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Review article

Back to the future: Hormone replacement therapy as part of a prevention strategy for women at the onset of menopause

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ABSTRACT

In the late 1980s, several observational studies and meta-analyses suggested that hormone replacement therapy (HRT) was beneficial for prevention of osteoporosis, coronary heart disease, dementia and decreased all-cause mortality. In 1992, the American College of Physicians recommended HRT for prevention of coronary disease. In the late 1990s and early 2000s, several randomized trials in older women suggested coronary harm and that the risks, including breast cancer, outweighed any benefit. HRT stopped being prescribed at that time, even for women who had severe symptoms of menopause. Subsequently, reanalyzes of the randomized trial data, using age stratification, as well as newer studies, and meta-analyses have been consistent in showing that younger women, 50–59 years or within 10 years of menopause, have decreased coronary disease and all-cause mortality; and did not have the perceived risks including breast cancer. These newer findings are consistent with the older observational data. It has also been reported that many women who abruptly stopped HRT had more risks, including more osteoporotic fractures. The current data confirm a "timing" hypothesis for benefits and risks of HRT, showing that younger have many benefits and few risks, particularly if therapy is predominantly focused on the estrogen component. We discuss these findings and put into perspective the potential risks of treatment, and suggest that we may have come full circle regarding the use of HRT. In so doing we propose that HRT should be considered as part of a general prevention strategy for women at the onset of menopause.

1. Introduction

In the late 1980s, several observational studies and meta-analyses suggested that hormone replacement therapy (HRT) for women after menopause was beneficial for prevention of osteoporosis, coronary heart disease (CHD), and dementia and decreased all-cause mortality [1–5]. Indeed it was a recommendation of the American College of Physicians to advocate the use of HRT as a prevention strategy in 1992 [6]. In the late 1990s and early 2000s, several randomized trials in mostly older women in which HRT was initiated 10 or more years after menopause suggested coronary harm and risks outweighed benefit [7–9]. Almost immediately after the initial publication of data from the hormone trial of the Women's Health Initiative (WHI) [9], HRT stopped being prescribed, even for women who had severe symptoms of menopause. Subsequently, reanalyzes of the older randomized trial data, using age stratification, as well as newer studies and meta-analyses have been consistent in showing that when initiated in younger women, 50–59 years or within 10 years of menopause onset, HRT decreases CHD and all-cause mortality; and did not have the perceived risks including breast cancer. These newer findings in younger women with initiation of HRT within 10 years of menopause are consistent with the older observational studies of younger women who initiated HRT at the time of menopause.

In public health, prevention strategies have been instituted with the expectation that it would be beneficial over time and reduce human suffering and mortality. Most aging-related diseases in women occur on average about 10 years after the onset of menopause [10]. Thus, an important opportunity is afforded by

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potentially intervening with preventative strategies at the onset of menopause. The coronary benefit in younger women using HRT, the reduced all-cause mortality and other benefits in terms of reduction in menopausal symptoms, osteoporosis prevention, prevention of new onset diabetes mellitus and improved quality of life; as well as the demonstration of cost effectiveness and the lack of effectiveness of other prevention strategies for younger healthy women make a compelling argument for the use of HRT for prevention. We propose here that use of HRT, and specifically the use of estrogen, should be part of a strategy for prevention of chronic diseases after menopause, and not restricted only for the treatment of moderate to severe hot flushes.

2. What was known about estrogen in women after menopause?

As introduced above, many observational studies showed a benefit of HRT for several endpoints. A meta-analysis and pooled analysis showing a coronary benefit of 0.65 (0.59–0.72) and a projected increase in longevity among users [5] led the American College of Physicians to publish guidelines in 1992 [6]. This statement suggested that "all women, regardless of race, should consider preventive hormone therapy" and that "women who have coronary heart disease or who are at increased risk for CHD are likely to benefit from hormone therapy" [6]. For many, the data on the cardioprotective effects of estrogen were so strong that there was serious concern over the potential attenuating effects of added progestogens; accordingly an International Consensus Meeting was convened in 1988 [11]. It was thought that even minor attenuation of the beneficial effects of estrogen would translate into less "lives being saved from ischemic heart disease " [11]. Although there was not clarity about the various mechanisms of potential cardioprotection by estrogen and attenuation of benefit with added progestogen, it was concluded that while progestogens were necessary in women with a uterus, different progestogens and regimens should be considered. This will be discussed in more detail below, but this conclusion is quite similar to the view today, almost 30 years later.

3. Randomized trials of HRT

Despite strong observational data, it was deemed important to carry out randomized trials to assess the purported coronary benefits of HRT in postmenopausal women. In the 1990's several secondary prevention trials were begun [7–9]. Just as WHI was beginning, reports from these trials, studying the effects of estrogen/progestogen *versus* placebo in women with established CHD showed no overall benefit with a complex pattern of "early harm" (more coronary events within first year of initiation) followed by a statistically significant reduction of coronary events with continued intervention [7].

WHI was a series of large randomized controlled clinical trials conducted mainly in older women more than 10 years from menopause, and an observational study, one aim of which was to investigate whether or not HRT could help prevent major chronic diseases in postmenopausal women. The primary outcome of the HRT studies was CHD end-points, with other clinical outcomes as secondary events, including breast cancer, which was also designated as the primary adverse event; it is important to recognize that breast cancer was a-priori defined as a secondary outcome. The preliminary results from the study with regard to combined estrogen-progestogen HRT were published in a blaze of publicity in 2002 [12]. It was claimed that HRT use increased the risk of CHD events, stroke, pulmonary embolism and breast cancer, and therefore the treatment was not safe. This had a huge global impact, with a significant decrease in the use of HRT world-wide. There has been much criticism about the results and interpretation of the findings in WHI and this discussion is beyond the scope of this review. The original results changed several time in terms of point estimates and confidence intervals, as reviewed by us previously [13]. In the most recent 13 year follow up of data from WHI, the early reported findings have been mainly negated. Indeed as will be reviewed below, the findings in younger women were extremely beneficial with decreases in coronary disease, all-cause mortality as well as cancer rates with very limited and rare side effects [14].

4. Aftermath of WHI: fractures, CV events, mortality

The large fall in use of HRT has had profound clinical consequences for postmenopausal women whose health and well-being has suffered. The reluctance of health care professionals to prescribe HRT has denied many women adequate and effective relief from menopausal symptoms and has impaired their quality of life. In addition, there are data showing that stopping HRT may result in increased CHD, stroke and all-cause mortality [15]. Of equal and well-documented concern is the substantial increase in hip fractures that has been seen due to HRT discontinuation following the WHI 2002 publication [16,17]; this burden is likely to grow. What will be the impact of the reduction in HRT use on cardiovascular disease (CVD)? It is too early to tell as yet, but it is likely that widespread avoidance of HRT use may have a serious negative impact (see below). The WHI had reported a reduction in CHD and in mortality in women initiating estrogen alone before age 60 years compared with those initiating placebo. When the excess mortality seen in this placebo group was related to similar women in the entire US population, it was estimated that during the 10 years following the WHI 2002 publication, avoidance of HRT would result in the premature deaths of anywhere between 19,000 and 92,000 women [18].

It was claimed that a fall in breast cancer incidence in the US was accompanied by the decline in HRT use following WHI 2002 [19]. But this was not borne out worldwide and in most cases the decreases in breast cancer incidence actually preceded the decline in HRT use [20].

5. Why the initial reports from WHI and the other secondary prevention trials were different from the observational data

Although the beneficial effects found in the earlier observational studies was hypothesized to be due to inherent biases of observational data such as a "healthy user effect", adjustments to the data have not negated these findings. A major difference between observational studies and randomized clinical trials of HRT is the age at initiation of therapy; observational studies included women who chose to start HRT around the time of menopause mainly for symptomatic relief, whereas the average age of women in WHI was 15 or more years older. Thus many women in WHI were outside the "window of opportunity", greater than age 60 years or more than 10 years post menopause. The areas that differ between the observational data and the randomized trials carried out in older women are the effects on CHD, and on cognitive decline and dementia. It is likely that these two disease processes are age dependent and also are affected by time from menopause onset.

The absent or diminished arterial response to estrogen in older *versus* younger women may be accounted for by several mechanisms. Loss of ERα, its methylation and interference by higher levels of 27-OH cholesterol with aging are all possible explanations for the lack of response in older atherosclerotic arteries [21–23]. The age effect may also be critically dependent on dose at initiation. Higher

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