Hormone replacement therapy

Lessons from the Women's Health Initiative: primary prevention and gender health

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The Women's Health Initiative (WHI) was designed to assess the risks and benefits of a number of primary prevention strategies in healthy postmenopausal women, including the use of hormone replacement therapy, calcium and vitamin D supplementation and a low-fat diet.[1] The outcome of the study of combined estrogen and progestin replacement, with risks exceeding benefits, is not surprising in 2002, although it was not expected when the study was designed in 1991–1992. The evidence for an increased risk of breast cancer with hormone replacement therapy has been steadily accumulating for the past 10 years.[2] We have become better informed about the increased risk of thromboembolic events, including stroke, deep vein thrombosis and pulmonary embolism.[3] Results of the HERS[4] studies suggested that hormone replacement therapy is associated with an increased risk of cardiovascular events, although this increased risk was not noted in healthy women in the Nurses Health Study.[3] On the other hand, there has been consistent evidence that hormone replacement therapy at menopause delays osteoporosis and decreases the incidence of hip fractures and a suggestion that it protects against colorectal cancer.

With the release of the WHI findings, the evidence is now unequivocal. There is more potential for harm than good in healthy postmenopausal women taking a combination of estrogen and progesterone to prevent chronic disease. The early termination of the portion of the WHI on combination hormone replacement therapy provides us with some important lessons on primary prevention, research and gender health.

As more of the population reaches old age with expectations of a significantly longer, healthier lifespan, there is an increasing focus on primary prevention strategies. Most randomized controlled trials are carried out to demonstrate the efficacy of a therapy for a single medical condition or the ability of a therapy to prevent a disease in people considered to be at increased risk for that condition. These studies are often funded by the pharmaceutical industry and are geared to end points that will allow licensing of new therapies or new uses of an existing product. Long-term studies that evaluate broader health effects are rarely funded by industry. The WHI, which is publicly funded by the US National Institutes of Health, demonstrates that the large, long-term, complex and costly studies that are needed to assess the efficacy of primary prevention interventions require the resources and support of the public sector.

The results of the WHI should make us evaluate whether we are targeting and funding primary prevention efforts appropriately. If the risks of hormone replacement therapy outweigh the benefits, what are the options for women who hope to avoid the fractures associated with osteoporosis? Recent studies demonstrate that the risk of osteoporosis is related to the peak bone mass achieved in the teens and twenties.[5] Primary prevention of osteoporosis could therefore consist of ensuring that teenagers and young adults maximize their bone mass with appropriate exercise and diet. Primary prevention of cardiovascular disease could consist of dealing with the societal tensions and marketing campaigns that drive young people to begin smoking, develop poor eating habits and choose a sedentary lifestyle. These types of nonpharmacologic interventions targeted at adolescents and young adults have barely been incorporated into our primary prevention strategies, and in many Canadian provinces there are no or minimal resources allocated to such interventions for any age group.

The results of this portion of the WHI also elegantly demonstrate that the scientific validity of ideas that appear to be intuitively correct must be proven through well-designed studies. Because women seem to be protected from coronary artery disease before menopause and have an accelerated risk of developing the disease in the 10 years after menopause, it seemed intuitively correct to hypothesize that hormone replacement therapy in postmenopausal women should provide them with protection from coronary artery disease. Good research demonstrated that our intuition was wrong.

Research panels and key opinion leaders fund research that is consistent with their perception of what is important. It is largely accepted that the WHI took place because of the leadership of people like Bernadine Healy, former Director of the National Institutes of Health, and Vivian Pinn, Associate Director for Research on Women's Health at the NIH. These women created a mandate to develop a research agenda to identify and address gaps in our knowl-

edge of women's health. They had the power necessary to push this research agenda forward in the face of considerable scientific opposition and the wisdom to recognize that a project on the scale of the mammoth, very expensive WHI was required.

Both men and women should be involved in making decisions about the allocation of funding for research and they should represent an appropriate balance of ethnic backgrounds and experience. For example, female researchers may ask different questions and propose different research methodologies than do male researchers, because of differences in their life experiences, perceptions of priorities and styles of interactions with peers. We must continually assess whether we are incorporating sufficient diversity into the processes that determine the direction and priorities of our research enterprise.

The WHI was carried out because of the vision and new-found power of women in the United States. Because women are different and more physiologically complex than men, there has been a tendency to exclude them from studies or to not carry out studies that are of importance to women. Of even more concern has been the tendency to extrapolate findings from studies of men to women. Some of the gaps in our knowledge of women's health, such as in the area of cardiovascular disease, are now being addressed. However, major issues in women's health remain unexplored, including the increased morbidity for women with asthma[6] and the lack of any evidence on the utility of annual chest x-ray screening for female smokers.[7] We are fortunate in Canada that as the Medical Research Council evolved into the Canadian Institutes of Health Research its directors recognized the importance of research relating to the differing health issues for women and men and established an Institute of Gender and Health to carry out this work.

The results of the WHI should also remind us that women seem to be particularly targeted to receive therapies to prevent future disease or to enhance or maintain their physical appearance. There is an increasing demand for breast implants, liposuction, facelifts and injections of botulinum toxin, despite the lack of adequate studies of their risks and benefits. Physicians and their female patients are willing to undertake even high-risk therapy if it is presented as primary prevention. Medications that produce anorexia, although known to be associated with a significant risk of pulmonary hypertension, were felt to be an acceptable therapy because obese women have an increased risk of coronary artery disease and diabetes.[8] Women of all ages are increasingly being prescribed medications for the treatment of depression and anxiety with little knowledge about the long-term effects of these drugs, although suggestions are emerging that users of selective serotonin reuptake inhibitors may be at a higher risk for suicide.[9]

The lessons learned so far from the WHI are important for both men and women. The norms and values of the society in which an individual and their physician reside often influence patient care. On the basis of a belief that hormones are associated with youth and health, hormone replacement therapy for women was believed to be good. In a similar fashion, we are now witnessing the discovery of andropause and the initiation of androgen therapy for men with the belief that it will lead to better overall health. The WHI has clearly demonstrated that it is imperative that trials assessing the overall risk and benefit of primary prevention interventions for both men and women be conducted before such therapies are broadly instituted. We must ensure that we understand the values and paradigms that drive our hypotheses and we must be willing to fund the research necessary to validate the effectiveness of our interventions. The WHI demonstrates the potential for doing harm … we cannot continue to do so.

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