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SHORT REVIEW



Hormone replacement therapy and prevention of chronic conditions

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ABSTRACT

Nowadays, postmenopausal women are largely undertreated. Analysis of conflicting results among different studies suggests that hormone replacement therapy (HRT) can prevent osteoporosis and cardiovascular disease in symptomatic, early postmenopausal women. In fact, climacteric symptoms are related to an increased risk of chronic conditions, including hypertension and cardiovascular disease. Different scientific societies have pointed out that patient selection, timing of initiation, and the choice of the type and dose of HRT used are the major determinants of the ultimate effect of HRT on women's health and quality of life in selected women. HRT may prevent chronic conditions when started in symptomatic women before the age of 60 years or within 10 years of the onset of the menopause, taking into consideration the characteristics and risk profiles of each given woman. The bulk of scientific evidence from preclinical, clinical, epidemiological, and also randomized studies indicates that wisely selected HRT is generally useful and rarely dangerous. Following simple and well-established rules, HRT benefits outweigh all of the possible risks. Progestogen choice can make the difference in terms of cardiovascular disease benefits.

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Introduction

During the climacteric, as many as 80% of women experience subjective symptoms and in a number of cases these are sufficiently unpleasant to significantly impair quality of life^{1,2}. In addition, the decline in estrogen production may have long-term health implications in that it is closely associated with the increased risk of cardiovascular disease (CVD) and osteoporosis (OP)^{3–6}. Thus, menopause in association with ageing is implicated in the genesis of major causes of death and disability in the western world and, as a consequence, is a major public health issue. Besides the effects on symptoms, hormone replacement therapy (HRT) exerts a bone-sparing effect, prevents the lowering in bone mineral density related to perimenopausal and postmenopausal hypoestrogenism, and reduces the risk of fractures in long-term treated subjects^{7,8}. Epidemiological and observational studies suggest that HRT can exert cardioprotective effects with a substantial reduction in morbidity and mortality for CVD in postmenopausal women^{9–16}. Conversely, the results of the randomized Women's Health Initiative (WHI) trial¹⁷ did not confirm these results, but rather showed an increased risk of coronary heart disease in older postmenopausal women. Being a large, long-term randomized controlled trial of HRT in women aged 50–79 years, although conducted in elderly, obese, and hypertensive patients, its findings were given prominent consideration. These results were shocking in the medical community and general population, and as a consequence HRT use dropped and nowadays HRT is largely underused in clinical practice. The latest report from the US Preventive Services Task

Force (USPSTF) on menopausal hormone therapy¹⁸ recommends against the use of postmenopausal hormone for prevention of chronic conditions. This statement against the use of HRT is an oversimplification leading to confusion and misunderstanding. The perception that can be generated by this type of report is that in general HRT is not useful and is potentially dangerous. Although the authors declare that their statement does not apply to HRT use for symptom management, this point is not highlighted and is even disregarded by the strong statement in the title and the assertions in the text. The medical community and lay public can perceive the USPSTF recommendation against the use of HRT for prevention of chronic conditions as advice basically against HRT, including the treatment of menopausal symptoms. This report may aggravate the misunderstanding and fear about HRT use, perpetuating the negative effect of the WHI trial¹⁷ and leading to even fewer women receiving proper treatment for symptoms that jeopardize their quality of life. Recommendations from scientific societies make clear that initiation of HRT is proper for symptomatic women without contraindications, when they are in the early postmenopausal period (i.e. younger than age 60 years or within 10 years of menopause onset)^{19–22}. A group of leading international experts wrote a commentary that highlights why the USPSTF statement is not acceptable²³. The decrease in HRT use and/or its premature discontinuation may even lead to an increased prevalence of chronic conditions such as CVD and OP^{2–36}. As for OP there is a general agreement that HRT is effective in the control of bone turnover rate and prevention of bone loss in postmenopausal women. HRT has been shown to significantly lower the risk of hip, vertebral,

and other OP-related fractures. Lower HRT doses can reduce the bone turnover rate and prevent the bone density decrease, although fracture data are not available. HRT is indicated for OP and fracture prevention in women suffering from premature menopause, in normal postmenopausal women at risk before the age of 60 years, or within 10 years after menopause. In addition, HRT is the only therapy proven to be effective in fracture reduction in normal postmenopausal women not selected for being at risk of fracture. This is really critical since the vast majority of fractures appear in osteopenic or even normal women who are not candidates for treatment with the expensive bone-specific drugs.

There are three major points to consider in order to understand the ultimate effect of HRT on women's health and quality of life: the timing, the patient selection, and the type and dose of HRT used (Table 1).

Hormone replacement therapy: timing

Preclinical, epidemiological, and clinical data, as well as solid meta-analyses, document the favorable benefit–risk profile for HRT use in early menopausal symptomatic women^{37–41}. Over the last decade, data clearly show that timing of HRT initiation relative to age and time since menopause is critical, with beneficial effects demonstrated in perimenopausal and early postmenopausal women, and null or even negative effect in elderly patients.

The most recent analysis of the WHI data clearly shows that in younger women, within 10 years of onset of menopause, the mortality is significantly reduced if they receive HRT⁴². When examined by 10-year age groups, the all-cause mortality was reduced by almost 40% (hazard ratio 0.61, 95% confidence interval 0.43–0.87) during the intervention phase in younger HRT-treated women (aged 50–59 years). These effects were not seen in older women, aged 60–69 or 70–79 years. It is noteworthy that this benefit was maintained (hazard ratio 0.87, 95% confidence interval 0.76–1.00) during cumulative 18-year follow-up⁴². The long-term protective effect of HRT on mortality that persists years after HRT discontinuation is similar to that demonstrated on bone, where the benefit of HRT on bone density and microarchitecture have been shown to persist after its withdrawal⁴³. These analyses on mortality and bone-sparing effects of HRT further support the timing hypothesis. In addition, these data show that the results of observational and randomized clinical studies do not differ if we examine a similar population of younger postmenopausal women. In fact, the women included in all observational studies, as well as those seen in everyday practice, are younger and start HRT during the menopause transition.

Hormone replacement therapy: patient selection

Since the chronological age and the time since menopause are critical, patient selection is almost consequential and concurrent. In fact, the main indication for HRT is the treatment of climacteric symptoms that are typically present in younger perimenopausal women, for sure before age 60 years and within 10 years since menopause. Women who suffer from

vasomotor symptoms (VMS), disruptive sleep, atrophic changes, and impaired quality of life are suitable candidates for HRT. However, these women nowadays are not receiving adequate treatment, thanks to the misinterpretation of the potential negative HRT effects on women's health. The VMS segregate perimenopausal and early postmenopausal women at higher risk of short-term decrease in quality of life but also identify a group of women that may have middle and long-term consequences⁴⁴. In fact, VMS have been clearly associated with a range of chronic conditions including CVD, OP, and cognitive decline, as a clinical marker of vulnerability to estrogen deprivation⁴⁴. This is the reason why the statements of different scientific societies^{19–22} have all reiterated the need to treat symptomatic women and to make a clear distinction about the use of HRT in young symptomatic versus elderly and asymptomatic women. By treating younger, healthy but symptomatic postmenopausal women we target the population that can benefit more from tailored HRT, with clear evidence of a net long-term benefit. This point was completely disregarded in the conclusion of the USPSTF document, based only on the misinterpretation of the overall WHI findings¹⁷. As a result, a good opportunity has been lost to clarify the issue of the difference of early HRT in young postmenopausal symptomatic women versus its use in the elderly asymptomatic population. This misconception is also reiterated in the conversation/interview published with the Framingham director, Dr Levy, where this eminent researcher repeats the WHI results as an untouchable icon⁴⁵.

Hormone replacement therapy: types and doses

The ideal product for all women of all ages cannot exist. Different products and combinations have peculiar characteristics that can be properly applied to different women. HRT includes a variety of different compounds with different doses and routes of administration that may have different benefits but mainly may carry different risk profiles. As a consequence, HRT has no generic and fixed 'class effect', chiefly regarding the potential side-effects and adverse events. Assuming a class effect is not appropriate and may generate misperceptions among clinicians and women. The concept of tailored HRT includes the choice of an effective and appropriate dose, type, and regimen that differs according to the age, goals, and clinical characteristics of each patient. The choice of the dose and type, but mainly the choice of the right progestin, is critical. The WHI trials clearly indicate that progestin can make the difference in terms of long-term outcomes. Estrogen treatment alone seems to be more beneficial than combined estrogen and progestin administration. Progestins may have unwanted effects and medroxyprogesterone acetate, the progestin used in the WHI trial, shows some mineralocorticoid, glucocorticoid, and residual androgenic effects⁴⁶. Conversely, other progestins such as drospirenone (DRSP) with antimineralocorticoid

Table 1. Key points in the ultimate effect of hormone replacement therapy on women's health and quality of life.

1. Timing
2. Patient selection
3. Types and doses

properties may have additional benefits on blood pressure control and the overall CVD risk. Postmenopausal women have a higher prevalence of hypertension than premenopausal women^{47–51}. High blood pressure is a modifiable risk factor for CVD^{52,53}. Menopausal VMS are associated with increased awake and sleep systolic blood pressure⁵⁴. Thus, when indicated for symptom control, HRT with blood pressure lowering properties may be very useful^{55–57}. Although antihypertensive effects have been demonstrated with a number of HRT preparations⁵⁸, DRSP in combination with 17- β -estradiol, as anticipated in a small prospective study⁵⁹, can reduce new-onset hypertension in early postmenopausal women⁶⁰. In fact, the initiation rate for antihypertensive treatment after start of HRT was substantially lower for women using DRSP/estradiol compared to the other cohorts of women treated with other HRT combinations⁶⁰. These results emphasize that the progestin choice is critical to the ultimate cardiovascular effect of HRT.

Conclusion

HRT is a proper treatment for VMS and other menopausal symptoms, in appropriate women. HRT may exert preventive effects against chronic conditions when started in symptomatic women before the age of 60 years or within 10 years of the onset of the menopause. It is important to take into consideration the characteristics and risk profiles of the women who may benefit from an HRT prescription (i.e. women in the early menopause with significant VMS or patients with premature menopause). The bulk of scientific evidence from preclinical, clinical, and epidemiologic studies and also randomized clinical trials clearly indicates that judiciously selected HRT is usually useful and rarely dangerous. Following simple and well-established rules, HRT benefits outweigh all of the possible risks. Progestogen choice can make the difference in terms of CVD benefits. Nowadays, postmenopausal women are largely undertreated, and menopause physicians should recommend a convenient HRT, eliminating the fear and encouraging its proper use.

Conflict of interest M. Gambacciani is a Speaker and Advisory Board member for Bayer, Fotona, Gedeon Richter, MSD, and Teva. A. Cagnacci is a Speaker and Advisory Board member for MSD, Bayer Italia, Gedeon-Richter, and Teva Italia. S. Lello reported no potential conflict of interest.

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