Hormone replacement therapy

To the Editor: The Women's Health Initiative (WHI) trial[1] constitutes the subject of an editorial in the September 2002 *SAMJ*[2] and deserves comment.

The following quotes from Professor Leon Speroff[3] put the results in perspective:

- 'It is not without some trepidation that I challenge the image of WHI as an unflawed study.'
- 'Quoting Trudy Bush "it takes many views to come close to the truth".'
- 'Combined HRT is unlikely to benefit the heart' (WHI). 'The results do not justify a definitive conclusion' (Speroff).
- 'In regard to cardiovascular disease: this may not be a pure primary prevention trial.'
- 'Contrary to the impression reported in the media the statistical calculations for coronary heart disease, stroke and breast cancer are not overwhelming in their strength.'
- 'I don't believe we should disregard a large body of biologic (including the monkey experiments in Tom Clarkson's group) and epidemiological evidence and make decisions solely based upon the WHI.'
- 'Hopefully with time, a more objective and less emotional understanding of post menopausal hormone therapy will be reached.'

Gynaecologically, the trial is unsound. In 1993 unopposed oestrogens were prescribed to 331 women with a uterus, and progestin was added in 1996! Also in 1993, about 9% of the trial subjects were reputed to be either past or current users of unopposed oestrogens and to have a uterus!

The hazard ration (HR) of venous thromboembolic disease is the only clinical outcome (Table II in the WHI study[1] to fulfil the statistical criteria of increased risk of disease (the HR must be in excess of 2.00)[4] and a statistically significant adjusted 95% confidence interval (CI). All the rest with HRs between 1.00 and 2.00 represent an increased risk but weak association only[5] and are not statistically significant because the adjusted 95% CI crosses one. Similarly, colerectal cancer, hip and vertebral fractures are also not statistically significant.

The ratio of disease outcome (Table I) shows impressive increases from year 4 to 5 and even larger reductions from year 5 to 6 and later. The significance of this unsustained rise in year 5 is uncertain.

The changes in the disease outcome results correlate more closely with the placebo outcome inversely than with the treatment incidence (Table I).

The year 6 and later drop is discounted by the writers: 'the narrowing of the difference by year 6 is because HR estimates tend to be unstable beyond 6 years after randomisation'. No references are given. The planned duration of the trial was 8.5 years. Over 25% of subjects had used HRT before the start of the trial!

If Table IV in the WHI study is analysed 2-yearly, no major impact is noted in the last 2 years (Table II). This reduces the risk of 1-year bias considering the small number of events involved.

Table I. Adapted from the WHI study Table IV[1]

Year	1	2	3	4	5	6 and later	Changes from year 4 to 5	Changes from year 5 to 6 and later
Ratio of disease outcome								
CHD	1.78	1.15	1.06	0.99	2.38	0.78	+1.39	-1.60
Breast cancer	0.62	0.83	1.16	1.73	2.64	1.12	+0.91	-1.52
VTE	3.60	2.26	1.67	1.84	2.49	0.90	+0.65	-1.59
Stroke	0.95	1.72	1.79	1.70	1.87	0.66	+0.17	-1.21
TREATMENT								
CHD	0.51	0.43	0.24	0.32	0.39	0.33	+0.07	-0.06
Breast cancer	0.12	0.31	0.34	0.50	0.57	0.53	+0.07	-0.04
VTE	0.58	0.31	0.25	0.34	0.27	0.23	-0.07	-0.04
Stroke	0.20	0.32	0.36	0.32	0.39	0.33	+0.07	-0.06
PLACEBO								
CHD	0.29	0.38	0.23	0.32	0.16	0.42	-0.16	+0.26
Breast cancer	0.21	0.38	0.29	0.29	0.22	0.47	-0.07	+0.25
VTE	0.16	0.14	0.15	0.19	0.11	0.26	-0.08	+0.15
Stroke	0.21	0.19	0.20	0.19	0.14	0.35	-0.05	+0.21

CHD = coronary heart disease; VTE = venous thromboembolism

Table II. Table IV in the WHI trial analysed 2-yearly[1]

	Years 1 and 2 average year	Years 3 and 4 average year	Years 5 and 6 average year
Ratio of outcome			
CHD	1.40	1.02	1.24
Breast cancer	0.73	1.52	1.60
VTE	2.97	1.74	1.35
Stroke	1.30	1.74	1.47

Other statistical problems include previous HRT use and a drop in rate for HRT of 6.2% and placebo of 10.7%. Drop-out rates for HRT (42%) and placebo (38%) exceeded design projection particularly early on. Does this allow the trial to retain the validity of a randomised trial?

With so few events it also decreases the power of the study from 90% to 70% to detect a 50% change in risk. The long-term benefits are difficult to assess using the intention-to-treat method of analysis with its high early drop-out rates.

The lack of cardiovascular benefit is due to the high percentage of women at high risk of events. Biological evidence shows that the action of oestrogens is blunted in the presence of atherosclerosis and hypertension. Coronary artery atherosclerosis is present in 25% of women aged 55 years and above.[6]

The editorial's two suggestions, viz. that the trial preparation not be used for long-term disease problems (although the authors state that there are currently no large randomised clinical trials on other preparations or routes), and that utilisation be limited to 4 years, need explanation. Neither statement is statistically justified on the WHI results, especially when the HERS trial[7] on cardiovascular health does not confirm the 4-year limit, showing increased risks for the first year only. A modest increase in the relative risk of venous thromboembolism mainly in the first years with a decreasing risk has been shown in case-controlled studies.[8] The possibility of an increased incidence of breast cancer has long been known and is probably promotion of an existing breast cancer, which possibly improves survival rate.

What is required are trials on various combinations and routes against each other as well as placebo. Would drug firms allow this? For cardiovascular protection 45 - 55-year-old women (within 5 years of the menopause) who are cardiovascularly healthy would be needed to assess long-term results.

As important are indications and contraindications. Medication of any sort should only be prescribed if there is an absolute indication or an informed request.

Before starting and during treatment, investigation should at least include baseline and yearly mammograms. A haematological opinion is required for high-risk women or women with a past or family history of venous thromboembolism while combined oral contraceptives used for 2 years or more will probably exclude an increased risk. Full cardiac evaluation is necessary, possibly with a cardiologist's opinion if the woman is over 55. Baseline cholesterol should be measured, and if the woman is on oral HRT triglycerides should be repeated at 6 months and 1 year. Blood pressure should be checked 2 - 4 weeks after commencement of treatment. If the patient is over 55 with cardiovascular risk, baseline lipoprotein (a), sensitive c-reactive protein (CRP), and homocysteine levels should be assessed, and if the patient is hypertensive, prothrombin variant estimations must be done.

Incremental changes from baseline CRP and interleukin 6 (IL6) independently predict future cardiac events in women from the WHI study irrespective of HRT status and show a two-fold increase in risk. Use or non-use of HRT has less importance as a predictor of cardiovascular risk than baseline levels of CRP.[9]

Additional reading on the WHI trial[10-14] is suggested. It should be noted that 5 of the 10 experts who formulated the North American Menopause Society Consensus report[14] were WHI investigators., An editorial entitled 'The end of wisdom'[15] concludes: 'The closure of this trial is a sad loss for women and the future health of our daughters. We have let them down.'

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