CAN WE REVERT TO OUR OLD HABITS OF HORMONE THERAPY PRESCRIPTION?

C. Christiansen, P. Alexandersen
Center for Clinical and Basic Research, Ballerup, Denmark

For more than five decades abundant animal experimental and observational data have supported the notion that estrogen alone replacement therapy (ERT) or combined estrogen plus progestin (‘hormone’) replacement therapy (HRT) provided significant protection against atherogenesis and coronary heart disease (CHD) due to its multiple effects on cardiovascular risk factors considered to be beneficial in nature.

All these results were recently challenged by the first large randomized placebo-controlled study in postmenopausal women without overt symptoms of CHD at baseline, the Women’s Health Initiative (WHI) that was planned to last for 7 years. However, the WHI study, that was prematurely stopped, indicated that 5.2 years of HRT, but not ERT, promotes cardiovascular harm in postmenopausal women (1,2). Because of on these surprising and ‘negative’ results, there still remains much confusion among laypeople and doctors alike as to the benefits and risks of using HRT for the control of menopausal symptoms or prevention of long-term consequences of the menopause, such as osteoporosis.

Since the publication of the WHI data in 2002, considerable controversy exists in the scientific community as the harm/benefit ratio of postmenopausal HRT. It has been argued that the women participating in the WHI study who were 63 years old at baseline and had a mean BMI 28.5 kg/m\(^2\) were not those who would chose HRT in the ‘real life’ because of their lack of menopausal symptoms. Furthermore, the use of medroxyprogesterone acetate (MPA) as the progestational agent was criticized, despite being the most widely used in the World. Nevertheless, today the general belief is that HRT – regardless of regimen, duration and the women taking it – is associated with an increased risk of CHD and stroke in all postmenopausal women.

However, there are several crucial points that should be kept in mind when addressing questions of who should and who should not take HRT. Recent evidence suggests that the potential harm of HRT is linked to a certain phenotype with respect to body fat distribution. Another important issue relates to the progestin itself.

A recent analysis of results from the Women’s Angiographic Vitamin and Estrogen (WAVE) study by Howard and colleagues (3) pointed out some interesting differences in the progression of CHD during 2.8 years of HRT depending on whether participants had a normal or an abnormal glucose tolerance test at baseline, the latter being a metabolic condition closely associated with central (abdominal) adiposity. Women with abnormal glucose tolerance had accelerated atherosclerotic progression and was further enhanced by HRT. In addition, subjects with an abnormal glucose tolerance test also responded to hormone therapy with increases in inflammatory markers.

We have recently investigated the influence of the progestational component used on the circulating levels of adiponectin, a adipokine with insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties (4). We found that at least some progestins (e.g. drospirenone) exert an inhibitory effect on circulating adiponectin concentrations, which could be a plausible mechanism of action underlying the adverse cardiovascular response, especially if exposing women who have low serum levels of adiponectin, i.e. women that are centrally obese. In contrast, when non-obese women take HRT for a period of 2-3 years after the menopause, both all-cause and cardiovascular mortality is significantly reduced compared to non-users (5).

Therefore, an essential question to ask is: can we identify the women who would most likely not benefit from HRT after the menopause? Accumulating evidence suggests that early initiation of HRT in the menopausal transition is crucial for a full benefit of the therapy, and that delaying this onset of HRT markedly reduces the cardioprotective influences (6). Hence, the beneficial/harm ratio of HRT may vary from primarily beneficial when started in the early menopause towards largely harmful if begun in the late menopause. However, regardless of time of HRT onset, body fat distribution per se seems to be a determining factor in atherosclerosis progression in postmenopausal women (7). In women who are centrally obese (i.e. have low adiponectin concentrations, low sex hormone binding globulin (SHBG) concentrations, but high estradiol concentrations, and also have low-grade inflammation) atherogenesis will progress 3-4 fold faster compared to women who are peripherally obese (i.e. have high adiponectin concentrations, high SHBG concentrations, but low estradiol concentrations) (7), and thus the
latter women are likely to benefit from the cardioprotective effects of HRT in contrast to the former. The pathophysiologic explanation behind this contrasting influence of central and peripheral fat tissue on atherogenic risk factors and on atherogenesis may be explained by decreased plasma adiponectin concentrations, increased estradiol concentrations, lower insulin sensitivity, and a chronic inflammation present in centrally obese women compared to peripherally obese women. Consequently, centrally obese postmenopausal women should avoid hormone therapy, and the relative contraindication is further stressed in the presence of metabolic syndrome and advancing age (8).

HRT is most frequently used for the control of menopausal symptoms impairing a woman's quality of life or for prevention of long-term consequences of estrogen-deficiency (e.g., osteoporosis). However, a history of breast cancer or other gynecological cancers is usually regarded as a relatively contraindication of estrogen use in early postmenopausal women. Likewise, in elderly women with a history of symptomatic CHD considering a prescription of estrogens today happens only after careful consideration of pros and cons and is done with caution. Nevertheless, in early as well as late postmenopausal women, being centrally obese (i.e. a high waist-hip ratio) or having signs of metabolic syndrome should also to be regarded as relative contraindications of estrogen use (8). For this purpose, it may be useful to measure the waist circumference (should not exceed 88 cm in women) that could be combined with a panel of parameters as fasting triglycerides levels (or the triglycerides/high density lipoprotein cholesterol ratio as an index of insulin sensitivity), SHBG, and inflammatory markers.

For women with an intact uterus, if hormone replacement is regarded relevant, an ultra-low dose estrogen-alone therapy without use of a progestin seems an interesting option, but this particular therapy warrants further investigation. For hysterctomized women, ERT either as patch or oral treatment, is a useful option, but the metabolic differences among the different progestins should also be taken into account.

References


