Hormone replacement therapy

Hormone replacement therapy: a time for pause

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Oh, what a tangled web we weave,
When first we practice to deceive!
— Sir Walter Scott, *Marmion*

A pill that prevents the ills of aging — fewer heart attacks, stronger bones and better quality of life — how can women be denied this wonder pill? Thus, some physicians have been prescribing various hormone preparations (estrogens with or without progestins) since the mid-1970s, and women in Western societies have been willingly taking them. Some "minor" side effects were known — clots in the legs and gallstones — but most believed that the benefits outweighed the inconveniences. All this has to be rethought with the early termination of one of the trial arms of the Women's Health Initiative (WHI) that was evaluating hormone replacement therapy (HRT).[1]

Menopause heralds the end of reproductive life for women, but why most species continue to have reproductive cycles into old age and humans do not has long perplexed anthropologists.[2] Some postulate that menopause frees up women from reproductive responsibilities and allows them to devote their energies to helping their offspring flourish.[3] Despite nature's designs, the process of menopause has become "medicalized" in Western society, such that many consider HRT to be physiologic.

In the first place, how good was the evidence in favour of the use of HRT? Women were prescribed HRT for several reasons: relief of hot flashes accompanying menopause, prevention of heart disease and osteoporosis, and a host of other supposed benefits such as improvement in quality of life.

There is strong evidence from randomized trials that HRT relieves hot flashes and that women who have severe symptoms experience immediate benefits.[4] But is there a need for the average postmenopausal woman to use HRT? The answer to this question has been far from clear. Although hot flashes and night sweats occur in about half of postmenopausal women, they are severe in only a quarter, with the symptoms generally subsiding over the next year or 2 after menopause.[5] It was also assumed that the prevention of heart disease and osteoporosis would outweigh any adverse effects — such as an increase in venous thromboembolism or breast cancer.

It was precisely to address the balance of benefit versus risks of long-term use that the WHI was established. This massive study involves a total of about 160 000 postmenopausal women between the ages of 50 and 79 years, of whom about 100 000 are included in an observational study and about 55 000 in various interventional trials, using a partial $2 \times 2 \times 2$ factorial design. The first component is the evaluation of low-fat diet in preventing breast cancer; the second component evaluates 2 HRT regimens (among women with a uterus, evaluation of conjugated equine estrogen at a dose of 0.625 mg/d in combination with 2.5 mg of medroxyprogesterone acetate v. placebo; and among women who have had a hysterectomy, evaluation of estrogen alone v. placebo). The third component of the trial evaluates the efficacy of calcium and vitamin D in preventing fractures.[6]

On May 31, 2002, after a mean of 5.2 years of follow-up, the trial arm evaluating estrogen plus progestin versus placebo was stopped because of an excessive number of cases of breast cancer (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.00–1.59; weighted z score –3.19) and major cardiovascular events (coronary heart disease [CHD]: HR 1.29, 95% CI 1.02–1.63; stroke: HR 1.41, 95% CI 1.07–1.85; pulmonary embolism: HR 2.13, 95% CI 1.39–3.25). Although there were fewer hip fractures (HR 0.66, 95% CI 0.45–0.98) and colorectal cancers (HR 0.63, 95% CI 0.43–0.92), a "global index" that incorporated several prespecified outcomes (heart disease, breast cancers, hip fractures, colorectal cancers) was significantly adverse (HR 1.15, 95% CI 1.03–1.28). Add to this the significant 40% excess in strokes and doubling in the risk of pulmonary embolism and it is clear that the hazards of HRT are much larger than the benefits.

Perhaps the trial results may be surprising to some, given that the findings of excess numbers of cases of CHD are in sharp contrast to the results of observational studies that claimed large reductions (by about a half) in the risk of CHD with prolonged use of HRT.[7] The potential biases and confounders (e.g., HRT users may have healthier lifestyles and are wealthier) that cannot be fully "adjusted" for by statistical manipulation in observational data are well known, and their potential for misleading results is recognized. Yet, the seductiveness of such promising effects with HRT from observational data and the extrapolation from a selective emphasis of the favourable effects on surrogate outcomes (vascular reactivity, impact on lipids) have had a profound impact.[8] Theoretical calculations, using decision analysis methodology,

suggested that the potential reductions in CHD would be much larger than any adverse impact on breast cancers and led to recommendations for the widespread use of HRT.[9] The increased risk of deep venous thrombosis has been recognized in previous studies, but the WHI is the first to report an excess number of cases of pulmonary embolism, which is a more serious complication. The results of previous randomized studies of HRTs had indicated a lack of benefit regarding CHD. For example, an increased risk of CHD and death was reported with 2 regimens of estrogens as early as in the 1970s in patients who had previously had an infarction,[10,11] but because the study was done in men, the applicability of the results to women was questioned. A meta-analysis of several small studies,[12] a recent study of secondary prevention,[13] a study of progression of atherosclerosis[14] and one in stroke patients[15] all showed no benefit for HRTs. Therefore, the lack of reduction in CHD in WHI should come as no surprise, and most reasonable and objective individuals would be hard pressed to now believe that HRT can reduce CHD. The excess numbers of cases of myocardial infarction, stroke and venous thromboembolism suggest a prothrombotic tendency affecting the venous bed and multiple arterial territories. Therefore, the collective data from randomized trials are conclusive that HRT increases the risk of vascular thrombosis.

When clinical trial results contradict observational and mechanistic studies, potential explanations for the lack of benefit or harm are often put forward. In the case of HRT, concerns regarding compliance, dose and route of administration have been raised and force us to ask if qualitatively different (i.e., beneficial) results could be obtained with other preparations of HRT? There are no data at present to address this question reliably, but the current verdict has to be "unlikely." Note that in the Coronary Drug Project (albeit in men), 2 doses of estrogens increased CHD risk;[10,11] in women, tamoxifen[16] and raloxifene[17] (2 selective estrogen receptor modulators) increase the risk of venous thromboembolism. The WHI is continuing a parallel study of estrogen alone compared with placebo in women who have undergone hysterectomy, a similar study is ongoing in the United Kingdom and there is a major study evaluating raloxifene. Given that different "directional" effects with similar agents or variations in dose are rare, one cannot assume that these alternative agents or preparations are safe or effective; and until proven otherwise, the use of other preparations cannot be advocated.[18]

Whereas the excess numbers of thrombotic events in the WHI trial emerged early and persisted throughout the study, the excess number of cases of breast cancer emerged after about 3–4 years with increasing risk with more prolonged exposure. Indeed, the risks of breast cancer were higher for individuals who had previously used HRT, which is consistent with epidemiologic data[19] and with the hypothesis that prolonged exposure to carcinogens is needed to cause cancers. A nominal decrease in colorectal cancers has been observed, but there was no time trend, with differences becoming apparent even in the first year. This rapidity of effect is surprising and may be an artifact. The reduction in fractures, including hip fractures, is noteworthy and consistent with data suggesting a decrease in the rate of osteoporosis.

The high rate of cessation of therapy in 42% of the subjects in the active group and use of HRT in 10.7% of the placebo group over 5 years (i.e., about a 50% contrast) in the trial would tend to underestimate any differences. This implies that had all women adhered to their initial treatment allocation (i.e., 100% contrast), the net hazards would probably have been substantially larger. Because the trial included women between the ages of 50 and 79 years, it could be asked whether the impact of HRT among women within the first few years after menopause had been evaluated. Subgroup analysis by age indicates no heterogeneity of results in different age categories (5522 trial subjects were aged between 50 and 59 years, which is a greater number of women than in all previous trials of HRT), suggesting that there is no reason to believe that the results would be different for women in the early years post menopause.

One of the important reasons why HRT is prescribed is to alleviate hot flashes after menopause. The WHI does not challenge its value in this situation. Severe hot flashes affect about a quarter of postmenopausal women, but usually become less severe in a few years. Contrary to popular belief, HRT does not improve the quality of life in all postmenopausal women, but only in the 20%–25% of women who suffer from severe hot flashes.[20] Although alternatives to HRT for the treatment of hot flashes, including selective serotonin reuptake inhibitors,[21] clonidine[22] or diets high in phytoestrogens,[23] have been suggested, these have not been evaluated in long-term studies such as the WHI, so that their risks and benefits during 2–4 years of therapy are uncertain. Since the publication of the WHI results, many physicians will likely consider that the risks do not justify using HRT in most postmenopausal women, and women may accept that some symptoms of menopause are inevitable; physicians should emphasize to patients the benefits of altering their lifestyle and that they should only resort to HRT if hot flashes are severe. Furthermore, patients should clearly understand the increased risks of vascular disease, even if HRTs are used for short periods, and of cancer if used long term. Even in these circumstances, it would be advisable to use HRT for as short a period as possible and gradually taper it. (Note that the increased risk of cardiovascular events is seen within the first year; CHD: HR 1.78, venous thromboembolism: HR 3.60.) Women who are currently taking HRT with the expectation of a health benefit should be advised to stop gradually, perhaps by "dose tapering" or "day tapering" to minimize the symptoms of withdrawal.[24]

For the prevention of cardiovascular disease, there are alternatives available, such as smoking cessation, maintenance of an ideal body weight, exercise, a healthy diet and, in those at high risk, aspirin, lipid lowering with statins, blood pressure lowering, angiotensin converting enzyme inhibitors and beta-blockers.[25] Collectively, these measures

could lower the risk of future vascular disease by over 80%. For the prevention of osteoporosis, there are alternatives including exercise, perhaps calcium and vitamin D, and, in high-risk women, bisphophonates (e.g., alendronate).

The results of the WHI may be viewed as "unwelcome news" by some, but for vast numbers of physicians and their patients, the information simplifies what has been a confusing past decade. We should not use HRT for its purported preventive effects, because it causes more harm than good. Instead, women, with the support of their physicians, should focus on adopting preventive strategies that are clearly proven to be helpful. The WHI also confirms the importance of well-designed, large randomized trials as the only reliable method to evaluate most common interventions. The direct and indirect costs related to the use of HRT probably run into a few billion dollars worldwide each year, with the cumulative costs over the last 2 decades probably in excess of a $100 billion. Had studies such as the WHI been conducted earlier, a significant proportion of this waste could have been avoided, not to mention the avoidance of adverse effects in several million women. The costs of conducting even "relatively expensive" trials pale in comparison to the economic costs saved and human suffering avoided. Other approaches to research have clearly been misleading in this and several other instances, and this should challenge our governments and health research funding bodies to consider whether their allocation of funds for clinical trials is inadequate.

In conclusion, the WHI is a large, well-designed and carefully conducted study that will have a tremendous impact on the health of women. The message for healthy women without severe symptoms of menopause is now clear: to avoid as far as possible HRT, which on balance does more harm than good.

The web of our life is of a mingled yarn, good and ill together.
— William Shakespeare, *All's Well That Ends Well*

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