

# HORMONE REPLACEMENT THERAPY IN POST MENOPAUSE STAGES AND EVOLUTION

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## Abstract

*From ancient times until the end of the 19th century, the literature comprises many indications of opotherapy, also in relation to hormone substitution.*

*The improvement of living conditions throughout the centuries has led to a substantial increase in the number of women who live many years after the age of menopause onset.*

*The discovery and marketing of female sex steroid hormones caused an addressability avalanche from women, but also a fierce battle between manufacturing companies to occupy the newly opened market.*

*There have been several waves of boosts and drops in sales determined by a variety of medical discoveries. The battle was fought between the patients' hope for a better life, the drug companies' desire for financial gain, and studies that have slowed down this impetus.*

*The manner in which the population perceives scientific truth is fairly limited and can be easily manipulated. Also, the scientific truth is historically bound with the level of knowledge of the moment. This paper reviews the evolution of the impact and the tortuous path of hormone replacement therapy and draws attention to the fact that significant changes may occur in the future. In the meantime, we follow the guidelines provided by competent professional institutions. The studies in this field must be continued.*

## Rezumat : Terapia de substituție hormonală în post menopauză, stadii și evoluție

*Din timpuri străvechi, până pe la sfârșitul secolului XIX, literatura cuprinde multe indicații ale opoterapiei, unele în scopul unei substituții hormonale.*

*Îmbunătățirea condițiilor de viață de-a lungul secolelor a condus la o creștere semnificativă a numărului de femei care vor trăi încă mulți ani după instalarea menopauzei.*

*Descoperirea și punerea în vânzare a hormonilor sexuali steroizi feminini a determinat o avalanșă de adresabilitate a femeilor dar și o bătălie acerbă între companiile de medicamente pentru ocuparea unei piețe noi.*

*Au fost mai multe valuri de creșteri și scăderi ale vânzărilor determinate de o serie de descoperiri medicale. Lupta a fost dusă între speranța pacientelor pentru o viață mai bună, dorința companiilor de medicamente pentru câștiguri mai mari și studiile medicale care au moderat acest avânt.*

*Modalitatea prin care populația percepe adevărurile științifice este destul de limitată și poate fi cu ușurință manipulată. În plus, adevărul științific este istoric, legat de gradul de cunoaștere al momentului. Această lucrare trece în revistă impactul și drumul sinuos al tratamentului de substituție hormonală și atrage atenția asupra faptului că în viitor pot să apară modificări semnificative. În același timp noi urmăm indicațiile de moment puse la dispoziție de instituțiile profesionale competente. Studiile în acest domeniu trebuie continuate.*

**Cuvinte cheie:** menopauză, tratament hormonal, estrogeni, istoria medicinei

## **Introduction**

The earliest written reference to menopause age can be traced back to Aristotle, in the 4<sup>th</sup> century BC: “the menstrual period stops in most women at the age of 40 and, if it lasts longer, it occurs up to the age of 50”.

Life expectancy was lower than 30 years in the Roman Empire, 33 years in the Middle Ages, 41 years in early 20<sup>th</sup> century, 75 years in 1970 and 79 years in 1989. In the United States, the average age of menopause is 51 years old, while in Iași, is it 47.7 years old (1). The age of menopause is, to a great extent, genetically determined (2).

A woman born in the United States in the second half of the 20<sup>th</sup> century is estimated to live between 71 and 83 years. It results that she will spend 20-30 years of her life in post menopause (3).

Throughout human history, the age of menopause has remained constant.

The Romanian clinical guide “Terapia menopauzei” (Menopausal Therapy) issued in 2010 states that menopause lasts until the age of 65, after which it is followed by senescence (4).

## **Menopausal therapy before estrogens**

One of the oldest known texts on menopause is an Egyptian medical text dated from 2000 BC (5). The ancient Egyptian writings recommend the use of animal organs or secretions to treat diseases.

Sushruta, who lived sometime between 400 and 500 BC, mentioned the use of substances of testicular origin to treat impotence in Ayurvedic writings.

Pliny and Galen’s writings comprise many references to the use of various concoctions of animal organs to treat diseases.

Hippocrates believed that many diseases were the result of “humours” and sought to treat them using corresponding healthy animal organs (6).

## **Menopausal therapy before estrogens discovery**

A book from the Renaissance period, approximately 500 years old, recommends about the

same treatment for menopause as the current one: plants and physical exercise. More specifically, a decoction with myrrh and apples is recommended for women with symptomatic menopause (5).

In 1849, Berthold drew attention to the importance of some glands without discharge canals. Five years later, the famous Claude Bernard paved the way for a new science.

The Merck Manual of Diagnosis and Therapy published in 1899 recommends a brown powder called “Ovariin” derived from dried cow ovaries for climacterium and other ovary-related issues. This was the first attempt at a medicalized treatment of menopausal symptoms.

In 1889, Dr. Brown-Sequard reported that he became rejuvenated after self-administrating testicular extracts of guinea pigs and dogs in sensitive parts of his body, which led to research on extracts of glands as a potential fountain of youth (5).

In the 1930s, Dr. Serge Voronoff made the first transplantation of a monkey’s testicles to a man, with limited results. The following attempts made regarded grafting monkey ovaries in women, with disastrous results, causing the deaths of women and monkeys alike (1).

## **The initial era of estrogens**

From 1923 until 1938, Dr. Allen and Dr. Doisy studied the structure of estrogens and described their effects.

The first commercial product appeared after Collip’s collaboration with Ayerst Labs in 1930; it was called Emmenin, it was administered by oral route, and it was extracted from the urine of pregnant women in their last trimester of pregnancy. The source of estrogens was subsequently changed to pregnant mares, the effect being considered twice as stronger than that of the product originating from women. Ayerst placed Premarin (PREgnant MAREs’s urINe) on the market.

The German company Schering initially produced Progynon, still from the urine of pregnant women, followed by Progynon 2, with estrogens from pregnant mares. In 1938, Hans Inhoffen and Walter Holweg from Schering synthesized ethinylestradiol.

Diethylstilbestrol (DES) was created by a team of English chemists in 1938.

Eli Lilly, Winthrop, Upjohn and Squibb joined hands to promote estrogens on the market. In 1941, the Food and Drug Administration (FDA) approved DES for the treatment of menopause-related symptoms, such as hot flushes, night sweats, vaginal dryness and atrophy (5).

Medroxyprogesterone acetate was discovered in 1956, and Tibolone was introduced in 1988.

In the 1960s, the drug industry found an opportunity to exploit the emotional problems caused by the society's perception of the decreasing role of the perception of femininity after the onset of menopause. This subject later became a billion dollar business (5).

### **Increasing sales of menopause-related drugs**

In 1966, Dr. Robert Wilson from New York wrote the highly successful book "Feminine Forever". The author sees menopause as degradation and recommends estrogens for older women in order to become more attractive. Wilson writes that the "tragedy of menopause" is that it destroys the women's character and health. The solution he proposes is for women to receive estrogens from puberty until death; menopause would no longer occur in this case, and women could be "feminine forever". At that time, the treatment consisted only of estrogens. Over 100,000 copies of the book were sold in the first 7 months following its release. In 1966, Wilson claimed to have already treated over 5,000 women with estrogens. The foundation created by Wilson for promoting estrogens received over 1.3 million dollars from drug companies, especially from Searle, Ayerst and Upjohn (5).

In November 1966, the FDA regarded Wilson as unacceptable for investigating menopause-related drugs.

By creating a new medical condition, the pharmaceutical companies ingeniously diagnosed menopause as a disease that requires treatment. Between 1966 and 1971, the women's uses of

tranquillizers, such as Valium, increased by 110%, while the use of antidepressants increased by 320%.

In the same period, 17% of women used psychotropic drugs compared with 8% of men at an average age of 44 years. This approach paved the way for drugs that "treat" menopause. The population in general is not aware of the fact that it is possible for pharmaceutical companies to have huge success by shaping the reception of the public opinion.

### **Highlighting negative side effects**

The DES received a major blow in 1971 once with the discovery of the risk of vaginal cancer in girls born to mothers who received treatment for maintaining their pregnancy. Four years later, the FDA withdrew its approval to use this treatment during pregnancy (5).

In December 1974, The New England Journal of Medicine published an article that revealed a 7.5-time higher risk of endometrial cancer in women who underwent this type of treatment and a 14 time higher in those who used it for more than 7 years (1).

In 1975, 25 million prescriptions were estimated to have been issued by physicians for estrogens therapy, 4 times higher than in 1972. The estrogens prescriptions decreased by 28% in the first 3 years, the sales dropping to a half until 1980.

### **Resuming sales**

The addition of progestin to estrogens in menopausal women who kept their uterus lead to the reappearance, in 1988, of an increased number of prescriptions for balanced estrogens, despite the fact that the new problems that arose were premenstrual syndromes and that some of the women who no longer had their period did not want its return.

Premarin became the best sold drug in the United States in 1992. Five years later, it became the first Wyeth product to have exceeded \$1 billion in sales (5).

With all its ups and downs, Premarin remained, until 2002, in top 50 of the best-selling drugs in the United States.

Far from being able to distinguish between the information provided by the media, and even by the doctors, women would buy these drugs in their hope for perpetual youth.

Like in the case of hypothyroidism or diabetes, hormone replacement in menopause, for an indefinite period, does not treat only the symptoms that appear, but also attempts to prevent any other effects produced by the lack of estrogens.

In December 1999, the American Association of Clinical Endocrinologists (AACE) issued guidelines for clinical practice for the management of menopause, stating that menopause is a consequence of hormone deficiency and that it should be treated (1).

The results of the Women Health Initiative (WHI) study published in 2002 changed the secondary enthusiasm and led, once again, to a decrease in prescriptions for estroprogestative drugs in menopause.

In developed countries, female gynaecologists and wives of male gynaecologists resort to this treatment in a percentage of 85-90%. In the Nordic countries, 30% of the female population aged between 50 and 70 uses HRT (1).

### **Current indications**

The current indications can be summarized in the form of the following guidelines accepted by the international scientific community: relieving symptoms caused by menopause; treatment is not recommended for asymptomatic women; women with hysterectomy should not receive progestogens; combined estroprogestogen treatment should not be applied as primary or secondary prophylaxis in cardiovascular disease (1,7).

The prophylactic treatment is approved by the FDA only for preventing osteoporosis; the time of administration should be limited to the lowest level that does not increase the risk of side effects; the use of doses to levels lower than the "standard" dose should be taken into consideration. Alternative routes of administration should also be considered.

The treatment must be individualised and women should make their decision knowingly.

The Society of Obstetricians and Gynaecologists of Canada has currently provided a series of indications on menopausal hormone therapy that are very similar to those in the United States, yet they are slightly more nuanced and more permissive (8).

The focus is shifted onto the detailed explanation of thromboembolism and breast cancer risks. If the patient wishes to benefit from this type of treatment, additional investigations are further prescribed in order to assess risks in dynamics.

The HRT contraindications are: present or suspected breast cancer, endometrial cancer, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, high risk of thromboembolism, active ischemic heart disease, cerebrovascular disease, active liver disease, porphyria cutanea tarda (9).

### **Financial implications**

The effects of the WHI study were severe for those who produce HRT. In 2001, Wyeth's Premarin had over 45 million prescriptions and other 21.4 million for the combination of Premarin and progestin – Prempro, used in the WHI study. The Premarin products brought sales of \$ 2.04 billion in 2001.

The hormone sales dropped by 38% for estrogens, while those for Prempro dropped by 74%. In 2002, 18.5 million women used hormone treatment, in comparison with only 7.6 million in January 2004. In the following years, the drops were between 2 and 8% per month also depending on the product (5).

In 2002, after a study conducted in 17 European countries, the estimated percentage of women aged between 45 and 69 who resorted to replacement therapy in menopause varied considerably from one country to another, from less than 5%, to over 25%. There was a major drop in all countries in the period 2002 - 2010, between 50% and 77%.

At the end of 2010, hormone replacement therapy was below 10% in all the countries studied, with the exception of Finland. These drops are not

related to the previous levels of adherence to HRT, or to the breast cancer rate, or to the number of gynaecologists per 100.000 women, or to the information released on HRT. The drops in the use of estrogens in menopause were much lower for tibolone or for local vaginal treatment (10).

Over 10 years after the publication of the results of the WHI study, we believe that the therapeutically changes brought about by the E+P study led to 126.000 fewer breast cancers, 76.000 fewer cardiovascular events, 263.000 more osteoporotic fractures and to 15.000 more colorectal cancers (5).

### **The moment for beginning treatment**

There seem to be greater health risks for older postmenopausal women than benefits.

The WHI data are less comprehensive than we would have liked when it comes to younger women (11).

So far, the specialists' attempts focused on increasing hormone levels in women in menopause. Some of the results have been unfavourable due to the unpleasant side effects. The current problem is the customization of indications for substitution therapy.

In any case, it seems that it is not recommended in women over the age of 65, unless the patient wants to undergo therapy and understands the potential risk (4).

If the treatment is beginning in the age range 50-59, it can have a positive role, but at a more advanced age, it can cause harm (12).

The use of hormone therapy must be regarded as a highly individual decision.

Oestrogens are usually recommended if there are symptoms (vasomotor and vulvovaginal). Hormone therapy is unquestionably the most effective one in treating symptoms. However, alternatives must be taken into consideration as well. Physicians must be flexible in their prescription because there is no such thing as an ideal treatment for all women.

The results of the WHI study were generalized for all women and many ceased hormonal treatments. After 10 years from the first publication

of the results of this study, it can be concluded that hormonal therapy is preferable for younger, healthy women, in early menopause. In most cases, the benefits exceed the risks (13).

In her book, *The Estrogen Elixir* (2010), Elizabeth Siegel Watkins argues that the WHI results are not able to close the chapter of the long-term use of estrogens in post menopause, in spite of the indications of the FDA to use them only in the short term (14).

The use of estrogens is a message about hope. The pressure of the industry, which is still exerted today, associates hormone replacement therapy with youth and beauty.

The Global Consensus Statement of 2013 also supports other potential effects, such as mood swings, sexual dysfunctions, sleep disorders or myalgia (9).

The lowest doses should be used for the shortest period of time necessary for therapy, without exceeding 5 years. Every 6-12 months, a re-evaluation must be performed (4).

### **Alternatives**

Oral estradiol, dermally administered estrogens and low oral doses of conjugated equine estrogens could be associated with a lower cardiovascular risk (15).

Tibolone and DHEA (dehydroepiandrosterone) are also effective in improving menopausal symptoms. Tibolone provides beneficial androgenic effects on mood and libido and has fewer side effects, but it is an expensive drug. DHEA has positive effects on psychological symptoms. The high cost and the androgenic side effects limit its long-term use (16).

The administration of 100 mg micronized progesterone per day in menopause does not increase the risk of thromboembolic disease or breast cancer, even in association with 50 micrograms of estradiol per day.

For cognition, oral, transdermal combined estrogens, associated with micronized progesterone, do not have great advantages.

The current research does not support the use of HT for preventing chronic diseases. Moreover,

a distinction must be made between using HT for menopausal symptoms and preventing chronic diseases. The risk of significant side effects is lower than 1% in younger women who use HT for 5 years and 4-5 times higher in older women.

The next logical step would be to conduct a random research of the effects of lower doses of HT, in the case of transcutaneous estradiol, and to compare the different routes of administration, and even products, conjugated estrogens compared to estradiol, micronized progesterone compared to another progestogen (17).

Alternative methods such as acupuncture, yoga, phytoestrogens, Omega 3, or physical exercise have not yet been proven and certified for relieving vasomotor symptom (7).

The autograft of ovarian tissue cryopreservation at a young age and reimplanted in menopause has not yet proven its effectiveness (18).

### **The link between science and the perception of knowledge**

In constructing a theory or a scientific study, the gaps in knowledge can be most often filled with elements related to the researcher's own values and convictions.

The epistemic ideal of the detachment and independence of results is a desideratum which is nearly impossible to realize. The study of hormone replacement therapy on the prevention of coronary disease also reveals the importance of the social condition of science. A pluralism of non-cognitive values is also involved in the process, highlighting the context in which discoveries are made, as well as the importance of the social condition of science.

A correct demarcation between what is inside or outside the epistemic process cannot be made (19).

Even if all the evidence-based data verification guidelines are complied with, the result of constructing a theory can still be judged as lacking value judgments, hence, objectivity.

The studies on the effects of HRT are an example that supports the involvement of value judgments in conducting and completing research on

this topic. We live in a time when the manifestation of doubt against the results provided by science has almost become a trend: from water fluoridation in the big cities, to the need for vaccinations, or climate change (19).

Science appeals to our rational brain, yet our beliefs are mostly motivated by emotions and the greatest motivation is to stay with people like us. Local values and opinions always influence science.

For some people, belonging to a tribe is more important than the truth; for the best scientists, the truth is most important than the tribe (20).

The truth value of an assertion also some historical component and hermeneutics (the methodology of text interpretation and understanding) can complement the semantic content of some of the norms of conduct of our time (21).

In developed countries, most of what women know about health comes from the media. In general, the more sensational a topic is, the more it is discussed. For example, the risk of breast cancer is real and serious, but the fear of breast cancer seems to direct all decisions, especially those related to hormonal treatment.

American women believe that the most important cause of death in women is breast cancer and they attach a marginal importance to cardiovascular diseases or osteoporosis. In reality, it is the other way around. Statistics show that one in three women over the age of 65 have signs of cardiovascular disease (13). Despite public perception, the overall incidence of breast cancer has remained constant in recent years.

### **Conclusions**

The significant decrease in estrogens levels is not a disease, but a distinct physiological stage, with many systemic consequences (3).

Medical menopause appeared after 1940 when the FDA approved estrogens to treat it and its symptom (22). This decision has created a multibillion dollar business.

HRT is neither good for everything, nor bad for everything. It certainly has benefits, but it depends

on how and to whom it is recommended. Negative side effects can otherwise occur.

A 40% decrease in overall death rate in patients who used the treatment long-term has been observed by several studies (13).

Low doses of estrogens and progestogens have marginal effects on the incidence of breast cancer in women with a uterus. The treatment should not be currently recommended for its cardiovascular benefits.

However, the mechanisms of hormones on the cardiovascular system are still unknown. The specialists have not yet discovered why women have fewer cardiovascular events than men of the same age (23).

The members of the research team must be independent of drug companies. The drugs for healthy people, for preventive purposes, must be used with the utmost caution.

The subject treated in this article will surely undergo many other changes in terms of the evolution of guidelines to be applied in the future.

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