ISSN: 2634 - 1255

Journal of Gynecology Research Reviews & Reports

SCIENTIFIC Research and Community

Short Communication

Open Access

A Brief History of THM

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Received: April 17, 2026; **Accepted:** April 22, 2026; **Published:** April 29, 2026

In the 20th century, interest in menopausal disorders steadily increased; however, it took a considerable amount of time to recognize the true impact of hormonal depletion on women's health. The clinical conditions associated with menopause were identified as "Hormonal Deficiency Syndrome", which encompassed—in addition to hot flashes—other late-onset chronic conditions such as osteoporosis, cardiovascular events, Alzheimer's disease, and vaginal atrophy [1].

The history of hormone therapy (HT) in climacteric women begins in the United States in the 1940s, stemming from Wilson's book *Feminine Forever* and the advent of orally active conjugated equine estrogens—derived from the urine of pregnant mares (Premarin®)—for the treatment of hot flashes [2].

Likewise, in Europe, its widespread prescription began with the synthesis of the 17β-estradiol molecule.

Hormone replacement therapy (HRT) was presented as a therapy that could allow women to liberate themselves from the curse of estrogen loss and preserve their femininity.

It has been confirmed: regarding the symptoms of climacteric syndrome, urogenital atrophy, and women's quality of life, the balance of MHT tips in its favor. Doctors, patients, and the media declared: "Estrogens for everyone, and for life".....

In the 1950s and 60s, other potential additional benefits emerged—such as cardiovascular and bone protection, positive effects on memory and cognitive processes, and benefits for the skin, skin appendages, and even the teeth. Everything was running smoothly, and the only points of contention related to cyclic versus continuous therapy.

In the 1970s, the finding that unopposed estrogen supplements were associated with an increased risk of endometrial cancer had a negative impact on the reputation of HRT. Ziel et al. observed a probable link between the administration of conjugated estrogen alone and the development of endometrial cancer. Panic ensued, and the cry went out: Hormones—not for any woman! [3-5]

However, in subsequent years, researchers discovered that reducing the estrogen dose and combining it with progesterone could reduce the risk of endometrial cancer. This combination therapy was recommended for women with an intact uterus, which generated renewed enthusiasm for HRT [6].

This combination of estrogen and progestogens gave rise to the concept of hormone replacement therapy. It was recommended to administer cyclic or continuous estrogen with the addition of progestins for 10 to 14 days per month.

Initially, the FDA approved HRT only for the treatment of hot flashes and not for the prevention of chronic diseases; however, in 1988, the prevention of osteoporosis was included among the indications approved by the FDA [7, 8].

Meanwhile, it was hypothesized that the cardiovascular protection attributed to estrogen depended not only—as initially assumed—on its effect on lipoproteins, but also on its actions on the vascular endothelium, its antioxidant effect, its inhibition of atheroma plaque formation, and—most notably—on its vasodilatory actions. It was suggested that, when administered sublingually, it could exert vasodilatory effects similar to those of nifedipine.

Furthermore, during the same years, numerous observational studies suggested that HRT offered various benefits—not only regarding the treatment of menopausal symptoms but also in the prevention of chronic diseases. Thus, the concept shifted from "feminine forever" to "healthy forever." [9-12]

Women also praised the pill for its potentially broad effects. Gloria Bachmann, MD, a professor of obstetrics and gynecology at the Robert Wood Johnson Medical School at Rutgers in New Brunswick, New Jersey, wrote in the *International Journal of Fertility and Menopausal Studies* in 1995 that HRT improved the appearance of the skin, breasts, and muscles—among other things—and therefore plays an important role in enhancing women's self-image and self-esteem.

Another effect of sequential therapy was the occurrence of vaginal bleeding in patients who had previously ceased bleeding. This was viewed favorably by younger menopausal women, who perceived this bleeding as a symbol of femininity, of eternal youth, and even as validation of the therapy's efficacy. It was prescribed with great fanfare: "HRT for Life!" Mothers and grandmothers menstruating just like their daughters and granddaughters... Eternal youth... Yet other women wished to avoid menstruation while still retaining the benefits of HRT.

To this end, continuous estrogen-progestogen regimens were developed, retaining many beneficial effects; however, their effects

on the cardiovascular system and the mammary gland began to be called into question.

However, the patients wanted HRT and were educating themselves about it, and we had to be prepared to address their concerns... and... it was always said to be beneficial, yet we had to wait four or five years for definitive answers regarding its risk-benefit ratio...

In the late 1970s, observational epidemiological studies drew attention to the increased relative risk of breast cancer among users of estrogen therapy, as well as its association with the type of estrogen used, dosage, duration of treatment, age, and other factors.

On the other hand, the addition of progestin appeared not to have the protective effect on the breast that it had on the endometrium, and even seemed to increase the risk.

In 1998, the Women's Health Initiative (WHI) was launched; it was the largest randomized study to date and aimed to evaluate the effect of HRT on the most common causes of death and disability in postmenopausal women, such as cardiovascular disease, cancer, and osteoporosis. Ultimately, approximately 160,000 women across the United States were enrolled in all phases of the study. The women were between 50 and 79 years of age, meaning that the majority had already gone through menopause.

Women with a uterus (16,608 participants) were randomized to receive a combination of 0.625 mg of conjugated equine estrogen (CEE) and 2.5 mg of medroxyprogesterone acetate, while women without a uterus (10,739 participants) were randomized to receive 0.625 mg of conjugated equine estrogen or a placebo.

The initial results of the WHI were published in 2002, following a mean follow-up period of 5.2 years. In the group with an intact uterus, a higher incidence of coronary heart disease and breast cancer was observed, alongside a reduction in osteoporotic fractures and colorectal cancer. The researchers found that, for every 10,000 person-years, women taking these pills would experience eight additional cases of invasive breast cancer, seven additional cardiac events, eight more strokes, and eight additional pulmonary embolisms. However, they also noted that there would be six fewer cases of colorectal cancer and five fewer hip fractures.

Given these results, it appeared that the risks outweighed the benefits, and the trial was suspended prematurely [13].

The data were widely disseminated among the media, which sparked panic among HRT users and compelled physicians to adopt new guidelines regarding the prescription of HRT.

The message was that HRT—without specifying the type or route of administration—was associated with more risks than benefits. However, no distinction was made between users and their age.

The estrogen-only trial (conducted in hysterectomized women) continued, and preliminary data were published in 2004. Furthermore, this trial was prematurely discontinued after 6.8 years of follow-up due to evidence of a small increase in the risk of ischemic stroke in the absence of other significant cardiovascular benefits [14].

Despite the benefits (such as a reduction in osteoporotic fractures and colon cancer) and the absence of an increased risk of breast cancer or cardiovascular disease, the general message regarding HRT remained negative. Following these announcements, regulatory authorities in the UK and the US issued an urgent safety restriction on HRT, recommending that physicians prescribe the lowest effective dose to alleviate symptoms, use it only as a second-line treatment for the prevention of osteoporosis, and not use it in asymptomatic postmenopausal women.

Since then, there have been ongoing discussions and controversies regarding the design and conclusions of the WHI, and many of its results have been widely debated. It turned out that a significant limitation of the WHI was that the majority of participants were more than a decade past their last menstrual period, raising the question of whether the trial's results could be applied to younger women. Furthermore, the WHI only analyzed CEE, either alone or in combination with a single progestin: medroxyprogesterone acetate. As a result, the WHI findings did not address questions regarding the safety and efficacy of other HRT formulations, regimens, and methods of administration. Despite its limitations, the WHI had a negative impact on the global perception of HRT, leading to a marked decline in the use of menopausal hormone therapy. Many physicians stopped prescribing HRT, and many women immediately discontinued it.

It has been suggested that the contradictory findings between the WHI and previous observational studies were a consequence of the differing ages of the women enrolled. Some observational studies had included symptomatic women who had initiated HRT close to the onset of menopause, whereas the women enrolled in the WHI trial were asymptomatic, older (average age 63.2 years), and frequently more than 10 years past the onset of menopause.

It has been suggested that a "window of opportunity" may exist—a period around menopause when the benefits of HRT outweigh the risks [15].

In 2002, at Clínica El Ávila, we—Dr. Franklin Mendoza (Gynecologist), Dr. Gerardo Hernández (Clínica Leopoldo Aguerrevere, Mastologist), Dr. David Martín (Gynecologist), and Dr. José Moreno Istúriz (Gynecologist)—initiated a series of conferences at our institution, as well as at various other clinics and hospitals and at scientific society congresses. During these events, we thoroughly analyzed this study and presented our conclusions regarding HRT in relation to its "influence" on breast cancer; our guiding principle was to "individualize therapy." It improves quality of life, protects bone health, and does not cause breast cancer (though it may potentially accelerate the rate of its onset); broadly speaking, the benefits outweigh the risks [16-18].

Those were years of great controversy, during which we received both criticism and applause for our opinions—opinions that were not solely our own, but were also endorsed by other researchers internationally.

Even today—despite all the complexities uncovered in this study, and all the recommendations and criticisms regarding its results—the warning persists: "Watch out for HRT and cancer."

Any therapy is beneficial if it is appropriately indicated—for the right duration, at the right age, at the right dosage, and for the right patient; therefore, it is essential to evaluate and individualize the approach in order to treat.

References

1. Keep PA, Kellerhals J (1973) The Elderly Woman. In: Lauritzen C, van Keep PA, editors. Aging and Estrogens: Frontiers in Hormone Research. Proceedings of the First International Workshop on Estrogen Therapy, Geneva, Switzerland, 1972 S. Karger; Basel, Switzerland 160-173.
2. Kling J (2000) The Strange Case of the Discovery of the Modern Drug Premarin. http://pubs.acs.org/subscribe/archive/mdd/v03/i08/html/kling.html
3. Wilson RA (1996) In: *Forever Feminine*. Evans M, editor. Lippincott & Co.; Philadelphia, PA, US. https://openlibrary.org/books/OL5982073M/Feminine_Forever.
4. Ziel HK, Finkle WD (1975) Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 293: 1167-1170.
5. Smith DC, Prentice R, Thomson DJ, Herrmann WL (1975) Association of exogenous estrogens and endogenous carcinoma. N Engl J Med 293: 1164-1167.
6. Woodruff JD, Pickar JH (1994) Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. The Menopause Study Group. Am. J. Obstet. Gynecol 170: 1213-1223.
7. Lobo RA (2017) Hormone replacement therapy. Current thinking. Nat. Rev. Endocrinol 13: 220-231.
8. The North American Menopause Society (2012) The 2012 hormone therapy position statement of The North American Menopause Society. Menopause 19: 257-271.
9. Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, et al. (1997) Postmenopausal hormone therapy and mortality. N. inglés. J. Med 336: 1769-1775.
10. Yaffe K, Sawaya G, Lieberburg I, Grady D (1998) Estrogen Therapy in Postmenopausal Women: Effects on Cognitive Function and Dementia. JAMA 279: 688-695.
11. Stampfer MJ, Colditz GA (1991) Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiological evidence. Prev. Med 20: 47-63.
12. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, et al. (1992) Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 117: 1016-1037.
13. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, et al. (2002) Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288: 321-333.
14. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, et al. (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: a randomized controlled trial of the Women's Health Initiative. JAMA 291: 1701-1712.
15. Hodis HN, Wendy JM (2011) A window of opportunity: the reduction of coronary heart disease and total mortality with menopausal therapies depends on age and time. Brain Res 1379: 244-252.
16. Watts NB, Cauley JA, Jackson RD, LaCroix AZ, Lewis CE, et al. (2017) Women's Health Initiative Investigators. No increased fractures after stopping hormone therapy: results from the Women's Health Initiative. J. Clin. Endocrinol. Metab 102: 302308.
17. NAMS POSITION STATEMENT (2022) The 2022 hormone therapy position statement of The North American Menopause Society. Menopause: The Journal of The North American Menopause Society 29: 767-794.
18. Maria Isabel Lorite, Angela Maria Cuadros, Mario Rivera-Izquierdo, Victoria Sanchez-Martin, Marta Cuadros (2023) Benefits of long-term hormone therapy on the cardiovascular system, bone density, and quality of life in hysterectomized women: a 20-year follow-up study. Menopause 30: 995-1001.