

# Menopause Medicine: Past, Present, and Future



R.L. Reid

## Robert L. Reid, MD

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynaecology, Queen's University, Kingston, ON

### THE PAST

The term “menopause” was coined by a French physician in 1821. A Canadian gynaecologist, Archie Cameron at Montréal General Hospital, was the first to use estrogen therapy, in 1930, using a human placental extract (Emmenin) discovered by James Collip.<sup>1</sup> The demand for this hormone therapy was such in the ensuing years that placental extracts proved insufficient, and the small pharmaceutical company providing Emmenin to the market (Ayerst, McKenna, and Harrison) switched to producing estrogenic compounds from pregnant mare's urine. Premarin, approved in Canada in 1941 and in the United States the following year, was the most widely prescribed menopausal therapy for the next 60 years.

Until the mid-1970s research on menopause was exclusively observational, and therapies were largely based on the experience and opinions of clinicians.<sup>2</sup> At the first International Conference on the Menopause in Montpellier, France in 1976, concerns about estrogen-induced endometrial cancer were emerging, and these led to concomitant progestin therapy becoming the standard of care for women with a uterus by the early 1980s. Estrogen-induced thrombosis was also identified as a concern. The role of estrogen in breast cancer was unclear, and whether progestin would ameliorate any risk was still being debated.<sup>2</sup>

Attitudes about the effectiveness and safety of hormone therapy shifted from a position of confidence in the early 1990s to one of caution at the turn of the century and then to outright fear following the alarming first reports from the Women's Health Initiative (WHI) in 2002.

Over the next decade, reports from the WHI dominated the news. The initial reporting of adverse effects of

menopausal hormone treatment (MHT) generated enormous media attention, and the ongoing one-sided coverage was fostered by consistent negative messaging from the WHI writing group.<sup>3</sup> Because of its enormous size, its randomized clinical trial design, and the worrisome findings, the WHI overshadowed many smaller, yet important, observations about the effects of MHT in the next decade. Reports from the WHI claiming that hormone replacement therapy would promote cardiovascular disease, stroke, and cancer had a domino effect with a broad range of adverse consequences on the health of menopausal women. Prescriptions for hormone therapy plummeted as both women and their health care providers became fearful of MHT. Many women were told either to just “put up with symptoms” or to try alternative therapies. Prescriptions for serotonin reuptake inhibitors soared, showing an inverse relationship with the fall in MHT prescribing.

Companies promoting complementary and alternative medicine (CAM) were largely unregulated and were under no obligation to demonstrate efficacy of their products through rigorous randomized clinical trials. The shelves of pharmacies were flooded with CAM products purporting to relieve vasomotor symptoms (VMS) and other menopausal concerns, and a burgeoning market emerged. Aggressive marketing with celebrity endorsement by celebrities such as Oprah and Suzanne Somers of “individualized therapy” based on salivary hormone testing and the use of “more natural and safer” compounded bioidentical

J Obstet Gynaecol Can 2019;41(S2):S347–S349

<https://doi.org/10.1016/j.jogc.2019.08.026>

© 2019 The Society of Obstetricians and Gynaecologists of Canada/La Société des obstétriciens et gynécologues du Canada. Published by Elsevier Inc. All rights reserved.

hormones reinforced the prevailing belief that traditional MHT was dangerous and something to be avoided. Most CAM products were found to function merely as placebos, and compounded bioidentical hormones lack standardization as well as proof of efficacy and safety.<sup>4,5</sup>

Consequently, menopausal symptoms in the population worsened, with more women reporting persistent distressing VMS, vaginal dryness, and dyspareunia. Largely ignored was the significant impact of untreated menopausal symptoms on quality of life and participation in the workforce.<sup>6</sup> Rates of osteoporotic fractures in large health maintenance organizations were seen to rise, and rates of cardiovascular disease and stroke increased in women who discontinued MHT compared with women who did not.<sup>7</sup>

## **THE PRESENT**

Now, almost 20 years after the first WHI report, the pendulum has swung back in favour of hormone replacement therapy for most symptomatic newly menopausal women. Not only has MHT been clearly established as the most effective treatment for VMS, it also ameliorates the genitourinary syndrome of menopause for many women. Observational studies and secondary analyses of WHI data provided evidence that MHT is cardioprotective when it is started close to the time of menopause.<sup>8</sup> A Cochrane analysis concluded that women who started MHT within 10 years of menopause had 30% lower mortality (relative risk (RR) 0.70; 95% CI 0.52–0.95) and 48% lower coronary heart disease (RR 0.52; 95% CI 0.29–0.96), and no effect on risk of stroke relative to placebo was found.<sup>9</sup>

Fear of breast cancer has long been a deciding factor in prescription and uptake of MHT. Mammography, although promoted as an ideal screening tool for breast cancer, is really a blunt instrument that leads to frequent overdiagnosis and overtreatment.

The apparent “harm” reported for combined MHT in the WHI has been overstated.<sup>8,10,11</sup> In the WHI, MHT caused no increase in breast cancer among first-time users. The small increase in breast cancer rates (8/10,000 users per year) seen in former MHT users in the combined estrogen-progestin trial appears to have resulted from an unexplained decrease in breast cancer diagnoses among women assigned to placebo. The annualized rate of breast cancer in women taking combined MHT was no different from the annualized rate of breast cancer in both arms of the much larger WHI diet modification

trial.<sup>8</sup> Findings of a review of randomized clinical trial data were as follows:

*After five decades of study, no conclusive evidence, including the WHI combined CEE/MPA (conjugated equine estrogen/medroxyprogesterone acetate) trial, proves that MHT causes breast cancer and, in fact, the overwhelming preponderance of data, including the WHI combined CEE/MPA trial, show that estrogen/progestogen therapy has a null effect on breast cancer.<sup>11</sup>*

Undoubtedly, some will challenge this assertion by citing biological plausibility and the accumulated evidence from observational studies. Nevertheless, the impact of MHT on breast cancer, if any, is small, and the potential preventive benefits for cardiovascular disease are enormous.

## **THE FUTURE**

New MHT approaches will be needed to address the clinical frustrations of women and their health care providers. Bleeding and breast pain rank high on the list of reasons why MHT is discontinued even when it is relieving VMS. Lower doses, different formulations (i.e., continuous vs. cyclic), and innovative products, such as the tissue-selective estrogen complex (TSEC) that combines an estrogen with a selective estrogen receptor modulator, all hold promise for relieving VMS while minimizing the nuisance adverse effects of traditional MHT.<sup>12</sup>

Venous thromboembolism, although a rare adverse event in MHT users between the ages of 45 and 60, remains a concern that may be reduced by greater awareness of concomitant risk factors (e.g., immobility, thrombophilia, family history), non-oral delivery, and newer formulations with less thrombogenic potential containing estradiol, estetrol, or TSEC.

## **REVISITING MHT AS A LONGER-TERM PREVENTIVE STRATEGY**

Not only does MHT relieve VMS, it also may afford other benefits to individual women. MHT can reduce new-onset somatic pain and, for some women, improve sleep, mood, and mental clarity. For women who feel better while on MHT, extended use may be appropriate after a review of individual benefits and risks.<sup>13</sup>

The short duration of MHT treatment in the WHI (mean of 5.2 years for combined MHT and 6.8 years for estrogen alone) leaves unanswered the question of whether early initiation and longer-term treatment with MHT would afford cardioprotection. Although there is evidence that aspirin,

statins, and angiotensin-converting enzyme inhibitors can reduce cardiovascular disease in men, no such evidence exists for women.<sup>7</sup> The MHT scares of the past and a lack of clinical trial data on the long-term impact of early initiation of MHT on cardiovascular end points have left most cardiologists and national organizations reluctant to support MHT for cardiac prevention in women. Others have challenged this position, pointing out that, other than lifestyle changes, MHT may be the best option to maintain cardiovascular health in aging women.<sup>7,8</sup> The risk of diabetes mellitus, another significant global health concern, is reduced by 15% to 20% in women taking MHT.<sup>14</sup>

Osteoporotic fractures lead to substantial morbidity and mortality and are considered one of the largest public health priorities by the World Health Organization.<sup>15</sup> Fears about MHT after the WHI reports led osteoporosis experts and organizations to recommend bisphosphonates as first-line treatment for primary prevention of osteoporosis. With the emergence of a much more reassuring benefit-to-risk profile for MHT, there are now arguments that this position should change, with MHT becoming first-line therapy—only oral conjugated equine estrogen has been proven to reduce the risk of fracture in both osteoporotic and non-osteoporotic women.<sup>15</sup>

Education and clarity about the true impact of MHT on breast cancer remain critical to the wider acceptance of long-term therapy. The combination of estrogen with a selective estrogen receptor modulator in the TSEC may ultimately prove to reduce the risk of breast cancer; however, there is currently insufficient evidence to establish this.

Taken together, these observations about the potential for MHT to prevent or delay several of the most serious conditions affecting women as they age suggest that it is time, once again, to evaluate the role of MHT as preventive therapy.

## REFERENCES

1. Baskett TF. *Eponyms and names in obstetrics and gynaecology*. 3rd ed. London: Cambridge University Press; 2019.
2. Barlow DH. A long and winding road: reflections on the evolution of menopause medicine over a professional lifetime. *Menopause* 2018;25:1395–400.
3. Langer RD. The evidence base for HRT: what can we believe? *Climacteric* 2017;20:91–6.
4. Nedrow A, Miller J, Walker M, et al. Complementary and alternative therapies for management of menopause-related symptoms: a systematic evidence review. *Arch Intern Med* 2006;166:1453–65.
5. Santoro N, Braunstein GD, Butts CL, et al. Compounded bioidentical hormones in endocrinology practice: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2016;101:1318–43.
6. Pinkerton JV. Money talks: untreated hot flashes cost women, the workplace, and society. *Menopause* 2015;22:254–5.
7. Lobo RA, Pickar JH, Stevenson JC, et al. Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. *Atherosclerosis* 2016;254:282–90.
8. Langer RD, Simon JA, Pines A, et al. Menopausal hormone therapy for primary prevention: why the USPSTF is wrong. *Menopause* 2017;24:1101–12.
9. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015(3):CD002229.
10. Reid RL. Hormone therapy and breast cancer: risk communication and the perfect storm. *Climacteric* 2019;22:13–6.
11. Hodis HN, Sarrel PM. Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials? *Climacteric* 2018;21:521–8.
12. Pinkerton JV. Tissue selective estrogen complex for menopausal hormone therapy. *Clin Obstet Gynecol* 2018;61:463–9.
13. Kaunitz AM. Extended duration use of menopausal hormone therapy. *Menopause* 2014;21:679–81.
14. Mauvais-Jarvis F, Manson JE, Stevenson JC, et al. Menopausal hormone therapy and type 2 diabetes prevention: evidence, mechanisms, and clinical implications. *Endocr Rev* 2017;38:173–88.
15. Levin VA, Jiang X, Kagan R. Estrogen therapy for osteoporosis in the modern era. *Osteoporos Int* 2018;29:1049–55.