MENOPAUSE

Our understanding deepens of the benefits and risks of hormone therapy in different formulations and populations

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Ten years have passed since the Women's Health Initiative (WHI) investigators published initial findings from the estrogen-progestin arm, shaking up the field of menopause management and leading to a sharp decline in the number of prescriptions being written for hormone therapy (HT). Over the course of the ensuing decade, numerous studies have filled in gaps in our understanding of the menopausal transition and the decades that follow—studies that have been detailed in OBG MANAGEMENT in this Update in Menopause and other articles. In this installment of the Update, I review:

- two studies that address the lower risk of venous thromboembolism (VTE) when transdermal HT is prescribed rather than oral estrogen
- the characteristics of a new oral medication to treat vulvar and vaginal atrophy
- a study highlighting the distinct effects on the breast of unopposed estrogen and combination estrogen-progestin HT
- two reports on ovarian conservation at the time of hysterectomy for benign indications
- a study from Sweden on the health impact of early menopause
- a closer look at the mood effects—or lack of them—of progestin therapy.

In addition, JoAnn E. Manson, MD, DrPH, NCMP, weighs in on what we have learned from the WHI and the Kronos Early Estrogen Prevention Study (KEEPS).

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Accumulating evidence points to a lower risk of VTE with transdermal versus oral HT

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What the KEEPS trial reveals about HT in younger menopausal women

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

The Kronos Early Estrogen Prevention Study (KEEPS) is a valuable adjunct to the Women's Health Initiative (WHI), as one of the principal investigators—of both trials—explains in this Q&A.

In the WHI, Dr. JoAnn E. Manson and colleagues set out to address a specific question: What is the balance of benefits and risks when hormone therapy (HT) is used to prevent chronic disease in postmenopausal women (ages 50–79 years; mean age 63)? Investigators concluded that the risks generally outweigh the benefits, especially for older women.

Contrast the KEEPS trial, which had a goal of exploring the effects of oral and transdermal HT in a younger, newly menopausal population. KEEPS found several favorable effects of HT, including significant relief of menopausal symptoms, improved sleep and quality of life, easing of dyspareunia and improvement of other aspects of sexual function, and preservation of bone mineral density (BMD). It also addressed effects of HT on atherosclerosis progression.

In this interview, Dr. Manson discusses both trials and the insights they have provided in menopausal medicine, as well as the need for continuing analyses of HT in younger menopausal women.

Dr. Manson is the Michael and Lee Bell Professor of Women's Health and Professor of Medicine at Harvard Medical School in Boston, where she is Chief of the Division of Preventive Medicine and Codirector of the Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital.

Q What is the biggest misconception about the WHI?

A Many clinicians are not aware that the WHI was designed to assess the role of HT in chronic disease prevention, not to study its efficacy in treating menopausal symptoms. The goal of the WHI was to evaluate the balance of benefits and risks of HT in preventing chronic disease, such as cardiovascular disease, cognitive decline, osteoporotic fracture, and other degenerative diseases of aging.

During the 1980s and 1990s (WHI was started in 1993), HT was commonly prescribed to prevent cardiovascular disease. Many older women—even women in their 70s and 80s—were being started on HT, some of them even after a coronary event. There was a perception that HT was not only protective of the heart but especially beneficial in higher-risk women. This was a grave misconception. As it turned out, older women at high risk of cardiovascular disease had adverse outcomes with HT—in fact, HT appeared to precipitate some coronary events in these women.

The WHI put a halt to the practice of initiating HT in older women for the express purpose of trying to prevent cardiovascular disease or cognitive decline and deserves credit for that. Regrettably, the WHI findings were generalized very broadly, including to recently menopausal women who had distressing vasomotor symptoms and good cardiovascular health and who stood to have a net benefit from HT. With the KEEPS trial and other studies, the pendulum is coming to rest in a more appropriate place.

Q What are the main findings of KEEPS?

A KEEPS evaluated two HT formulations—oral conjugated equine estrogens (CEE) at a daily dose of 0.45 mg and transdermal estradiol in a weekly patch of 50 µg/d (both with the addition of cyclic oral micronized progesterone, 200 mg daily for 12 days each month)—as well as placebo. Overall, HT produced many favorable effects, including significant improvement in hot flushes, night sweats, and sleep disturbances; preservation of BMD; and

postmenopausal hormone therapy in a large prospective study [published online ahead of print September 10, 2012]. J Thromb Haemost. doi:10.1111/j.1538-7836.2012.04919.x.

The estrogen-progestin arm of the WHI clarified the most statistically prominent risk associated with combination HT: a higher incidence of VTE in women allocated to oral conjugated equine estrogen and medroxyprogesterone acetate (MPA).[1]

Although no randomized trials have been large enough to compare the safety of oral versus transdermal HT with respect to VTE in a statistically meaningful manner, the issue has been investigated in observational (case-control and cohort) studies. In past Updates in Menopause, I have detailed studies from France,[2,3] the United Kingdom,[4]

improvement in sexual function in terms of pain and lubrication. For the transdermal formulation, there was also improvement in libido. And with oral estrogen, there was the intriguing finding that it improved mood, depressive symptoms, anxiety, tension, as well as cognitive function in a subset of women who had good cardiovascular health and a low level of cardiovascular risk factors.

Neither form of HT increased blood pressure. (In the WHI, where a higher dose of CEE was given, systolic blood pressure increased significantly.) We also observed the expected first-pass liver effects of oral estrogen on lipids—a reduction in low-density lipoprotein (LDL) and an increase in high-density lipoprotein (HDL) cholesterol. With oral estrogen, there was also an increase in triglycerides and C-reactive protein (CRP). With the transdermal formulation, however, lipids were generally unchanged, while glucose tolerance improved and insulin resistance declined. (In the WHI, oral HT had a beneficial effect on glucose tolerance and diabetes, lowering the incidence of diabetes.)

As for vascular health, the KEEPS trial had insufficient statistical power to examine the clinical events studied in the WHI, so it relied on surrogates, such as noninvasive imaging of the carotid intima-media thickness and accrual of coronary artery calcium. The results were neutral. There was no evidence of an adverse effect on carotid intima-media thickness. For coronary artery calcium, there was a nonsignificant trend toward less calcium accumulation in the HT arms, compared with placebo.

Q What does KEEPS reveal about the different routes of estrogen administration?

A One surprising finding, as I mentioned, is that mood, depression, anxiety, and tension tended to improve with oral estrogen but not with the transdermal formulation. And among healthy women who had a very low risk of cardiovascular disease, oral estrogen improved memory and cognitive function. On the other side of the equation, transdermal estradiol reduced insulin resistance and enhanced libido-related domains of sexual function.

Q What can clinicians take away from KEEPS?

A I think that the KEEPS trial helps to inform clinical decision-making about HT and assists us in individualizing the care of menopausal women. For example, because transdermal estradiol had favorable effects on glucose tolerance and insulin resistance and did not increase CRP or triglycerides, it may be a better choice than oral estrogen for an obese patient or a woman with metabolic syndrome who has significant vasomotor symptoms and really wants to take HT.

However, many KEEPS findings are preliminary and require confirmation in other studies. The evidence is not conclusive—for example, it is likely too soon to conclude that only oral estrogen benefits mood or memory, or that only transdermal estradiol improves insulin resistance. Other studies may show similar effects for oral and transdermal routes. Overall, the findings on cognition were neutral; only in one subgroup was there a signal for some benefit with HT.

Q The WHI had a significant impact on clinical practice. What impact will the KEEPS findings have?

A I do believe that as further evidence emerges on the benefits of HT in managing symptoms and improving quality of life in newly menopausal women, it will be used appropriately, when benefits are likely to outweigh risks. I think that HT should be reserved for management of menopausal symptoms when there is a clear indication for treatment. The decision should be individualized, and women need to be fully informed about benefits and risks. This requires risk-stratification strategies, as younger and lower-risk women are the best candidates. Also, with estrogen-progestin therapy, there is a concern about breast cancer, especially with longer treatment. When prescribing unopposed estrogen, there may be a little more latitude in terms of duration—but, again, treatment should be for symptom management among women who choose to take HT. The research is helping to inform clinical decision-making and leading to more personalized health care.

and the United States,[5] each of which has suggested that, in contrast with oral HT, transdermal HT does not increase the risk of VTE.

One British study also indicated that while oral estrogen therapy slightly increased the risk of stroke (as demonstrated by the WHI), transdermal estradiol at a dose of 0.05 mg or less did not.[6] In 2012, two additional observational reports—one from the United Kingdom and one from Holland—provided additional data confirming the safety of transdermal HT with respect to thrombosis.

Sweetland and colleagues drew from a large population

Using data from the massive British Million Women's Study (MWS), investigators compared the risk of VTE between oral and transdermal HT. Of 1,058,259 postmenopausal women followed in the MWS cohort, 36%

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although the data comparing the risk of VTE between oral and transdermal estrogen is observational, my perspective is that it would be inappropriate to wait for randomized trials before informing our patients that transdermal estrogen appears to be safer than the oral route. Given the costs, logistical challenges (including likely low adherence to study medications) and time involved, we are unlikely to see randomized trials of HT large enough to more definitively compare the risks and benefits between oral and transdermal HT.

In my practice, although I continue to prescribe both oral and transdermal HT, a high percentage of my prescriptions are for transdermal formulations. For women who have an elevated baseline risk of VTE (especially overweight and obese women), I emphasize the safety benefits of transdermal HT in my counseling.

were current HT users. Of current users, 23% were using oral and 14% were using transdermal HT.

The risk of VTE—including deep venous thrombosis and pulmonary embolism—was significantly elevated with the use of oral HT, with a relative risk (RR) of 1.42, compared with nonuse of HT (95% confidence interval [CI], 1.21–1.66).

The risk of VTE was not elevated among users of transdermal therapy (RR, 0.82; 95% CI, 0.54–1.06).

Roach and colleagues studied VTE among 1,000 HT users

In a large case-control study from the Netherlands, investigators identified 1,082 cases of VTE among women older than age 50. Women who used oral estrogen-progestin HT had four times the risk of VTE, compared with nonusers. Although oral unopposed estrogen therapy was also associated with an elevated risk of VTE, this risk was lower than with combination HT and appeared to be dose-dependent.

In contrast, the risk of VTE associated with transdermal estrogen therapy was almost identical to the risk observed in nonusers.

With the addition of these two new studies, there are now six observational studies that agree that transdermal estrogen is safer than oral estrogen with respect to the risk of VTE.[2-5]

ACOG weighs in

In April 2013, ACOG published a Committee Opinion on the route of administration of HT and the risk of VTE, stating: "When prescribing estrogen therapy, the gynecologist should take into consideration the possible thrombosis-sparing properties of transdermal forms of estrogen therapy."

FAST TRACK

ACOG: "When prescribing estrogen therapy, the gynecologist should take into consideration the possible thrombosis-sparing properties of transdermal forms"

FDA approves a new oral drug for vulvar and vaginal atrophy

Portman DJ, Bachmann GA, Simon JA; the Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy [published online ahead of print January 28, 2013]. Menopause. doi:10.1097/gme.0b013e318279ba64.

Simon JA, Lin VH, Radovich C, Bachmann GA. The Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause. 2013;20(4):418–427.

In February 2013, the US Food and Drug Administration (FDA) approved ospemifene (Osphena), an orally administered, tissue-selective estrogen agonist/antagonist, for the treatment of dyspareunia caused by vulvar and vaginal atrophy (VVA) in menopausal women. As with its pharmacologic relatives tamoxifen and raloxifene, ospemifene acts as an estrogen agonist in some tissues and an estrogen antagonist in others. In clinical trials, ospemifene has been found to reduce pain with sexual intercourse and increase vaginal mucosal maturation and vaginal pH to a greater extent than placebo.

Contraindications listed in package labeling for ospemifene include estrogen-dependent neoplasia, VTE (or a history of VTE), stroke, and myocardial infarction (or a history of it).

Although ospemifene acts as an estrogen agonist on the endometrium, no cases of endometrial cancer were noted in clinical trials, the longest of which was 12 months.

Adverse reactions most frequently reported in clinical trials were hot flushes (7.5% with ospemifene vs 2.6% with placebo), vaginal discharge (3.8% vs 0.3%), and muscle spasms (3.2% vs 0.9%).

VVA has reached epidemic proportions

Although most women expect to continue their sexual lives during postmenopause, fewer of them are using hormone therapy. The result is an epidemic of symptomatic VVA. Against this backdrop, new treatment options represent good news for women.

Ospemifene may have special appeal for symptomatic women who prefer not to use vaginal cream, tablets, or the vaginal ring. However, in contrast with vaginal estrogen therapy, ospemifene increases hot flushes. In addition, like tamoxifen and raloxifene, it may increase the risk of VTE.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Package labeling recommends that clinicians consider adding a progestin to prevent endometrial neoplasia in women with an intact uterus using ospemifene, and that endometrial monitoring also be considered in long-term users. As with all menopausal women, any vaginal bleeding in a woman using ospemifene should be evaluated.

The use of vaginal or systemic estrogen is contraindicated in women with a history of breast cancer. As the ospemifene package label indicates, the drug has not been studied adequately in women with breast cancer; therefore, the FDA advises against the use of ospemifene in women with known or suspected breast cancer or a history of the malignancy.

Unopposed estrogen and combination hormone therapy have distinctly different effects on the breast

Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 2012;13(5):476–486.

As I reported in this Update last year, a key finding of the WHI estrogen-only arm was a persistently reduced risk of invasive breast cancer among women without a uterus who used unopposed oral conjugated equine estrogen (CEE) for a median of 5.9 years.[7] Since then, WHI investigators have reported additional details about breast cancer incidence and mortality after a median follow-up of 11.8 years.

They found CEE to be associated with a lower incidence of invasive breast cancer than placebo (annual incidence, 0.27% vs 0.35%; HR, 0.77; P = .02). The level of protection against breast cancer associated with CEE did not vary by duration of use during the intervention or postintervention phases. The incidence of breast cancer was even lower (HR, 0.68) when the analysis was restricted to patients most adherent to the study medication.

Among women given a diagnosis of breast cancer, both overall and breast cancer–related mortality were significantly lower in the CEE arm (HR, 0.62 and 0.37, respectively).

Detection bias is unlikely

Although many observational studies have reported a modestly elevated risk of breast

FAST TRACK

The FDA advises against the use of ospemifene in women with known or suspected breast cancer or a history of the malignancy

WHAT THIS EVIDENCE MEANS FOR PRACTICE

These findings should reassure women who use estrogen to manage menopausal symptoms or prevent osteoporosis after hysterectomy that this therapy does not increase the risk of breast cancer.

The findings also underscore the importance of distinguishing between estrogen-only and estrogen-progestin therapy as we help our patients make sound decisions about HT.

New data support the practice of ovarian conservation during benign hysterectomy

Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the Nurses' Health Study. Obstet Gynecol. 2013;121(4):709–716.

Perera HK, Ananth CV, Richards CA, et al. Variation in ovarian conservation in women undergoing hysterectomy for benign indications. Obstet Gynecol. 2013;121(4):717–726.

FAST TRACK

Women who use unopposed estrogen after hysterectomy to manage menopausal symptoms should be reassured that this therapy does not increase the risk of breast cancer

In recent years, studies have documented the health risks of routine bilateral salpingo-oophorectomy (BSO) at the time of hysterectomy for benign indications. The body of evidence of the potential risks of BSO continues to expand, with publication, in April 2013, of two large analyses.

In the first analysis, investigators from the Nurses' Health Study (NHS), a large prospective cohort, extended follow-up to 28 years. Among more than 30,000 participating nurses who underwent hysterectomy for benign indications, 16.8% of those who underwent BSO died during follow-up, compared with 13.3% of those with ovarian conservation (hazard ratio [HR], 1.13; 95% CI, 1.06–1.21).

BSO was associated with a lower risk of fatal ovarian cancer and, if performed before age 47.5 years, a lower risk of breast cancer as well. However, at all ages, BSO was associated with higher other cause-specific deaths (coronary artery disease, stroke, lung cancer, colorectal malignancy) as well as all-cause mortality. Similar increases in overall and breast cancer deaths were associated with BSO regardless of family history (sibling or mother) of breast or ovarian cancer.

Among women younger than age 50 who had never used estrogen therapy at the time of BSO, the surgery was associated with significantly increased all-cause mortality (HR, 1.41; 95% CI, 1.04–1.92). However, BSO before age 50 was not associated with significantly higher all-cause mortality in current or previous users of estrogen (HR, 1.05; 95% CI, 0.94–1.17).

Ovarian conservation is more common in younger women

In the second large analysis published this year, Perera and colleagues used records that include approximately 15% of all US hospital discharges to explore recent practices with respect to ovarian conservation at the time of hysterectomy for benign indications. They found that, among more than 750,000 women who underwent hysterectomy between 2000 and 2010, the ovaries were conserved in 53.6% of cases.

Ovarian conservation was more common in younger women, as it was practiced

in 74.3% of cases involving women younger than age 40 and in 31% of cases involving women aged 60 to 64 years.

Ovarian conservation was also more common in recent hysterectomies than in surgeries performed more remotely in time.

It is heartening to observe that US gynecologists are practicing ovarian conservation more often at the time of hysterectomy for benign indications. The new analysis from the NHS supports this practice unless the patient has a mutation (BRCA, Lynch) that substantially increases her risk of ovarian cancer.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Unless contraindications apply, ObGyns should encourage women who undergo BSO before age 50 to use HT, at least until they reach the normal age of spontaneous menopause.

Clinicians who are considering performing elective BSO at the time of hysterectomy despite this guidance should recognize that in the aftermath of the WHI, and in the absence of contraindications,it may not be wise to perform BSO in women younger than age 50, since many women currently are reluctant to use estrogen therapy.

Swedish cohort confirms the ill effects of early menopause

Svejme O, Ahlborg HG, Nilsson JA, Karlsson MK. Early menopause and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. BJOG. 2012;119(7):810–816.

Although early menopause has been linked to osteoporosis and fragility fractures, most studies documenting this association have been cross-sectional and retrospective, raising concerns about recall bias (inaccurate recall of when menopause occurred).

In 1977, investigators began a study of women living in Malmö, Sweden, who were born in 1929. This ethnically homogeneous (white, Northern European) cohort of 390 women (age 48 at enrollment) underwent bone mineral density (BMD) assessment and were stratified into two groups:

- early menopause – those who entered menopause before age 47
- late menopause – those who became menopausal at or after age 47.

At age 77, 198 of the 298 surviving participants underwent BMD reassessment. Fracture history and mortality were documented at the study's end in 2011.

BMD measurement at age 77 revealed osteoporosis in 56% of women with early menopause, compared with 30% of those with late menopause ($P = .01$). The incidence of fragility fractures per 1,000 person-years was 19.4 in the early menopause group, compared with 11.6 for late menopause ($P = .01$). The death rate during the 34-year follow-up was 52.4% for the early menopause group, compared with 35.2% for late menopause ($P = .01$). Twenty-two percent of women with early menopause had used HT, compared with 10% of those with late menopause ($P = .05$).

Because it tracked health and mortality over multiple decades, this prospective, population-based study is particularly credible.

The use of HT was uncommon among women in this cohort.

FAST TRACK

BMD measurement at age 77 revealed osteoporosis in 56% of women with early menopause, compared with 30% of those with late menopause

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Given our current understanding of the efficacy of HT in lowering the risk of osteoporotic fractures in menopausal women and reducing coronary artery disease and overall mortality among women in their 50s (or within 10 years of the onset of menopause), it is important to advise women who undergo early menopause to use HT unless they have specific contraindications.[8,9]

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Progestin therapy may not impair mood, after all

Rogines-Velo MP, Heberle AE, Joffe H. Effect of medroxyprogesterone on depressive symptoms in depressed and nondepressed perimenopausal and postmenopausal women after discontinuation of transdermal estradiol therapy. Menopause. 2012;19(4):471–475.

Although many ObGyns have noted anecdotally that progestin therapy precipitates negative mood reactions in some menopausal women, data addressing this issue have been scarce and inconsistent.

Rogines-Velo and colleagues analyzed the results of two short-term trials involving perimenopausal and postmenopausal women. One trial enrolled 52 nondepressed women, and the other enrolled 72 women with clinical depression. Participants were randomly allocated to transdermal estradiol or placebo for 2 or 3 months.

In both trials, women in the estradiol group who had a uterus received medroxyprogesterone acetate (MPA; 10 mg daily) for an additional 2 weeks to prevent endometrial hyperplasia. Depressive symptoms were assessed using the Beck Depression Inventory at study entry, after estradiol therapy, and again at the conclusion of MPA treatment.

Among women who received estradiol, 24 of 26 nondepressed women and 14 of 21 depressed women completed the course of MPA. Estradiol therapy was associated with mood improvement in both trials, with greater improvement among depressed women (P = .02). Subsequent use of MPA did not affect mood significantly in either depressed or nondepressed women, even after adjustment for educational status and presence of vasomotor symptoms.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although considerable anecdotal experience suggests that progestational treatment can cause mood deterioration in some women, this effect had not been studied in depressed populations.[10,11] The two short-term trials on which this report is based confirm that estrogen has a positive effect on mood. Their findings suggest that progestin need not be withheld from depressed women on the assumption that it will worsen mood.

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