Women's health in menopause with a focus on hypertension

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In menopause transition many women have vasomotor symptoms which may affect their normal daily activities. With the decline in oestrogen levels, risk factors for coronary heart disease (CHD) become more apparent, especially hypertension. The onset of hypertension can cause a variety of complaints that are often attributed to the menopause. Risk factor identification is poorly managed in middle-aged women and should be the first step in the evaluation and treatment of women with perimenopausal symptoms. In women at low risk for CHD, there is still a window of opportunity for safe hormone prescription in the first years proximal to menopause. (*Neth Heart J* 2009;17:68-72.)

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Although the use of hormone therapy (HT) is very effective in women with moderate to severe menopausal symptoms, its clinical prescription has declined dramatically since the first randomised trials of HT in elderly postmenopausal women were published ten years ago.^{1,2} The use of HT caused more harm than benefit compared with placebo in secondary prevention and even in the Women's Health Initiative (WHI) primary prevention studies, negative effects of HT on the cardiovascular system were found in women aged 50 to 79 years.^{3,4} Over the past years the discussion has gradually changed from an emotional debate into a more rational approach to women's

health in the menopausal transition period. Cardiologists and gynaecologists have joined their efforts for a better patient management, summarised in a consensus document that underscores the importance of cardiovascular (CV) risk assessment in perimenopausal women.⁵ With this integrated approach there is still a window of opportunity for safe HT prescription in the perimenopausal period when women have severe symptoms and if they are at low risk for coronary heart disease (CHD) events.

The timing hypothesis

There is abundant evidence that premenopausal oestrogen levels inhibit the progression of atherosclerosis. Women with lower oestrogen levels before menopause, such as smokers, are at increased risk to develop premature CHD.⁶ Young women with endogenous oestrogen deficiency have a more than sevenfold increase in coronary artery sclerosis.⁷ With the decline in endogenous oestrogen production after 40 years of age, women gradually develop atherosclerotic lesions with fibrous cap formation. Signs of subclinical atherosclerosis can already be found with intima-media thickness measurements in women before menopause, especially when several CHD risk factors are present.⁸ After menopause, atherosclerosis becomes more extended with the involvement of inflammation and the appearance of calcified atheromas in the vessel wall.⁹ Most CHD events occur in women after 63 years of age. Once more advanced atherosclerotic lesions are present, the biology of the vascular wall is altered with a markedly reduced expression of the oestrogen receptor.¹⁰ While oestrogen dilates the endothelium in the healthy vessel wall, the administration of hormones has serious side effects in diseased atherosclerotic arteries through the activation of vascular inflammation and the production of vasoconstrictive factors that further promote plaque instability.^{11,12} Early adverse CHD events after initiating HT were observed in the randomised trials such as the Heart and Estrogen/progestin Replacement Study (HERS), the WHI and in the most recent Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) trial.^{1-3,13} Mean age of the

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women included in these trials, however, was 63 to 67 years, with a mean interval of 10 to 15 years since menopause when the use of HT is no longer appropriate. As the absolute risk of CHD events is low in women below 60 years of age, there is a time-span of ten years from the onset of menopause when healthy women with severe menopausal symptoms may profit from the beneficial effects of HT.^{11,14,15} In a subanalysis in women below 60 years of age, who were included in the WHI primary prevention trials, it was even shown that women who initiate HT proximal to the onset of menopause have a reduced risk for CHD events.¹⁶ Further, in a subset of 1064 younger (50 to 59 years) WHI participants, it was demonstrated that mean coronary artery calcium scores were lower in women receiving HT compared with women on placebo.¹⁷ Others found that flow-mediated dilatation with oestrogen administration is time dependent and reduced by a longer period since menopause.¹⁸ It appears that the potential for HT to have CV benefits is decreased by advancing age, the time since menopause and the stage of subclinical atherosclerosis of the individual woman. Cardiovascular risk assessment should therefore be the first step in the evaluation and treatment of women with perimenopausal symptoms.

Determinants of perimenopausal symptoms

Symptoms of vasomotor dysfunction ('hot flashes') occur in 50 to 70% of women in the menopausal transition period and are directly related to the decline in endogenous oestrogen production. It is assumed that these hormonal changes affect the levels of the neuro-transmitters norepinephrine and serotonin which interfere with the thermoregulation in the hypothalamus.¹⁹ Other general symptoms that are commonly reported are night sweating, mood changes, concentration disturbances, palpitations, fatigue, headache, anxiety etc. Besides specific urogenital symptoms that are related to lower oestrogen levels, it is uncertain whether all the complaints that women may have during their menopausal transition period are caused by hormonal changes.²⁰ From several surveys it is known that important determinants of perimenopausal symptoms are lower socioeconomic class, racial differences, smoking, overweight, higher alcohol intake and reduced physical fitness.²¹⁻²³ Although many of these factors are also important in the development of hypertension, data on the relation of hypertension with hot flashes are relatively scarce.^{24,25} Treatment with an angiotensin II-antagonist has been shown to reduce perimenopausal symptoms in women with hypertension.²⁶ Further, women with hot flush symptoms have more serum metabolites of cerebral norepinephrine than women without these symptoms, indicating an increase in sympathetic activity.²⁷

Hypertension as a key risk factor in menopause

The loss of ovarian hormones around menopause has many adverse effects on CHD risk factors. Clinical

manifestation of CHD occurs ten years later in women compared with men and the risk increases rapidly after the age of 63 years.²⁸ In the Framingham study it was shown that the ten-year intermediate and high-risk chance of having a CHD event in the age group between 50 and 60 years is 37% for men and only 6% for women.¹⁴ Hypertension is by far the most important risk factor that affects women in the early postmenopausal years. About 30 to 50% of women develop hypertension (RR >140/90 mmHg) before the age of 60 and the onset of hypertension can cause a variety of symptoms that are often attributed to menopause.^{29,30} Mild to moderate hypertension may cause complaints such as non-specific chest pain, sleep disturbances, headaches, palpitations, hot flushes, anxiety, depression, tiredness, etc.^{26,31} Women with a family history of hypertension and women with a history of hypertension in pregnancy are at increased risk to develop hypertension in this age period.³² Hypertension often clusters with other risk factors such as overweight, elevated insulin resistance, diabetes and lipid abnormalities. In the Women's Health Study it was shown in almost 40,000 healthy women (≥ 45 years) that an elevated blood pressure increases CV risk and that hypertension is a strong predictor for the development of type II diabetes.^{33,34} Even in premenopausal women, hypertension has been shown to be a potent risk factor for the presence of coronary artery disease.³⁵ Despite the high prevalence of hypertension in middle-aged women, less than half of the patients receive adequate treatment, especially in the older age group when the risk of CHD morbidity and mortality is highest.^{30,36}

Menopause-related changes in blood pressure

The rise in systolic blood pressure with ageing is mainly caused by an increase in vascular stiffness of the great arteries in combination with atherosclerotic changes in the vessel wall. Systolic blood pressure rises more steeply in ageing women compared with men, and this may be related to the hormonal changes per se during menopause.^{29,37} Several other hormone-related factors have an additive effect on the increase in blood pressure during menopausal transition (table 1).³⁸⁻⁴¹ The decline in the oestrogen/androgen ratio dilutes the vaso-relaxant effects of oestrogens on the vessel wall and promotes the production of vasoconstrictive factors such as endothelin.⁴² Both male and female sex steroids have a regulating effect on the renin-angiotensin system (RAS) and affect angiotensinogen production and sodium metabolism. The decline in oestrogen levels around menopause causes an upregulation of the RAS with an increase in plasma-renin activity.⁴³ Oral oestrogen replacement, however, increases the hepatic production of angiotensinogen, which is not observed with transdermal oestrogen. This potentially disadvantageous effect of HT seems to be counteracted by a substantial decrease in renin levels that overall reduces RAS activity. Several clinical studies have

Table 1. Effects of the decline in oestrogen levels on blood pressure.

- Relative increase in androgen levels
- Activation RAS, higher renin levels
- Increase plasma-endothelin levels
- Higher salt sensitivity
- Increase in insulin resistance
- Higher sympathetic activity
- Increase in weight

RAS=renin-angiotensin system.

shown that salt sensitivity is higher in postmenopausal women compared with premenopausal women, which may explain the effectiveness and good tolerance of diuretics and ACE inhibitors in ageing women.⁴⁴ Further, sympathetic activity is higher in postmenopausal women than in age-matched men, especially in women who are overweight.^{45,46} Sympathetic overactivity is associated with abdominal visceral fat which is strongly related to increased inflammatory markers and oxidative stress. Another important change around menopause is an increase in insulin resistance which causes unfavourable changes in blood pressure, lipid metabolism, bodyweight and the development of the metabolic syndrome.⁴⁷ It remains to be further clarified which mechanisms are involved in the interaction of oestrogens with insulin sensitivity.

Treatment advice for women with perimenopausal symptoms

Cardiologists and gynaecologists have recently reached consensus on the importance of CV risk factor assessment as the first step in managing women with perimenopausal symptoms.⁵ From the Framingham study it is known that women without established risk factors at the age of 50 have a low lifetime risk for the development of CHD.⁴⁸ The treatment of risk factors should be addressed according to the current guidelines that underscore lifestyle changes as the initial goal of therapy.⁴⁹⁻⁵¹ A healthy lifestyle is equally important in the treatment of women with perimenopausal symptoms. Hormone therapy should not be prescribed in women >60 years of age and in women at high risk for CHD, such as women with a previous CHD event or stroke. Caution should be taken in women who are current smokers, women with diabetes, women with the metabolic syndrome and women with ≥ 2 CHD risk factors (table 2). Although HT is not indicated for CHD prevention, its use may be very effective in the treatment of women with severe vasomotor symptoms, in women with specific urogenital complaints or in women at risk for osteoporosis.^{20,52} According to the latest position statement of the North American Menopause Society (NAMS) the recommendation is

Table 2. Cardiac risk in menopause and safety of hormone therapy (HT)

High-risk HT

- Documented atherosclerosis
- Previous CHD event, stroke, PVD
- Current smokers
- Diabetes mellitus
- Metabolic syndrome
- Age >60 years

Intermediate-risk HT

- ≥ 2 CHD risk factors

Low-risk HT

- 1 risk factor (no smoking or DM)
- Age 45-55 years

CHD=coronary heart disease, PVD=peripheral vascular disease, HT=hormone therapy, DM=diabetes mellitus.

to use HT at the lowest possible dose in the years proximal to menopause.⁵³ The choice of the many available HT regimens and the route of administration should be discussed with the woman herself and her gynaecologist or her primary care physician. The use of HT is contraindicated in women at elevated risk for breast cancer (previous history, family history). In these women the use of clonidine or antidepressants may be helpful when disabling hot flush symptoms are present.⁵⁴ Other alternative medical therapies, such as herbs and phyto-oestrogens, have not been proven effective for the treatment of perimenopausal symptoms.^{20,52}

A new development for combined HT in women with mild hypertension (RR <160/90 mmHg) and perimenopausal symptoms is the use of a low dose of 17 β -oestradiol (1 mg) in combination with drospirenone as a novel progestin. Drospirenone is related to spironolactone and has aldosterone-antagonistic properties.⁵⁵ It lowers ambulatory blood pressure by a mean of 7 mmHg compared with placebo and can easily be combined with other antihypertensive drugs.⁵⁶

Conclusion

The years proximate to menopause are accompanied by an increase in blood pressure and the prevalence of hypertension that may lead to complaints that are often attributed to menopause.

Assessment of the CV risk of the individual woman should be the first step in the evaluation and treatment of perimenopausal symptoms, with the treatment of lifestyle factors and hypertension as a priority. In women with severe menopausal complaints and who are at low risk for CHD the use of HT in the years proximal to menopause may be very helpful. ■

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