



MENOPAUSE

Recent trial results on the cardiovascular safety of hormone therapy in early menopausal women are reassuring, while survey data reveal millions of women are using unvetted and unregulated custom compounded hormone therapy for menopausal symptoms



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IN THIS ARTICLE

Cardiovascular safety of HT

page 39

JoAnn E. Manson discusses new data on HT benefits vs risks

page 40

Use of compounded hormones growing

page 42

In this Update, I discuss important new study results regarding the cardiovascular safety of hormone therapy (HT) in early menopausal women. In addition, I review

survey data that reveal a huge number of US women are using compounded HT preparations, which have unproven efficacy and safety.

Earlier initiation is better: ELITE trial provides strong support for the estrogen timing hypothesis

Hodis HN, Mack WJ, Henderson VW, et al; for the ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med. 2016;374(13):1221-1231.

Keaney JF, Solomon G. Postmenopausal hormone therapy and atherosclerosis—time is of the essence [editorial]. N Engl J Med. 2016;374(13):1279-1280.

A substantial amount of published data, including from the Women’s Health Initiative (WHI), supports the timing hypothesis,

which proposes that HT slows the progression of atherosclerosis among recently menopausal women but has a neutral or adverse effect among women who are a decade or more past menopause onset.¹ To directly test this hypothesis, Hodis and colleagues randomly assigned healthy postmenopausal women (<6 years or ≥10 years past menopause) without cardiovascular disease (CVD) to oral estradiol 1 mg or placebo. Women with a uterus also were randomly assigned to receive either vaginal progesterone gel or placebo gel. The primary outcome was the rate of

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In an editorial accompanying the published results of the ELITE trial, Keaney and Solomon concluded that, although estrogen had a favorable effect on atherosclerosis in early menopause, it would be premature to recommend HT for *prevention* of cardiovascular events. I agree with them, but I also would like to note that the use of HT for the treatment of menopausal symptoms has plummeted since the initial WHI findings in 2002, with infrequent HT use even among symptomatic women in early menopause.³ (And I refer you to the special inset featuring JoAnn E. Manson, MD, DrPH, on page 40.) The takeaway message is that this important new clinical trial provides additional reassurance regarding the cardiovascular safety of HT when initiated by recently menopausal women to treat bothersome vasomotor symptoms. This message represents welcome news for women with bothersome menopausal symptoms considering use of HT.

A word about the vaginal progesterone gel used in the ELITE trial in relation to clinical practice: Given the need for vaginal placement of progesterone gel, potential messiness, and high cost, few clinicians may prescribe this formulation, and few women probably would choose to use it. As an alternative, micronized progesterone 100-mg capsules are less expensive and well accepted by most patients. These capsules are formulated with peanut oil. Because they may cause women to feel drowsy, the capsules should be taken at bedtime. In women with an intact uterus who are taking oral estradiol 1-mg tablets, one appropriate progestogen regimen for endometrial suppression is a 100-mg micronized progesterone capsule each night, continuously.

change in carotid artery intima-media thickness (CIMT), which was assessed at baseline and each 6 months of the study. (An earlier report had noted that baseline CIMT correlated well with CVD risk factors.²) Coronary artery atherosclerosis, a secondary outcome, was assessed at study completion using computed tomography (CT).

Details of the study

Among the 643 participants in the Early versus Late Intervention Trial with Estradiol (ELITE), the median years since menopause and the median age at enrollment were 3.5 and 55.4, respectively, in the early postmenopause group and 14.3 and 63.6,

respectively, in the late postmenopause group.

Among the younger women, after a median of 5 years of study medications, the estradiol group had less progression of CIMT than the placebo group ($P = .008$). By contrast, in the older group, rates of CIMT progression were similar in the HT and placebo groups ($P = .29$). The relationship between estrogen and CIMT progression differed significantly between the younger and older groups ($P = .007$). Use of progesterone did not change these trends. Coronary artery CT parameters did not differ significantly between the placebo and HT groups in the age group or in the time-since-menopause group.



ELITE provides reassurance of HT's cardiovascular safety when it is started in early menopause for bothersome menopausal symptoms

FDA-approved HT is preferable to compounded HT formulations

Pinkerton JV, Santoro N. Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. Menopause. 2015;22(9):926-936.

Pinkerton JV, Constantine GD. Compounded non-FDA-approved menopausal hormone therapy prescriptions have increased: results of a pharmacy survey. Menopause. 2016;23(4):359-367.

CONTINUED ON PAGE 40



WHI, ELITE, and the timing hypothesis: New evidence on HT in early menopause is reassuring

Q&A with JoAnn E. Manson, MD, DrPH



In this interview, Dr. JoAnn Manson discusses the reassuring results of recent hormone therapy (HT) trials in early versus later postmenopausal women, examines these outcomes in the context of the Women's Health Initiative (WHI) trial and ELITE trial, and debunks an enduring common misconception about the WHI.

Q You have said for several years that there has been a misconception about the WHI trial. What is that misconception, and what has been its impact on clinicians, women, and the use of HT?

A The WHI HT trial has been largely misunderstood. It was designed to address the balance of benefits and risks of long-term HT for the prevention of chronic disease in postmenopausal women across a broad range of ages (average age 63).^{1,2} It was not intended to evaluate the clinical role of HT for managing menopausal symptoms in young and early menopausal women.³ Overall, the WHI study findings have been inappropriately extrapolated to women in their 40s and early 50s who report distressing hot flashes, night sweats, and other menopausal symptoms, and they are often used as a reason to deny therapy when in fact many of these women would be appropriate candidates for HT.

There is increasing evidence that younger women in early menopause who are taking HT have a lower risk of adverse outcomes and lower absolute risks of disease than older women.^{2,3} In younger, early menopausal women with bothersome hot flashes, night sweats, or other menopausal symptoms and who have no contraindications to HT, the benefits of treatment are likely to outweigh the risks, and these patients derive quality-of-life benefits from treatment.

Q How do the results of the recent ELITE (Early versus Late Intervention Trial with Estradiol) trial build on cardiovascular safety, in particular, of HT and when HT is optimally initiated?

A The ELITE trial directly tested the “timing hypothesis” and the role of HT in slowing the progression of atherosclerosis in early

menopause (defined as within 6 years of menopause onset) compared with the effect in women in later menopause (defined as at least 10 years past menopause).⁴ The investigators used carotid artery intima-media thickness (CIMT) as a surrogate end point. In this trial, 643 women were randomly assigned according to whether they were in early or later menopause to receive either placebo or estradiol 1 mg daily; women with a uterus also received progesterone 45 mg as a 4% vaginal gel or matching placebo gel. The median duration of intervention was 5 years.

The ELITE study results provide support for the “critical window hypothesis” in that the estradiol-treated younger women closer to onset of menopause had slowing of atherosclerosis compared with the placebo group, while the older women more distant from menopause did not have slowing of atherosclerosis with estradiol.

The ELITE trial was not large enough, however, to assess clinical end points—rates of heart attack, stroke, or other cardiovascular events. So it remains unclear whether the findings for the surrogate end point of CIMT would translate into a reduced risk of clinical events in the younger women. Nevertheless, ELITE does provide more reassurance about the use of HT in early menopause and supports the possibility that the overall results of the WHI among women enrolled at an average age of 63 years may not apply directly to younger women in early menopause.

Q What impact on clinical practice do you anticipate as a result of the ELITE trial results?

A The findings provide further support for the timing hypothesis and offer additional reassurance regarding the safety of HT in early menopause for management of menopausal symptoms. However, the trial does not provide conclusive evidence to support recommendations to use HT for the express purpose of preventing cardiovascular disease (CVD), even if HT is started in early menopause. Using a surrogate end point for atherosclerosis (CIMT) is not the same as looking at clinical events. There are many biologic pathways for heart attacks, strokes, and other cardiovascular events. In addition to atherosclerosis, for example, there is thrombosis, clotting, thrombo-occlusion within a



It is unclear whether the findings for CIMT would translate into a reduced risk of clinical events in younger women

blood vessel, and plaque rupture. Again, we do not know whether the CIMT-based results would translate directly into a reduction in clinical heart attacks and stroke.

The main takeaway point from the ELITE trial results is further reassurance for use of HT for management of menopausal symptoms in early menopause, but not for long-term chronic disease prevention at any age.

Q Another recent study, published in the *Journal of Clinical Endocrinology and Metabolism*, addresses HT and the timing hypothesis but in this instance relating to glucose tolerance.⁵ What did these study authors find?

A This study by Pereira and colleagues is very interesting and suggests that the window of opportunity for initiating estrogen therapy may apply not only to coronary events but also to glucose tolerance, insulin sensitivity, and diabetes risk.⁵

The authors investigated the effects of short-term high-dose transdermal estradiol on the insulin-mediated glucose disposal rate (GDR), which is a measure of insulin-stimulated glucose uptake. Participants in this randomized, crossover, placebo-controlled study included 22 women who were in early menopause (6 years or less since final menses) and 24 women who were in later menopause (10 years or longer since final menses). All of the women were naïve to hormone therapy, and baseline GDR did not differ between groups. After 1 week of treatment with transdermal estradiol (a high dose of 150 µg) or placebo, the participants' GDR was measured via a hyperinsulinemic-euglycemic clamp.

The investigators found that in the younger women, estradiol had a favorable effect on insulin sensitivity and GDR, whereas in the older women, there was no evidence of a favorable effect and, in fact, there was a signal for risk and more adverse findings in this group.

Several studies in the WHI also looked at glucose tolerance and at the risk of being diagnosed with diabetes. While the results of

the WHI estrogen-alone trial revealed a reduction in diabetes and favorable effects across age groups, in the WHI estrogen-plus-progestin trial we did see a signal that the results for diabetes may have been more favorable in the younger than in the older women, somewhat consistent with the findings of Pereira and colleagues.^{2,5}

Overall this issue requires more research, but the Pereira study provides further support for the possibility that estrogen's metabolic effects may vary by age and time since menopause, and there is evidence that the estrogen receptors may be more functional and more sensitive in early rather than later menopause. These findings are very interesting and consistent with the overall hypothesis about the importance of age and time since menopause in relation to estrogen action. Again, they offer further support for use of HT for managing bothersome menopausal symptoms in early menopause, but they should not be interpreted as endorsing the use of HT to prevent either diabetes or CVD, due to the potential for other risks.

Q Where would you like to see future research conducted regarding the timing hypothesis?

A I would like to see more research on the role of oral versus transdermal estrogen in relation to insulin sensitivity, diabetes risk, and CVD risk, and more research on the role of estrogen dose, different types of progestogens, and the benefits and risks of novel formulations, including selective estrogen receptor modulators and tissue selective estrogen complexes.

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The author reports no financial relationships relevant to this article.

FAST TRACK

Estradiol had a favorable effect on insulin sensitivity and GDR in younger women, but there was no evidence of a favorable effect in older women

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CONTINUED ON PAGE 42



WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clinicians should be alert to the growing prevalence of use of compounded HT and should educate themselves and their patients about the differences between non-FDA-approved HT and FDA-approved HT. Further, women interested in using “natural,” “bioidentical,” or “custom compounded” HT should be aware that FDA-approved estradiol (oral, transdermal, and vaginal) and progesterone (oral and vaginal) formulations are available.

Because the FDA does not test custom compounded hormones for efficacy or safety and the standardization and purity of these products are uncertain, the American College of Obstetricians and Gynecologists has stated that FDA-approved HT is preferred for management of menopausal symptoms.⁸ Similarly, the North American Menopause Society does not recommend the use of compounded HT for treatment of menopausal symptoms unless a patient is allergic to ingredients contained in FDA-approved HT formulations.⁹

Gass ML, Stuenkel CA, Utian WH, LaCroix A, Liu JH, Shifren JL.; North American Menopause Society (NAMS) Advisory Panel consisting of representatives of NAMS Board of Trustees and other experts in women's health. Use of compounded hormone therapy in the United States: report of The North American Menopause Society Survey. Menopause. 2015;22(12):1276-1284.

Millions use compounded HT for menopausal symptoms

A recent study by Pinkerton and Santoro that analyzed data from 2 national surveys suggested that as many as 2.5 million US women currently use non-FDA-approved custom-compounded HT. The authors also found that more than three-quarters of women using compounded HT are unaware that these medications, which include oral, topical, injectable, and implantable (pellet) formulations, are not FDA approved. In a study by Pinkerton and Constantine, total annual sales of compounded HT were estimated at approximately \$1.5 billion. The dramatic growth in the use of compounded HT appears to have stemmed from celebrity endorsements, aggressive and unregulated marketing, and beliefs about the safety of “natural” hormones.⁵

Spurious laboratory testing. Women seeking care from physicians and clinics that provide compounded HT are often advised to undergo saliva and serum testing to determine hormone levels. Many women are unaware, however, that saliva testing does not correlate with serum levels of hormones. Further, in contrast with conditions such as thyroid disease and diabetes, routine laboratory testing is neither indicated nor helpful in the management of menopausal symptoms.⁶ Of note, insurance companies often do not reimburse for the cost of saliva hormone testing or for non-FDA-approved hormones.⁵

Inadequate endometrial protection.

Consider how you would manage this clinical scenario: During a well-woman visit, your 54-year-old patient mentions that, after seeing an advertisement on television, she visited a clinic that sells compounded hormones. There, she underwent some testing and received an estrogen-testosterone implant and a progesterone cream that she applies to her skin each night to treat her menopausal symptoms. Now what?

The use of HT for menopausal symptoms declined considerably following the 2002 publication of the initial findings from the WHI, and its use remains low.⁴ Symptomatic menopausal women often find that their physicians are reluctant to consider prescribing treatment for menopausal symptoms because of safety concerns regarding HT use. Further, confusion about HT safety has opened the door to the increasing use of compounded bioidentical HT formulations, which are not approved by the US Food and Drug Administration (FDA).³ Since the publication of my 2015 Update on menopause (*OBG Manag.* 2015;27(6):37-40,42-43), several reports have addressed the use of “custom compounded” bioidentical menopausal HT in US women.



ACOG states that FDA-approved HT is preferred over compounded hormones for menopausal symptom management

Topical progesterone cream, which is not absorbed in sufficient quantities to generate therapeutic effects, is often prescribed by practitioners who sell bioidentical compounded hormones to their patients.⁷ According to a report by the North American Menopause Society, several cases of endo-

metrial cancer have been reported among women using compounded HT. These cases may reflect use of systemic estrogen without adequate progesterone protection, as could occur when topical progesterone cream is prescribed to women with an intact uterus using systemic estrogen therapy. 🚫

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