Hormone replacement therapy and blood pressure in normotensive and hypertensive women

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decline in incidence since 1980 to post-menopausal hormone use [1].

Introduction

Oral contraceptives are one of the recognized causes of secondary hypertension, and although the condition occurs much less frequently with the preparations employed today compared with those used 20 years ago, clinicians continue to be concerned about the effects of hormonal preparations on blood pressure. Pregnancy is associated with a decrease in blood pressure. Nevertheless, apart from pre-eclampsia, certain women develop milder forms of pregnancy-associated hypertension that may be hormonally related. Thus, the possibility that hormone replacement therapy (HRT) might indeed increase blood pressure in at least some recipients, is a notion worth testing. Menopause affects half the citizenry at some point or other and the putative advantages of HRT in terms of cardiovascular and skeletal health, as well as wellbeing, comfort, and perhaps appearance, have received much attention. The likelihood that many if not most women will select HRT during or after menopause, to increase their survival superiority compared to men still further, is considerable. Furthermore, in addition to the issue of risk in terms of blood-pressure increases, the possibility remains that HRT in menopausal women might decrease blood pressure and protect from hypertension. A recent study on the trends of coronary heart disease in women ascribed 9% of the observed 31%

Putative mechanisms

Blood pressure is determined by an interplay between peripheral vascular resistance and volume-regulatory mechanisms. Thus, effects that HRT has on vascular and endothelial function, as well as on renal sodium excretion should receive focused attention. Oestrogen has a vasodilatory effect both in vitro and in vivo [2,3]. The predominant mechanism involves improvement in or restoration of endothelial function [4,5]. These effects have been shown on the forearm circulation and the coronary circulation. HRT increases nitric oxide (NO) production [6]. However, the actions appear to extend beyond NO release because even when the endothelium is denuded, vasodilatation continues to occur [7]. HRT increases circulating levels of bradykinin, which could also decrease blood pressure [8]. Oestrogen also antagonizes the effects of endothelin-1, a powerful vasoconstrictor and remodeller [9].

HRT may increase aortic compliance through mechanisms that are as yet unclear [10]. Since systolic hypertension is highly prevalent in post-menopausal women, and since pulse pressure is the overriding risk factor with increased blood pressure, an effect on large-vessel behaviour would be extremely important. A very interesting observation concerns the interrelationship between oestrogen-related effects and the AT1 receptor. Recently, oestrogen was reported to down-regulate the AT1 receptor in rat aortic tissue and vascular smooth-muscle cells [11]. The responsiveness of aorto to angiotensin (Ang) II was strongly attenuated by oestrogen treatment in ovariectomized animals. A detailed study of HRT-related effects on the
renin–angiotensin system was conducted in cynomolgus monkeys [12]. HRT increased plasma renin activity and Ang I concentrations, but reduced angiotensin-converting enzyme activity, so that Ang II and Ang (1-7) concentrations were unchanged. Oestrogens also exert effects on autonomic function [13]. Heart rate variability studies indicate that high-frequency sympathetic spectral power is reduced relative to the low-frequency parasympathetic spectrum by oestrogen treatment. There is also some evidence that HRT may have direct effects on the heart. In a comparative study of post-menopausal women treated with conjugated oestrogens or placebo, exercise echocardiography after 6–9 months showed that women with HRT had reduced left ventricular cavity dimensions, diminished resting aortic blood flow velocity, and lower resting-mean and post-exercise blood pressures [14].

Oestrogen in contraceptive doses may increase salt and water retention, thereby supporting an increase in blood pressure. However, a decrease in AT1 receptor expression coupled with a decrease in angiotensin converting enzyme activity would be expected to offset such an effect [15]. The effects of progesterone in normal individuals include a tendency to antagonize the actions of aldosterone. Nevertheless, mutations of the mineralocorticoid receptor have been described which alter the configuration of the receptor such that progesterone becomes a receptor agonist instead of an antagonist [16]. Whether or not more common polymorphisms could influence the receptor’s behaviour in this regard is unknown.

Less is known about selective oestrogen modulators.Raloxifene is a benzothiophene derivative that binds to the oestrogen receptor in a unique area of DNA called the raloxifene-response element [17]. The compound produces oestrogen-agonistic effects in some tissues and oestrogen-antagonistic effects in others. Raloxifene appears to have an oestrogen-antagonistic effect on breast tissue, while its effects on bone and lipid metabolism are oestrogen agonistic in nature.

On balance, HRT would be expected to leave blood pressure unchanged or to actually promote a blood-pressure reduction in post-menopausal normotensive and hypertensive women. However, the preparations and their dosages are variable and only data from prospective clinical trials can settle the issue.

Data from clinical trials

Lip et al. [18] conducted an observational study in 75 hypertensive women who required HRT to avert post-menopausal symptoms. The women were followed up for 14 months (range 8–32 months). Body weight increased significantly in the women, but blood pressure did not. No differences were observed when comparing oestrogen only, oestrogen combination, or transcutaneous-delivery patch therapy. Medication requirements were not altered. Lack of a placebo control group limits the interpretations that can be made from this observation; however, serious deleterious consequences from HRT appear unlikely. Kornhauser et al. [19] conducted a randomized double-blind study over 90 days in menopausal women with mild to moderate hypertension. The 55 women first discontinued their antihypertensive medications. The patients were then allocated to three groups: placebo, oestradiol, and oestradiol plus a progesterone analogue. Blood pressure decreased in the placebo group and remained unchanged in the other two groups. Thus, HRT did not change blood pressure in these patients. The unexpected blood-pressure-lowering action of the placebo preparation remains unexplained. The effects of transdermal oestrogen were tested by Manhem et al. [20]. They conducted a placebo-controlled, double-blind, cross-over study and relied on 24-h ambulatory blood pressure measurements. Transdermal oestrogen had a small blood-pressure-lowering effect on daytime blood pressure and did not interfere with nocturnal blood pressure dipping. Lloyd et al. [21] performed a randomized placebo-controlled trial of tibolone on blood pressure in hypertensive women. They found that the preparation had no effect on blood pressure.

The effects of discontinuing HRT have also been investigated. Zarifis et al. [22] reported that hypertensive women in whom HRT was discontinued for various reasons exhibited no change in systolic or diastolic blood pressure after the preparations were stopped. Also at issue is whether or not oestrogen alone or oestrogen combined with a second preparation have similar effects on blood pressure. Jespersen [23] observed that artificial oestrogens combined with progestogens increased blood pressure, while genuine oestrogens did not, even when used in combination. In the United States, Premarin® (Wyeth–Ayerst, Philidelberg, PA) is a commonly employed mixture of conjugated oestrogens obtained from the urine of pregnant mares. According to Jespersen [24], this preparation also increases blood pressure. Wong et al. [25] demurred in their report that involved the treatment of 25 hypertensive post-menopausal women who received 0.625 mg Premarin®. They observed no increases in blood pressure with this preparation.

Larger trials with different primary endpoints do not suggest that HRT influences blood pressure to a significant degree. The post-menopausal oestrogen/progestin interventions (PEPI) trial focused on systolic blood pressure among various endpoints [26]. Patients were randomized to placebo, conjugated oestrogens, either without or with progestin, in a cyclic or consecutive fashion. No treatment-related effects on systolic blood pressure were observed. In the Heart and Estrogen/progestin Replacement Study (HERS), blood pressure was documented to be no different in the groups at the beginning of the trial [27]. The investigators did not comment on blood pressure further. Cardiovascular endpoints were not decreased by treatment while thromboembolic events and gall bladder disease were increased. The investigators studying the effects of raloxifene on cardiovascular
risk factors also first assured themselves that blood pressure levels were not different in the treatment groups at the outset of the study but did not otherwise comment on blood pressure [28]. Presumably, blood pressure was not influenced by raloxifene.

Conclusions

Earlier reports have indicated that our knowledge on the use of HRT in hypertensive women is hindered by lack of large prospective trials [29,30]. We agree. The evidence at hand points to a neutral effect on blood pressure. The introduction of new HRT products and particularly oestrogen-receptor modulators clearly warrants more emphasis on blood-pressure monitoring in these patients. The earlier investigations have focused almost exclusively on lipids and coagulation factors. Although HRT has great appeal as part of a multiple risk factor intervention particularly in hypertensive women, concerns about breast cancer, the association of HRT with deep-vein thrombosis and gall-bladder disease, and the possibility that inflammatory markers may increase, necessitates close clinical follow-up of these patients [31–33].

References

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