Blood Pressure

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: informahealthcare.com/journals/iblo20

Hormone replacement use and cardiovascular function and structure in postmenopausal women

Joseph Tomson, Ingrid Os & Gregory Y. H. Lip

To cite this article: Joseph Tomson, Ingrid Os & Gregory Y. H. Lip (2005) Hormone replacement use and cardiovascular function and structure in postmenopausal women, Blood Pressure, 14:1, 3-5, DOI: 10.1080/08037050510008841

To link to this article: https://doi.org/10.1080/08037050510008841

Published online: 08 Jul 2009.

Blood Pressure. 2005; 14: 3–5

Taylor & Francis
Taylor & Francis Group

GUEST EDITORIAL

Hormone replacement use and cardiovascular function and structure in postmenopausal women

JOSEPH TOMSON[1], INGRID OS[2] & GREGORY Y. H. LIP[2]

[1]*Haemostasis, Thrombosis, and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK, and* [2]*Department of Pharmacotherapy, University of Oslo, N-0407 Oslo, Norway*

The incidence of cardiovascular disease (CVD) in women increases substantially following the menopause, making CVD the leading specific cause of death in postmenopausal women. As the menopause is characterized by a lack of estrogen, the increased CVD risk was initially attributed to this phenomenon. Synthetic estrogen was first used in the 1930s for the relief of menopausal symptoms, and since then, hormone replacement therapy (HRT) grew in popularity due to observational studies that suggested potential benefits in reducing the incidence of CVD, osteoporotic fractures and colorectal cancer (1–3). However, these studies also suggested an increased incidence of endometrial cancer, breast cancer, stroke and venous thromboembolism – but this was perceived to be outweighed by the presumed benefit of CVD prevention.

However, all this was soon to change. In 1998, the Heart and Estrogen/progestin Replacement Study (HERS) (4,5) showed that women with established coronary heart disease who were assigned to HRT had rates of recurrent coronary events similar to those in the placebo group. The Women's Health Initiative study (WHI) published in 2002 (6,7), found that the rate of coronary heart disease was higher among women assigned to combination HRT than among those assigned to placebo. Thus, perhaps the bubble has burst for HRT and CVD prevention. Current CVD prevention guidelines do not even recommend HRT for primary (or secondary) prevention of CVD in postmenopausal women.

However, many questions were raised after publication of HERS and WHI. For example, women with severe menopausal symptoms were dissuaded from enrolling in the study. The participants had a higher average age than those in other studies. Would the results be different had the form of administration been different? When compared to observational studies, why was there a divergence in CHD results but a concordance with the other findings? Perhaps, the route of administration and formulation could have shown a different outcome (8). Rather than answering the question of the usefulness of HRT in postmenopausal women, these trials have thrown open the doors for more debate.

The so-called ''cardioprotective effects'' of HRT were based on the assumption that the longer life expectancy in women and the natural protection against CVD was due to cyclical endogenous ovarian hormonal production before menopause. Indeed, after menopause, the risk of CVD in women increases substantially (9). HRT has been shown to have a range of potentially cardioprotective effects by altering the lipid profile, vascular reactivity, hemodynamic and fibrinolytic variables (8,10). Estrogens also preserve low-density lipoproteins (LDLs) from oxidation and protect cells against cytotoxic effects of oxidized LDL, as well as raise high-density lipoprotein (HDL)-cholesterol levels. Diabetes and dyslipidemia are also deemed to be more prevalent in post-menopausal than premenopausal women (11).

Correspondence: Professor, G. Y. H. Lip, Haemostasis, Thrombosis, and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK. Tel: 0121 5075080. Fax: 0121 554 4083. E-mail: g.y.h.lip@bham.ac.uk

ISSN 0803-7051 print/ISSN 1651-1999 online
DOI: 10.1080/08037050510008841

In this issue of *Blood Pressure*, Wong et al. (12) add to the debate by presenting data on HRT use, arterial distensibility, cardiac structure and circadian blood pressure profile in menopausal women. They studied the effect of HRT in 38 women who were subdivided into normotensives and hypertensives, and further into HRT users and non-users. Though no differences were noted in arterial stiffness and left ventricular mass index (LVMI), they found that the clinic diastolic blood pressure was inversely related to the duration of use of HRT. The 24-hour pulse pressure was also found to be associated to duration of HRT use in normotensive women. Interestingly, arterial distensibility was unchanged between groups, possibly due to the effect of aging on blood vessels.

Nonetheless, they provide limited information on the type of HRT used, and the number and class of antihypertensive agents used by the hypertensive patients. Also, estrogen plus progestin does not confer much cardiac protection and may even increase the risk of CVD among generally healthy postmenopausal women, especially during the first year after the initiation of HRT use (13). The various anti-hypertensive agents used could have influenced the neurohormonal mechanisms studied, e.g. the formulation and site of administration of HRT could have influenced the type and magnitude of blood pressure response. The duration of hypertension may also be a confounder as vascular mechanisms may be altered in chronic hypertension, and whether some non-users had been excluded from HRT because of high BP is unknown. A clearer definition of ''dipper/non-dipper'' differences, based on a comparison of the ''awake'' period and ''asleep'' period (perhaps by a diary) may also be useful. Nevertheless, the drop in diastolic blood pressures amongst HRT users is notable. Notwithstanding the limitations of classifying the groups as dippers and non-dippers, the average body mass index (BMI) in the non-dippers seemed higher than the dippers. A raised BMI and hypertension are important components of the metabolic syndrome (14), and whether HRT could influence this risk factor would need further longitudinal studies.

However, would functional vascular studies or mechanistic data assist our understanding of the benefits (or otherwise) from HRT? Purists would argue that randomized clinical trials are all that matter. Indeed, vascular reactivity improves after estrogen treatment in postmenopausal women, with a favorable effect on arterial vasomotility and improved arterial compliance. It is apparent that not all HRT preparations are the same (8). Some studies have found no net effect of HRT on vascular and cardiac function in postmenopausal women (15–21). Certainly, endothelium-dependent vasodilation is impaired after menopause and restored by estrogen treatment (20). However, the available evidence is not definitive due to small numbers of participants, the studies being observational, a lack of coherence in study design and pooling of data from women treated with a variety of hormonal treatment (natural, conjugated, semi-synthetic and non-oral).

For now, what should we do with HRT use in hypertensive women? In keeping with current guidelines, HRT should not be prescribed solely for primary or secondary CVD prevention. However, symptomatic women with hypertension should not be denied access to HRT as long as blood pressure levels can be adequately controlled by antihypertensive medication. As previously suggested, suitable guidelines for the management of hypertensive women taking HRT are summarized as follows (22):

- All clinicians should measure blood pressure before starting HRT.
- In a normotensive postmenopausal woman, blood pressure should be measured annually following the start of HRT. One exception may be the use of premarin, where a follow-up blood pressure measurement should probably be made at 3 months (in view of reports of a possible rare idiosyncratic rise in blood pressure).
- In hypertensive menopausal women, blood pressure should at least be measured initially and at 6-monthly intervals thereafter. If blood pressure is labile or difficult to control, 3-monthly measurements should be taken. If a hypertensive woman on HRT demonstrates a rise in blood pressure, careful monitoring or observation and even an alteration or increase of their antihypertensive treatment should be considered.

It may be unjustifiable to attribute cardioprotective effects to HRT solely based on mechanistic studies, especially due to the possibility of selection bias and small numbers. However, it can be argued that there could well be a subset of menopausal women who may benefit from HRT, but the problem is the identification of such individuals. Only further well-structured randomized and well-designed clinical trials, using the different hormonal therapies available, on a large umber of postmenopausal women, would be the solution. As current evidence stands, there is so much more to understand from the physiological mechanisms of menopause affecting the cardiovascular system, which could well direct us towards a better grasp of the evolution of cardiovascular morbidity in general.

References

1. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med. 1992; 117:1016–1037.
2. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000; 133:933–941.
3. Keating NL, Cleary PD, Rossi AS, Zaslavsky AM, Ayanian JZ. Use of hormone replacement therapy by postmenopausal women in the United States. Ann Intern Med. 1999;130:545–553.
4. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, 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;280:605–613.
5. Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al. HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. JAMA. 2002;288:58–66.
6. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA. 2002; 288:321–333.
7. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA. 2004;291:1701–1712.
8. Foster W, Lip GYH. Hormone replacement therapy and cardiovascular disease: Does route of administration and formulation matter? Br J Haematol. 2004;124:836–840.
9. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. N Engl J Med. 1987;316:1105–1110.
10. Lip GYH, Felmeden DC. Hormone replacement therapy and cardiovascular risk: Do abnormalities of coagulation and fibrinolysis matter? J Intern Med. 2001;249:201–204.
11. Barret Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? JAMA. 1991;265:627–631.
12. Wong J, Wong S, Handa SP, Abbott EC. Hormone replacement use, arterial distensibility, cardiac structure and circadian blood pressure profile in menopausal women. Blood Press. 2005;14:12–20.
13. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003;349:523–534.
14. Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults, Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–2497.
15. Pines A, Fisman EZ, Levo Y, Averbuch M, Lidor A, Drory Y, et al. The effects of hormone replacement therapy in normal postmenopausal women: Measurements of Doppler-derived parameters of aortic flow. Am J Obstet Gynecol. 1991; 164:806–812.
16. Gangar KF, Vyas S, Whitehead M. Pulsatility index in internal carotid artery in relation to transdermal estradiol and time since menopause. Lancet. 1991;338:839–842.
17. Volterrani M, Rosano G, Coats A, Beale C, Collins P. Estrogen acutely increases peripheral blood flow in postmenopausal women. Am J Med. 1995;99:119–122.
18. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO. Acute vascular effects of estrogen in postmenopausal women. Circulation. 1994;90:786–791.
19. Samaan SA, Crawford MH. Estrogen and cardiovascular function after menopause. J Am Coll Cardiol. 1995;26:1403–1410.
20. Taddei S, Virdis A, Ghiadoni L, Mattei P, Sudano I, Bernini G, et al. Menopause is associated with endothelial dysfunction. Hypertension. 1996;28:576–582.
21. Fischer G, Swain M. Effect of sex hormones on blood pressure and vascular connective tissue in castrated and noncastrated male rats. Am J Physiol. 1977;232:H617–H621.
22. Edmunds E, Lip GYH. Cardiovascular risk in women: The cardiologist's perspective. Q J Med. 2000;93:135–145.