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Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 position 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), European Menopause and Andropause Society (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 BMI, life-style and diet. In women experiencing an early menopause (<45 year) current data support a specific overall benefit of HRT. At present,

Abbreviations: CCHRTcontinuous combined (estrogen + progestogen) therapy; CHD, coronary heart disease; CEE, conjugated estrogens; DVT, deep venous thrombosis; EPT, estrogen progestin therapy; HERS, The Heart And Estrogen/Progestin Replacement Study; HRT, hormone replacement therapy; RCT, randomised placebo-controlled clinical trial; WHI, Women's Health Initiative

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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.

Keywords: EMAS position statement; Climacteric medicine; Perimenopause; Postmenopause; HRT

1. Introduction

European Menopause and Andropause Society (EMAS) considers that the clinicians' main goal is to provide safe and effective relief of climacteric complaints and advice on all aspects of climacteric medicine. Even if relative risks and benefits of hormone replacement therapy (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 of 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 Women's Health Initiative Study (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 cardiovascular disease (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 remains mismatched throughout Europe 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