



Published in final edited form as:

*Sex Med Rev.* 2019 July ; 7(3): 416–421. doi:10.1016/j.sxmr.2019.03.006.

## The History of Estrogen Therapy

Grace E. Kohn<sup>1</sup>, Katherine M. Rodriguez<sup>2</sup>, Alexander W. Pastuszak, MD, PhD<sup>3</sup>

<sup>1</sup>Baylor University, Waco, TX

<sup>2</sup>Baylor College of Medicine, Houston, TX

<sup>3</sup>Department of Surgery - Urology, University of Utah, Salt Lake City, UT

### 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 1800's when cow ovarian tissue was injected into German women in a successful attempt to reverse the sexual symptoms of menopause. The early 1900's 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:** Here we tell a 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**Methods:** A literature search was conducted using PubMed to identify relevant studies and historical documents regarding the history of estrogen therapy.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 to be cardioprotective for post-menopausal women, though 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.

### Keywords

Estrogen; Menopausal hormone therapy; breast cancer

---

**Correspondence:** Alexander W. Pastuszak, MD, PhD, Assistant Professor, Division of Urology, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Rm #3B420, Salt Lake City, UT, 84132, alexander.pastuszak@hsc.utah.edu.

Conflict of Interest Statement

Dr. Pastuszak

- Endo Pharmaceuticals – advisor, speaker, consultant

- Boston Scientific – advisor

- Bayer AG – speaker

## Introduction

There is ongoing debate about the use of menopausal hormone therapy (MHT) in women, stemming from conflicting study findings and Federal Drug Administration (FDA) statements. The Women's Health Initiative was one such study which 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. MHT is safest to initiate in women less than 60 years old or less than 10 years from onset of menopause. While 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 B.C., when Aristotle (384-322 B.C.) described the cessation of menstruation as occurring around the age of 40.[2] 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[3]. This initiated the thinking that women's aging deserved medical attention.

## 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, where advancements in manufacturing and globalization were rapidly changing. Two studies in Germany published in March and April 1886, 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/day of dried ovarian tissue from reproductive age cows, resulted in symptomatic improvement in four of seven patients, six of whom were ovariectomized and one with physiological menopause. These studies were quickly followed by another by Mainzer, in June 1896, demonstrating that 1.0-7.5 g/day of dried bovine or porcine ovarian tissue was successful for reducing the symptoms of sexual dysfunction.[4]

Dr. Charles Edward Brown-Séguard, 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.[5]

## Twentieth Century Leaps and Bounds

In 1917, near the conclusion of WW1, Stockard and Papanicolaou were the first to describe estrogen and the role of the hypothalamic-pituitary-adrenal (HPA) axis in guinea pigs.[6] 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.[7] Long and Evans, in 1922, defined the oestrous cycle in the rat, and were the first to discover and explain the tissue changes during the menstrual cycle its relationship to pregnancy.[8]

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.[9] This was further illustrated with two 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 oestrous (estrogen) cycle in rats and assumed that the corpus luteum and interstitial tissue would contain the “estrus hormone”. In 1923, Allen and Doisy reported localizing, extracting, and partially purifying estrogen. They also determined some actions of estrogen in animal models.[9] 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. [10]

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. See picture 1. 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.[11] The name Premarin derives from the pregnant mare urine from which these estrogens were derived.[12] 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.[13, 14] 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.[14]

Several books and publications during the 1940s-1950s suggested use of estrogen therapy for “menopausal disorders” promoted steady increases in use of MHT, eventually doubling and tripling in use by the 1960s to mid-1970s. This trend was further encouraged by a book by Robert Wilson, 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.’[15] This created a market for drug companies and physicians to increase prescription and synthesis of estrogen therapy.[3] By 1975, estrogen was the fifth most prescribed drug in the United States.[16]

## 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.[17, 18] However, evidence in the mid-1980s stated that the addition of progestin would reverse endometrial hypertrophy associated with endometrial cancer by over 98%. This would counteract the estrogen-induced endometrial changes, initiating a revival in MHT use.[14, 19] Estrogen use increased through the 1980s and 1990s among all women, with a corresponding increase in use of progestin by women with a uterus. Also, during this time, the link between decreasing rates of osteoporosis, coronary heart disease, 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).[14] The use of estrogen therapy for male to female transgendered patients is based on the recommendations for post-menopausal 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. [20]

During the 1980s and 1990s, Albright et al. concluded that bone loss was linked to low ovarian hormone levels and that DES could represent a viable solution for improving bone density.[21] In 1972, the FDA stated that estrogen therapies were “probably effective” for the prevention of osteoporosis.[14] Evidence in the 1984 NIH Consensus Development Conference on Osteoporosis declared estrogens as the best way to prevent bone loss.[22] Women’s Health Initiative (WHI) trials in 1992 demonstrated that the use of estrogen for prevention of diseases is variably effective. This study was composed of three components: hormone therapy, dietary modification, or observational study if they 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 one year, women were offered to begin calcium plus vitamin D, if qualified. Combination estrogen and progestin therapy was thought to decrease the risk of coronary heart disease and hip fracture, but increased the risk of endometrial and breast cancer in long-term use, up to 10% per year of use. Estrogen only therapy indicated a possible decrease in risk of breast cancer. Bone density was shown to slightly, but significantly, increase in the calcium plus Vitamin D component of the study [23] In the WHI studies, Prempro showed an increase in cardiovascular disease, 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 cardiovascular events. This suggests that progestins were possibly responsible for the adverse outcomes.[24]

The WHI hormone trials began in order 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. This study was not meant to determine the efficacy of estrogen therapy in menopause. Rather, women who were selected for this study (50–97 years old) had higher risk for cardiovascular events, which would power the study with a smaller number of participants.[29] These were multicenter, parallel, randomized, controlled prevention trials which 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 0.625mg) and progesterone (medroxyprogesterone acetate 2.5mg) with a placebo to study cardiovascular disease.[1] Five years into the eight 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. [30, 31] The group of women without a uterus, solely on estrogen (0.625 mg conjugated equine estrogen) was also terminated, as an increased risk of stroke was observed, although no increased risk of CHD was found.[31] Following 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, 31]

Following the publication of the WHI studies, estrogen therapy use declined by 45% and estrogen / progestin therapy use declined by 22%.[32] However, a study that followed women after stopping treatment with estrogen or progestin therapy observed a 12% increased risk of malignancies for women who received conjugated equine estrogens (CEE) plus medroxyprogesterone (MPA).[33] 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.[34]

The FDA Generic Drugs Advisory Committee became aware of issues of safety and efficacy of generic conjugated estrogens in 1990 and proposed to remove all generic forms of estrogen from the market.[14] In 1995, Wyeth-Ayerst petitioned the FDA to include

$\delta$ -dehydroestrone sulfate (DHES) as a required component for all conjugated estrogens. Prior to this, in 1970, the US Pharmacopeia (USP) conjugated estrogens contained sodium estrone sulfate and sodium equilin sulfate. This was only amended in 1992 to include three additional estrogens, as well as  $\delta$ -dehydroestrone sulfate (DHES) in 1995.[25] 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 having 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 potential for bioequivalence and safety and efficacy of the generic drugs [14] Premarin continued to rise in popularity, becoming the number one prescribed drug in 1992.[26]

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.[27] In 1993, the first large randomized control trial (RCT) for menopausal hormone therapy began. The Heart and Estrogen/Progestin Replacement Study (HERS) 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 (CEE) (0.625mg) and medroxyprogesterone acetate (MPG) (2.5mg), 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 three years, when the two groups were compared. Overall, no benefit was found in women with CHD taking hormone therapy. A second large RCT, HERS II, followed 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 (USPSTF) advised that all postmenopausal women consider using preventative hormone therapy.[28]

In 2005, the Kronos Early Estrogen Prevention Study (KEEPS) interventional clinical trial began in order 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  $\mu$ g), cyclic progesterone, or placebo. It was found that there was no significant differences in arterial wall thickness over the 4 years of study between the groups. Coronary artery calcium, a marker for atherosclerotic plaque, was smaller among the hormone therapy groups. Although the differences were not significantly different, a trend was found. Although blood pressure was increased in the WHI trials, due to smaller dosage of estrogens in the KEEPS trials, neither the oral or transdermal patch significantly increased blood pressure. This study was unable to make definitive conclusions on the differences in breast cancer, endometrial cancer, MI, TIA, stroke, or venous thromboembolic disease between the three groups. As such, it would be important to further investigate these results.

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 was started at least five years after menopause occurred. This was investigated and supported by the data from the prospective, observational Million Women study in Britain. [35] However, the authors found a significant increase in risk of breast

cancer in women who had begun therapy less than five years before menopause, regardless of type or length of therapy, or weight of women. In a study by Coombs et al., the risk of breast cancer in women using hormone therapy increased from a baseline 6.1% to 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, as breast cancer risk increased 2.75% if hormone therapy had been used for more than five years and 1.85% if used two to five years.[30]

In 2016, it was still not known whether cardiovascular effects associated with MHT varied with time of initiation, between two to ten years after menopause, of MHT. Early versus Late Postmenopausal Treatment with Estradiol (ELITE), with support of the clinical trials EPAT and 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, rather than placebo, for women who were less than 6 years past menopause, but not those who were 10+ years past menopause.

Today, MHT in women is used to manage symptoms of menopause which impair quality of life. In 2017, The North American Menopause Society (NAMS) concluded that hormone therapy is still the most effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause as well as prevents 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 less than 60 years old or less than 10 years from onset of menopause have favorable outcomes of hormone therapy for symptoms of menopause. However, women who begin hormone therapy more than 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.[36]

## 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 reduce heart disease in women, to concerns of thromboembolic disease, breast and endometrial cancer, it has been a highly debated topic in the last 50 years. While new research is emerging every day, oral estrogen use in post-menopausal 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.

## Acknowledgements

A.W.P. is a National Institutes of Health K08 Scholar supported by a Mentored Career Development Award (K08DK115835-01) from the from the National Institute of Diabetes and Digestive and Kidney Diseases. This work is also supported in part through a Urology Care Foundation Rising Stars in Urology Award (to A.W.P.)

## REFERENCES:

1. Investigators, W.G.f.t.W.s.H.I., Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *Jama*, 2002. 288(3): p. 321–333. [PubMed: 12117397]
2. O'dowd MJ and Philipp EE, *The history of obstetrics and gynaecology*. 2000: CRC press.
3. Singh A, Kaur S, and Walia I, A historical perspective on menopause and menopausal age. *Bulletin of the Indian Institute of History of Medicine (Hyderabad)*, 2002. 32(2): p. 121–135. [PubMed: 15981376]
4. Kopera H, *The dawn of hormone replacement therapy*. 1991, Elsevier.
5. Rooke T, *The quest for cortisone*. 2012: MSU Press.
6. Stockard CR and Papanicolaou GN, The existence of a typical oestrous cycle in the guinea-pig— with a study of its histological and physiological changes. *Developmental Dynamics*, 1917. 22(2): p. 225–283.
7. Tan SY and Tatsumura Y, George Papanicolaou (1883–1962): discoverer of the Pap smear. *Singapore medical journal*, 2015. 56(10): p. 586. [PubMed: 26512152]
8. Long JA and Evans HM, *The oestrous cycle in the rat and its associated phenomena*. Vol. 6. 1922: University of California Press.
9. Allen E and Doisy EA, An ovarian hormone: Preliminary report on its localization, extraction and partial purification, and action in test animals. *Journal of the American Medical Association*, 1923. 81(10): p. 819–821.
10. Lieberman S, Are the differences between estradiol and other estrogens, naturally occurring or synthetic, merely semantical? *The Journal of Clinical Endocrinology & Metabolism*, 1996. 81(2): p. 850–851. [PubMed: 8636315]
11. D'Souza C, *The Hot Topic: A life-changing look at the Change of Life*. 2016.
12. Vance DA, *Premarin: The intriguing history of a controversial drug*. *International journal of pharmaceutical compounding*, 2007. 11(4): p. 282. [PubMed: 23974785]
13. Barrett-Connor E, An epidemiologist looks at hormones and heart disease in women. *The Journal of Clinical Endocrinology & Metabolism*, 2003. 88(9): p. 4031–4042. [PubMed: 12970259]
14. Stefanick ML, Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *The American journal of medicine*, 2005. 118(12): p. 64–73. [PubMed: 16414329]
15. Wilson MDRA, *Feminine Forever*. 1968.
16. Bell SE, Sociological perspectives on the medicalization of menopause. *Annals of the New York Academy of Sciences*, 1990. 592(1): p. 173–178. [PubMed: 2197942]
17. Smith DC, et al. , Association of exogenous estrogen and endometrial carcinoma. *New England journal of medicine*, 1975. 293(23): p. 1164–1167. [PubMed: 1186789]
18. Ziel HK and Finkle WD, Increased risk of endometrial carcinoma among users of conjugated estrogens. *New England journal of medicine*, 1975. 293(23): p. 1167–1170. [PubMed: 171569]
19. Gambrell RD, Use of progestogen therapy. *American Journal of Obstetrics & Gynecology*, 1987. 156(5): p. 1304–1313. [PubMed: 3578452]
20. Unger CA, Hormone therapy for transgender patients. *Translational Andrology and Urology*, 2016. 5(6): p. 877–884. [PubMed: 28078219]
21. Albright F, Smith PH, and Richardson AM, Postmenopausal osteoporosis: its clinical features. *Journal of the American Medical Association*, 1941. 116(22): p. 2465–2474.
22. Panel, N.I.o.H.C.D., National Institutes of Health Consensus Development Conference statement: adjuvant therapy for breast cancer, November 1–3, 2000. *JNCI Monographs*, 2001. 2001(30): p. 5–15.
23. Grady D, et al. , Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals of internal medicine*, 1992. 117(12): p. 1016–1037. [PubMed: 1443971]
24. Rossouw JE, et al. , Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *Jama*, 2007. 297(13): p. 1465–77. [PubMed: 17405972]



25. Seaman B, et al., The history of hormone replacement therapy: a timeline. Kleinman, Kinchy and Handelsman, 2005: p. 219–35.
26. Watkins ES, The Estrogen Elixir: A History of Hormone Replacement Therapy in America. 2010: The Johns Hopkins University Press.
27. Bush TL, Whiteman M, and Flaws JA, Hormone replacement therapy and breast cancer: a qualitative review. *Obstetrics and gynecology*, 2001. 98(3): p. 498–508. [PubMed: 11530137]
28. Force UPT, Guide to clinical preventive services. 1996, Alexandria, VA: International Medical Publishing.
29. Utian WH, A decade post WHI, menopausal hormone therapy comes full circle--need for independent commission. *Climacteric*, 2012. 15(4): p. 320–5. [PubMed: 22762439]
30. Alexander IM, The history of hormone therapy use and recent controversy related to heart disease and breast cancer arising from prevention trial outcomes. *Journal of Midwifery & Women's Health*, 2012. 57(6): p. 547–557.
31. Committee W.s.H.I.S., Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative Randomized Controlled Trial. *ACC Current Journal Review*, 2004. 13(6): p. 19.
32. Buist DS, et al. , Hormone therapy prescribing patterns in the United States. *Obstetrics & Gynecology*, 2004. 104(5, Part 1): p. 1042–1050. [PubMed: 15516400]
33. Heiss G, et al. , Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *Jama*, 2008. 299(9): p. 1036–1045. [PubMed: 18319414]
34. Hackley B and Rousseau ME, CEU Managing Menopausal Symptoms After the Women's Health Initiative. *Journal of Midwifery & Women's Health*, 2004. 49(2): p. 87–95.
35. Beral V, et al. , Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst*, 2011. 103(4): p. 296–305. [PubMed: 21278356]
36. Pinkerton JAV, et al. , The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause*, 2017. 24(7): p. 728–753. [PubMed: 28650869]



**Picture 1.**  
Emmenin tablets.