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Review

Perspective on hormone therapy 10 years after the WHI

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ABSTRACT

The Women's Health Initiative (WHI) hormone trials are among the most influential and debated research studies in women's health in recent medical history [1,2]. This year (2013) marked the 10th anniversary of the publication of the WHI results and this past decade has been nothing less than revolutionary. We have witnessed a transformative evolution in our understanding of, and in the practice of, menopause management and herein summarize the strides the field has traversed over the past 10 years.

Contents

1. Introduction

From a historical perspective, cardioprotective implications of menopausal hormone therapy (MHT) had been suggested by several observational studies in women with and without existing coronary heart disease (CHD) [3–6]. In 1992, the American College of Physicians published guidelines *advising* postmenopausal women with a prior hysterectomy and women at risk for coronary heart disease that they are likely to benefit from preventative hormone replacement therapy [7]. Ensuing years witnessed an escalation in the use of MHT not just in the United States, but across the globe, and MHT use was encouraged by both providers and the lay media almost as a risk reduction strategy against CHD [5,6,8]. In the late 1990s, the medical as well as the lay community believed in the promise of long term benefits of MHT use. In the rouse of a wealth of observational data therefore, results of the randomized controlled trials from the Women's Health Initiative left the community, providers and patients, bewildered [9–13].

The stringently designed WHI hormonal trials studied the effects of unopposed estrogen (E-alone trial), and of combined estrogen–progestin therapy (E + P trial) on risk for CHD (primary objective); effects of MHT on additional organ systems such as skeleton, breast and thrombotic risk constituted secondary outcomes of interest. Over 16,600 menopausal women between

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the ages of 50–79 (average age was 63 years) were enrolled across 40 clinical centers in the United States between 1993 and 1998; notably, the enrolled age range for MHT reflected the clinical practice norms of then. After a mean of 5.2 years of follow-up, the data and safety monitoring board recommended discontinuing the E + P trial in July 2002 due to concerns that the potential for "net harm" outweighed the observed "health benefit" from MHT use. At trial inception, an increased risk of breast cancer diagnosis and of thromboembolism related to MHT use had been anticipated but the purported benefit against CHD and possibly stroke was expected to outweigh any potential for harm. And indeed, over the duration of the E + P trial, the incidence of invasive breast cancer and of venous thrombosis was higher in the hormone users compared to those assigned to the placebo [1]. Although reduced fracture and colon cancer risks came as welcome surprises, the much anticipated and believed cardioprotection related to MHT was not evident. An increased risk of stroke along with of invasive breast cancer, venous thrombosis and pulmonary embolism with MHT tipped the scales in the direction of "net harm" with hormone use and the investigators concluded that the risk-benefit profile in the trial did not support the use of combined (E + P) hormonal therapy for the primary prevention of coronary heart disease [1].

In the E alone WHI trial [2], over 10,000 previously hysterectomized women were randomized to E-alone or placebo; again coronary heart disease was the primary outcome of interest, with similar secondary end points as the E + P trial. Similar to the E + P results, elevated risks of stroke and of thromboembolism were evident, and deemed to outweigh the observed risk reduction in fragility fractures seen with E use. The risk of breast cancer was not increased with E alone use, but the E alone trial failed to demonstrate cardioprotective benefits of E and the National Institutes of Health (NIH) ended the E-alone trial early in February 2004 on grounds of "lack of overall health benefit relating to E use" [2].

The unexpected findings of the WHI hormone trials were highly publicized, widely disseminated and extensively debated. A major shift in opinion on role of MHT followed with a consequent change in the then existing paradigm for menopause management; the place of hormone replacement therapy in postmenopausal women was redefined [12–14]. The U.S. Preventative Services Task Force published recommendations *against* the use of estrogen and progestin therapy for the primary prevention of chronic conditions in postmenopausal women [14]. A precipitous global decline in the dispensation and use of MHT followed in the wake of WHI [9,10,13].

Since the initial publication of the WHI hormone trial results, multiple secondary analyses have yielded interesting data which suggested that the risk of CHD was dependent upon both the timing of initiating hormone exposure as well as the age of the woman at the time of MHT initiation [15,16]. Specifically, in the E-alone trial, a non-statistically significant reduction in CHD risk was noted in participants of ages between 50 and 59 years [16]. In the E + P trial, a decreased risk of CHD was noted in MHT users who were within 10 years since the onset of menopause. A similar non-significant trend for benefit was observed for total mortality with MHT use [16]. Results from these post hoc analyses published the initial WHI data have helped calm patients and providers fears relating to MHT and refine the *timing hypothesis* which identifies time since menopause is a critical determinant of the net benefit versus potential for harm relating to MHT initiation and use [16]. Nonetheless, the lacking unanimity of understanding and the interpretative heterogeneity has muddied the waters for providers seeking guidance about how to best to counsel their patients. The most recent Position Statement of the North American Menopause Society on hormone therapy published in early 2012 laudably crystallizes our understanding of the existing data and provides easy to follow recommendations for menopause management [17]. In a follow-up publication, the North American Menopause Society published an article with the support of several other key organizations including the American Society for Reproductive Medicine and the Endocrine Society to reassure patients and providers that despite the debate that followed the WHI trials the experts in the field are in agreement about the role of hormone therapy in menopause management [18]. The many national and international organizations are unified in their stance that MHT *not* be used to prevent chronic disease in postmenopausal women [18,19]. A similar consensus exists regarding a role of MHT in the management of menopausal symptoms wherein the balance of risk versus benefit of short term use of MHT must be individualized when considering the use of MHT for the temporary treatment of vasomotor symptoms in aging women. A lack of consensus on long term safety underscores a need for continued investigation into the safety and efficacy of hormone replacement therapy.

2. Changing landscape of menopause management – *then and now*

Vasomotor symptoms (VMS) occur in approximately 70% of women in menopause [20] and may be severe enough to adversely impact on quality of life [21]. Estrogen is the most efficacious of available therapies for the management of menopause related symptoms and relief of VMS is the primary indication for initiating MHT, especially in younger perimenopausal or postmenopausal women. It is important to recognize that frequency and severity of symptoms dominates early in the process of reproductive aging, i.e. the younger peri and early menopausal women bear the brunt of vasomotor symptoms. It is imperative to appreciate that the WHI trials were not designed with the intent to study the efficacy of MHT on menopausal symptoms and that only a fraction of women enrolled in the WHI hormone trials was symptomatic. However, menopausal symptom data were collected on women enrolled in the estrogen plus progestin trial, which included over 16,000 patients across all ages of menopause. Detailed data analyses from these participants showed that estrogen with or without a progestin as an effective therapy to treat vasomotor symptoms related to menopause [22,23].

2.1. Estrogen dose – then and now

MHT related risks highlighted in the post WHI era gave impetus to efforts aimed at exploring the safety and efficacy of lower hormone dose regimens (conjugated equine estrogen and estradiol based regimens with and without a progestin) for treatment of menopausal symptoms. A reduction in the risk of venous thromboembolism is suggested through lowering in E content of MHT, thus offering some reassurance to the patient and provider alike [24]. *Significant reduction in the frequency and severity of hot flushes compared to placebo has been observed with regimens utilizing E in doses that are ½ to ¼ of dose employed in the WHI trials* [25].

2.2. Progestin component of MHT – then and now

In non-hysterectomized postmenopausal women, the use of estrogen alone, unopposed by periodic progesterone exposure, confers a risk for endometrial hyperplasia and even endometrial cancer and combination hormone therapy (i.e. E + P) is therefore now the standard of care when considering hormone replacement therapy in women with intact uteri [26]. While mitigating the risk for endometrial cancer with continuous progestin in combination with estrogen, the WHI E + P trial paradoxically demonstrated an increased incidence of invasive postmenopausal breast cancer [1]. Interestingly, the number of new cases of breast cancer in the E alone users was less than that seen in the placebo treated population in the WHI [2]; these discrepant findings suggested that