*REVIEW (Derleme)*

# SHOULD WE GIVE UP HORMONE TREATMENT IN MENOPAUSE ?

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**SUMMARY**

*Hormone treatment (HT) is an add back regimen of declining hormone or hormones in a postmenopausal woman in order to eliminate unfavorable conditions caused by hormone deficiency, although it does not meet the actual levels secreted from the ovary. Leading indications are hypoestrogenemia and disturbing symptoms related to hypoestrogenic state. Vaginal atrophy, genitourinary symptoms like urinary incontinence, increased risk for osteoporosis and cardiovascular diseases are the other main concerns of HT. On the other hand, postmenopausal women who were treated with HT protocols including estrogen preparations as well as estrogen/progestogen combinations have been indicated as being exposed to increased risk for breast cancer development. Moreover, HT preparations were demonstrated to be ineffective in protection from cardiovascular diseases and thromboembolic events, in contrast to the prior beliefs. Therefore, today in the light of new data, use of hormone therapy in postmenopausal women seems to lose its relevance. Nevertheless, alternative therapies have been developed to serve for the relief of menopausal disorders. Among them, tibolone, micronized testosterone, dihydroepiandrosterone, selective serotonine noradrenaline re-uptake inhibitors (SNRI), selective estrogen receptor modulators, combined oral contraceptives and fitoestrogens could be preferred. For all that, the most efficacious treatment on menopausal and genitourinary symptoms seems to be HT, yet. Furthermore, HT was indicated to be effective on osteoporosis and reducing postmenopausal bone fractures. HT should be the first choice of treatment in patients with premature ovarian failure and early onset menopause without any familial history of cancer. At the present time, it is advised to use hormone treatment choosing the appropriate preparation with the lowest effective dose with respect to above mentioned indications. If HT was introduced, there are valuable recommendations to keep the duration of therapy less than 5 years.*

***Key words:*** *breast cancer, colon cancer, endometrial cancer, estrogen, hormone therapy, menopause, progestogen, thromboembolism*

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# MENOPOZDA HORMON TEDAVİSİNİ TERK ETMELİ MİYİZ ?

**ÖZET**

*Hormon tedavisi (HT); postmenopozal bir kadının azalan hormon ya da hormonlarının, overlerden salgılanan düzeylerde olmasa da yerine konulması ile hormon yetmezliğine bağlı gelişen olumsuz durumların ortadan kaldırılmasını hedefleyen tedavi biçimidir. En temel endikasyon hipoöstrojenemi ve ona bağlı görülen olumsuz durumlardır. Vajinal atrofi, idrar inkontinansı gibi genitoüriner semptomlar, osteoporoz ve kardiyovasküler hastalıklar için yüksek risk varlığı HT için öngörülen diğer ana endikasyonlardır. Ancak, hem östrojenlerin hem de östojen/progestajen kombinasyonlarının kullanıldığı HT protokolleri postmenopozal kadınlarda artmış meme kanseri gelişim riski ile ilişiklendirilmektedir. Ayrıca, HT preparatlarının, düşünüldüğünün aksine kardiyovasküler hastalıklar ve tromboembolik olaylarla ilişkili koruyucu etkilerinin bulunmadığı gösterilmiştir. Günümüzde yeni verilerin ışığı altında, HT'ne eskiden*

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*olan ilgi kaybolmaktadır. Bununla birlikte HT'ne alternatif tedaviler geliştirilmiştir. Bunların arasında Tibolon, mikronize testosteron, dihidroepiandrosteron, selektif serotonin noradrenalin geri alım inhibitörleri (SNRI), selektif östrojen reseptör modülatörleri, kombine oral kontraseptifler ve fitoöstrojenler gösterilebilir. Ancak, menopozal semptomlar ve genitoüriner atrofi üzerinde en etkin tedavi olarak HT görülmektedir. Yine, osteoporoz ve postmenopozal kemik kırıklarının önlenmesinde HT'nin etkin olduğu bildirilmektedir. Ailesel kanser hikayesi olmayan prematür overyan yetmezlik olgularında ve erken menopozda HT ilk düşünülmesi gereken tedavi seçeneğidir. Günümüzde, belirttiğimiz endikasyonlarla, menopozal HT'nde mümkün olan en düşük doz tercih edilmelidir. HT'ne karar verilmişse, toplam sürenin 5 yıldan kısa tutulmasında fayda vardır.*

***Anahtar kelimeler:*** *endometrium kanseri, hormon tedavisi, kolon kanseri, meme kanseri, menopoz, östrojen, progestajen, tromboembolizm*

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## INTRODUCTION

The mature woman concept typically includes women of age 40 or more who completed their fertility. Most of those women enter menopausal transition period in their late 40s. Since it is genetically coded, this transition period which is accepted as physiological is completed between the ages 51 and 56. Estrogen deficiency which is observed physiologically has recently become a pathological process due to negative effects of long term absence of circulating estrogen, particularly due to advances in average human life. The low estrogenic status which is experienced after the failure of the ovaries has specific effects on diverse tissues. Low estrogen levels cause vasomotor and cerebrovascular symptoms as well as metabolic and structural changes such as osteopenia, osteoporosis, thinning of the skin, and increase in adipose tissue content of the breast. As a result, special problems may be observed on postmenopausal women both due to aging and decrease in estrogen levels which negatively influence their individual life conditions. In fact, this estrogen deficiency is at a level which should be treated for most women, however, less than 20% of women receive hormone treatment (HT).

### What is hormone treatment?

Since the menopause was considered as a disease of deficiency like hypothyroidism, HT concept was formed as a replacement therapy for this specific condition. Accordingly, different forms of HT were defined. HT is the therapy form which aims the replacement of decreasing hormones of a postmenopausal woman.

The most basic indication is hypoestrogenemia and negative conditions based upon it. The prescribed indications for HT are genitourinary complaints such as hot flashes, vaginal atrophy, urinary incontinence, and existence of increased risk for osteoporosis and cardiovascular diseases. Existence of pregnancy, undiagnosed uterine bleeding, untreated endometrial hyperplasia, acute gall bladder disease, liver disease, and malignant melanoma are absolute contraindications for HT. Although acute phases of myocardial infarction, cerebrovascular ischemic disorders, deep vein thrombosis, and post-venous thromboembolism are considered amongst absolute contraindications, presence of such diseases in past medical history forms a relative contraindication. Breast cancer, endometriosis, big leiomyomas, migraine headache, convulsive diseases, hepatic porphyria, and familial hyperlipidemia are also relative contraindications for HT.

### Treatment protocols

Estrogen preparations or estrogen-progesterone combinations are used in HT. Estrogens are divided into two categories as natural and synthetic estrogens. 17-ß- estradiol, micronized estradiol, estradiol valerate, estriol, conjugate estrogens, conjugate equine estrogens are being used as natural estrogen forms. Particularly, the ethinyl estradiol which is included within oral contraceptive agents is a synthetic estrogen form. Other than oral tablets, estrogens are available in parenteral forms such as flasters (transdermal carrier systems-TCS), percutaneous gel, vaginal cream, vaginal tablets, vaginal rings, intranasal spray, and implants. Due to particularly the abundance of side effects encountered with oral forms, transdermal forms have started to be preferred nowadays. Transdermal forms can be chosen in the existence of comorbidities such as hypertriglyceridemia, hypertension, type II diabetes mellitus, cholelithiasis, extensive varicosities in the lower extremities, and history of venous thromboembolism,

myocardial infarction and cerebrovascular ischemic stroke. In the treatment of vaginal atrophy and other genitourinary symptoms, vaginal forms are quite helpful.

Progestogen agents are divided into three categories: These are pregnanes, estranges, and gonanes. Medroxyprogesterone acetate (MPA), megestrol acetate, chlormadinone acetate, and cyproterone acetate are encountered in the pregnane group. Norethindrone, norethindrone acetate (NETA), norethinodrel, and ethynodiol acetate are included in estrane group. Among new era progestogen agents; levonorgestrel, desogestrel, norgestimate, and gestoden form gonane group progestogen agents. Recently, out of new progestogen agents, drospirenon and dienogest are drawing attention. Drospirenon is a gestagen which is derived from 17-α-spironolactone. It has antimineralocorticoid and antiandrogenic effects. Increase in blood pressure, weight gain, breast sensitivity and androgenic side effects are less observed with drospirenone. It is known that progestogen agents have no cardioprotective effects, and even may form negative effects on the heart. However, there are some studies which demonstrate that drospirenone may provide cardioprotective effect by decreasing triglyceride and LDL cholesterol levels and increasing HDL cholesterol levels. Another new agent, dienogest, is a strong progestogen as well. It has antiandrogenic and antiproliferative effects. It was even advocated that it might have an anticarcinogenic effect on endometrium and breast tissue with its antiproliferative effect. Although not being used solely (without estrogens) for HT, progestogen agents have also oral, TCS, intrauterine device and vaginal preparation forms.

Estrogen and progesterone combinations or estrogen only regimens were developed as HT protocols. The combined estrogen and progesterone treatment can be applied as cyclic (intermittent-sequential) or continuous (without interruption). Cyclic regimen is particularly preferred in premature ovarian failure and perimenopausal period. The patient is regularly menstruated during drug use. And the continuous treatment is often used in postmenopausal period. During drug use, no menstruation is observed on patients. The aim for adding progesterone to the therapy is to protect endometrium from the effect of unopposed estrogen. For hysterectomised patients, only estrogen can be used. However; progesterone should again be added on patients who have endometriosis history, whose hysterectomy was performed due to a grade 1 or 2 endometrium cancer or endometrioid tumor of the ovary, and on whom supraservical hysterectomy is applied.

Since side effects of estrogen and progesterone are coming into forefront day by day, different treatment protocols have started to be researched. Tibolon, a 19-nortestosterone derivative, which has progestogenic and androgenic effects, has started to be used for this purpose. Tibolone was particularly found effective in eliminating vasomotor symptoms and increasing the libido, but since it led to an increase in endometrium and breast cancer in long term use, its usage remained limited[1]. Again belonged to androgens, micronized testosterone and dehydroepiandrosterone were observed to be effective in increasing the libido. The effects of these two preparations were not apparent on vasomotor and genitourinary symptoms. Amongst the selective estrogen receptor modulators, raloxifene was started to be used on women presenting menopausal symptoms due to positive estrogenic effects on bone and lipid metabolism and antiestrogenic effects on breast and endometrium. Previously, its range of usage has widened because it did not allow breast cancer to increase[2,3], however, its prescription was limited due to being associated particularly with venous thromboembolism risk in recent studies as well as hypoestogenemic status and related symptoms. Combined oral contraceptives were also being used on perimenopausal women both for contraception and hormonal therapy purposes. But due to very low estrogen dosage they contain, particularly after entering into menopausal period, it is suggested to go on with HT form at appropriate dosage and protocol.

**Specific Health Risks and Particular Incidents**

In a book published in 1970s, after being stated that women shall enjoy the life more and they shall not feel themselves boring and unattractive in their postmenopausal period by using estrogen, a general increase in estrogen usage was observed and HT usage became common among the people who want to stay young and are aiming to prevent chronic diseases. However, observing the life threatening side effects after long term usages have shown the requirement of comprehensive studies on this subject. Postmenopausal Estrogen/Progesterone Interventions (PEPI) study

which was started in 1995 is a randomized study performed on women in menopause with an average age of 56[4]. Placebo, only estrogen, estrogen and cyclic MPA, estrogen and continuous MPA, estrogen and micronized progesterone therapies were started for the participants; effects and side effects, advantages and disadvantages of such therapies were evaluated. In the Heart and Estrogen Progestin Replacement Study (HERS) which was started in 1998, the effect of hormone therapy on cardiovascular diseases has been researched[5]. 2763 volunteer patients who have a known cardiovascular disease were involved in the study, and estrogen/progesterone therapy was compared to placebo on the patients.

The most extensive study performed on this subject is the Women's Health Initiative (WHI) study which was started in 1993. Acceptable benefits of HT and its protective effect against diseases were researched against chronic diseases which develop with aging. 16608 healthy postmenopausal women between ages 50 and 79 were involved in the study, and effects of combined conjugated equine estrogen and MPA were compared to placebo on these women. Additionally, coronary heart diseases, venous thrombotic events, breast cancer, colon cancer, and bone fractures were the special results evaluated in this study. The study also compared conjugated equine estrogens and placebo on hysterectomized postmenopausal women.

In the Million Women Study - data of which was collected and evaluated in 2003-, the data were obtained from extensive observational cohorts, national tumor and death records data were evaluated. 1084110 women between ages 50 and 64 were involved in the study. Different from the WHI study, effects of hormone therapies which are applied by many routes including transdermal, implant applications, and oral preparations other than conjugated equine estrogen and MPA combination were evaluated.

At the end of such studies, general opinion is that the negative effects which are observed based on HT usage are generated depending on dosage and time. Yet, the existence of tissues sensitive to estrogen makes this fact important.

**Breast Cancer Risk**

The first studies made on this subject were towards no increase in breast cancer risk based on HT[6]. Nevertheless, the recent studies emphasized that a risk increase might be available based on time[17,8]. In the WHI study, it is stated that there was a risk increase with regard to breast cancer not only in estrogen group but also in estrogen/progesterone treatment group (RR=1.24)[8]. And the Million Women Study has detected breast cancer risk in both estrogen/progesterone treatment arm and estrogen-only arm (RR=1.3 and RR=2.0, respectively)[1]. In another study evaluating the estrogen/progesterone treatment, there was an increase detected in breast cancer risk based on progesterone combined with estrogens, and it was emphasized that this risk might be reduced by micronized progesterone usage[9]. And in another study evaluating KRAS variant on sporadic and familial cases of breast cancer, HER2 overexpression which is based on KRAS variant and poorly differentiated breast cancer development were observed on postmenopausal women taking HT[10].

HT was considered not to be effective on benign breast lesions. Additionally, benign lesions were not considered to transform into malign form with HT. But in recently performed studies, HT was found to be associated with increased breast cancer risk particularly in postmenopausal women with familial history of breast cancer, and having benign breast lesions with high risk[11].

**Endometrium Cancer Risk**

As it is known, endometrium cancer risk increases with usage of estrogens alone. Even in some studies, 4 to 7 times of risk increase is stated[12]. Adding progesterone to the therapy provides a significant reduction in endometrium cancer risk[13]. In recent studies, effects of both the body mass index and HT with endometrial cancer risk were evaluated. It was emphasized that endometrium cancer risk would increase with estrogen-only regimens free from the body mass index, and thus combined estrogen/progesterone therapy should be preferred[14]. In another study, risk of recurrence based on HT usage was evaluated in patients who were followed up due to endometrium cancer, and it was stated that HT usage in those women particularly having stage 1 and 2 endometrium cancer would not cause a risk increase for the recurrence[15,16]. The common result is; HT shall not cause an increased risk in recurrence of early stage female genital organ malignancies. However, HT is clearly contraindicated due to increased risk of

recurrence particularly on women who are followed up due to endometrial stromal sarcoma[16].

**Colon Cancer Risk**

In WHI study, it was revealed that HT with combined estrogen/progesterone preparations has reduced the colorectal cancer risk compared with the ones using only estrogens or placebo in postmenopausal period. However in that study, increased risk for invasive breast cancer was observed in both patients who take either estrogens alone or estrogen/progesterone combinations. This raised the question of how hormone therapy causes an increase in one cancer risk while reducing another cancer risk. In another study comparing WHI databases, it was particularly emphasized that certain period of time should be elapsed for breast cancer and colorectal cancer to progress to invasive form, that the time evaluated in WHI study was inadequate for such case, that hormone therapy might cause increase in both cancer risks and thus more extensive studies were needed for this case[17].

**Cardiovascular Disease and Thromboembolic Event Risk**

In a study performed on this subject, 50% increase on cardiac morbidity and 100% increase on cerebrovascular disease risk is stated[18]. In another study published in the same issue, the rate of heart disease for women receiving postmenopausal estrogen was detected to be significantly lesser than the non-receivers[19]. The contradictory results in these two studies can be explained with the better health standards of the volunteers in the second study (i.e. volunteers in the latter one were slimmer, richer and healthier). The contradictory results have revealed the need for more extensive studies to be done. In PEPI study, a decrease in LDL level, an increase in HDL level and thus, a possible cardioprotective effect is mentioned for all 4 groups to which estrogen was applied in comparison with the placebo group[4]. However, in the first year findings of HERS, study performed afterwards PEPI, an increase in myocardial infarction frequency was detected in women taking continuous MPA together with conjugated estrogen. Nonetheless, it was observed that there was no difference in terms of cardiovascular death or nonfatal myocardial infarction risk between the groups after 4 years of treatment period (RR=0.99, 95 % CI: 0.81-1.22)[5].

After an average follow-up of 5.2 years, WHI study was finished since the hazardous effects of estrogen/progesterone combinations have exceeded its benefits. The results obtained from the initial data of the study revealed that the rate of risk for death and nonfatal myocardial infarction was 1.24 (95% CI: 1.00-1.54). It was also observed that there were no significant differences with respect to hospitalization for coronary artery revascularization, angina, chronic angina, acute coronary syndrome and congestive heart failure[8].

In another study associated with the WHI study, a reduction in coronary artery disease risk was shown with HT which is started at a close period after menopause when compared with HT which is started long after the menopause[20]. Similarly, increased risks were stated for cardiovascular and thromboembolic diseases based on HT which is started long years after menopause[21].

The recent studies are particularly pointing out the increased venous thromboembolic event risk which is developed particularly based on estrogen and MPA usage. Therefore, prescription of transdermal estrogen and micronized progesterone is particularly emphasized as menopausal HT[22].

In another study researching the effect of estrogen/progesterone treatment on lipid profile and cardiovascular risk of menopausal women, it was stated that early-started low dosage HT would provide protection with respect to cardiovascular aspect due to its positive effect on lipid profile[23]. Nevertheless, according to the current literature and analyses carried out in Cochrane database, there is no indication for the long term HT in perimenopausal and postmenopausal women in order to prevent cardiovascular diseases primarily or secondarily. Additionally, the data investigating the risk related with the long term HT usage in perimenopausal and postmenopausal women who are younger than 50 years of age are still inadequate [24].

**Liver and Gallbladder Diseases**

Estrogen is metabolized in the liver. The detection of higher estrogen levels in circulation of women with normal ovarian function who have chronic liver disease has shown that care should be taken in estrogen usage on women having liver disease. It is known that oral contraceptives lead to increase in symptomatic gallbladder disease. And in another study, it is stated

that the increase in gallbladder disease risk is 2 times more for women who had estrogen therapy to women who had not received hormone[25].

**Other Treatment Options for Menopausal Patient**

It was emphasized that treatment with estrogens was the most effective method on cognitive functions and vasomotor symptoms. However, due to current risks brought by the estrogen usage, search has began for alternative treatments, and particularly the medications which are considered as likely to be effective on eliminating vasomotor symptoms were studied. Among such medications, in a study performed on effects of selective serotonin noradrenalin reuptake inhibitors (SNRI), very small recovery was detected in hot flashes compared with placebo[26]. And in another study, it was shown that venlafaxine, from SNRI group, and clonidine, a central acting α-2 receptor agonist agent, have significantly reduced the hot flash scores on patients with breast cancer, with a superiority for venlafaxine[27]. In a similar study, clonidine was shown to be effective in reduction of vasomotor symptoms, but clonodine treatment could not be continued effectively since the side effects such as hypotension, dry mouth, constipation, dizziness, and sedation were prominent[28]. In a study aiming to reveal the effects of SNRI group medicines, fluoxetine was shown to be effective in thermoregulation in the animal model[29]. In order to eliminate the vasomotor symptoms, escitalopram was tried and it was seen efficient in reducing hot flashes[30]. In another study in which gabapentin, estrogen, and placebo were compared, it was observed that estrogen and gabapentin took similar and higher effects in preventing hot flashes but placebo had a less effect on that issue, and that the side effects developing based on gabapentin such as headache, dizziness and disorientation led the therapy to be ceased [31].

Since the phytoestrogens (isoflavones) show estrogenic effects they were considered to be likely to eliminate hypoestrogenemia as a complementary and an alternative medicine. Particularly, the soya products and red clover were used as phytoestrogen sources. However, the effects of isoflavones were very limited when compared to placebo on menopausal symptoms, particularly on hot flashes. Nonetheless, it was stated that soya and purified isoflavones did not increase endometrium or breast cancer risk. Moreover, soya particularly reduced endometrium and ovary cancer risk and had cholesterol lowering effect[32]. But failing to evaluate their side effects in estrogen sensitive tissues clearly and requirement for more extensive studies on this case has limited the usage of such products[33]. Moreover, in order to enable isoflavones to show effect in the human body, they should be transformed into equol form which is a nonsteroid estrogen. Equol form is created by some intestinal bacteria, and this form can be produced only at 25 to 30% of human[34]. And we come across with another reason which limits common use of phytoestrogens. Two extensive studies related with red clover and black gentian root extract continue under the sponsorship of National Institute of Health (NHI).

**Conclusion**

According to the decisions given by Hormone Therapy Consensus Group in 2003, there is no other option today as effective as HT for menopausal symptoms (vasomotor disorders and related sleep disorders), and genitourinary atrophy. Estrogen/progesterone therapy should not be used only for purposes of primary and secondary cardiovascular protection. There is no adequate proof for the use of estrogens for the latter mentioned indications. In terms of protecting endometrium, no adequate information is available on different forms of progesterone.

According to Million Women Study, no difference was found between HT content, application route, and therapy regimes with regard to increased breast cancer risk. Breast cancer risk observed with HT disappears 5 years after the withdrawal. Increment of the risk for breast cancer which is brought by HT is not different from the risk factors such as alcohol use, excess weight (i.e. body mass index 30 or more), first childbirth after the age of 30, and late menopause. All these data are compatible with the previous studies researching the relationship between HT and breast cancer.

It was proven that estrogen/progesterone treatment is effective in preventing osteoporosis and fractures based upon it. In treatment of osteoporosis; biphosphonates, selective estrogen receptor modulators and calcitonin can be used. Moreover; exercise, calcium and sunlight should be utilized during menopause period.

The mentioned suggestions do not comprise the premature menopause (menopause before age of 40) and premature ovarian failure. In premature ovarian

failure and early menopause, long term HT is recommended until natural menopause age[35]. Particularly in treating vasomotor symptoms, no therapy option effective than the hormone therapy could be found[36]. Again for women who entered menopause surgically, an increase is mentioned on frequency of their sexual problems and menopausal symptoms when compared to women who entered menopause in natural way[37]. Again, HT is considered as the most effective treatment option for this case as well. According to the current literature data and analyses performed in Cochrane database, long term hormone therapy is not indicated in preventing dementia and regulating cognitive functions on perimenopausal and postmenopausal women[24].

Today, the possible lowest dosages should be preferred for menopausal HT. In our country, there is no available lowered-dose HT preparation yet.

WHI study was finished after an average 5.2 years of follow-up, and therefore HT period should be taken less than 5 years. As it is particularly emphasized, possible hazards exceed current benefits after a time period, the shortest therapeutic period should be determined.

Benefit-hazard balance and costs of HT for menopausal women should always be considered and the answers of "Should the hormone therapy be started? / quitted?" questions should be discussed with the patient considering the current benefits and damages, and informed consent of the patient should be taken along with the doctor's decision.

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