Estrogen and Progestogen use in Postmenopausal Women: 2010 Position Statement of The North American Menopause Society

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2010 Position Statement

- The Panel also recognized that the WHI trials had several characteristics that limit the ability to generalize the findings to all postmenopausal women.
- These include the use of only one formulation of estrogen (conjugated estrogens [CE]), alone or with one progestin (medroxyprogesterone acetate [MPA]) and only one route of administration (oral).
- Moreover, women studied in the WHI were older (mean age, 63 y), mostly more than 10 years beyond menopause and with more risk factors than younger women who typically use HT, and largely without menopause related symptoms.

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Hormone Therapy Terminology

- EPT: combined estrogen-progestogen therapy
- ET: Estrogen therapy
- HT: Hormone therapy (encompassing both ET and EPT)
- Local therapy: vaginal ET administration that does not result in clinically significant systemic absorption
- Progestogen: Encompassing both progesterone and progestin
- Systemic therapy: HT administration that results in absorption in the blood high enough to provide clinically significant effects
- Timing of HT initiation: length of time after menopause when HT is initiated

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Menopausal Terminology

►Early menopause: Natural or induced menopause that occurs well before the average age of natural menopause (51 y), at or under age 45

►Early postmenopause: The time period within 5 years after the final menstrual period (FMP) resulting from natural or induced menopause & Induced menopause. Permanent cessation of menstruation after bilateral oophorectomy (i.e., surgical menopause) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or pelvic radiation therapy)

►Natural/spontaneous menopause: The FMP, confirmed after 12 consecutive months of amenorrhea with no obvious pathologic cause

►Perimenopause/menopause transition: Span of time when menstrual cycle and endocrine changes occur a few years before and 12 months after an FMP resulting from natural menopause

► Premature menopause: Menopause reached at or under age 40, whether natural or induced

►Premature ovarian insufficiency: Loss of ovarian function before age 40, leading to permanent or transient amenorrhea (often described as premature ovarian insufficiency or premature menopause)

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Hormone Therapy Use

- Use of HT should be consistent with treatment goals, benefits, and risks for the individual woman. The benefit-risk ratio for an individual woman continually changes with her age and her menopause-related symptoms (e.g., vasomotor symptoms, sleep disturbance, vaginal atrophy, dyspareunia, or diminished libido), any of which may have an adverse impact on quality of life (QOL).

- Risk factors are related to: a woman's baseline disease risks, her age, age at menopause, cause of menopause, time since menopause, and prior use of any hormone including type, route of administration, dose, and medical conditions that emerged during treatment.

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Vasomotor Symptoms

- ET, with or without a progestogen, is the most effective treatment for menopause-related vasomotor symptoms (i.e., hot flashes and night sweats) and their potential consequences (e.g., diminished sleep quality, irritability, and reduced QOL).
- Treatment of moderate to severe vasomotor symptoms remains the primary indication for HT. Every systemic ET and EPT product has regulatory agency approval for this indication.

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Vaginal Symptoms

- ET is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy (e.g., vaginal dryness, dyspareunia, and atrophic vaginitis). Many systemic ET and EPT products and all local vaginal ET products have regulatory agency approval for treating these vaginal symptoms.
- Lower doses than previously used, and less frequent administration, often yield satisfactory results. Some systemic ultralow dose regimens may be inadequate for relief of vaginal symptoms.
- When HT is considered solely for urogenital atrophy, local vaginal ET is generally recommended.

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Sexual Function

- Relief of moderate to severe vaginal atrophy with systemic or local HT can be effective in relieving dyspareunia, a common cause of intercourse avoidance. Local estrogen may improve coital satisfaction by improving lubrication and increasing blood flow and sensation in vaginal tissues.
- One oral systemic ET product is approved in the United States for the treatment of pain with intercourse.
- HT is not recommended as the sole treatment of other problems of sexual function, including diminished libido.

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Urinary Health

- Local ET may benefit some women with urge incontinence who have vaginal atrophy. Whether ET by any route is effective in treating overactive bladder is unclear. There is controversy as to whether local ET can improve certain cases of pure stress incontinence. On the other hand, systemic HT may worsen or provoke stress incontinence, perhaps related to changes in uterine volume or periurethral collagen.
- Clinically, only ET administered by the vaginal route has been shown in an RCT to be effective in reducing the risk of recurrent UTI.
  - However, no ET/EPT product has regulatory agency approval for any urinary health indication.

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Change in Body Weight/Mass

- Body mass index (BMI) increases with age in midlife, with the peak BMI occurring between ages 50 and 59. At this time of life, other factors may also contribute to weight gain, including a decrease in energy expenditure and an increase in energy intake coupled with a decrease in metabolic rate.
- In women, the hormonal changes associated with the menopause transition can affect body composition and add to the tendency to gain weight.
    - No statistically significant difference in mean weight gain or BMI has been demonstrated between women who use HT and those who do not.

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Quality of Life

- Although no HT product has regulatory agency approval for enhancing QOL, an improvement in health-related quality of life (HQOL) can result with HT use because of decreased menopause symptoms and perhaps other mechanisms, including improved sleep and a possible elevation of mood that leads to a feeling of well-being.
- Whether HT improves HQOL in asymptomatic women is unknown, nor are data available to determine the effect of HT on global QOL (the sense of well-being with or without symptoms or physical impairments).

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Osteoporosis

- Bone strength depends on both bone quality and bone mineral density (BMD). Changes in BMD alone may not always reflect fracture risk.
- There is RCT evidence that HT reduces postmenopausal osteoporotic fractures, including hip fractures, even in women without osteoporosis, although no HT product has regulatory agency approval for treatment of osteoporosis.
- Many systemic HT products, however, have regulatory agency approval for prevention of postmenopausal osteoporosis through long-term treatment

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Osteoporosis

►Extended use of HT is an option for women who have established reduction in bone mass, regardless of menopause symptoms; for prevention of further bone loss and/or reduction of osteoporotic fracture when alternate therapies are not appropriate or cause side effects; or when the benefits of extended use are expected to exceed the risks.

►The optimal time to initiate HT and the optimal duration of therapy have not been established, but HT would largely be used in the early years after menopause.

►The benefits of HT on bone mass dissipate quickly after discontinuation of treatment.

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Coronary Heart Disease

- Most observational and preclinical studies support the potential benefits of systemic HT in reducing the risk of CHD. Most RCTs do not.
- However, it is now understood that the characteristics of women participating in observational studies are markedly different from those of women enrolled in RCTs, and that some of these demographic or biologic differences, or both, influence baseline cardiovascular risks and may modify the effects of HT on cardiovascular risk.

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Coronary Heart Disease

- When analyzed by age and time since menopause at initiation of HT, the ET arm of the WHI is in general agreement with observational studies indicating that ET may reduce CHD risk (coronary revascularization and composite outcomes) when initiated in younger and more recently postmenopausal women.
- In a secondary analysis of WHI data, there was a statistically significant reduction in the composite endpoint of myocardial infarction, coronary artery revascularization, and coronary death in women who were randomized to ET during ages 50 to 59.
- However, statistical modeling of the combined WHI data, including further data from WHI observational studies, did not find that CHD risks varied by the timing of HT initiation.

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Coronary Heart Disease

- **Duration of therapy:** Observational studies suggest that longer duration of HT use is associated with reduced risk of CHD and related mortality.
- The WHI RCTs and the WHI observational study suggest a pattern of lower risk of CHD among women who used HT for 5 or more years, but this is not conclusive, and should be considered in light of other factors altered by duration of therapy, such as breast cancer.
- In contrast, in the short term, HT is associated with an increase in CHD risk among women who are more distant from menopause at the time of HT initiation.

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Coronary Heart Disease

►**Coronary artery calcium:** Observational studies show that long-term HT is associated with less accumulation of coronary artery calcium, which is strongly correlated with atheromatous plaque burden and future risk of clinical CHD events.

►In an ancillary substudy of younger women (< 60 y) in the WHI ET trial, after an average of 7 years of treatment, women who had been randomized to ET had lower levels of coronary artery calcium than those randomized to placebo.

►These findings suggest that ET initiated by recently postmenopausal women may slow the development of calcified atherosclerotic plaque.

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Stroke

- The WHI EPT and ET trials demonstrated an increased risk of ischemic stroke and no effect on risk of hemorrhagic stroke. In these trials, there were 8 additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET when the entire cohort was analyzed.
- In recent analyses that combined results from the WHI EPT and ET trials, HT in younger women (ages 50-59) at study entry had no significant effect on risk of stroke (relative risk [RR], 1.13; 95% confidence interval [CI], 0.73-1.76).
- In the Framingham Heart Study, natural menopause at age 42 or younger was associated with elevated risk of ischemic stroke.

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Stroke

- No studies indicate that postmenopausal HT is effective for reducing the risk of a recurrent stroke among women with established cardiovascular disease (CVD) or for prevention of a first stroke, and it may increase the rate of first strokes particularly in women initiating HT over age 60.
- HT cannot be recommended for the primary or secondary prevention of stroke. Although stroke was not increased in the group ages 50 to 59 in the combined analysis of the WHI, it was almost doubled in the ET group less than 10 years since menopause.
    - This apparent contradiction in the data is hard to explain, but may be due to relatively few events and the difficulty in accurately timing onset of menopause in the ET group.

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Venous Thromboembolism

►Data from both observational studies and RCTs demonstrate an increased risk of VTE with oral HT. In the WHI trials, there were 18 additional VTEs per 10,000 women per year of EPT and 7 additional VTEs per 10,000 women per year of ET when the entire cohort was analyzed. VTE risk in RCTs emerges soon after HT initiation (i.e., during the first 1-2 y), and the magnitude of the excess risk seems to decrease somewhat over time.

►In the WHI trials, the absolute excess VTE risk associated with either EPT or ET was lower in women who started HT before age 60 than in older women who initiated HT after age 60. This falls into the rare category.

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Venous Thromboembolism

►The baseline risk of VTE also increases relative to BMI. For obese women (BMI 930), the baseline risk was almost threefold greater. At any BMI, the risk of VTE doubled with HT, and returned to baseline soon after HT discontinuation.

►Growing evidence suggests that women with a prior history of VTE or women who possess factor V Leiden are at increased risk for VTE with HT use.

►There are limited observational data suggesting lower risks of VTE with transdermal than with oral ET, but there are no comparative RCT data on this subject. Lower doses of oral ET may also confer less VTE risk than higher doses, but no comparative RCT data are available to confirm this assumption.

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Cardiovascular Conclusions

- HT is currently not recommended as a sole or primary indication for coronary protection in women of any age.
- Initiation of HT by women ages 50 to 59 years or by those within 10 years of menopause to treat typical menopause symptoms (e.g., vasomotor, vaginal) does not seem to increase the risk of CHD events.
- There is emerging evidence that initiation of ET in early postmenopause may reduce CHD risk.

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Diabetes mellitus

- Although no HT product has regulatory agency approval to prevent DM, large RCTs demonstrate that HT reduces the new onset of T2DM.
- Women who received active treatment in the WHI EPT arm had an annualized incidence of DM requiring treatment of 0.61% versus 0.76% in placebo-treated women. This translates into a statistically significant 21% reduction (hazard ratio [HR], 0.79; 95% CI, 0.67-0.93) in incident-treated DM, or 15 fewer cases per 10,000 women per year of therapy.
- A similar statistically significant risk reduction was also noted in the HERS trial (HR, 0.65; 95% CI, 0.48-0.89). In the WHI ET trial, there was a 12% reduction (HR, 0.88; 95% CI, 0.77-1.01) in incident DM, or 14 fewer cases per 10,000 women per year of ET.

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Diabetes mellitus

- It is presently unclear whether the mechanism for this benefit is through less centripetal weight gain, reduced insulin resistance in women receiving combined EPT, or some other factor.
- Meta-analysis data suggest that HT is associated with an improvement in insulin resistance in postmenopausal women. There is inadequate evidence to recommend HT as the sole or primary indication for the prevention of DM in peri- or postmenopausal women.

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Diabetes mellitus

- In women with T2DM, measures to reduce CHD risk are probably of greatest concern. If HT is prescribed, the specific agent, dose, regimen, and route of administration may be important.
- Transdermal ET administration may offer advantages over the oral route. Serum triglyceride levels and thrombotic factors, which are often increased in patients who have DM, are not increased further with transdermal HT.
- Moreover, adverse alterations in blood pressure in both nonhypertensive and hypertensive women (although viewed as being rare, if not idiosyncratic, reactions) have been reported only with oral therapy.

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Endometrial Cancer

- Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the ET dose and duration of use.
  - Standard-dose therapy (0.625 mg/d CE or the equivalent), when used for more than 3 years, is associated with up to a fivefold increased risk of endometrial cancer; if used for 10 years, the risk increases up to tenfold. This increased risk persists for several years after ET discontinuation.
- To negate this increased risk, adequate concomitant progestogen is recommended for women with an intact uterus when using systemic ET.
- HT is not recommended in women with a history of endometrial cancer.

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Breast Cancer

►**Estrogen-progestogen :** Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years. In the WHI, this increased risk, in absolute terms, was 8 total breast cancers per 10,000 women using EPT for 5 or more years.

- ►Studies have not clarified whether the risk differs between continuous and sequential use of progestogen, with observational studies suggesting risk may be greater with continuous use of progestogen.
- ►It is also not clear whether there is a class effect from the progestogen or whether the specific agent used influences breast cancer risk.

►Early data from a large observational trial suggest that EPT with micronized progesterone may not be associated with an increased risk of breast cancer if used for up to 5 years, but these findings should not be overemphasized and require confirmation.

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Breast Cancer

►**Estrogen therapy:** Women in the ET arm of the WHI demonstrated no increase in risk of breast cancer after an average of 7.1 years of use, with 6 fewer cases of invasive breast cancer per 10,000 women per year of ET use, which is not statistically significant. The decrease in risk was observed in all three age groups studied

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Ovarian Cancer

- Published data on the role of HT and risk of ovarian cancer are conflicting. Most epidemiologic studies have shown no association or a modest increase. There is a relatively large volume of observational trial data that points to an association between HT use and increased ovarian cancer risk.

In the WHI (the only RCT to date to study ovarian cancer), postmenopausal women taking daily continuous-combined EPT for an average follow-up of 5.6 years did not exhibit a statistically significant increase in ovarian cancer.

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Ovarian Cancer

- The association between ovarian cancer and HT beyond 5 years, if any, would fall into the rare or very rare category.
- Women at increased risk of ovarian cancer (e.g., those with a family history) should be counseled about this rare association.

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Lung Cancer

- The overall data, including the WHI analysis, suggest that initiating EPT in older women with a history of smoking may promote the growth of existing lung cancers.
- However, evidence from the WHI and some case-control and cohort studies of HT in a younger population (Gage 60) shows some protection against lung cancer.
- Although the findings are confusing with regard to any relationship between lung cancer and HT use, they reinforce the need to encourage prevention or cessation of smoking and possibly to increase surveillance in older smokers who are current or past users of HT.

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Mood

- For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood.
- Several small, short-term trials among middle-aged women suggested that HT improves mood, whereas other trial results showed no change. Progestogens in EPT may worsen mood in some women, possibly in those with a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression.
- Although HT might have a positive effect on mood and behavior, HT is not an antidepressant and should not be considered as such. Evidence is insufficient to support its use for the treatment of depression.

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Cognitive Aging and Dementia

- Natural menopause has little effect on memory performance or other areas of cognitive function.
- For postmenopausal women over age 65, findings from several large, well-designed clinical trials indicate that HT does not improve memory or other cognitive abilities.
- One trial within WHI Memory Study (WHIMS) of women ages 65 to 79 reported an increase in dementia incidence with HT use. The estimate of dementia cases attributed to HT was 12 per 10,000 persons per year of ET use and 23 per 10,000 persons per year of EPT use.

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Cognitive Aging and Dementia

- HT cannot be recommended at any age for the sole or primary indication of preventing cognitive aging or dementia.
- HT seems to increase the incidence of dementia when initiated in women age 65 and older.
- Similarly, HT should not be used to enhance cognitive function in younger postmenopausal women with intact ovaries, although very small clinical trials support the use of ET initiated immediately after menopause induced by bilateral oophorectomy.
  - Available data do not adequately address whether HT used soon after menopause increases or decreases later dementia risk.

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Premature Menopause

- Premature menopause and premature ovarian insufficiency are associated with a lower risk of breast cancer and earlier onset of osteoporosis, CHD, Parkinson's disease; premature bilateral oophorectomy is possibly associated with cognitive decline as well. There are
- inadequate data regarding HT in these populations. Most observational reports suggest an increased risk of CHD with early natural or surgical menopause in the absence of HT and a protective effect of HT when HT is administered.

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Total Mortality

- The WHI trials are consistent with observational studies indicating that HT may reduce total mortality when initiated soon after menopause.
- The WHI suggests that both ET and EPT nonsignificantly reduce total mortality by 30% when initiated in women younger than age 60, and when data from the ET and EPT arms were combined, that reduction with HT use was statistically significant. In contrast, HT was not associated with mortality reduction among women who initiated HT at age 60 or older.

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Progestogen Therapy

- The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use. All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen.
- Postmenopausal women without a uterus should not be prescribed a progestogen with systemic ET.
- A progestogen is generally not indicated when ET at the recommended low doses is administered locally for vaginal atrophy or transdermally at the ultralow dose approved for prevention of bone loss.

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Dosages

- The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman should be the therapeutic goal, with a corresponding low dose of progestogen added to counter the adverse effects of systemic ET on the uterus.
- Lower ET and EPT doses are better tolerated and may have a more favorable benefit-risk ratio than standard doses. However, lower doses have not been tested in long-term trials to support an assumed more favorable risk-benefit ratio.
- Some women may require additional local ET for persistent vaginal symptoms while on systemic therapy.

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Routes of Administration

►There is currently no clear benefit of one route of administration versus another for systemic ET.

►Nonoral routes of administration including transdermal and intrauterine systems may offer both advantages and disadvantages compared with the oral route, but the long-term benefit-risk ratio has not been demonstrated.

►Differences would be related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of ingredients. With transdermal therapy, there is no significant increase in triglycerides, no change in C-reactive protein, no increase in sex hormone-binding globulin, and little effect on blood pressure.

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Regimen

- There is insufficient evidence regarding endometrial safety to recommend as alternatives to standard EPT regimens the off-label use of long-cycle regimens, vaginal administration of progesterone, the contraceptive levonorgestrel-releasing intrauterine system, or low-dose estrogen without progestogen.
- If any of these approaches is used, close surveillance of the endometrium is recommended pending more definitive research, much of which is currently in progress.
- Tissue-selective estrogen complex - a combination of estrogen with an estrogen agonist/antagonist may become an alternate option.

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Bioidentical Hormone Therapy

- The US Food and Drug Administration (FDA) has ruled that compounding pharmacies have made claims about the safety and effectiveness of BHT unsupported by clinical trial data and considered to be false and misleading.
- Pharmacies may not compound drugs containing estriol without an investigational new drug authorization.
- The FDA also states that there is no scientific basis for using saliva testing to adjust hormone levels.

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Treatment Issues

- Before initiating HT, a comprehensive history and physical examination are essential. NAMS recommends assessment of risk factors for stroke, CHD, VTE, osteoporosis, and breast cancer and discussion of these results with each woman before initiating therapy.
- Mammography should be performed according to national guidelines and age, but preferably within the 12 months before initiation of therapy. Other specific examinations, such as bone densitometry, may be considered on a case-by-case basis.

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Treatment Issues

- Women older than age 60 who experienced natural menopause at the median age and have never used HT will have elevated baseline risks of CHD, stroke, VTE, and breast cancer, and **HT should therefore not be initiated** in this population without a compelling indication and only after appropriate counseling and attention to CVD risk factors.

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Treatment Issues

- Premature menopause and premature ovarian insufficiency are conditions associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD, but there are no clear data as to whether ET or EPT will affect morbidity or mortality from these conditions.
- Despite this, it is logical and considered safe to recommend HT for these younger women, at least until the median age of natural menopause.
- Younger women with premature menopause might also require higher doses of HT for menopause symptom relief than the doses currently recommended for women ages 50 to 59.

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Duration of use

- One of the most challenging issues regarding HT is the duration of use. Existing data do not provide a clear indication as to whether longer duration of therapy improves or worsens the benefit-risk ratio.
- Extending HT beyond the years around menopause may be a concern for healthcare providers and their patients. The benefits outweigh the risks in some women, whereas the reverse is true for others. Treatment recommendations are different for women experiencing premature menopause, those who are first users of HT, or women who are in their 60s and have previously used HT for several years.

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Duration of use

- Provided that the lowest effective dose is used, that the woman is well aware of the potential benefits and risks, and that there is clinical supervision, extending HT use for an individual woman's treatment goals is acceptable under some circumstances, including:
- The woman for whom, in her own opinion, the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop HT
- The woman with established reduction in bone mass for whom alternate therapies are not appropriate or cause unacceptable side effects, or the benefit-risk ratio of extended use is unknown.

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Discontinuance

- Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use.
- The decision to continue HT should be individualized on the basis of severity of symptoms and current benefit-risk ratio considerations, provided the woman in consultation with her healthcare provider believes that continuation of therapy is warranted.
- Current data suggest that the rates of vasomotor symptom recurrence are similar when HT is either tapered or abruptly discontinued. No recommendation can be made as to how to discontinue therapy.

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Discontinuance

- Growing data indicate that discontinuance of HT will lead to expected complications such as increased incidence of bone fracture, including hip fracture. When HT is discontinued after several years of use, bone mineral density should be monitored

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Individualization

Each woman is unique, having her own risk profile and preferences.

When HT is desired by patients, individualization of therapy is key to providing health benefits with minimal risks, thereby enhancing QOL.

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