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Postmenopausal hormone therapy for disease prevention: have we learned any lessons from the past?

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Use of hormone replacement therapy became widespread from 1966 onwards following the publication of the book “Feminine Forever” and speaking tours by gynecologist Robert Wilson promoting his belief that every woman needed to replace the “deficient” ovarian hormones after menopause. This belief was based on clinical observations that older women who took hormone therapy appeared to be younger, more attractive, and healthier than those that did not. From 1985 onwards, several dozen observational studies added impetus to the growing belief that hormone replacement therapy (HRT) would prevent not only osteoporosis, but also heart disease, dementia, and urinary incontinence, and would improve the quality of life of postmenopausal women. Pervasive industry advertising illustrated how the therapy would benefit the skin, bones, heart, and brain. The industry sponsored research, symposia, and speaking tours by opinion leaders in the field of gynecology, osteoporosis, and heart disease. The concept being promoted was that cessation of ovarian function was an endocrinopathy, much like those resulting from failure of the thyroid, adrenal, or the pancreas. This medical model of menopause logically would lead to the conclusion that every postmenopausal woman is diseased and in need of HRT.

By the early 1990’s the scientific establishment had convinced itself that postmenopausal estrogen was indeed good for most women. Professional societies recommended estrogen for osteoporosis, and increasingly also for the prevention of coronary heart disease (CHD). If estrogen did prevent heart disease, then the benefits would clearly outweigh the risks such as breast cancer. The recommendations had a seemingly reasonable basis: the lag in age-related CHD in women compared to men, mostly consistent findings from observational studies of estrogen users, and small clinical trials demonstrating lipid benefits of estrogen. At meetings of the American Heart Association, one or more sessions were devoted to laboratory studies showing mechanisms by which estrogen could reduce coronary risk. However, these kinds of evidence do not prove causality: observational studies cannot resolve the problem of healthy user biases, intermediate outcomes do not necessarily predict clinical effect, and laboratory models looking for mechanisms of benefit are destined to find them. The disappointing results of trials of estrogen to lower cholesterol in men performed decades earlier were dismissed as irrelevant, and the warning signals from studies of oral contraceptive use were ignored.

Prescriptions for HRT continued to climb steadily until 1998, when the first definitive trial published its results. The Heart and Estrogen/Progestin Replacement Study (HERS) investigators chose to study women with existing heart disease because of their high absolute risk and because the epidemiologic studies showed strong associations with reduced risk of second heart attacks. The combination of estrogen-plus-progestin increased the rate of CHD in the treated group in the first year, and with longer term follow-up there was no overall benefit. Following HERS, HRT was no longer recommended for women with existing heart disease, and it was accepted that HRT may increase the early risk of heart attacks in women with

diseased arteries, possibly through mechanisms of coagulation or inflammation. Attention now focused on the potential for HRT in primary prevention. In 2002 the Women's Health Initiative (WHI) trial of estrogen-plus-progestin in generally healthy women with a uterus was stopped early because of increased risks of breast cancer, heart disease, stroke, and blood clots. These risks were not offset by reduced risks of colorectal cancer and hip fractures. As in HERS, the increased risk of CHD was observed in the first few years of the trial, and risks tended to be lower in subsequent years.

The findings from the WHI trial had far-reaching repercussions. The Food and Drug Administration required a black box warning that what was now recast as postmenopausal hormone therapy (omitting the "replacement") should not be used for prevention of coronary heart disease, and when used for the existing indications (vasomotor symptoms, vaginal atrophy, and osteoporosis prevention) it should be used at the lowest dose and the shortest duration needed for management. Professional societies followed suit, and recommended against the use of hormone therapy for primary or secondary prevention of heart disease. Prescriptions of hormone therapy plummeted across the board, and the prescriptions of estrogen plus progestin in particular decreased by two-thirds.

The continuation of the WHI trial of estrogen-alone in women with hysterectomy provided some hope that the results might be different in the absence of progestin. However, in 2004 the estrogen-alone trial was also stopped early, because of increased risk of stroke, and no benefit for prevention of heart disease. Like estrogen-plus-progestin, estrogen-alone increased the risk of blood clots and decreased the risk of hip fracture, but unlike estrogen plus progestin it had no effect on risk of breast or colorectal cancer. Hence, while the results were different in some respects, the overall message was the same: hormone therapy is not suitable for the prevention of cardiovascular disease. Both drugs had adverse effects on cognitive function and dementia, gallbladder disease, urinary continence, and neither drug showed a clinically significant benefit for health-related quality of life.

Why were the trial results for cardiovascular disease so different from those predicted by observational studies? The obvious explanation is that the observational studies overestimated benefit, for a variety of plausible reasons: women who choose hormone therapy are healthier to start with, women who persist with hormone therapy are unusually compliant (and compliance is associated with healthier outcomes), women who develop complications stop hormone therapy, the observational studies failed to account for the early increase in CHD risk, amongst others. Indeed, concern that the observational studies overestimated benefit was the reason for doing the clinical trials. Direct comparisons of the WHI clinical trial and observational study data showed that this observational study did overestimate CHD benefit in hormone users by about 23–30%, after adjusting for a range of potential confounders. The early elevation in CHD risk declined with longer term use, with most of the data on this issue emanating from the observational study where many women had already used hormone therapy for some years prior to enrollment. After allowing for duration of use the overestimate of CHD benefit in the observational study decreased to a non-significant 7–11%.

The timing (a.k.a. the "window of opportunity") hypothesis arose post-hoc as another potential explanation for the discrepant findings for CHD in clinical trials and observational studies. In "primary prevention" observational studies hormone therapy would typically commence at the age of menopause, while most women in the clinical trials were well past the age of menopause. There is support for the hypothesis that estrogen may have beneficial effects on relatively healthy arteries, but adverse effects on diseased arteries, from basic science and animal studies. However, it is important to appreciate that timing cannot be the entire explanation, because "secondary prevention" observational studies suggest a similar reduced risk of CHD in hormone users who already have diseased arteries. The hypothesis can be deconstructed as

having two dimensions: the first is that estrogen may be beneficial in younger women with healthy arteries; the second is that if initiated at this younger age, the benefit will continue into older ages. Additional analyses of observational study and clinical trial data offer support for the first dimension of the hypothesis. Specifically, the data from the combined WHI trials suggest that, if hormone therapy is started within 10 years of the menopause and continued for an average of 4–5 years, there is a trend towards reduced risk of CHD on hormone treatment and a reduction in coronary artery calcium on estrogen-alone in women aged 50–59.

The second dimension (of continued benefit over decades of hormone use) cannot be answered definitively from either clinical trial or observational data. Interpretation of clinical outcomes associated with long term use of estrogen in observational cohorts (including the WHI observational cohort) is fraught with confounding by powerful factors such as compliance bias and survivor bias in this highly selected subset of long term users. From the clinical trials it is known that initiating hormone therapy in women more distant from the menopause is harmful, therefore at some point the effects of estrogen may transition from benefit to harm as women and their arteries age. It is possible that the age at which this transition occurs may be postponed by estrogen, as with other prevention strategies. However, it seems extraordinarily unlikely that estrogen will keep aging at bay indefinitely, which would be akin to its being an “elixir of life.” A definitive very long term trial with clinical outcomes is infeasible. Even if the timing hypothesis is correct, we are dealing with a drug with a very narrow therapeutic window—an important consideration given the existence of better alternatives for prevention of heart disease. The possibility of eventual CHD harm from hormone therapy, in addition to the undoubted harm for stroke, venous thrombo-embolism, and breast cancer (on combined therapy), is incompatible with its use as viable long-term prevention strategy. On the basis of what we do know from the existing clinical trials, most benefit in terms of both symptom relief and possibly reducing an already-low risk of CHD may be obtained by short-term treatment immediately after the menopause, followed by a long-term focus on more acceptable prevention strategies.

It seems unlikely that the mainstream medical community will again consider hormone therapy for prevention of CHD. However, there are constituencies that have found it difficult to give up on the overall beneficence of hormone therapy. A recent survey of gynecologists indicated that almost half did not believe the results of the WHI trials, though they did concede that prevention of CHD was not a suitable indication for hormone therapy. It is possible that more recent publications will help gynecologists and other health care providers put hormone therapy in a more balanced perspective, in that short term use for relief of vasomotor symptoms remains a reasonable option, while the converse applies to long term use for cardiovascular benefit. Others have used these recent data to buttress their belief that long-term hormone therapy will reduce CHD risk, if started during the “window of opportunity.” This belief is eerily reminiscent of the “feminine forever” mythology expounded by Dr. Robert Wilson 42 years ago.