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Prescribing postmenopausal hormone therapy to women in their 50s in the post-Women's Health Initiative era

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Originally used primarily for the treatment of menopausal symptoms, prescriptions for menopausal hormone therapy (MHT) rose sharply from the late 1980s onwards following the publication of several epidemiologic studies showing that use of MHT was associated with a lower risk of osteoporosis and coronary heart disease. These studies also showed an increased risk of venous thrombo-embolism, and with prolonged use also of breast cancer, in addition to a previously demonstrated risk of endometrial cancer. Whereas the increased risk of endometrial cancer could be abolished by the addition of a progestin to estrogen, breast cancer risk appeared to be further increased by progestin. Nonetheless, towards the turn of the new century the consensus opinion of most professional societies was that the benefits of MHT outweighed the risks, and MHT was widely recommended for all post-menopausal women and in particular for women at high risk of coronary heart disease. The perceived favorable risk-benefit ratio depended heavily on the assumption that MHT would reduce the risk of coronary heart disease, a major affliction of women in the postmenopausal and older age groups.

The findings from the first large-scale randomized controlled clinical trials caused a reevaluation of this favorable paradigm for MHT. In 1998 the Heart and Estrogen-Progestin Replacement Study (HERS) showed that MHT did not in fact reduce risk of recurrent myocardial infarction.¹ Subsequently, in 2002 and 2004 the Women's Health Initiative (WHI) primary prevention trials showed that neither estrogen plus progestin nor estrogen alone reduced risk of coronary heart disease—in fact the risk was increased compared to placebo in the first several years.^{2,3} In addition the combination of estrogen plus progestin increased the risk of stroke, venous thromboembolism, and breast cancer; these risks were not offset by the benefits for fractures and colorectal cancer. Similarly, estrogen alone increased the risks of stroke and venous thromboembolism (but not of breast cancer) and reduced the risk of fracture; again with no overall benefit. As a result of these findings, most professional societies no longer recommend MHT for either primary or secondary prevention of coronary heart disease, and MHT is now a second-line drug for the prevention of osteoporosis. Prescriptions for MHT dropped precipitously around the world and appear to be decreasing further over time. Within the WHI cohort breast cancer has decreased after stopping estrogen plus progestin, and in the US population the national decrease in hormone use has been accompanied by reduced rates of breast cancer and coronary heart disease.

The observational studies clearly overestimated the coronary heart disease benefits of MHT, and over time the reasons for this have become clearer. Within the WHI program the results

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of the (initially more favorable) observational study could be reconciled with those of the trials by taking into account age, risk factors, and most importantly the differences in duration of therapy.⁴ Duration of therapy is critical, because in general clinical trials are of shorter duration but capture all initial events, while observational studies have longer periods of exposure but often are poor at capturing initial events; since most coronary heart disease risk occurs in the first two years after initiation observational studies may overestimate benefit. Joint analyses of the WHI observational study and clinical trial data showed no overall effect on coronary heart disease, albeit with significantly increased initial risk and no significant benefit with prolonged therapy. Re-analysis of the Nurses' Health Study (NHS) observational data using a methodology similar to that of a clinical trial, and which (unlike all previous analyses) includes coronary heart disease events in the first two years after starting MHT, yielded results very similar to those of the WHI trial of estrogen plus progestin: no benefit overall, increased initial risk, and no significant benefit with prolonged therapy.⁵ Thus, data from an observational study whose findings were key to creating the enthusiasm for MHT can no longer be regarded as being supportive of a role for MHT in the prevention of coronary heart disease.

The major remaining reason for prescribing MHT is for the relief of vasomotor symptoms; but even here caution is warranted. Older women and especially those with vasomotor symptoms appear to be at higher risk of coronary heart disease if given MHT, but this is not a major concern because only a small proportion of older women have persistent severe symptoms and MHT should rarely if ever be prescribed to older women.⁶ On the other hand, re-analyses of both the WHI and NHS data suggest that MHT does not affect the overall risk of coronary heart disease in younger women.^{5,6} However, there is a trend towards increased risk of coronary heart disease in the first two years after initiation which does not differ significantly from the initially increased risk in older women, and even with prolonged therapy there is no significant benefit. Furthermore, both WHI and NHS have found that the increased risk of stroke is not modified by age. The risk of venous thrombo-embolism due to MHT is also not modified by age. More disturbing is the finding from the joint WHI observational and clinical trial data that women who initiate estrogen plus progestin close to the menopause, and who continue it for a long period of time, are at higher risk for breast cancer.⁴

These new insights should be considered when prescribing MHT to younger women. While they might expect relief of vasomotor symptoms, they should be counseled that there is small chance of coronary heart disease, stroke, or venous thrombo-embolism even with short-term therapy. They should not expect long-term benefit for coronary heart disease; rather, they should be cautioned that long-term use carries with it an increased risk of breast cancer.

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