OPINION

Hormone replacement therapy — finally, good data

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In recent decades, long-term use of hormone replacement therapy (HRT) has been widely and heavily promoted as a prophylaxis against heart disease and other illnesses. Millions of women have taken these medications based on their physicians' recommendations, which were made despite the absence of data from clinical trials demonstrating benefit. Belief in a protective effect of HRT against heart disease was based on the results of observational studies,[1] the effect of HRT on selected lipid and other parameters,[2] and the widely held but unsubstantiated belief that endogenous female hormones protect women against coronary heart disease.[3,4]

Data from randomised trials, the gold standard for assessing the potential protective effect of a medication, are now available on the effect of oestrogen taken with a progestin.[5-7] The largest and most definitive trial is the Women's Health Initiative (WHI),[7] in which women with a uterus were randomised to take placebo or oestrogen together with progestin, and women with hysterectomies were randomised to placebo or oestrogen alone. The oestrogen-with-progestin arm of the trial was stopped after 5.2 years rather than the planned 8.5 years because of greater risk than benefit in the women taking oestrogen with progestin. The increased incidence of breast cancer, venous thromboembolism and stroke, and decreased incidence of colon cancer and fractures in users of oestrogen with progestin in the WHI was in agreement with results of observational studies, but the increased incidence of coronary heart disease in HRT users was in conflict with much of the observational data.

The WHI findings on heart disease seem particularly difficult for some to accept, but they do not stand alone. A meta-analysis of small randomised trials[8] also found an increased risk in users, and the Heart and Estrogen/Progestin Replacement Study (HERS) trial found no overall protective effect of HRT and an increased risk in the first year of use.[5] Nonetheless, recent comments in the *SAMJ* indicate an unwillingness to accept that these results are valid[9] and to give up the belief that some oestrogens and progestins *must* be protective against coronary heart disease or that the benefit/risk ratio for HRT will become favourable if other outcomes are factored in.[10]

In a recent article in the *SAMJ*[9] Cheifitz presented an analysis of changes in disease incidence from year to year in the WHI and argued that they indicate no major impact in the final 2 years. Cheifitz's analysis is incorrect. As in any well-designed trial, 'stopping' rules were devised at the start so that the trial would be ended prematurely if there was evidence of benefit or adversity beyond some defined boundary. After 5.2 years there was clear evidence in the oestrogen-plus-progestin arm of greater harm than benefit — the increase in a 'global index' of disease occurrence was statistically significant, and the incidence of breast cancer, coronary heart disease, stroke and venous thromboembolism exceeded the decreases in the incidence of colon cancer and fractures. The breast cancers among women on HRT were more advanced than those among women on placebo.[11] No randomised data are available on survival, but a recent follow-up study of a million women in the UK[12] found increased breast cancer mortality in oestrogen users compared with non-users.

In his article Cheifitz suggested that the WHI results are invalid because some women used HRT previously, some women changed their use during the trial (e.g. discontinuation of HRT use), and the analysis of the data was according to intention to treat.[9] None of these criticisms stands up. Owing to the randomisation, the prevalence of previous HRT use was closely similar among the HRT users and placebo users; therefore previous HRT use could not have distorted the results. Indeed, inclusion of women who used HRT before the trial allowed for analyses according to previous use, which indicated that breast cancer incidence in the oestrogen-with-progestin users who had used HRT previously was greater than that among oestrogen-with-progestin users who had no previous use. Intention to treat is the correct analysis for randomised trials. Changes in drug use during the trial are likely to have resulted in underestimation of the effects of use, not in the creation of spurious associations, as indicated by subanalyses carried out by the WHI investigators.[7]

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In a recent *SAMJ* editorial Sonnendecker and de Villiers[10] suggested that the WHI may have failed to find a protective cardiovascular effect of HRT because the participants may have been at higher risk of heart disease from HRT because of previous risk factors or cardiovascular disease. However, the women in the trial were typical of postmenopausal women aged 50 - 79 years in the USA and also similar to women in many of the observational studies that suggested a protective effect of HRT.[1,7]

Cheifitz[9] suggested that younger women, aged 45 - 55 years, who have not already developed atherosclerosis would receive cardiovascular protection from HRT. Even if this were so, there is no reason to believe that younger women would not also be at increased risk of breast cancer, venous thromboembolism, stroke and other illnesses caused by HRT use through the same mechanisms operating in older women.

Sonnendecker and Villiers[10] suggested that the benefit-risk equation will not be complete until randomised data are available on the effects of HRT on the brain and dementia. Results from randomised trials have now been published and indicate no benefit. The HERS trial[13] found that quality of life among women without menopausal symptoms is poorer among users of HRT than among users of placebo. The WHI study suggests that the incidence of dementia was increased in users relative to placebo.[14,15] These findings go against the oft-made suggestions that quality of life and brain function are improved by the use of HRT.

Sonnendecker and de Villiers[10] suggested that other oestrogens and progestins might have a more favourable benefit-risk profile and that assessment of their effects should be a research priority. The most compelling data on the effects of different oestrogens and progestins comes from the Million Women Study.[12] This study found that the adverse effect of HRT on breast cancer incidence differed little according to the type of oestrogen or progestin, the dose, or the route of administration.

Given the millions of women around the world who have taken HRT, these drugs are responsible for the occurrence of thousands of cases of illness and death. Many effective and safe methods for disease prevention are readily available. For example, treatment of hypertension and diabetes, smoking cessation, and weight loss decrease the incidence of coronary heart disease without increasing the risk of other illnesses. It is not necessary or justified to cause breast cancer and other serious diseases in women who are essentially healthy in order to decrease the risk of some other disease.

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