Menopausal Hormone Therapy

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Abstract

Background: Although estrogen has been clinically available for more than 6 decades, women have been confused by different opinions regarding the risks and benefits of menopausal hormone therapy (HT), estrogen therapy (ET), and estrogen–progestin therapy (EPT). The publication of recent randomized controlled trials (RCTs), notably, the Heart and Estrogen Replacement Study (HERS), Women's Health Initiative (WHI), and Women's Health Initiative Memory Study (WHIMS), has intensified the risk versus benefit controversy and prompted this review.

Objective: We provide a systematic, comprehensive, and critical review of selected literature that addresses the basic and clinical aspects of menopausal HT.

Results: Solid, consistent evidence based on observational, epidemiologic, and randomized controlled trials underpins the efficacy of menopausal HT for its regulatory agency–approved indications: vasomotor symptoms, vulvovaginal atrophy symptoms, and osteoporosis-related fracture prevention. ET and EPT increase the risk for venous thromboembolism, although the absolute number of events and the risk are both small. Though there is a small increase in the number of breast cancers in women who have used menopausal HT for more than 10 years, the biological meaning of this observation (cause versus unmasking versus chance) is unresolved. Most evidence shows that menopausal HT does not affect breast cancer recurrence and that overall longevity is higher in breast cancer survivors who select menopausal HT. Strong basic science and clinical observational evidence show a benefit of menopausal HT in the cardiovascular and central nervous systems. Data from recent RCTs that included predominantly overweight women aged between 63 and 71 years have been reported to show more harm than benefit; the rush to generalize these studies to all women and all menopausal HT regimens is unjustified.

Conclusion: Menopausal HT improves vasomotor symptoms and vulvovaginal atrophy symptoms and prevents osteoporosis-related fracture. Menopausal HT increases the likelihood of venous thromboembolism, but other harms such as breast cancer require further controlled studies. A clinical benefit of menopausal HT for cardiovascular or central nervous system disease prevention is unproven. RCTs of menopausal HT in newly menopausal women, or in women less than 3 years from menopause, are urgently needed to investigate the prevention of cardiovascular and central nervous system aging diseases.

Key Words: Coronary heart disease, neurodegeneration, breast cancer, osteoporosis, venous thromboembolism, colon cancer, ovarian cancer, endometrial cancer, vasomotor symptoms, vulvovaginal atrophy, WHI, WHIMS, HERS

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Résumé

Contexte : Bien que les œstrogènes constituent une option de traitement depuis plus de six décennies, l'existence de différentes opinions a semé la confusion chez les femmes au sujet des risques et des avantages du recours à l'hormonothérapie (HT), à l'œstrogénothérapie (OT) et à un traitement œstrogènes–progestatif (TOP) pendant la ménopause. La publication d'essais comparatifs randomisés (ECR) récents, notamment la *Heart and Estrogen Replacement Study* (HERS), la *Women's Health Initiative* (WHI) et la *Women's Health Initiative Memory Study* (WHIMS), a eu pour effet d'exacerber la controverse entourant le rapport risques-avantages et est à l'origine de la présente analyse.

Objectif : Nous offrons une analyse systématique, exhaustive et critique d'articles sélectionnés qui traitent des aspects fondamentaux et cliniques du recours à l'HT pendant la ménopause.

Résultats : Des données fiables et systématiques, fondées sur des essais comparatifs randomisés, observationnels et épidémiologiques, sous-tendent l'efficacité du recours à l'HT pendant la ménopause dans le cadre de ses indications approuvées par les organismes de réglementation : symptômes vasomoteurs, symptômes associés à l'atrophie vulvovaginale et prévention des fractures ostéoporotiques. L'OT et le TOP entraînent une hausse du risque de thrombo-embolie veineuse, encore que le nombre absolu d'incidents et que les risques en tant que tels soient plutôt faibles. Bien qu'il y ait une faible hausse du nombre de cas de cancer du sein chez les femmes qui ont eu recours à une HT pendant leur ménopause au cours d'une période supérieure à 10 ans, la signification biologique de cette constatation (rapport cause–démasquage–chance) n'a pas encore été élucidée. La plupart des résultats d'étude indiquent que le recours à l'HT pendant la ménopause n'entraîne aucun effet sur la récurrence du cancer du sein et que la longévité globale est accrue chez les femmes qui, après avoir survécu à un cancer du sein, ont recours à l'HT pendant la ménopause. De fiables données, issues de la science fondamentale et des études cliniques observationnelles, indiquent que le recours à l'HT pendant la ménopause entraîne des effets bénéfiques pour le système nerveux central et le système cardiovasculaire. On a signalé que des données issues de récents ECR, lesquels portaient principalement sur des femmes présentant un excès de poids et étant âgées entre 63 et 71 ans, indiquaient que l'HT entraînait plus d'effets nuisibles que d'avantages; la généralisation hâtive de ces études à toutes les femmes et à tous les schémas posologiques d'HT visant la ménopause est injustifiée.

Conclusion : Le recours à l'HT pendant la ménopause entraîne une amélioration des symptômes vasomoteurs et des symptômes associés à l'atrophie vulvovaginale et permet la prévention des fractures ostéoporotiques. Bien que le recours à l'HT pendant la ménopause entraîne une hausse du risque de thrombo-embolie veineuse, l'élucidation de son rôle dans le cadre d'autres pathologies, telles que le cancer du sein, nécessite la tenue d'autres études comparatives. Les avantages cliniques du recours

à l'HT pendant la ménopause, en ce qui concerne la prévention des pathologies affectant le système cardiovasculaire ou le système nerveux central, restent à prouver. Des ECR portant (chez des femmes récemment ménopausées ou qui en sont à moins de trois ans de la ménopause) sur le rôle du recours à l'HT visant la ménopause dans la prévention des pathologies liées à la sénescence du système cardiovasculaire et du système nerveux central sont requis de toute urgence.

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BACKGROUND

Each day, almost 5000 women in North America enter menopause. It is true that this is a physiological change, as are birth and puberty; however, there must be a difference. We are quick to prevent infections in toddlers with vaccines that carry a small chance of allergic reaction. We easily prescribe systemic therapies for teen acne, using hormones that might rarely cause thromboembolism and isoretinoin, which might rarely threaten vision. However, we debate proven, low-risk therapy to treat symptoms experienced by most menopausal women and to prevent metabolic diseases experienced by many women.

Estrogen therapy (ET) with conjugated equine estrogens (CEE) in postmenopausal women was initiated in 1942 for various symptoms that were thought to result from the loss of ovarian estrogen. The average age for onset of menopause in healthy white women is 50 to 51 years; current smokers and black women reach menopause on average 1.5 to 2 years earlier.[1] Because the average life expectancy for women in Canada and the US is 81 years,[2] most women can expect to live more than one-third of their lives in the postmenopausal years. This aging process is accompanied by health problems such as osteoporosis, cardiovascular disease, neurodegenerative diseases including Alzheimer's disease, and cancer. Basic and clinical investigators have striven to develop preventive and interventional strategies that will help postmenopausal women maintain a healthy and productive quality of life. Fieser and Fieser, in their book *Steroids*, published in 1959, wrote, "An extract from a pregnant mare's urine is a potent oral estrogen, and it is said to produce a feeling of well-being."[3] Observational studies using different formulations indicated that estrogens protect against osteoporosis and may reduce the risk of heart disease, Alzheimer's disease, and colorectal cancer. Millions of women entering menopause sought menopausal hormone therapy (HT, ET, and estrogen–progestin therapy[EPT]) benefits. This all changed following the publication of the Women's Health Initiative (WHI) study.[4] This study, along with an earlier randomized controlled trial (RCT), the Heart and Estrogen Replacement Study (HERS I and HERS II), and the Women's Health Initiative Memory Study (WHIMS),[5–8] resulted in confusion in the minds of both practising physicians and postmenopausal women who had faithfully ingested these hormones on the advice of their physicians over a period of 60 years. This review

Figure 1. Source of estrogens in postmenopausal women (adapted from Bhavnani).[1]