Understanding the WHI gap

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“IMPACT OF AGING VS. ESTROGEN loss on cardiac gene expression: estrogen replacement and inflammation” by Pechenino et al. (7) is an exciting addition to the literature that helps explain the discrepancy between the observational studies and the randomized clinical trials with regard to hormone therapy (HT) and cardiovascular disease. As clinicians, we have always and still believe that the Women’s Health Initiative (WHI) cohort was not representative of the women we care for in our practices. The release of the WHI revealed a “gap” in our understanding of how HT works. Some will argue Brown Norway rats may not also be representative of women transitioning into menopause, but the authors’ results go a long way toward explaining the deleterious effects of estrogen administration resumed in women remote from menopause.

We continue to believe in the critical window (8), the “timing is everything” hypothesis (1), and our Eu-estrogenemia hypothesis (4, 11) and thank Pechenino et al. (7) for contributing to those concepts with their excellent study. Hypoestrogenemic hiatuses appear to lead to atherosclerotic changes in the heart (1), worsening verbal memory (5), osteoporosis (3), urogenital atrophy, impaired retinal artery blood flow (2), and renal stones (10). Furthermore, we suggest that a true and good concentration of estrogen may be necessary for optimal function of all estrogen receptors for homeostasis, eu-estrogenemia, in most women and perhaps also in men for all of their lives (4, 11).

In the 1980s and 1990s, clinicians prescribed hormone replacement therapy (HRT) in physiological and pharmacological doses to optimize our patients’ health through improved estrogen receptor function. Since the release of the WHI in 2002 and the recommendations for the lowest dose for the shortest duration for vasomotor symptoms and urogenital atrophy (6), a large number of women stopped HRT completely and became hypoestrogenic. We call this group Rossouw’s cohort (9). If our clinical concepts and the author’s animal model concepts of hypoestrogenemia are correct, then we should soon begin to see a clinical increase in the disease entities attributed to the absence of estrogen, as we are already seeing with hip fractures (3). As genomic medicine becomes more prevalent in our practice of medicine, discoveries such as the authors’ will help us understand the role of estrogen in the disease processes of hypoestrogenic women.

REFERENCES