Menopausal hormone therapy in women with medical conditions

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Abstract

Hormone therapy is the most effective treatment for menopausal symptoms. Current evidence supports its use in young healthy menopausal women, under the age of 60 years and within 10 years of menopause, with benefits typically outweighing risks. However, decision making is more complex in the more common clinical scenario of a symptomatic woman with one or more chronic medical conditions that potentially alter the risk-benefit balance of hormone therapy use. In this review, we present the evidence relating to the use of hormone therapy in women with chronic medical conditions such as obesity, hypertension, dyslipidemia, diabetes, venous thromboembolism, and autoimmune diseases. We discuss the differences between oral and transdermal routes of administration of estrogen and the situations when one route might be preferred over another. We also review evidence regarding the effect of different progestogens, when available.

Keywords

Menopause; hormone therapy; chronic disease; diabetes; hypertension; venous thromboembolism; obesity

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Introduction

The recommendations for use of menopausal hormone therapy (HT) have been outlined in several guidelines and are consistent in suggesting that the benefits of HT typically outweigh the risks in younger symptomatic menopausal women who are under the age of 60 years and within a decade of the final menstrual period.[1–4] The more difficult decision making comes into play when faced with a symptomatic woman who also has one or more chronic medical conditions that may impact the risk associated with HT use, and thus have an altered risk benefit balance. Given that 80% of women over the age of 55 years have at least one chronic medical condition,[5] this is more the norm than an aberrancy. As common as this clinical scenario is, decision making regarding HT use in women with chronic medical conditions can be complex and is often less supported by robust evidence. In this review, we outline the state of the science regarding HT use in women with common chronic medical conditions such as obesity, hypertension, dyslipidemia, diabetes and prior history of venous thromboembolism (VTE) as well as less common conditions which prompt questions about HT use in clinical practice including autoimmune diseases, gallbladder disease, liver hemangiomas and meningiomas. We discuss clinical situations in which transdermal estrogen preparations may be preferred over oral and point out areas of uncertainty where additional research is needed to better inform clinical practice.

Obesity

According to the WHO statistics from 2016, nearly half of all the adult women in the world are affected by overweight (body mass index, BMI 25–29.9 kg/m^2) or obesity (BMI 30 kg/m^2).[6] Obesity rates in women are on the rise, with a notable age-related increase in prevalence.[7] Nearly half of the U.S. women in the age range of 40–59 years are affected by obesity, compared to one-third of those in the 20–39 year age range.[8] In addition to an overall increase in adiposity and BMI with aging, women going through the menopause transition experience significant changes in body composition, characterized by a loss of lean body mass and an increase in abdominal fat mass, particularly visceral adipose tissue.[9,10] This change in body fat distribution pattern, from gynoid (lower-body) to android (upper body), is of even greater significance than the overall increase in adiposity and BMI because it poses a higher risk for multiple metabolic complications including type 2 diabetes (T2DM), hypertension, dyslipidemia, metabolic syndrome, and ultimately coronary heart disease (CHD).[10] In the Women's Health Initiative (WHI) observational study and randomized controlled trials, postmenopausal women with abdominal obesity (as defined by waist circumference 88 cm) were shown to have a greater risk of cardiovascular disease-related and all-cause mortality compared to those with no abdominal obesity, even in the presence of a normal BMI. The excess risk posed by abdominal obesity in women with normal BMI was comparable to that in women with obesity and abdominal obesity.[11] Other studies have similarly shown incremental metabolic and cardiovascular risk associated with abdominal obesity independent of that conferred by obesity per se, as defined by BMI criteria.[9,12]

Carefully conducted longitudinal studies have shown that weight gain in women across the menopause transition is not affected by the menopausal state, but rather is predominantly a

consequence of chronological aging.[13] In the Study of Women's Health Across the Nation (SWAN) and Healthy Women Study, women gained an average of about 2 kg across the menopause transition during a 3 year follow-up period, but this change was not dependent on menopausal status, and it was not detectable after adjustment for aging.[14,15] On the other hand, the body composition changes that are characteristic of midlife women seem to be a menopause-related phenomenon, and are largely related to estrogen deficiency.[10,15]

In addition to the metabolic complications and increased risk for CHD, obesity also confers an increased risk for VTE and certain hormone-sensitive cancers including breast and endometrial cancers. These factors need to be considered when making decisions regarding HT use. On the other hand, perimenopausal women with obesity are more likely to report more severe or frequent VMS, thereby posing a greater need for effective therapies, including HT.[16] While HT has not consistently been shown to impact weight, it does result in favorable effects on body composition and fat distribution by preserving lean body mass and reducing visceral adiposity. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, women in the conjugated equine estrogen group (with or without concomitant progestogen) weighed about 1 kg less than the women randomized to placebo after a 3-year follow-up period. Women in the estrogen only (conjugated equine estrogen-CEE) group had a smaller increase in the waist circumference compared to those on placebo over a 3-year follow-up.[17] Similarly, in the WHI trials there were no differences in the change in BMI between the HT and placebo groups over a 6-year follow-up, but women in the CEE plus medroxyprogesterone acetate (MPA) group had preservation of lean body mass and better upper body fat distribution as assessed by the change in ratio of trunk to leg fat mass compared to those in the placebo group over a 3 year follow-up.[18] HT use is neither appropriate nor recommended for management of abdominal obesity, but if used for management of bothersome menopausal symptoms, it is likely to result in favorable body composition changes. Oral CEE may have a more favorable impact on body composition compared to transdermal estradiol,[19] but this has not been adequately investigated.

Cardiovascular disease (CVD) outcomes with different HT formulations and routes of administration have not been investigated in clinical trials, but there is substantial evidence from large observational studies to suggest the potential for differential effects on the basis of type of estrogen, route of administration and the type of progestogen used. In general, there appears to be a lower risk of CVD and related mortality with transdermal estradiol compared to oral estrogens.[9,20,21] This is likely due to the more favorable effects of transdermal estradiol on clotting factors, inflammatory markers, and triglycerides related to the avoidance of first-pass hepatic metabolism. In addition, 2 recent large nested case-control studies have shown an increased risk of VTE with oral HT preparations (risk greater with CEE than with oral estradiol), but not with transdermal estradiol.[22,23] Among oral regimens, CEE plus MPA was associated with the highest risk. Given the elevated risk of VTE and CVD associated with obesity, particularly abdominal obesity, transdermal estradiol preparations are preferred over oral estrogens in women with obesity. In addition, a progestogen with a lower risk of VTE and minimal effects on metabolic parameters is preferable, such as micronized progesterone, dydrogesterone, or transdermal norethisterone.[24–27]

Hypertension

Hypertension is the most common modifiable risk factor for CVD with a global prevalence in women of 30%.[28,29] It is more common in men than women under the age of 50 years, but this trend reverses gradually in midlife when it becomes more prevalent in women.[30] In addition, unfavorable vascular changes resulting from hypertension may not only develop earlier in women, but also progress more rapidly, setting the stage for heart disease later in life.[31] Postmenopausal women are also less likely than men to experience a nocturnal fall in blood pressure, predisposing them to greater end organ damage.[32] Risk factors for hypertension in postmenopausal women include genetic predisposition, aging, obesity, physical inactivity, increased sodium intake, diabetes and history of preeclampsia.[33]

Women have lower blood pressure prior to the menopause transition, which suggests that sex hormones play a prominent role in the genesis of hypertension.[34] However, longitudinal and cross-sectional studies have examined the association between menopausal status and blood pressure changes and found mixed results[35–38] As such, whether the presence of estrogen protects against an increase in blood pressure in premenopausal women, and conversely, whether the lack of estrogen contributes to hypertension women after menopause remains controversial and unknown. The increased predisposition to hypertension in midlife women may be a result of chronological aging.

HT is sometimes avoided in women with hypertension due to the belief that it has an adverse effect on blood pressure. However, the current overall evidence, including randomized controlled clinical trial data, does not support a deleterious effect of HT on blood pressure in young postmenopausal normotensive or hypertensive women.[39]

Few studies have examined the effect of HT on blood pressure in women with pre-existing hypertension, with most, but not all, reporting reductions or no changes in blood pressure in women using HT.[40,41] Transdermal estrogen has been shown to have a beneficial effect on blood pressure in normotensive women, and a neutral effect in hypertensive women.[42] With regard to progesterone, most data suggest that blood pressure increases when synthetic progestins are used, either for contraception or for hormone therapy, possibly due to androgenic activity.[43] On the other hand, micronized progesterone, dydrogesterone, and drospirenone, appear to have a beneficial or neutral effect on blood pressure.[44–46]

When making decisions regarding HT use in a woman with pre-existing hypertension, her overall risk of CVD should be considered. HT use is appropriate for management of bothersome menopausal symptoms in women who are under the age of 60, within 10 years of the final menstrual period, and who are not at high risk for CVD. Oral estrogen is associated with increased production of renin substrate which may lead to an increase in the vasoconstrictive action of angiotensin II and/or increased sodium retention in hypertensive women with dysregulation of the renin-angiotensin-aldosterone system.[47] Thus, in women with underlying hypertension, a transdermal route of estrogen administration is preferable due to avoidance of first-pass hepatic metabolism, particularly in the presence of comorbidities such as obesity or diabetes; a progestogen that is neutral

or beneficial with respect to blood pressure is preferable (e.g., micronized progesterone, dydrogesterone, or drospirenone).[39]

Dyslipidemia

The menopause transition is accompanied by changes in several lipid parameters. Total cholesterol, low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B levels increase abruptly during the menopause transition and are independent of aging. .[15,48] The menopause transition is also characterized by important functional changes in high density lipoprotein cholesterol (HDL-C), as well as altered HDL particle distribution.[49] These changes lead to a reversal in the direction of association between HDL-C and CVD risk. A higher HDL-C level may portend a greater CVD risk after menopause, in contrast to a reduced risk of CVD with higher HDL-C prior to menopause.[50] All in all, these changes in the lipid parameters, along with adverse changes in blood pressure and glycemic control during the menopause transition, increase the prevalence of the metabolic syndrome and contribute to the heightened CVD risk noted in women after menopause.[9]

When considering HT use in a woman with dyslipidemia, her overall CVD risk should be considered in the context of co-morbidities that impact the risk. HT should be avoided in women with pre-existing CVD and in those at high risk for CVD. In women who are under age 60 and within 10 years of the final menstrual period, HT has favorable or neutral effects on the lipid parameters and overall CVD risk. HT use decreases LDL-C and lipoprotein(a) levels and increases HDL-C and triglyceride levels.[51,52] It is important to take into account the dose of estrogen used given that the lipoprotein effects are dose-dependent and are attenuated with lower doses of estrogen.[53] The route of estrogen administration also impacts lipid parameters. The increases in triglyceride and HDL-C levels is mainly seen with oral estrogen monotherapy, whereas the combination of estrogen plus a progestogen appears to result in less of an increase in triglyceride and HDL cholesterol levels.[54,55] Oral estrogen lowers LDL-C and increases HDL-C and triglycerides, whereas transdermal estrogen has been shown to be neutral in short-term studies. However, longer-term studies show that transdermal estrogen may result in lower total and LDL-C levels without significantly affecting HDL-C and triglycerides levels.[56] Progestogens can modulate the effect of oral estrogen on HDL-C and triglycerides, but micronized progesterone, dydrogesterone and intrauterine levonorgestrel are essentially neutral in this regard. Norethisterone acetate may lower HDL-C, along with a favorable effect on triglyceride and LDL-C concentrations, and the effect of medroxyprogesterone acetate is unclear.[57]

In the absence of contraindications, clinicians should not hesitate to use HT in symptomatic menopausal women with dyslipidemia. The transdermal route of administration of estrogen is preferable in women with pre-existing hypertriglyceridemia, moderate CVD risk and in those with comorbidities including obesity, hypertension, and diabetes.

Diabetes

There is substantial evidence to suggest that HT improves glycemic control and insulin resistance in postmenopausal women with and without type 2 diabetes (T2DM).[58] In a

meta-analysis of 107 trials evaluating the effect of HT in women, in those without T2DM, there was a 13% reduction in the homeostatic model assessment-insulin resistance (HOMA-IR) and a 30% decrease in the risk of T2DM. In women with T2DM, there was an even greater reduction in fasting glucose and HOMA-IR by 36%, along with improvements in other CVD risk parameters, including lipids, blood pressure and coagulation markers. The beneficial effect of HT on glycemic control seems to be the result of a variety of physiological mechanisms, including alterations in body fat distribution, with amelioration of visceral adiposity, lowering of insulin resistance and augmentation of insulin secretion. Oral estrogens seem to have a greater benefit with regard to improving insulin sensitivity compared to bioequivalent transdermal estradiol doses.[59] Nevertheless, the use of HT in women with T2DM is nearly 50% lower than in the general population,[60] mostly because of the conventional thinking that T2DM is a CVD equivalent.[61] Clinicians have therefore been reluctant to utilize HT for management of bothersome menopausal symptoms in women with T2DM.

Given its beneficial effects on glycemic control and other components of the metabolic syndrome, HT use in postmenopausal women with T2DM should not be avoided, but it should be individualized. Women with T2DM, may in fact be excellent candidates for HT in the appropriate clinical circumstances and after assessment of their CVD risk.[4,60,62,63] Given its beneficial effects on glycemic control, HT use should be considered in menopausal women with bothersome menopausal symptoms and T2DM who are under age 60 and within 10 years of the final menstrual period who are not at high risk for CVD.[64] Oral estrogens provide a greater benefit in terms of improving insulin sensitivity and have a greater beneficial effect on high density and low-density lipoprotein cholesterol compared to transdermal estradiol preparations. However, the oral route should only be considered in normal weight women at low risk of CVD. In women with obesity or those with moderate CVD risk, a transdermal route of administration of estrogen is preferred due to the more favorable effects on inflammatory markers and triglycerides as well as a lower risk of VTE. The choice of progestogen in women with a uterus may also have an impact, and use of micronized progesterone, dydrogesterone, or transdermal norethisterone appears to have minimal effects on glycemic control.[24–27]

Venous thromboembolism

The overall annual incidence of VTE is 117 per 100,000 persons, and the incidence increases with age, nearly doubling for women from age 25 to 50 years of age (51 to 123 per 100,000 per year).[65] Risk factors specific to women include pregnancy and use of combined oral hormonal contraceptives. Other risk factors associated with VTE include obesity, major surgery, trauma, immobility, malignancy, previous thromboembolism, and smoking.[66] The risk of VTE with HT overall compared to placebo is elevated, but that risk is somewhat lower if treatment is started within 10 years of menopause.[67] However, like most outcomes related to HT use, the type, dose, formulation and route of administration impact associations with VTE. Lower doses of oral estrogen may confer less risk than high doses,[68] while transdermal formulations are associated with lower risk than oral formulations of estrogen in observational studies.[23,69–72] Similarly, the type of progestogen used in women with an intact uterus likely influences VTE risk, with micronized progesterone

and dydrogesterone associated with lower VTE risk than other progestogens.[69,70] In a case control study, oral estrogen combined with progestogen was associated with a higher risk than oral estrogen alone, while transdermal estrogen combined with progestogen or local vaginal estrogen was not associated with increased VTE risk.[22] Likewise, a large case-control study from the United Kingdom found that transdermal estrogen preparations were not associated with VTE risk.[23]

In women with a history of VTE, shared decision making that takes into account individual risk factors, such as whether the VTE was provoked or associated with an underlying thrombophilia, the severity of menopausal symptoms and impact on quality of life, as well as a review of non-hormonal options for treatment of menopausal symptoms should be considered. If estrogen therapy is used, a transdermal route is recommended to avoid the first-pass hepatic metabolism associated with the oral route and to minimize VTE risk.[73] In a study of women with a history of VTE, oral but not transdermal estrogen was associated with higher risk of VTE recurrence.[71] It is important to distinguish that the VTE association has only been noted with systemic estrogen. Although clinical trial safety data are limited to 52 weeks, observational data have not shown any long-term adverse health outcomes, including VTE risk, associated with low dose vaginal estrogen therapies.[74–76] Clinicians in the U.S. will need to reassure patients in this regard because the U.S. Food and Drug Administration (FDA) class labeling included in the package insert for estrogen therapies does not distinguish between systemic and low dose vaginal estrogen when reporting risks.[76]

Autoimmune disease

Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), Sjogren's syndrome and multiple sclerosis (MS) are more common in women, with a second peak in incidence that occurs at midlife.[77,78] It is hypothesized that a link may exist between menopause and autoimmune disease risk and course. Changing estrogen levels may be a modifying factor,[79] which is supported by findings such as the association described between earlier age of menopause and an increased risk of SLE and RA.[80] A relationship between age at menopause and progressive MS has also been identified. Specifically, age at onset of progressive MS has been associated with menopausal age, and women with premature menopause were found to have a shorter duration from onset of relapses to onset of progressive MS.[81] Symptoms of autoimmune diseases can be further exacerbated by menopausal changes. For example, mucosal dryness in women with Sjogren's syndrome may worsen with loss of estrogen at menopause and changes associated with genitourinary syndrome of menopause.[82,83]

However, it is unclear whether HT may mitigate or reduce autoimmune disease incidence, risk or severity. Some studies have found links between lower risk of autoimmune disease and fewer symptoms in those with diseases such as rheumatoid arthritis with certain forms of HT,[84,85] while others have not.[86] There have been no reports of increased risk of severe SLE exacerbations with HT initiation.[87] Furthermore, oral estradiol has been explored as a treatment for MS due to immunomodulatory and neuroprotective pathways.[88] Beyond relief from menopause symptoms, treatment with HT has been shown to improve physical function in women with MS[89]

For women with an established diagnosis of autoimmune disease and bothersome symptoms of menopause, or those who have or are at increased risk for osteoporosis, HT can be considered if there are no contraindications to use. Women with antiphospholipid syndrome, a disorder characterized by the presence of antibodies to phospholipids, commonly seen with SLE and associated with thrombosis, thrombocytopenia, and recurrent fetal loss, HT is best avoided because data are limited regarding safety of HT use in this setting.

Although data specific to women with Sjogren's syndrome are sparse, and while treatment of the underlying autoimmune disorder is key,[90] the addition of low dose vaginal hormonal therapy (estrogen or prasterone/dehydroepiandrosterone-DHEA) could be considered to treat menopause-related genitourinary symptoms in this population.

Other medical conditions

There are many other medical conditions that may be impacted by HT use. A few that have data that may guide decisions regarding HT use include gallbladder disease, liver hemangiomas and meningiomas. Oral estrogen is associated with an increased risk of cholecystitis and cholelithiasis, likely as a result of the first-pass hepatic metabolism.[91] Observational studies demonstrate that transdermal estrogen may be associated with a lower risk of gallbladder disease.[92] Therefore, in women at risk for or with established gallbladder disease, a transdermal route of administration of estrogen should be considered.

Similarly, relationships have been identified between estrogen use and increased risk for or growth of meningiomas and hepatic hemangiomas.[93,94] The impact of estrogen on hepatic hemangiomas is not fully understood, but these liver lesions have been shown to increase in size during pregnancy.[95] A small study following 94 women found higher rates of hemangioma enlargement over time in those on hormone treatment than those not on treatment, although only 4 of the participants were using menopausal HT, while the remainder were on oral contraceptives, either combined estrogen plus progestin or progestin only.[94] There are no studies that have evaluated the impact of the lower doses of estrogen contained in menopausal HT regimens on the growth of either hemangiomas or meningiomas. Women with either of these diagnoses should engage in shared decision-making with their health care providers as well as their disease-specific subspecialists regarding initiation or continuation of HT based on their menopausal symptoms, personal risk factors, preferences, and goals.

Conjugated equine estrogen and bazedoxifene-based hormone therapy regimens

The tissue-selective estrogen-complex (TSEC) that combines oral conjugated equine estrogen (CE) with bazedoxifene (BZA, a third-generation selective estrogen receptor modulator) offers the advantages of estrogen therapy while obviating the need for concurrent progestogen therapy. It should generally be avoided in all situations where oral estrogen is not recommended. Additionally, there is an increased risk of VTE with BZA, and the combination should be avoided in women at increased risk for or with a prior history of VTE.[96] The Selective Estrogens, Menopause, and Response to Therapy (SMART) Trials

evaluated the effect of the TSEC on lipid profile with findings similar to those seen with oral estrogen, namely an increase in HDL-C and triglyceride levels, and a reduction in total cholesterol and LDL-C levels.[57] The effects of CE/BZA on obesity and glucose homeostasis are unclear. While animal studies have shown improvements in obesity and the risk for T2DM, data in postmenopausal women are limited to small, short term studies, and larger studies are needed to confirm these findings.[97]

Tibolone

Tibolone is a synthetic steroid with metabolites that have estrogenic, androgenic and progestogenic properties. Approved for use in Europe, but not in the US, it is associated with weight gain, impaired glucose tolerance, decreased HDL-C, but also a decrease in LDL-C, lipoprotein (a) and triglycerides.[57,98] Tibolone increases the stroke risk in women over the age of 60 years, but based on low or very low quality evidence, there does not appear to be an increased risk of other cardiovascular events including VTE. However, the cardiovascular safety of tibolone requires further study.

Summary

Decision making surrounding the use of HT in symptomatic menopausal women can be complex, especially in women with chronic medical conditions. Some of the more common conditions including obesity, hypertension, dyslipidemia, and diabetes are not contraindications to the use of HT, although the decision-making is nuanced. The transdermal route of administration of estrogen may be preferred over oral in women with obesity, diabetes, gallbladder disease, and especially in women with a greater number of comorbidities. Women with a history of VTE are at increased risk for recurrent VTE, but transdermal estrogen does not appear to further increase that risk in observational studies. Decision making regarding HT use in women with a prior VTE should be individualized and include assessment of risk for subsequent VTE and severity of menopausal symptoms. Data on HT use in women with autoimmune diseases are limited, although HT can be considered in women with MS or RA. In women with SLE, individualized decision making is needed, accounting for factors such as disease activity and presence of antiphospholipid antibodies, which if present, would prompt the use of non-hormonal treatments. There are very limited data to inform clinical decisions regarding the use of HT in women with liver hemangiomas or meningiomas, and shared decision-making in collaboration with the treating subspecialist is recommended. Low dose vaginal hormonal therapies are not contraindicated and can be used in any of these patient populations if needed for management of genitourinary symptoms.

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Practice points

- The majority of symptomatic menopausal women will have one or more chronic medical conditions which need to be taken into account when considering HT use.

- HT use does not appear to greatly impact blood pressure in either hypertensive or normotensive women. It has either no effect or favorable effects on lipids and a beneficial effect on glycemic control.

- A transdermal route of administration appears to confer lower risk than oral and is preferred for women with certain medical conditions including obesity, diabetes, and gallbladder disease.

- An individualized approach that takes into account individual risk factors, the severity of menopausal symptoms and impact on quality of life, personal preferences, and includes shared decision-making in collaboration with a woman's medical providers is needed in the setting of medical conditions such as VTE, autoimmune disease, liver hemangioma and meningioma.

- Low dose vaginal hormonal therapies can and should be used to treat genitourinary symptoms in women with chronic medical conditions, even if systemic estrogen therapy is not indicated or recommended

Research agenda

- Comparative trials of longer duration investigating differences in outcomes with various HT regimens that include oral versus transdermal routes of administration, different formulations of estrogens and progestogens, and different dosages are needed in order to better inform clinical HT decision making in women with chronic medical conditions.

- Studies investigating the impact of HT on CVD risk factors singly and in combination are warranted to better understand the value of the use of CVD risk scores in HT clinical decision making.

- The safety of the use of transdermal estrogen in symptomatic menopausal women with a history of or at high risk for VTE needs to be established in randomized controlled clinical trials.

Table 1.

Recommendations for menopausal hormone therapy use in women with chronic diseases

Condition	Comments	Recommendations for HT
Obesity	While estrogen is not recommended for management of abdominal obesity, it is likely to result in favorable body composition changes. Progestogens with lower VTE risk and minimal effects on metabolic parameters are preferred.	Estrogen: Transdermal route of administration preferred Progestogen: Consider micronized progesterone, dydrogesterone or transdermal norethisterone
Hypertension	Current evidence does not support a deleterious effect of HT on BP in young postmenopausal normotensive or hypertensive women. Progestogens with beneficial or neutral BP effects preferred.	Estrogen: Transdermal route of administration preferred Progestogen: micronized progesterone, dydrogesterone, drospirenone
Dyslipidemia	Oral estrogen lowers LDL-C and increases HDL-C and TG; transdermal estrogen may lower total and LDL-C without significantly impacting HDL-C and TG.	Estrogen: Transdermal route of administration preferred in women with pre-existing hypertriglyceridemia, moderate CVD risk and in those with comorbidities including obesity, hypertension, and diabetes.
Diabetes	HT is associated with reduction in fasting glucose, insulin resistance and risk of T2DM. While oral estrogens may provide greater benefit in terms of improving insulin sensitivity versus transdermal routes of administration, transdermal is preferred given the more favorable effects on inflammatory markers, TG, and lower risk of VTE. Progestogens with minimal effects on glycemic control preferred.	Assess overall CVD risk and consider HT use in women with T2DM with bothersome symptoms who are not at high risk for CVD. Estrogen: Transdermal route of administration preferred, particularly in obese women and in those with moderate CVD risk. Progestogen: micronized progesterone, dydrogesterone, or transdermal norethisterone
Venous thromboembolism	Oral HT is associated with increased risk for VTE. Lower doses of oral estrogen may confer less risk than higher doses. Observational data show less risk with transdermal compared to oral estrogens. Safety data for low dose vaginal estrogens limited to 52 weeks; observational data have not shown increased risk for VTE. The type of progestogen likely also influences VTE risk. Other factors to consider: whether VTE was provoked, presence of inherited thrombophilia, obesity, malignancy, smoking, or immobility.	Non-hormonal treatment options preferred. Estrogen: If considered, use shared decision making that takes into account history, risk factors, menopause symptom severity, quality of life. Transdermal route of administration preferred if estrogen is used. Progestogen: micronized progesterone, dydrogesterone
Autoimmune disease	Some evidence suggests a link between autoimmune diseases and estrogen. It is unclear whether HT mitigates or reduces autoimmune disease incidence, risk or severity.	Individualize treatment and consider HT in symptomatic women with no contraindications to use. Avoid HT in women with antiphospholipid antibodies. Consider treating menopausal women with SS and vaginal dryness with low dose vaginal hormonal therapy.

HT=hormone therapy; VTE=venous thromboembolism; BP=blood pressure; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides; CVD=cardiovascular disease; T2DM=type 2 diabetes mellitus; SS=Sjogren's syndrome