and sexual functioning: a review of the population-based studies. *Annu Rev Sex Res* 2003;14:64–82.
23. Graziottin A. Sexuality in Postmenopause and Senium. In: Lauritzen C, Studd J, eds. *Current Management of the Menopause*. London: Martin Dunitz: 2004. pp 185-203.
24. Rees M Unravelling the confusion about HRT in women. *Journal of Men's Health & Gender* 2005; 2(3): 287-291
25. Graziottin A. Treatment of sexual dysfunction. in: Bo K, Berghmans B, van Kampen M, Morkved S. (Eds), *Evidence Based Physiotherapy for the Pelvic Floor - Bridging Research and Clinical Practice*, Elsevier, Oxford, UK (2005, in press)
26. Donati Sarti C, Chiantera A, Graziottin A, Ognisanti F, Sidoli C, Mincigrucci M, Parazzini F. Gruppo di Studio IperAOGOI Hormone therapy and sleep quality in women around menopause *Menopause*. 2005; 12 (5): 545-551
27. Luborsky, JL, Meyer,P, Sowers, MF, Gold, EB, Santoro, N. Premature menopause in a multiethnic population study of the menopause transition. *Hum Reprod* 2003; 8(1):199-206.
28. Adamopoulos DA, Karamertzanis MD, Thomopoulos A, Pappa A, Koukkou E, Nicopoulou SC. Age at menopause and prevalence of its different types in contemporary Greek women. *Menopause* 2002;9(6):443-448.
29. Anasti JN. Premature ovarian failure: an update. *Fertil. Steril* 1998,70:1-15.
30. Laml T, Schultz-Lobmeyr I, Obruca A, et al. Premature ovarian failure: etiology and prospects. *Gynecol Endocrinol* 2000;14:292-302.
31. Rauck A, Green DM, Yasui Y, Mertens A, Robinson LL. Marriage in the survivors of childhood cancer: a preliminary study description from the Childhood Cancer Survivor Study Medical and Pediatric. *Oncology* 1999;33:60-63.
32. Larsen EC, Muller J, Schmiegelow K, Rechnitzer C, Andersen AN. Reduced ovarian function in long term survivors of radiation- and chemotherapy-treated childhood cancer. *J Clin Endocrinol Metab* 2003;88:5307-5314.
33. Thomson, AB, Critchley, HOD, Kelnar, CJH, Wallace WHB. Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. *Bailliere S Best Pract Res Clin Endocrinol Metab* 2002;6(2):311-334

34. Dennerstein L, Koochaki PE, Barton I, Graziottin A. Surgical menopause and female sexual functioning: a survey of western european women. *Menopause* (2005 in press)
35. Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA et Al. Safety and efficacy of a testosterone patch for the treatment of Hypoactive Sexual Desire Disorder in Surgically Menopausal Women *Arch. inter Med* 2005; 165: 1582-1589
36. Simunic V, Banovic I, Ciglar S, Jeren L, Pavicic Baldani D, Sprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynecol Obstet* 2003;82:187-197.
37. IMS Writing Group. Hormone Replacement Therapy – practical recommendations – meeting report. *Climacteric* 2004; 7 (Suppl) I:11-35
38. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MI A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-941.
39. Grodstein F, Stampfer MI, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease *N Engl J Med* 1996; 335:453-461
40. Speroff L. Alternative therapies for postmenopausal women. *Int J Fertil Womens Med.* 2005; 50(3):101-14.
41. Haimov-Kochman R, Hochner-Celnikier D. Hot flashes revisited: pharmacological and herbal options for hot flashes management. What does the evidence tell us? *Acta Obstet Gynecol Scand.* 2005 Oct;84(10):972-9. Review.
42. Nagata H, Nozaki M, Nakano K. Short-term combinational therapy of low-dose estrogen with selective serotonin re-uptake inhibitor (fluvoxamine) for oophorectomized women with hot flashes and depressive tendencies. *J Obstet Gynaecol Res.* 2005; 31(2):107-14.
43. Pandya KJ, Morrow GR, Roscoe JA et Al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet.* 2005 Sep 3-9;366(9488):818-24.
44. Martino S, Disch D, Dowsett SA et Al. Safety assessment of raloxifene over eight years in a clinical trial setting. *Curr Med Res Opin.* 2005;21(9):1441-52.

Table 1 - Typical premenopausal and postmenopausal serum steroid hormone concentrations

Steroid Hormone	Typical Serum Level, pg/mL		
	Reproductive Age	Natural Menopause	Iatrogenic Menopause
Estradiol	100–150	10–15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
DHEA	5000	2000	1800
DHEAS	3,000,000	1,000,000	1,000,000

DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate.

Adapted from Lobo RA, 1999 [2]

Table 2 - Terminology for peri- and postmenopausal therapy *

ET	Estrogen therapy
EPT	Combined estrogen and progestogen therapy
Progestogen	Encompassing both progesterone and progestin
Systemic ET/EPT	Preparations of ET or EPT that have a systemic, not solely vaginal effect
Local ET	Preparations of ET that have a predominantly vaginal, not systemic, effect
HT	Hormone therapy (encompassing both ET and EPT) in <i>asymptomatic</i> women such as those in RCT (late therapy)
HRT	Hormone Replacement Therapy, which includes administration of hormones to <i>symptomatic</i> estrogen deficient women, in the late perimenopause or early postmenopause, such as those in observational studies
CC-EPT	Continuous combined estrogen progestogen therapy (daily administration of both estrogen and progestogen)
CS-EPT	Continuous-sequential estrogen-progestogen therapy (estrogen daily, with progestogen added on a set sequence)

* adapted from Sturdee & MacLennan, 2003 [13], the North American Menopause Society Position statement [11], the European Menopause and Andropause Society position statement [12], and the International Menopause Society (IMS) Hormone Replacement Therapy- practical recommendations [14]

Table 3 - Factors affecting sexual outcome after premature menopause

1. Etiological Factors

- POF vs. PM associated with chronic disease
- iatrogenic: benign vs. malignant
- debility from associated medical conditions
- severity of the residual chronic pelvic pain & deep dyspareunia in endometriosis
- type of cancer, stage and prognosis, conservative vs. radical surgery
- cancer hormone-dependence (breast cancer and genital adenocarcinomata)
- adjuvant chemo/radiotherapy/bone marrow transplant.

2. Factors Associated with Life Stage

- more complex negative effects on sexuality in younger women
- teenage PM interrupts psychosexual maturity
- fulfilment of life goals prior to diagnosis

3. Factors Personal to the Woman

- coping strategies
- premenopausal sexual experiences and quality
- premorbid personality and psychiatric status
- previous erotic self-perception, sexual self-confidence
- education, social and professional role

4. Contextual Factors

- family dynamics (attachment vs. autonomy, in peripubertal children and adolescents)
- couple's dynamics and marital status
- support network (family, friends, colleagues, self-help groups)
- quality of medical and psychosexual care
- ethnicity & sociocultural issues

Legend: POF: premature ovarian failure; PM: premature menopause

Adapted from Graziottin & Basson, 2004 [4]

Table 4 - EMAS* 2005 position statement on peri- and post-menopausal hormonal therapy, with grade of recommendation

Positive statements:

- **Life style management**, with emphasis on exercise, dietary intake and cessation of smoking is recommended, to increase the quality of life and reduce the risk of cardiovascular disease, osteoporotic fractures and also breast cancer (**Grade A clinical recommendation**).

- **Systemic ET or EPT alleviates moderate and severe climacteric symptoms, especially vasomotor symptoms (Grade A recommendation).** No alternative treatment exists with similar effect.
- **HRT can beneficially affect QoL in women with climacteric symptoms (Grade A-B clinical recommendations).** The effect is independent from the route of administration.
- **An overall beneficial risk-benefit ratio of HRT in women with an early (<45 years) natural or iatrogenic menopause is documented (Grade A-B recommendation).** In particular, the risk of breast cancer corresponds to the risk found in premenopausal women of similar age, who have not suffered an iatrogenic or premature menopause.
- **ET and EPT reduce the risk of both spine and hip as well as other osteoporotic fractures.** HRT is an effective method of preventing fracture in **all age groups** of women who are most susceptible (**Grade A recommendation**). HRT may be the best option in young women or menopausally symptomatic women. Alternatives to HRT use are available and may generally be preferable for the long term prevention and treatment of osteoporosis in elderly women.
- **HRT decreases the risk of developing type 2 diabetes (Grade A-B recommendation).**

Risks and controversies:

- **HT should *not* be used as prevention against CHD (Grade A clinical recommendation).** Results from both the secondary prevention HERS and the EPT of the WHI study show that EPT does not confer cardiac protection and may increase the early risk of CHD. However, the information from the ET WHI study indicates no harmful effect of ET on the CHD rate.
- **HT should *not* be used as prevention against Alzheimer disease (Grade A. clinical recommendation).** HT does not improve *established* brain damage.
- **HRT is associated with an increase risk of breast cancer.** The magnitude of the excess relative risk is greater when estrogen is combined with progestogen, sequentially or continuously. The absolute excess risk corresponds to 1-2 cases per 100 women among the age groups of 50 to 70 years of age.

adapted from S. Skouby [12] and the EMAS Writing Group: *Sven O. Skouby (President), David Barlow, Martina Dören, Göran Samsioe, Anne Gompel, Amos Pines, Farook Al-Azzawi, Alessandra Graziottin, Decebal Hudita, Erdogan Ertüngealp, Joaquin Calaf-Alsina, Serge Rozenberg and John C. Stevenson*

* **EMAS: European Menopause and Andropause Society, which has 21 affiliated National Menopause Societies**

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