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Review

The hormone replacement therapy (HRT) of menopause: focus on cardiovascular implications

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Abstract. The hormone-replacement therapy for menopause has recently become matter of debate, especially after the first large randomized controlled trials failed to confirm the potential benefits on cardiovascular risk suggested by previous observational studies. On the contrary, the treatment has tuned out as to be potentially harmful, increasing the risk of stroke and of venous thromboembolism, without any benefit on coronary heart disease. Some factors, such as cardiovascular comorbidity, age and the time of treatment initiation since menopause, influence the clinical response to HRT, so that it can be considered relatively safe only in younger women, asymptomatic for cardiovascular disease and within 10 years from menopause. Evidences from studies on surrogate endpoints, including levels of the independent risk factors for atherosclerosis, suggest both beneficial and detrimental effects of female hormones on different steps of the process of plaque development, although with differences among different treatment regimens, depending on the type of estrogen and progestin employed, the dosage and the route of administration. Regimens including natural progestogens and using transdermal route, but, above all, Selective Estrogen Receptor Modulators (SERMs) such as raloxifene, are promising alternative to the oral estrogen-progestin treatment experimented in most trials, although no specific regimen can be considered completely safe. So, the updated guidelines on menopause management recommend a careful balance of risks and benefits for selection of women for therapy on an individual basis. (www.actabiomedica.it)

Key words: Hormone replacement therapy (HRT), menopause, cardiovascular risk

The hormonal replacement therapy (HRT) of menopause has long been widely employed for symptom relief, at least in United States, well before the availability of experimental and observational evidences supporting a role for female hormones in cardiovascular prevention.

It was in the early 1990s, when a report of the World Health Organization was published, first establishing that, according to observational cohort reports, HRT use might be associated with a near 50% reduction in the risk of non fatal myocardial infarction and coronary heart disease (CHD) death.

To confirm this finding, interventional studies were planned, with results rather unexpected.

Five large randomized controlled trials (RCTs) were published (1-5), two of them in secondary prevention, the Heart Estrogen-progestin Replacement Study (HERS) and the Estrogen-Progestin Replacement Intervention Trial (ESPRIT), employing either oral estrogens alone or estrogen-progestogen regimens.

The potential benefit on CHD risk was not confirmed, and, in one study, the combined-treatment trial of Women Health Initiative (WHI-EP), a significant increase of risk was found (OR 1.25; 95% CI 1.00-1.59). Besides, a detrimental effect in terms of an increase in risk for stroke and venous thromboembolic events was reported in most studies.

Results were particular disappointing from the HERS trial, showing, in women with CHD, an early increase of coronary events, followed by a progressive reduction, which accounted for the null effect on the primary endpoint at the end of the study. This finding were interpreted as the result of an early pro-thrombotic effect of oral estrogens, due to a first-passage impact on liver, with an increase of risk for plaque complication in already affected coronary arteries.

As a whole, according to meta-analyses, HRT has no beneficial effect on CHD risk (OR 1.00; 95% CI 0.90-1.11), while increasing the risk for stroke (OR 1.24, 95% CI 1.09-1.41) and venous thromboembolism (OR 2.05; 95% CI1.44-2.92) (6).

Interestingly, a recent meta-analysis, including both observational and intervention studies, showed that the increase in risk for venous thrombo-embolism in response to HRT can be influenced by several factors, such as hormone administration route (oral versus transdermal), the presence of some specific prothrombotic genetic mutations and obesity (7).

The discrepancy between observational studies and randomized trials has been widely discussed and can be interpreted in several ways.

First of all, one must consider the potential for a so called "healthy cohort effect" in observational studies, which can be defined as the confounding effect on the association between therapy and the outcome of some prognostic factors, which can be more frequently associated with the exposure to the treatment under investigation. In the Nurses Health Study (8), some of these potential confounders, such as exercise, social and economic issues, compliance to prevention measures and the access to health resources, were not entered into the analysis of the relationship between HRT use and cardiovascular risk. As a matter of fact, according to a retrospective review of the original data of the Nurses Health Study, the cohort of HRT users was actually "healthier" in terms of life style habits than non users, which could partly explained the lower rate in cardiovascular events, independent of hormone therapy. Accordingly, other cohort studies, adjusting for these variables, failed to demonstrate any benefits from therapy, and documented, in diabetic women, an increase in risk associated with estrogen exposure.

Furthermore, cohort and trial participants differ in terms of several characteristics, which can partly explain the differences in results. In HRT trials, women were less frequently symptomatic in term of neurovegetative symptoms, were older and weightier. Besides, treatment period was shorter and the endpoints included also atypical and silent myocardial infarction.

Sub-analyses of WHI trials (9), with sample stratification according to age and years since menopause at study entry, confirmed a significant increase in risk only for the oldest women (aged 70-79 yrs) and in those more than 20 years from menopause. Some age difference was found also for stroke risk, although in this case, the risk was significantly higher in the intermediate age group (60-69 yrs). Interestingly, the same sub-analyses confirmed that estrogen plus progestin treatment is associated with a more consistent risk in CHD than therapy with unopposed estrogen. As a whole, these secondary analyses of WHI trials are consistent with the so called "timing" theory, by which the time of HRT initiation since menopause is crucial for cardiovascular system response.

Finally, for a full understanding of the potential harm of HRT, one can consider the evidences from studies on surrogate endpoints, showing that estrogens can play different roles in atherogenesis, both protective and detrimental (10).

As a whole, we have evidences that estrogens can affect the occurrence of some independent risk factors, as well as directly act at different steps of the process of plaque formation and evolution, , such as endothelial dysfunction, oxidative stress, inflammation and thrombosis

As for risk factors, trials with oral estrogens have demonstrated both positive and negative effects. Considering for instance lipid metabolism, they can decrease plasma concentrations of Low Density Lipoproteins-Cholesterol (LDL-C) and Lipoprotein (a) [LP(a)] and increase High Density Lipoprotein-Cholesterol (HDL-C), but they also can increase triglycerides and small and dense LDL particles.

As for other surrogate endpoints, oral estrogens can improve endothelial function and reduce LDL oxidation and the plasma levels of some inflammation indexes, such as Tumor Necrosis Factor (TNF) and adhesion molecules, but they can also increase Reac-

tive C Protein (RCP), Interelukin-6 (IL6) and Metalloproteinase-9 (MMP-9). Finally, the effects on hemostasis are all detrimental, with both an increase in pro-thrombotic factors and a decrease in pro-fibrinolytic factors.

So, artery responses to estrogen must be considered as the result of two opposite sorts of effects, with the predominance or either positive or negative effects depending on the endothelium basal condition. It has been hypothesized that in presence of a healthy endothelium, as in younger and healthy women, the positive effects of estrogens prevail, while, in older women, especially if already affected with CHD, the negative effects can play some role in plaque evolution and complication, mainly in terms of inflammation, destabilisation and thrombosis.

Another aspect that can potentially contribute to differences in the clinical response to HRT, is the treatment regimen, in term of type of either progestogen or estrogen and the route of administration (11).

In WHI trials, the increase in CHD risk was associated with the dual-HRT (Conjugated Equine Estrogens, CEE, and Medroxyprogesterone-acetate, MPA) but not with CCE alone. Accordingly, synthetic progestogens, such as MPA, have been shown to exert detrimental effects on surrogate endpoints, in particular lipid and glucose metabolism and endothelial function, opposite to estrogens. It is noteworthy that natural progestogens do not exert such effects and, as such, might be safer in combined regimens. Similarly, some detrimental effects of oral estrogen on lipids and other surrogate endpoints, have not been reported for transdermal estradiol, although the pro-thrombotic effects on hemostasis, although decreased, are still detectable.

Recently, Selective Estrogen Receptor Modulators (SERMs) have been investigated as a promising substitute for estrogens in HRT for menopause, to reduce some adverse effects, in particular the potential increase in breast and endometrial cancer risk, while maintaining the benefits in terms of bone density loss prevention.

Recent RCTs on raloxifene (12-14), while confirming the potential benefits on osteoporosis and on breast cancer risk, did not show significant changes in CHD risk, although subgroup analysis showed a trend toward a reduction in risk associated with the lowest dosage of 60 mg daily, in younger women (aged < 60 years) as well as in those with high cardiovascular risk at study entry.

However the increase in risk for stroke and venous thromboembolism documented in response to oral estrogens has been reported also for raloxifene.

So, the evidence so far available do not support any indications for HRT to prevent cardiovascular disease in postmenopausal women, as it has been clearly stated in the 2007 update of the American Heart Association (AHA) guidelines (15). On the contrary, an increase in risk is possible, especially in older women and when the menopause onset interval is over 10 years. As a whole, venous thromboembolism risk is increase at any age.

In clinical practice, to decide for treatment on and individual basis, these potential harmful effects, along with the increased risk in breast cancer and dementia, must be weighted against the well established benefits on neurovegetative symptoms, osteoporosis and colon cancer risk.

According to the North American Menopause Society and its 2008 position statement (16), "pending additional data, HT is currently not recommended as a primary indication for coronary protection in women of any age". However, " initiation of HT by women aged 50 to 59 years or by those within 10 years of menopause to treat typical menopause symptoms (eg. Vasomotor and vaginal) does not seem to increase the risk of CHD events" and "there is emerging evidence that initiation of HT in early postmenopause may reduce CHD risk". On the contrary "women older than 60 years who experienced natural menopause at the typical age and have never used HT will have elevated baseline risk of CHD, stroke, VTE and breast cancer and HT should not be initiated in this population without a compelling indication and only after appropriate counselling".

In conclusion, HRT for menopause can have as adverse effect an increase in cardiovascular risk, in terms of CHD events, stroke and venous thromboembolism, with some slight differences among different treatment regimens. The risk is lower in younger women, asymptomatic for CHD and within 10 years from menopause. These effects must be taken into ac-

count, in the process of balancing benefits and risks to select women for treatment on an individual basis. Treatment regimens other than those experimented in clinical trials, employing either transdermal route of hormone administration or SERMs, might be of some advantage in terms of vascular risk, although to date no specific treatment has been proven to be completely safe.

References

1. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women (Heart and Estrogen/progestin Replacement Study (HERS) Research Group). *JAMA* 1998; 280: 605-13
2. Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomized placebo controlled trial. *Lancet* 2002; 360: 2001-8.
3. Writing Group for Women's Health Initiative Investigators. Risks and benefits of estrogens plus progestins in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002; 288: 321-33.
4. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006; 166: 357-65.
5. Vickers MR, MacLennan AH, Lawton B, et al. Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ* 2007: 335: 239-51.
6. Sare JM, Gray LJ, Bath PMW. Association between Hormone Replacement Therapy and subsequent arterial and venous vascular events: a meta-analysis. *Eur Heart J* 2008; 29: 2031-41.
7. Canonico M, Plu-Bureauu G, Lowe GDO, Scarabin P. Hormone replacement therapy and venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008; 336: 1227-31.
8. Grodstein F, Manson JE, Colditz GA, et al. A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease. *Ann Intern Med* 2000; 133: 933-41.
9. Rossouw JR, Prentice RL, Manson JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA* 2007; 297: 1465-77.
10. Arnal J-F, Gourdy P, Elhage R, et al. Estrogens and atherosclerosis. *Eur J End* 2004; 150; 113-7.
11. Warren MP. A comparative review of the risks and benefits of hormone replacement therapy regimens. *Am J Obs Gynecol* 2004; 190: 1141-67.
12. Barrett-Connor E, Mosca D, Collins P. Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women. *N Engl J Med* 2006; 355: 125-37.
13. Barrett-Connor E, Cauley JA, Kulkarn PM, Sashegyi A, Cox DA, Geiger MJ. Risk-Benefit Profile for Raloxifene: 4-Year Data From the Multiple Outcomes of Raloxifene Evaluation (MORE) Randomized Trial. *J Bone Min Res* 2004; 19: 1270-5.
14. Mosca L, Grady D, Barrett-Connor E, et al. Effect of Raloxifene on Stroke and Venous Thromboembolism According to Subgroups in Postmenopausal Women at Increased Risk of Coronary Heart Disease. Stroke 2009;40;147-155.
15. Mosca L, Banka CL, Benjamin EJ et al. 2007 Update Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 update. *Circulation* 2007; 115; 1481-501.
16. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008; 15: 147-55.

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