Menopausal Hormone Therapy: Current Considerations

Cynthia A. Stuenkel, MD

KEYWORDS

• Menopausal hormone therapy • Estrogen • Progestogen
• Selective estrogen receptor modulator • Bazedoxifene • Ospemifene

KEY POINTS

- Menopausal hormone therapy (MHT) is the most effective method to improve vasomotor and vaginal symptoms associated with the menopause; for carefully selected women, benefits exceed risks.
- Optimal candidates for MHT include women younger than age 60 or within 10 years of menopause, without contraindications, and without increased risk of cardiovascular disease or breast cancer.
- Individualization is a key factor when formulating a treatment plan for relief of menopausal symptoms.
- Currently available choices of MHT allow for tailoring therapy to integrate personal preference, consideration of varying risk profiles, and individual treatment requirements.
- The decision to use MHT should be revisited at least annually or whenever a change in the patient's medical status, treatment priorities, or personal preferences occurs.

Practicing evidence-based medicine, in the realm of menopausal hormone therapy (MHT), is an ever-evolving challenge, and one that requires an ongoing awareness of emerging scientific findings and updated recommendations. In this article, a practical approach to navigating the use of MHT and available options are presented.

MENOPAUSAL HORMONE THERAPY: THE STATE OF THE EVIDENCE

For many years, menopausal medicine was more eminence-based than evidence-based.[1] Women were encouraged to use MHT to stay *Feminine Forever* (the title of a 1966 bestseller,[2] which was very persuasive, but received mixed reviews).[3] Eventually, small clinical trials confirmed symptom relief by various MHT preparations; others showed benefit on bone density measurements and lipid determinations.[4]

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Department of Medicine, University of California, San Diego, School of Medicine, 6376 Castejon Drive, La Jolla, CA 92037, USA
E-mail address: castuenkel@ucsd.edu

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During the 1980s, impressive evidence from several prospective cohort and case-control studies began to accumulate, and with few exceptions, consistently described reduction of coronary heart disease (CHD) and osteoporotic fractures in women who used MHT. In 1992, in response to mounting supportive data from studies examining surrogate endpoints and accompanying enthusiasm of the medical community, the American College of Physicians recommended MHT for postmenopausal women, particularly those with history of CHD or at risk for CHD, primarily for cardioprotection and osteoporosis prevention.[5] Breast cancer was a recognized risk, but the overwhelming cardiovascular benefit seemed to outweigh concerns.

Randomized clinical outcome trials (RCT) lagged decades behind clinical practice. The Postmenopausal Estrogen and Progestogen Intervention (PEPI) trial,[6] funded by the National Institutes of Health and published in 1995, evaluated effects of commonly prescribed MHT preparations on surrogate cardiovascular disease (CVD) risk factors and endometrial safety (**Table 1**). The results were reassuring and consistent with the anticipated benefits, but the trial was too small and too short to assess the effects of MHT on hard clinical endpoints, such as heart attack, stroke, blood clots, osteoporotic fractures, and breast cancer risk.

Although a lightning rod for more than a decade of controversy, the subsequent landmark Women's Health Initiative (WHI) trials have provided the best available RCT evidence for assessing risks and benefits of MHT. Conceived in the late 1980s as an effort to confirm the validity of prevailing practice recommendations at the time to prescribe MHT for prevention of CHD, osteoporosis, and possibly cognitive decline, the WHI was designed to evaluate the preventive benefits of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), the most commonly prescribed drugs in America in postmenopausal women ages 50 to 79.[7] CHD was the primary outcome, with breast cancer as the primary safety outcome (see **Table 1**). The WHI was not designed to evaluate symptom relief because this had previously been shown in many adequately powered RCTs.[4] Furthermore, women who had severe vasomotor symptoms (VMS) were intentionally excluded from the WHI, because investigators hoped to minimize dropout of highly symptomatic women assigned to placebo therapy.

In 2002, the initial results of the WHI combined estrogen plus progestin (E + P) MHT trial were prematurely announced after 5.6 years (rather than 8.5 as planned), because MHT-related risks (CHD, stroke, breast cancer, and venous thromboembolic events [VTE]) were noted to exceed preventive benefits (reduced fractures, reduced colon cancer) (see **Table 1**).[7] In response to the unanticipated negative results of the WHI E + P trial, prescriptions for MHT declined by 70%.[11] In early 2003, the US Food and Drug Administration (FDA) required package labeling changes for all MHT products, with the assumption that risks and benefits were similar.

The initial results of the 7.2-year WHI conjugated equine estrogen (CEE-alone) trial, published in 2004, differed from the combination trial in several ways (see **Table 1**).[8] With CEE-alone, there was no overall increase in CHD or breast cancer, while fractures were reduced, as anticipated.[8] In women ages 50 to 59, the risk of CHD, although not statistically different from rates in older age groups, suggested a trend consistent with observational studies showing that CEE use may offer CHD benefit.

In the intervening decade, since the WHI results were initially reported, continued participant follow-up and outcome analyses have accentuated the divergent findings between the WHI CEE-alone and the WHI E + P clinical trials[12] (**Box 1**, **Table 2**). Furthermore, when data were stratified by participant age and years since menopause, the effect of timing of initiation of MHT on clinical outcomes, particularly CHD and breast cancer, was brought into sharper focus.[13,17] Most recently, the