SEXUAL MEDICINE REVIEWS REVIEW

# The History of Estrogen Therapy

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ABSTRACT

**Introduction:** Menopausal hormone therapy (MHT) has proven an effective treatment for the amelioration of symptoms of menopause. The idea that a substance was the missing factor in a woman's body after menopause dates to the 1800s, when cow ovarian tissue was injected into German women in a successful attempt to reverse the sexual symptoms of menopause. The early 1900s saw the rise of commercialized menopause "treatments" that ranged in substance and even theoretical efficacy. The role of estrogen was first accurately described in Guinea pigs in 1917 by Dr. Papanicolaou.

**Aim:** To tell the detailed history of how estrogen was discovered and the controversy surrounding MHT.

**Methods:** A literature search was conducted using PubMed to identify relevant studies and historical documents regarding the history of estrogen therapy.

**Results:** The history of estrogen supplementation and its controversies are interesting stories and relevant to today's ongoing investigation into hormone replacement.

**Conclusion:** The controversy of MHT remained until the first randomized trials examining MHT in the early 1990s that suggested MHT is cardioprotective in postmenopausal women, although this conclusion was contradicted in subsequent trials. In the present day, MHT is approved only for short-term use for the symptomatic treatment of menopause. **Kohn GE, Rodriguez KM, Hotaling J, et al. The History of Estrogen Therapy. Sex Med Rev 2019;XX:XXX–XXX.**



**Key Words:** Estrogen; Hormone Replacement Therapy; Breast Cancer

## INTRODUCTION

There is ongoing debate about the use of menopausal hormone therapy (MHT) in women, stemming from conflicting study findings and Food and Drug Administration (FDA) statements. The Women's Health Initiative was 1 such study that showed a relationship between MHT and cancer beginning in 1992.[1] The use of estrogen as effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause, testosterone to relieve symptoms of low sexual desire in women, and estrogen/testosterone use in transgender patients continues to be an evolving conversation. Women in whom MHT is indicated can experience improvements in quality of life and sexual symptoms, as well as an improvement in genitourinary symptoms, which include night sweats, hot flashes, flushes, and vulvovaginal atrophy. However, it is important to note that there is an evolving understanding of the role of sex steroid hormones in genitourinary tissues, as well as receptor types and signaling pathways. This exciting field will undoubtedly increase understanding and treatment options.[2] MHT is safest to initiate in women <60 years old or <10 years from onset of menopause. Whereas modern debates regarding the safety and efficacy of MHT have become nuanced and complicated, the history of estrogen therapy is a story of scientific inquiry to improve symptoms of a non-life-threatening medical condition that affects women, a novel idea for the time.

References to menopause date back to the 300s BC, when Aristotle (384–322 BC) described the cessation of menstruation as occurring around the age of 40.[3] Discussions on the cessation of menstruation continue throughout literature, including mentions in the Bible. Although mentioned throughout literature, little is said about the actual experience of menopause. The term menopause, derived from the Greek words *men,* meaning month, and *pauses,* meaning stop, was not even used until the early 1800s, when it was coined by the French physician Gardanne.[4] This initiated the thinking that women's aging deserved medical attention.

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## NINETEENTH CENTURY ADVANCEMENTS IN FEMALE HORMONE THERAPY: THE START OF AN ERA

The late 1800s and beginning of the 1900s saw the beginning of the Second Industrial Revolution, during which advancements in manufacturing and globalization were rapidly changing the world. 2 studies in Germany, published in March and April 1886, reported on women who were either ovariectomized or experiencing menopausal symptoms with injected ovarian tissue. F. Mainzer and R. Mond prescribed oral therapy of 5−20 g/day of bovine ovarian tissue. The patients experienced a dramatic reduction in sexual dysfunction. After switching to non-ovarian tissue, the treatment was ineffective. A third publication from Austria, in May 1896, showed that 0.2−0.8 g/d of dried ovarian tissue from reproductive-age cows, resulted in symptomatic improvement in 4 of 7 patients, 6 of whom were ovariectomized and 1 with physiological menopause. These studies were quickly followed by another by Mainzer, in June 1896, demonstrating that 1.0−7.5 g/d of dried bovine or porcine ovarian tissue was successful for reducing the symptoms of sexual dysfunction.[5]

Dr. Charles Edward Brown-Séquard, known as the "Father of Endocrinology," experimented on himself with an extract of guinea pig and dog testicles in 1889. This injection resulted in his claim that he had "rejuvenated himself" and suggested that these extracts may have the same effect on women. Ultimately, this was the seed for commercialization of sex hormone therapy. In the 1890s, Merck & Company produced Ovariin in both powder and pill form, a treatment for menopause made from powdered cow ovaries that successfully treated symptoms of menopause.[6]

## TWENTIETH CENTURY LEAPS AND BOUNDS

In 1917, near the conclusion of WWI, Stockard and Papanicolaou[7] were the first to describe estrogen and the role of the hypothalamic-pituitary-adrenal axis in guinea pigs. By 1920, George Papanicolaou had turned his attention to the human reproductive system and was able to distinguish between normal and malignant cervical cells from cultured swabs. He is best known for creating the Papanicolaou test, a revolutionary discovery that transformed the detection of cervical cancer in 1943.[8] Long and Evans,[9] in 1922, defined the estrous cycle in the rat and were the first to discover and explain the tissue changes during the menstrual cycle its relationship to pregnancy.

Although it was believed that hormones were present in ovarian preparations, as indicated by the maintenance of cyclic changes when ovaries were transplanted to other parts in the body, the actual hormones or their specific effects, as well as the efficacy of commercial extracts for clinical use, remained unknown.[10] This was further illustrated with 2 reviews by Frank and Novak in 1922, claiming distrust in the popular commercial preparations, given that there was no reliable test to measure the activity of the hormones (or extracts). Allen had discovered the estrous (estrogen) cycle in rats and assumed that the corpus luteum and interstitial tissue would contain the "estrus hormone." In 1923, Allen and Doisy[10] reported localizing, extracting, and partially purifying estrogen. They also determined some actions of estrogen in animal models. This bioassay for detecting estrogenic activity would provide a basis for future hormone research and facilitated the identification of estrogens in many different sources, including mammalian tissues, excreta, and plants. Perhaps as significantly, the new assays facilitated estrogen synthesis.[11]


**Figure 1.** Photograph of Emmenin, an early form of female hormone therapy.

Although during the Great Depression in the United States, the first MHT product, Emmenin, was commercially produced and sold in 1933 in the United States by James Collip at Ayerst (Figure 1).[12] This was the first form of bio-identical hormone therapy and was derived from the urine of pregnant women. However, Emmenin was expensive to produce and was replaced in 1941 by Premarin, which was made from conjugated equine estrogens.[13] The name Premarin derives from the pregnant mare urine from which these estrogens were derived.[14] Premarin was marketed to orally "replace" a woman's estrogen. Later, other routes of administration included an estrogen patch, produced by Searle in 1928, as well as oral ethinyl estradiol, produced by Schering in 1937.[15,16] The synthetic estrogen, diethylstilbestrol (DES), was discovered in 1938 and was granted FDA approval in 1941. It was suggested that DES might stimulate bone growth.[16]

Several books and publications from the 1940s−1950s that suggested use of estrogen therapy for "menopausal disorders" promoted steady increases in use of MHT, eventually doubling and tripling in use by the 1960s−mid-1970s. This trend was further encouraged by a book by Robert Wilson,[17] called *Feminine Forever.* This book promoted the use of estrogen therapy as a way to eliminate emotional complaints and menopause, making a woman "feminine forever."[17] This created a market for drug companies and physicians to increase prescription and synthesis of estrogen therapy.[4] By 1975, estrogen was the fifth-most prescribed drug in the United States.[18]

## CONTROVERSY ARISES

A sharp decline in the use of estrogen therapy occurred in the 1970s, when reports of a 4−14 times increased risk of endometrial cancers was linked to estrogen therapy. As a result, the FDA required a warning on all estrogen products that indicated a risk for blood clots and cancer.[19,20] However, evidence in the mid-1980s stated that the addition of progestin would reverse endometrial hypertrophy associated with endometrial cancer by >98%. This would counteract the estrogen-induced endometrial changes, initiating a revival in MHT use.[16,21] Estrogen use increased through the 1980s−1990s among all women, with a corresponding increase in the use of progestin by women with a uterus. Also, during this time, the link between decreasing rates of osteoporosis, coronary heart disease (CHD), and the use of estrogen therapy was being investigated.

The Coronary Drug Project began in 1966 and examined the effect of estrogen therapy on men with previous myocardial infarction. An increased risk of thromboembolic events and myocardial infarction was observed in men taking Premarin (5 mg and 2.5 mg).[16] The use of estrogen therapy for male-to-female transgendered patients is based on the recommendations for postmenopausal women, although no studies to date have compared the efficacy of different routes of administration. Interestingly, transgender women are at increased risk for bone loss, despite the use of estrogen therapy, in part likely due to concomitant anti-androgen therapy. The use of estrogen therapy in transgender women shows a trend toward increased risk of cardiovascular disease, although studies remain inconclusive.[22]

During the 1980s and 1990s, Albright et al[23] concluded that bone loss was linked to low ovarian hormone levels and that DES could represent a viable solution for improving bone density. In 1972, the FDA stated that estrogen therapies were "probably effective" for the prevention of osteoporosis.[16] Evidence in the 1984 NIH Consensus Development Conference on Osteoporosis declared estrogen therapy as the best way to prevent bone loss.[24] A Women's Health Initiative (WHI) trial in 1992 demonstrated that the use of estrogen for prevention of diseases is variably effective. This study was composed of hormone therapy, dietary modification, or observational study if women did not qualify for the clinical trial or did not want to participate. Within the hormone therapy component, women were randomized to combination estrogen and progestin therapy or estrogen-only therapy. However, after 1 year, women were offered to begin calcium plus vitamin D.[25] Combination estrogen and progestin therapy was thought to decrease the risk of CHD and hip fracture, but it increased the risk of endometrial and breast cancer with long-term use (≤10% per year of use). Results from the estrogen-only group suggested a possible decrease in the risk of breast cancer. Bone density was shown to slightly, but significantly, increase in the calcium plus vitamin D component of the study.[26] In the WHI studies, conjugated estrogen (Prempro; Pfizer, New York, NY, USA) showed an increase in cardiovascular disease risk, which caused the studies to be terminated early. This may be because the WHI trials were composed of women with an average age of 63, of whom one-third had hypertension and one-half had a history of smoking. However, when a reanalysis of the data was performed, the estrogen therapy without progestin did not increase the risk of cardiovascular events. This suggests that progestins were possibly responsible for the adverse outcomes.[27]

The WHI hormone trials were intended to clearly define the effects of estrogen as a primary prevention measure for CHD. This study was led by cardiologists, and the main outcome measure was cardiac in nature. The WHI trial and resulting follow-up studies were not meant to determine the efficacy of estrogen therapy in the setting of menopause. Instead, women who were selected for these investigations (50−97 years old) had higher risk for cardiovascular events, which would power the study with a smaller number of participants.[28] These were multicenter, parallel, randomized, controlled prevention trials that investigated the effects of hormone therapy in postmenopausal women with an intact uterus on CHD risk. The study used Prempro, a daily estrogen (conjugated equine estrogen 0.625 mg) and progesterone (medroxyprogesterone acetate 2.5 mg) with a placebo to study cardiovascular disease.[1] 5 years into the 8 years of anticipated follow-up, the WHI study demonstrated an increase in breast cancer, stroke, pulmonary embolism, and myocardial infarction risk in women on hormone therapy who had a uterus, although a lower incidence of fracture due to osteoporosis was also observed.[29,30] The group of women without a uterus, solely on estrogen (0.625 mg conjugated equine estrogen) was also terminated, because an increased risk of stroke was observed, although no increased risk of CHD was found.[30] After the publication of these results, the use of HT decreased significantly, with concerns from patients and providers.

The WHI studies have been criticized, with critiques including concerns with the median age and range of ages of participants, overstatement of the conclusions, and the use of a single form and formulation of female hormone therapy. As women age, there is a natural increase in risk of myocardial infarction and thromboembolic events; therefore, it is difficult to determine the underlying cause of the increased risk observed in the WHI studies. Another critique is that the authors overstated the conclusions, excluding absolute risk and rather focusing on relative risk. The final major critique is that the estrogen-progesterone combination used for the trials was a single dose and single formulation, limiting the ability to make more global conclusions regarding female hormone therapy.[1,30]

After the publication of the WHI studies, estrogen therapy use declined by 45%, and estrogen/progestin therapy use declined by 22%.[31] However, a study that monitored women after stopping treatment with estrogen or progestin therapy observed a 12% increased risk of malignancies for women who received conjugated equine estrogens plus medroxyprogesterone.[32] Short-term use of estrogen therapy has been approved by the FDA for

menopausal symptoms but not for prevention of CHD. Currently, estrogen therapy is used to reduce the frequency of hot flashes, insomnia, and vaginal discomfort, as well as potentially reducing stress incontinence and urinary symptoms using the lowest possible dose for relief.[33]

The FDA Generic Drugs Advisory Committee became aware of issues of safety and efficacy of generic conjugated estrogens in 1990 and proposed removing all generic forms of estrogen from the market.[16] In 1995, Wyeth-Ayerst petitioned the FDA to include δ-dehydroestrone sulfate as a required component for all conjugated estrogens. Before this, in 1970, the US Pharmacopeia conjugated estrogens containing sodium estrone sulfate and sodium equilin sulfate. This was only amended in 1992 to include 3 additional estrogens, as well as δ-dehydroestrone sulfate in 1995.[34] However, in 1997, the FDA's Center for Drug Evaluation and Research indicated that it would not approve generic forms of Premarin that did not have the same active ingredients as the brand formulation because, without these, the drugs were unable to effectively treat menopausal symptoms and prevent osteoporosis. There were also concerns regarding the bioequivalence and safety and efficacy of the generic drugs[16] Premarin continued to rise in popularity, becoming the number 1—prescribed drug in 1992.[35]

Medical knowledge about the actual effects of estrogen therapy was varied, with some healthcare professionals indicating it was beneficial and some stating that it was not.[36] In 1993, the first large randomized control trial for MHT began. The Heart and Estrogen/Progestin Replacement Study examined the effects of estrogen-progestogen therapy on postmenopausal women with CHD. No significant differences in the progression of CHD were observed in women taking conjugated equine estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg), and the placebo group. However, after the first year of the study, the incidence of cardiac events in women in the treatment group was higher than that in women on placebo. This was, however, found to be negligible over the next 3 years, when the 2 groups were compared. Overall, no benefit was found in women with CHD taking hormone therapy. A second large randomized control trial, Heart and Estrogen/Progestin Replacement Study II, monitored the participants for another 2.7 years, in which no significant benefits for CHD risk were identified. As a result, HT was recommended against for secondary prevention of CHD.[1] Despite this conclusion, in 1996, the United States Preventive Services Task Force advised that all postmenopausal women consider using preventative hormone therapy.[37]

In 2005, the Kronos Early Estrogen Prevention Study interventional clinical trial began to explore the correlation of early initiation of MHT, within 3 years post-menopause, to delay cardiovascular disease using low-dose oral Premarin (0.45 mg) or transdermal estrogen (50 μg), cyclic progesterone, or placebo. No significant differences in arterial wall thickness over the 4 years of study between the groups were observed, and coronary artery calcium, a marker for atherosclerotic plaque, was lower among the hormone therapy groups. Although the differences were not significantly different, a trend toward significance was identified. Although blood pressure was increased in the WHI trials, due to lower dosage of estrogens in the Kronos Early Estrogen Prevention Study trials, neither the oral nor the transdermal patch significantly increased blood pressure. This study was unable to make definitive conclusions regarding the differences in breast cancer, endometrial cancer, myocardial infarction, transient ischemic attack, stroke, or venous thromboembolic disease among the 3 groups.[38]

The relationship between the effect of estrogen therapy and breast cancer led to the Gap Hypothesis, which posited that there is very little or no increased risk for breast cancer if hormone therapy is started ≥5 years after menopause occurred. This was investigated and supported by the data from the prospective, observational Million Women study in Britain.[39] However, the authors found a significant increase in risk of breast cancer in women who had begun therapy <5 years before menopause, regardless of type or length of therapy, or weight of women. In a study by Coombs et al,[40] the risk of breast cancer in women using hormone therapy increased from a baseline 6.1—6.3% with use of estrogen therapy and 6.7% with use of estrogen-progestogen use, although the risk returned to baseline rapidly when therapy was stopped. Length of time on therapy was also important, because breast cancer risk increased 2.75% if hormone therapy had been used for >5 years and 1.85% if used for 2—5 years.[29]

In 2016, it was still not known whether cardiovascular effects associated with MHT varied with time of initiation, between 2—10 years after menopause. The Early versus Late Postmenopausal Treatment with Estradiol study, with support of the clinical trials Estrogen in the Prevention of Atherosclerosis Trial (EPAT) and Women's Estrogen/Progestin Lipid Loweing Hormone Atherosclerosis Regression Trial (WELL-HART), began to study the timing hypothesis. This indicates that the timing of initiation of hormone therapy will affect CHD and atherosclerosis. This study specifically looked at atherosclerosis with estradiol therapy with or without progesterone and found that progression of carotid-artery intima-media thickness was lower in the estradiol group, in comparison with placebo, for women who were <6 years post-menopause but not those who were ≥10 years post-menopause.[41]

Today, MHT in women is used to manage symptoms of menopause that impair quality of life. In 2017, The North American Menopause Society concluded that hormone therapy is still the most effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause, as well as preventing bone loss and fracture, although risks depend on type, dose, duration of use, route of administration, and timing of initiation. For longer duration of hormone therapy, estrogen therapy is more favorable than estrogen-progesterone therapy. Women who are <60 years old or <10 years from onset of menopause have favorable outcomes of hormone therapy for symptoms of

menopause. However, women who begin hormone therapy >10 years after menopause or are older than 60 years old at the time of initiation of hormone therapy appear to have greater risks of CHD, stroke, venous thromboembolism, and dementia.[42]

## CONCLUSION

The history of our understanding of menopause and estrogen supplementation is an interesting story that highlights many pitfalls of new therapies and evolving understanding of mechanisms of disease. From exciting claims that estrogen could be "the fountain of youth," help with osteoporosis and reducing heart disease in women, to concerns of thromboembolic disease and breast and endometrial cancer, it has been a highly debated topic in the last 50 years. Although new research is emerging every day, oral estrogen use in postmenopausal women is currently limited to the short-term treatment of vasomotor flushing, and topical estrogen for vaginal atrophy. Overall, the risks and benefits of female hormone therapy should be considered by clinicians and patients, and treatment decisions made on an individual basis.

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