Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 positions statements on peri- and postmenopausal hormone replacement therapy


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Abstract
In women experiencing distressing climacteric symptoms during the peri- and postmenopause there is conclusive evidence from abundant randomised controlled trials that systemic hormone replacement therapy (HRT) of any type affords symptom relief, with no alternative treatment producing similar effect. Though this evidence is accumulating, the question of how to provide best clinical practice in an attempt to both alleviate the menopausal symptoms and prevent the more long-term postmenopausal degenerative diseases is still under debate. When providing climacteric medicine, the dose and regimen of HRT needs to be individualised based on the principle of choosing the lowest appropriate dose in relation to severity of symptoms and on the menopausal age. However, few long-term data on different HRT formulations exist in symptomatic women, which also account for baseline risk of cardiovascular disease (CVD), breast cancer and osteoporosis. In most cases an individualized prescription together with life-style management will sustain possibilities for net beneficial effects on climacteric symptoms, quality of life (QoL), sexuality and osteoporosis, with only rare risk of severe adverse effects. With the perspective provided by recent epidemiological findings, not least from the estrogen only arm of the Women’s Health Initiative Study (WHI), EMAS supports research activities in symptomatic women with new HRT formulations in order to affect positively the balance of clinical benefit and risk, including specific information on QoL and also account for the traditional differences in treatment modalities between the US and Europe, and the difference in of BMI, life-style and diet. In women experiencing an early menopause (<45 year) current data support a specific overall benefit of HRT. At present, more long-term systemic HRT may be considered in women at high risk of osteoporotic fractures, in particular when alternate therapies are either inappropriate or insufficiently effective, as benefits will outweigh any risks. In contrast, urogenital symptoms may be addressed efficiently and safely with long term local estrogen therapy.

Introduction
EMAS considers that the clinicians’ main goal is to provide safe and effective relief of climacteric complaints, and advice in all aspects of climacteric medicine. Even if relative risks and benefits of HRT may appear impressive, the absolute figures are generally much smaller and may or may not apply to a given individual or situation in clinical practice. Particularly in symptomatic women the phrasing HRT should be preferred to hormone therapy (HT) which may be appropriate for more long-term therapy. There are few absolute indications and contra-indications for HRT, but it is now timely for both the health care provider and the user to re-appraise the risk/benefit situation. It is evident from both
meta-analysis on observational studies and the recent large randomized clinical trials (RCTs), the Heart and Estrogen/progestin Replacement Study (HERS), the Estrogen Replacement and Atherosclerosis Study (ERAS) and the WHI, that the information on the risks and benefits associated with HRT use in peri- and postmenopausal women must be weighed against the expected morbidity in relevant age groups and against existing individual risk factors. WHI and HERS involved predominantly asymptomatic postmenopausal with mean ages of 63 and 67, respectively. Hence external validation in younger more relevant age groups is crucial for translating study results into best clinical practice. Moreover the most used hormonal compounds, the average BMI, the diet, the prevalence of CVD, breast cancer and osteoporosis are different in Europe compared to the US. Notwithstanding the efforts made by the European Committee for Proprietary Medicinal Products (CPMP) in 2003 to harmonise prescribing information for all HRTs following the work of an expert group formed by the European Agency for the Evaluation of Medicinal Products (EMEA), the attitude of clinicians therefore still remains mismatched throughout Europe in particular towards what is the minimum effective HRT dose, what is the shortest duration and which alternative therapies are equivalents to HRT for prevention of postmenopausal osteoporosis.

Considering the source of evidence, observational studies have the advantages of being able to include large numbers of subjects and long-term follow-up, but the disadvantages of incomplete adjustment for confounding factors such as time trends, heterogeneity between users and non-users (healthy user effect) and also imprecise information on HRT dosage and type. In contrast RCT studies are widely acknowledged as the gold standard of clinical trials because they use the study design least affected by bias and, therefore, have the greatest objectivity. The methodology is, however, not flawless. It can only study perceived benefits, and the use of exclusion and inclusion criteria together with the planned visits can influence life style. RCTs select a specific population, emphasize short term effects in new acceptors, and study relatively small numbers due to costs. The results of a given RCT can only be applied to the specific population, the considered treatment, and circumstances applicable to the study in question. Subgroups of individuals may react in a unique way to medication and also influence a placebo arm. In addition, the interventions usually do not allow clinical adaptability to the treatment. Consequently, no single study should lead to general health recommendations.

Considering the most recent finding from the estrogen only arm of the WHI study it is essential to improve our current knowledge on risks, benefits and unsolved clinical issues, since estrogens remain the most efficient and cheapest therapy of clinical symptoms. EMAS has previously (1) published a position paper reflecting the clinical conclusions drawn by the Society and the affiliated member societies on the ongoing debates related to the recent clinical HRT trials and the recommendations made by the regulatory authorities. With this paper EMAS has updated its clinical recommendations, following the same procedures as with the previous version in retrieving source data and in obtaining endorsement from the affiliated members translating the message into evidenced based (Table 1) clinical recommendations.

Recommendation Statements for Clinical Practice

• Terminology for peri- and postmenopausal therapy:
  ET: Estrogen therapy
  EPT: Combined estrogen and progestogen therapy
  Progestogen: Natural or artificial compounds with progesterone like effect
  HRT: Hormone replacement therapy (local or systemic ET, EPT or progestogen, regardless of the route of administration)
• **Biological identity of products**
  Systemic HRT administered as EPT has the two principal components, estrogen and progestogen. Both hormones may be natural or artificial in constitution. Therefore it may be of clinical relevance to discuss specific drug classes, but the results from large epidemiological studies are in general assumed to apply to all systemic HRT regiments regardless of hormonal structure or route of delivery. The principal difference between oral and non-oral (transdermal, subcutaneous, nasal) route of administration is the first-pass metabolism in the gut and liver changing markedly the pharmacokinetics of the hormonal compound. As estrogen, natural estradiol valerate or micronized 17-β estradiol is often used in Europe whereas the conjugated equine estrogen (CEE) derived from pregnant mare’s urine is the preferred product in the US. After oral intake the equipotent dose of 2 mg 17-β estradiol corresponds to approximately 0.625mg of conjugated estrogens and to 50 µg delivered by patches or 1.5 mg given as percutaneous gel.

  Progesterone is not available from any natural source without extraction and synthesis. In contrast to progesterone, the progestogens used in HRT are all rapidly absorbed after oral intake. The most common products are those based on the C19 steroid testosterone (i.e. norethisterone, levonorgestrel), the 17_-hydroxyprogesterone derivatives (i.e. medroxyprogesterone acetate (MPA), megestrol acetate), 19-norprogesterone derivatives (i.e. nomegestrol, promegestone, trimegestone) or the retroprogesterone, dydrogesterone.

  Endometrial protection can be obtained with all the progestins when given sequentially or continuously in systemic HRT.

• **Route of administration**
  The epidemiological data cannot discriminate in detail between pharmacodynamic effects of systemic oral or non-oral treatment. In contrast, a single case-control study reported no increase in the risk of VTE using transdermal estradiol. Concerning the risk of breast cancer, a single cohort study did not report any increase in the risk of breast cancer with transdermal estradiol combined with micronized progesterone in contrast to transdermal estradiol combined with synthetic progestogens. However this single finding requires much further study confirmation before any clinical recommendations can be made.

  The use of an intrauterine progestogen delivering system is promising, but endometrial safety data are still awaited.

• **Continuous versus sequential EPT**
  The recent RCTs were conducted with continuous combined regimens. Cohort and case-control studies do not allow conclusions in favour of any regimen with regard to the breast. Concerning the cardiovascular risk, no information is available for this comparison, and there are no additional data from other RCTs comparing other relevant clinical endpoints during systemic sequential versus continuous combined EPT.

• **Clinical examination prior to prescription -monitoring**
  The clinical examination will include a complete questionnaire about the personal and familial medical and gynaecological history of the patients, sexuality, evaluation of the risk for cardiovascular disease, breast cancer and osteoporosis. A questionnaire on detailed diet and calcium intake, exercise, and sunlight exposure is warranted. The procedure should include a gynaecological and breast examination, and measurement of blood pressure and BMI.
Pre-prescription mammograms with follow-up every 2 years may be considered. The clinical follow-up will include regular examinations on a yearly basis. An educational effort should address, smoking risks, exercise, and appropriate interventions on metabolic abnormalities.

- **Early or premature menopause (<45 years)**
  Current data support an overall beneficial risk benefit ratio of HRT in women with natural or iatrogenic premature menopause (Grade A-B clinical recommendation). In particular the risk of breast cancer after HRT corresponds to the risk found in premenopausal women of similar age who have not suffered a premature menopause. Women with premature menopause are significantly more distressed by sexual dysfunction(s) precipitated or maintained by the loss of sexual hormones. Their – and their couple’ - sexuality may specifically benefit from a well tailored HRT.

- **Treatment of vasomotor symptoms**
  There is compelling evidence (Grade A clinical recommendation) that systemic ET or EPT, alleviates climacteric symptoms, especially vasomotor symptoms and sleep disturbance. Improvement is usually obtained within a few weeks. The beneficial effect on vasomotor symptoms is independent of route of administration, and is seen in the late perimenopausal period as well as after the menopause. Effects of ET are present in low dose (0.25 – 0,50 mg oral β-estradiol) and may be enhanced in EPT. As progestogen is only used for endometrial safety, women without a uterus should not usually be prescribed a progestogen. Although self-limiting, 20% of all women will still endure distressing vasomotor symptoms more than 4 years following the menopause. The incidence of hot flushes after cessation of HRT has not been studied in detail and benefits from gradual treatment withdrawal versus abrupt cessation have not been fully elucidated.

- **Quality of life**
  HRT has a beneficial effect on the health related QoL) in women with climacteric symptoms (Grade A-B clinical recommendation). The beneficial effect on vasomotor symptoms is independent of route of administration, and is seen in the late perimenopausal period and after the menopause. Evidence from RCT indicates as well the specific benefits HRT can give to different dimensions of women’s sexuality (increase of sexual desire, sexual arousal, orgasm and reduction of vaginal dryness and dyspareunia). Validated measurement of QoL or extended life quality is essential in climacteric medicine. Using mathematical modelling, postmenopausal women with mild to severe symptoms, with little risk of CVD and with HRT use for 2 years, may add 3 to 4 months or 7 to 8 months of quality adjusted life expectancy respectively. In clinical practice, the individual QoL improvement can also be judged by using a validated self-rating score. In a subset of in the WHI QoL, there was no effect of EPT on perceived general health, vitality, mental health, depressive symptoms or sexual satisfaction. There was only a small benefit on sleep disturbance. This, of course, is hardly surprising, given that the women were largely asymptomatic with respect to menopause symptoms.

- **Urogenital and sexual symptom**
  Symptoms such as vaginal dryness, soreness, dyspareunia, recurrent vaginitis and cystitis from colonic germs, post coital cystitis, nocturia, urinary frequency and urgency respond well to estrogens (Grade A recommendation). Improvement may take several months and in cases of severe atrophy, initial combination of EPT and local therapy may be followed by local therapy alone which may be given topically. Long-term treatment is often required as
• Endometrial cancer
In women with an intact uterus, ET causes a dose- and duration-dependent increase in the risk of endometrial hyperplasia and cancer and should therefore be combined with progestogen therapy (Grade A recommendation). Endometrial protection is currently the only menopause-related indication for progestogen use. Continuous combined EPT is slightly more efficient in prevention of hyperplasia compared with sequential EPT in particular sequential therapy with less than 12 days of progestin per cycle (Grade A-B). In hysterectomized women, ET is preferable to EPT.

• Osteoporosis
There is evidence from RCTs that both ET and EPT reduce the risk of fractures of both spine and hip as well as other osteoporotic fractures. The most recent epidemiological studies suggest that HRT is an effective method of preventing fracture in all age groups of women who are at increased osteoporosis risk (Grade A recommendation). Whilst alternatives to HRT use are available and may in general be preferable for the long-term treatment of osteoporosis in elderly women, HRT may still remain the best option for osteoporosis prevention, particularly in younger and/or symptomatic women. Established alternative treatments have not been shown to have the same beneficial effects of HRT in younger women with increased risk rather than established disease. Extended HRT use may be considered appropriate in such women. Lower doses then previously believed necessary are now proving effective.

• Colorectal Cancer
EPT reduces the risk of colorectal cancer (Grade A recommendation). Both previous observational data and the EPT part of the WHI trial show a significantly reduced risk. It is unknown how long the effect of combined HRT persists after treatment is stopped or how HRT affects mortality from colorectal cancer. The reduction of risk has not been shown with ET. At present, we do not recommend the use of HRT solely for this indication.

• Breast cancer
EPT is associated with increased risk of breast cancer. There is good evidence that the excess relative risk increases with duration of use, returning to baseline levels within a few, at most five, years after stopping the intake. The magnitude of the excess relative risk is greater when the estrogen is combined with both progestogen given sequentially or continuously. In contrast the ET part of the WHI trial has shown no increased risk of breast cancer during the study. The absolute excess in life-time risk attributable to EPT corresponds to 1-2 cases per 100 women after HRT from the age of 50 years to 70 years, whereas ET results in a small reduction in risk. The risk is very low during HRT for less than 5 years. The increased risk of breast cancer risk due to HRT is not significantly different or even lower than from the increase in risk due to other risk factors such as alcohol use, obesity, lack of exercise, late first child-birth and late menopause and disappears 5 years after cessation of therapy. EPT may cause increased mammographic density and may thus reduce the sensitivity of mammographic screening. The WHI study showed no increase on ET up to 7 years. Due to a possible risk of recurrence, HRT should not be prescribed to women with a
Ovarian cancer
Results from observational studies like the WHI trial indicate that EPT may be associated with a slightly, albeit significant, risk of epithelial ovarian cancer after long-term use.

Venous thromboembolism
Oral HRT should not be prescribed to women with a previous episode of deep venous thromboembolism (DVT) (Grade A recommendation). Oral HRT increases risk of DVT three fold with the highest risk occurring in the first year of use. The overall risk in menopausal women years 50-59 is of the order of 3-4 in 10,000 per year. The absolute rate increase is impacted by 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 taking HRT for 5 years there would be an additional 2 cases. Transdermal estradiol could be different in that respect.

Coronary heart disease
EPT should not currently be used as prevention against CHD (Grade A clinical recommendation). Results from both the secondary prevention HERS and the EPT of the WHI study showed that EPT does not confer cardiac protection and may increase the early risk of coronary heart disease (CHD) among elderly postmenopausal women. These trial data appear to contradict numerous previously published observational data that have showed a reduction of 30-40% of any type of HRT on CHD risk. The information from the WHI studies indicates a possible protective effect in women aged 50-59y, and warrants further studies of the CHD effects of different HRT dosages and regimens in different age groups. Some women may be at risk for early thrombotic events. Further studies including special clinical features in subgroups, clusters of risk markers, genetics and functional proteomics may assist in identifying the women at increased risk.

Stroke
HRT should not be prescribed to women with previous TCI or stroke (Grade A recommendation). The WHI trial evidence that both ET and EPT increase the risk of stroke with an excess of 8 more strokes per year for every 10,000 women on HRT. When separating by stroke subtypes, EPT was associated with an excess risk of ischemic stroke only. In women 50-59 years five years use of HRT would yield 1 additional case of stroke per 1000 women.

Diabetes
HRT may decrease the risk of developing type 2 diabetes by increasing insulin sensitivity (Grade A-B recommendation). The EPT part of the WHI study as well as the HERS demonstrated a significant decreased risk of developing diabetes in the hormone treated women. Large observational studies have not indicated any increased CHD risk from HRT use in diabetic women with established secondary CHD although HRT may be associated with increased risk of MI in women with history of a recent MI.
Cognitive function

HRT should not be prescribed to women suffering from dementia (Grade A –B recommendation) as there is insufficient evidence of a beneficial effect of HRT on cognitive function or risk of dementia. The EPT part of the WHI study found a two-fold increased risk of dementia (possibly of thrombotic origin) in women. However, this increased risk was only significant in the group of women over the age of 75 years. The results are oppose of earlier findings from observational studies.

Life style

Over and above defining the afore mentioned best clinical HRT strategy, EMAS warrants special attention to the possibility of increasing quality of life and prevention of not only CHD and osteoporotic fractures but also breast cancer by life-style management, with particular emphasis on exercise, dietary intake and cessation of smoking.

Conclusions

The main indication for HRT use in postmenopausal women remains the relief of menopausal symptoms. Treatment for up to five years does not add significantly to lifetime risk of breast cancer, but significantly decreases bone loss and risk of osteoporotic fractures. Some women may be susceptible to early thrombotic risk, but when appropriate HRT is given after individual clinical evaluation, the benefits will far outweigh any potential risks and the treatment should be recommended. Future research is needed to identify new indications for HRT and to diminish or abolish its potential risks.

Acknowledgement

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Terminology and abbreviations


Table 1

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