By Karen Roush, MSN, RN, FNP-BC

MENOPAUSAL HORMONE THERAPY: WHAT WE KNOW NOW

Nurses need to understand the evidence regarding potential risks and benefits, current recommendations, and the questions that remain.

OVERVIEW: This article describes the findings and limitations of the major research thus far on hormone therapy, particularly that of the Women's Health Initiative; examines practice recommendations; clarifies common terminology related to menopause and hormone therapy; and provides the implications for nurses. This is part one of a four-part series on postmenopausal health.

KEYWORDS: bioidentical hormones, combined estrogen and progestogen therapy, estrogen, estrogen therapy, hormone therapy, menopause, menopausal transition, postmenopause, progestin, progestogen, women's health, Women's Health Initiative

> *"I don't know what to do. The hot flashes are so debilitating. I'm having them 10, 20 times a day. And every time I get them I get this terrible, anxious feeling. It's affecting my job and my family. I'm just exhausted and miserable all the time. I've thought about taking estrogen, but with everything you hear lately, I don't know what to think. I don't want to end up with breast cancer or a stroke! What do you think?"*—Marcia

Marcia doesn't exist, but her questions reflect the concerns expressed by many of the women I cared for in my NP practice and also of the estimated 37.5 million women in the United States today who have reached menopause or are within a few years of its beginning or end.[1] Many of these women will look to nurses to help them navigate through the morass of information about menopausal hormone therapy. If Marcia were your patient, what would you advise her about postmenopausal hormone therapy? It's crucial that nurses have a clear understanding of the research to date and the current recommendations.

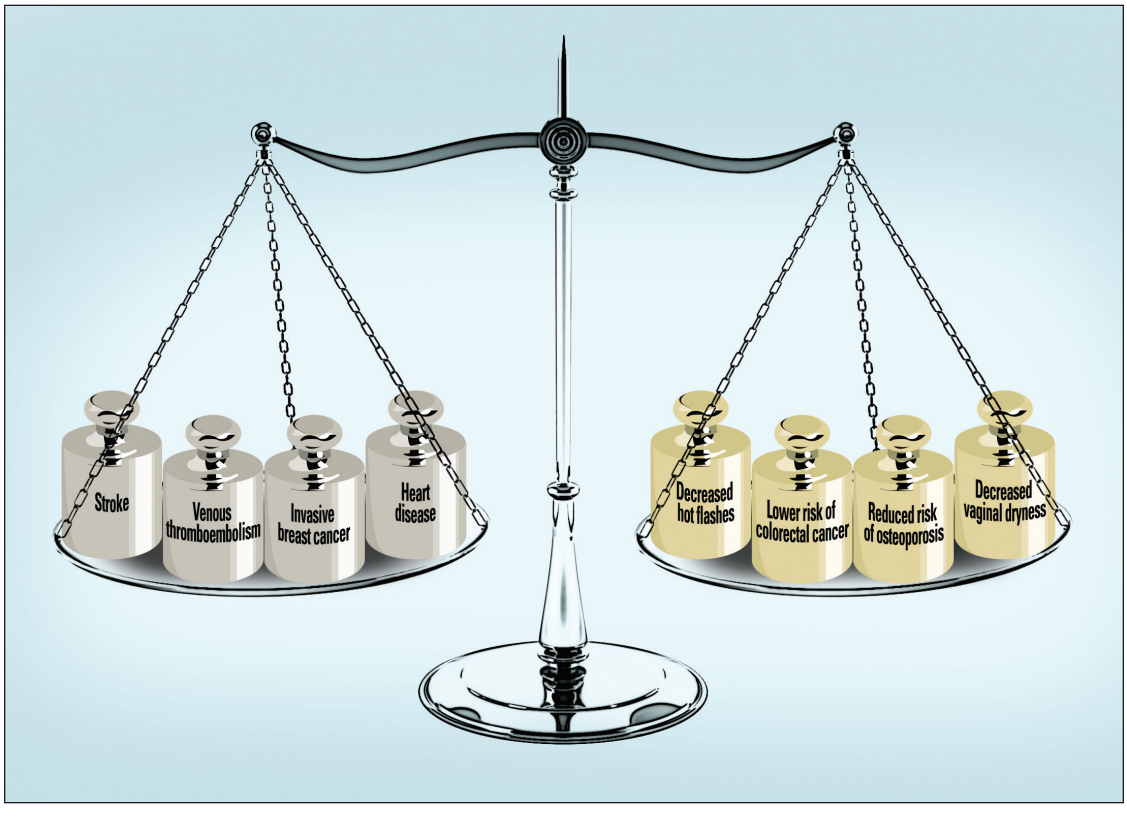
Hormone therapy has a long and varied history. Estrogen began to be used routinely for the treatment of menopausal symptoms in the 1940s, when it was discovered that it could be extracted from the urine of pregnant mares. At first, there wasn't much of a market for it—but in 1966, Dr. Robert Wilson published the book *Feminine Forever* as well as numerous articles espousing estrogen as the answer to what he called the "living decay" of menopause.[2-4] Sales of estrogen rose quickly, reaching a peak in 1975 of 28 million estrogen-containing prescriptions dispensed from pharmacies.[5] It was recommended as a panacea for all of an aging woman's woes, from wrinkles to cardiovascular disease (CVD). It promised to ease and even erase the changes associated with menopause, relieving hot flashes and insomnia, improving mood, and reinvigorating libido. Then in the 1970s, studies found that postmenopausal women with an intact uterus who were taking estrogen had significantly higher rates of endometrial cancer.[6,7] The use of estrogen dropped dramatically. However, further research revealed that if estrogen was combined with a progestogen (a term for both progestin and progesterone), there was no longer an increased risk of endometrial cancer.[8,9] Once again it became routine for postmenopausal women to be prescribed hormone therapy—combined estrogen and progestogen for those with a uterus, and estrogen alone for those without.

This practice continued for about 20 years, until 2002, when results of the Women's Health Initiative (WHI) estrogen-plus-progestin study,[10] indicating an increased risk of coronary heart disease (CHD), breast cancer, stroke, and pulmonary embolism, shocked the women's health community. Many women reacted with fear and immediately stopped taking hormone therapy. By 2004, estrogen-only prescriptions had dropped by 49% and estrogen-plus-progestin prescriptions by 70%.[11] For many, this was a healthy decision—but not all of these women needed to stop hormone therapy. A more in-depth examination of the findings, coupled with an individualized approach, will ensure the appropriate use of menopausal hormone therapy in women who can most benefit from it, particularly for bone protection and relief of severe vasomotor symptoms. With up-to-date knowledge, nurses can help each woman understand the implications of the WHI findings and what they mean for her.

THE WHI HORMONE STUDIES

The WHI was a research program started in 1991 by the National Heart, Lung, and Blood Institute and the National Institutes of Health (NIH).[12] A total of 161,808 postmenopausal women were enrolled in the WHI studies. The overall purpose of the WHI was to gather information about the major health issues facing women after menopause, including heart disease, bone fractures, breast and colon cancer—and hormone therapy. It continued for 15 years and consisted of a number of different clinical trials and an observational study.

There were two arms to the hormone research—the estrogen-plus-progestin study and the estrogen-alone study. Both were randomized, double-blind, placebo-controlled trials with primary outcomes of CHD and invasive breast cancer. Secondary outcomes were stroke; venous thromboembolism (VTE), both pulmonary embolism and deep vein thrombosis; endometrial cancer (in the estrogen-progestin study) and colorectal cancer; fractures, including hip, vertebral, and total osteoporotic; and death due to other causes.[10,13] Each had a planned duration of 8.5 years. The estrogen-plus-progestin study was stopped in July 2002, three years early, when it became apparent that the risks of the therapy outweighed the benefits. The estrogen-alone study was stopped two years later, after the researchers concluded that enough data had been collected to determine the



Hormone Therapy Terminology

The term *hormone replacement therapy*, or HRT, though commonly used, is inaccurate and doesn't conform to current recommendations. The inaccuracy is in the use of the word *replacement*. Exogenous hormones do not "replace" the levels or complex balance of endogenous estrogen and progestogen maintained by a woman's body during her reproductive years. The more accurate, and recommended, term to describe the use of hormone therapy is *supplementation*. The following is a list of correct terms for hormone therapy and their abbreviations, as recommended by the North American Menopause Society:

- ***Estrogen therapy (ET)*** for estrogen supplementation
- ***Combined estrogen and progestogen therapy (EPT)*** for combined estrogen and progestogen supplementation
- ***Hormone therapy (HT)*** for either estrogen or combined estrogen and progestogen supplementation

North American Menopause Society. *Menopause* 2010;17(2):242-55.

risks and benefits of that therapy.[14] All of the women in both studies continued to be followed and data was collected through 2010.

Estrogen-plus-progestin study. This study enrolled 16,608 postmenopausal women ages 59 to 70 years with an intact uterus. The women were randomized to receive either daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate (Prempro) (n = 8,506) or a placebo (n = 8,102).[10] Both groups received the same follow-up, which included phone calls, office visits every six months, fasting blood samples at baseline and year 1, annual mammograms and clinical breast exams, and electrocardiograms at baseline and years 3 and 6.

Problems began emerging early in the study. By 1999, just two years after the start of data and safety monitoring, five preliminary analyses indicated "small but consistent early adverse effects in cardiovascular outcomes and in the global index" in women taking estrogen plus progestin.[10] However, the designated stopping boundary hadn't been reached; study participants were informed of the findings and the study continued. The 10th interim analysis, performed in May 2002, found that the breast cancer boundary had been crossed and the global index indicated a finding of "overall harm." It was determined that the increased risk of breast cancer, as well as of CHD, stroke, and pulmonary embolism, outweighed the benefits of decreased risk of fracture and possible decreased risk of colon cancer. The study was stopped and participants informed of the results.

Study findings.[10]

- **CVD increased** among women taking estrogen plus progestin compared with the control group. Women taking estrogen plus progestin had a 29% increased rate of CHD, most often nonfatal myocardial infarction, compared with women in the control group ($P \leq 0.05$). Women taking estrogen plus progestin had double the risk of VTE and a 41% increased rate of stroke compared with controls ($P \leq 0.05$).
- **Invasive breast cancer was increased** by 26% in the estrogen-plus-progestin group compared with the control group. Women with a history of postmenopausal hormone use had higher rates of breast cancer than those without. There was no significant difference in rates of breast cancer in situ between the groups.
- **Colorectal cancer rates were lower** (37%) in women taking estrogen plus progestin compared with controls. There were no significant differences in the incidences of endometrial cancer or lung cancer between the groups.
- **Fracture rates were significantly lower** (24%) in women taking estrogen plus progestin than in women taking placebo. Rates of hip and vertebral fractures, the two most common osteoporosis-related fractures, were one-third lower in the estrogen-plus-progestin group.

Race, ethnicity, age, and preexisting risk factors made no difference in the increased risk of CVD or breast cancer. There was also no difference in all-cause mortality between groups, but the researchers noted that not enough time had elapsed to assess this outcome.

Estrogen-alone study. The primary purpose of the estrogen-alone study was to examine claims that estrogen therapy decreased the risk of CVD[15, 16] and increased the risk of invasive breast cancer.[17-19] The design was the same as that of the estrogen-plus-progestin study. Researchers enrolled 10,739 postmenopausal women ages 50 to 79 years who'd had a hysterectomy. Participants were randomized to receive either 0.625 mg of conjugated equine estrogen (Premarin) (n = 5,310) or a placebo (n = 5,429), and they received the same follow-up as those in the estrogen-plus-progestin study.[13]

Problems began to emerge early in this trial as well. By 2000, interim analyses showed increases in CHD, strokes, and VTE in women taking estrogen. Rates of breast cancer didn't increase in this group as they had in the estrogen-plus-progestin group. None of the adverse effects reached the predefined stopping boundary, although the stroke results came close. By February 2004, the NIH decided to stop the study about a year and a half early. Researchers had enough data to conclude that estrogen alone wasn't cardioprotective and didn't have an effect on breast cancer risk, and the latest interim analyses had shown that the increased rate of stroke had crossed the predefined adverse effect boundary. It was determined that continuing the study placed participants at unacceptable risk. The study was stopped and all participants were advised to stop taking the study medications.

Study findings.[13]

- **CVD findings were mixed.** There was no significant difference in the rate of CHD between the conjugated equine estrogen group and the placebo group. However, compared with the placebo group, the conjugated estrogen group had a 39% greater risk of stroke ($P = 0.007$) and a 33% greater overall risk of VTE (the increase in deep vein thrombosis was statistically significant [$P = 0.03$], but the increased rate of pulmonary embolism wasn't). Despite these findings, there was no difference in the global index or in total mortality between the groups.
- **Invasive breast cancer rates were 23% lower** in the conjugated estrogen group than in the placebo group, just missing statistical significance ($P = 0.06$). There were no differences in rates of other cancers between groups.
- **Fracture rates were significantly lower** in the conjugated estrogen group than in the placebo group. Hip fractures were lower by 39% ($P = 0.01$), vertebral fractures by 38% ($P = 0.02$), and total osteoporotic fractures by 30% ($P < 0.001$).

Race, ethnicity, body mass index, and preexisting risk factors made no difference in the risk of any of the outcomes. Age, however, did appear to be a factor; preliminary subgroup analyses indicated that conjugated estrogen might decrease CHD in younger women.

An estimated 15 million women were taking hormone therapy at the time of the study[20]—while the risk for any particular woman may have been small, the overall number of events could have been in the tens of thousands.

Study follow-up. The WHI continued to follow the study participants after stopping the trials. In the estrogen-plus-progestin study, the period of time from July 2002, when the study was stopped, to August 2005, its planned end date, was defined as the *post-intervention phase*; during it, participants continued to receive the same monitoring they'd had in the intervention phase.[21] During the postintervention phase, the increased risk of CHD, VTE, and stroke seen in the estrogen-plus-progestin group disappeared—but so did the decreased risk of fracture; and the overall rate of cancer increased. This was due to a continued higher—though trending downward—rate of breast cancer in the estrogen-plus-progestin group than in the placebo group and to an increase in the rate of colorectal cancer in the estrogen-plus-progestin group that brought it up to the level of the placebo group.[21]

THE WHI MEMORY STUDY (WHIMS)

The WHI also looked at how hormone therapy affects women's cognitive function. They enrolled women participating in the estrogen-plus-progestin and estrogen-alone studies who were between 65 and 76 years of age and determined to be dementia free. Out of 3,200 eligible participants in the estrogen-alone study, 2,947 agreed to take part in a substudy[22] and of 4,894 eligible participants in the estrogen-plus-progestin trial, 4,532 agreed to do so.[23] Participants in each substudy completed a baseline and an annual Modified Mini-Mental State Examination (3MSE); those who scored below a preset cut point completed further testing and a neuropsychiatric examination. The possible range of scores on the 3MSE is 0 to 100, with higher scores reflective of better cognitive functioning.

Evidence from earlier observational studies indicated that postmenopausal hormone therapy improved cognitive function. The results of the substudies, however, were inconsistent with those findings. In the estrogen-alone substudy, Espeland and colleagues found that the mean 3MSE scores of women taking conjugated equine estrogen were 0.26 units lower than those of women taking a placebo ($P = 0.04$).[22] Also, more

ALTHOUGH THE RESULTS OF THESE STUDIES WERE DISTRESSING TO WOMEN USING POSTMENOPAUSAL HORMONE THERAPY AND THEIR HEALTH CARE PROVIDERS, IT'S IMPORTANT TO UNDERSTAND THAT THE RISK OF HARM TO EACH INDIVIDUAL WOMAN IS VERY SMALL.

Putting it in perspective. The results of these studies were distressing to the millions of women using postmenopausal hormone therapy and their health care providers. It's important to understand, though, that the risk of harm to each individual woman is very small. Looking at the increased risks in absolute numbers is helpful in understanding this distinction.

The increased risk of CHD in the estrogen-plus-progestin study can be understood as seven more cardiac events in 10,000 women taking estrogen plus progestin for a year. The increased risk of invasive breast cancer, stroke, and pulmonary embolism in that study can be interpreted as eight more women out of 10,000 taking estrogen plus progestin experiencing each of those outcomes.[10]

In the estrogen-alone study, the increased risk of stroke can be explained as 12 additional cases of stroke for every 10,000 women taking estrogen for one year.

women taking conjugated equine estrogen had a decrease in 3MSE scores of at least 12 units compared with women taking a placebo (3.89% versus 2.96%, respectively). In the estrogen-plus-progestin substudy, Rapp and colleagues found no difference in mean study scores between women taking estrogen plus progestin and those taking a placebo; however, a greater proportion of women taking estrogen plus progestin had a clinically significant decline (≥ 2 SDs) in cognitive function compared with women taking placebo (6.7% versus 4.8%, respectively; $P = 0.008$). Once again, WHI results added unsettling new information to the postmenopausal hormone therapy debate.

Research has shown that estrogen has different effects on the blood vessels of younger and older women. This may be related to its differing biologic effects on the healthy vessels of women in early menopause versus the vessels of women later in menopause, when atherosclerosis has already been established.[31-33] A substudy of women ages 50 to 59 in the estrogen-alone WHI trial supported this idea, finding a 60% reduction in coronary artery calcification among women with at least an 80% adherence to the study estrogen.[24] However, to date there's no epidemiologic evidence to support the timing hypothesis, and the debate continues.[25, 34]

A SECONDARY ANALYSIS FOUND THAT WOMEN WHO STARTED HORMONE THERAPY WITHIN 10 YEARS OF MENOPAUSE HAD A DECREASED RISK OF CHD, WHEREAS THOSE WHO STARTED IT LATER HAD AN INCREASED RISK.

WHY THE DIFFERENCE IN RESULTS?

Healthy user bias. The surprising findings of the WHI trials created a lot of controversy and discussion. Experts wondered why the results were so different from those of earlier observational studies, which indicated that use of hormone therapy reduced the risk of CVD. One possibility discussed was that the observational studies suffered from *healthy user bias*; that is, there were better cardiovascular outcomes among estrogen users because the choice to use estrogen was associated with other health-promoting factors, such as higher education levels and greater physical activity.[24-26]

A matter of timing? Another possibility was what became known as the *postmenopausal timing hypothesis*.[27] This hypothesis posited that hormone therapy started within 10 years of menopause would have favorable effects on health outcomes, particularly CVD, while hormone therapy started in late menopause would not.

The WHI researchers did a number of secondary analyses of the hormone trials' data. One looked at the effect of age and years since menopause on the risk of CVD. They found that women who started hormone therapy within 10 years of menopause had a decreased risk of CHD, whereas those who started it later had an increased risk.[28] Although this finding just missed statistical significance ($P = 0.06$), it was the first indication that the timing of initiation of hormone therapy might have an impact on risk. Proponents of the postmenopausal timing hypothesis claimed that this phenomenon explained the difference between the WHI trials and earlier observational studies because a large proportion of WHI participants were older (mean age, 63.6 years), and therefore farther from menopause.[29, 30]

OTHER EVIDENCE: DIGGING DEEPER

Heart disease is the number one killer of women in the United States.[35] Therefore it's imperative to follow up on any evidence suggesting that early initiation of postmenopausal estrogen therapy may be cardioprotective.[36] While there's clear evidence of an increased risk of breast cancer with estrogen-plus-progestin therapy, it's been argued that because every year far more women die of CHD than breast cancer (315,930 versus 40,820, respectively, in 2006),[35, 37] for many women the slightly increased risk of breast cancer would be far outweighed by the benefit of CHD prevention.

It's also been noted that, just as the older age of participants in the WHI hormone studies might have been a factor in the results, so might the fact that each trial tested only one dose of an oral formulation of hormones. Prior research has shown that transdermal estrogen doesn't have the same procoagulation effects that oral estrogen has.[38, 39] Is it possible that different routes of administration or dosages would have an impact on CVD outcomes?

Route and dose. This possibility is supported by studies that looked specifically at estrogen use and VTE. A case–control study in France, the Estrogen and Thromboembolism Risk (ESTHER) study, found that the odds ratios for VTE were 0.9 (95% confidence interval [CI], 0.4-2.1) in women taking transdermal estrogen and 4.2 (95% CI, 1.5-11.6) in women taking oral estrogen, compared with those not taking estrogen.[40] A more recent, large observational study, also in France, had similar results.[41] Canonico and colleagues found that transdermal estrogen didn't increase risk of VTE (hazard ratio, 1.1; 95% CI, 0.8-1.8), while oral estrogen did (hazard ratio, 1.7; 95% CI, 1.1-2.8). Both studies also found that the

type of progestogen used determined VTE risk (only norpregnanes increased risk).[40, 41]

A recent study of oral and transdermal estrogen and stroke adds further support to the possibility that route of administration and dose make a difference.[42] A population-based case–control study used a cohort of women drawn from the UK General Practice Research Database, a large database of anonymous medical records from about 400 general medical practices in the United Kingdom. The study included all women ages 50 to 79 years in the database from January 1987 to October 2006. There were 15,710 women with a history of stroke (the cases) matched to 59,958 controls. Renoux and colleagues found that compared with no estrogen use, the use of low-dose transdermal estrogen didn't increase the risk of stroke (rate ratio, 0.81; 95% CI, 0.62-1.05), but the use of high-dose transdermal estrogen (rate ratio, 1.89; 95% CI, 1.15-3.11) and any dose of oral estrogen (rate ratio, 1.28; 95% CI, 1.15-1.42) did.

KEEPS. The Kronos Early Estrogen Prevention Study (KEEPS) is a randomized controlled trial begun in 2005 and designed to more closely examine the postmenopausal timing hypothesis and the question of differences in the effects of oral versus transdermal estrogen.[43] A 5-year, multisite trial, KEEPS enrolled 720 women, 42 to 58 years of age, who had reached menopause within the previous 36 months. Participants were randomized to one of three treatment groups: daily 0.45 mg oral conjugated equine estrogen (Premarin) plus 200 mg micronized progesterone (Prometrium); daily 50 micrograms of transdermal estradiol (Climara) plus micronized progesterone; or daily placebo.

The primary research question of the trial is whether hormone therapy initiated at or shortly after menopause prevents or slows the development of atherosclerosis. KEEPS is also investigating whether there are differences in how oral and transdermal estrogen affect the development of atherosclerosis. Finally, it is looking at how hormone therapy affects other risk factors for atherosclerosis and what, if any, significant interactions there are among them. The study was scheduled to end in 2010.

A number of ancillary studies are planned as well, including those to evaluate data on effects in bone, metabolic processes, and cognitive functioning in the three groups. The researchers hope to resolve questions raised by the WHI results, providing women and clinicians with the information they need to make decisions about the use of hormone therapy during the menopausal transition and postmenopause.

CURRENT RECOMMENDATIONS

Immediately after the WHI trials were stopped, the NIH recommended that hormone therapy not be used for the prevention of chronic diseases, including CVD. The NIH also recommended that when estrogen was used, whether alone or in combination with progestin, it should be prescribed at the lowest effective dose for the shortest duration needed to meet treatment goals.[14] A black box warning with this information was added to the label of all postmenopausal hormone therapies. Overall, most experts agreed that it was acceptable to use estrogen to treat menopausal symptoms for a short period of time in early menopause.[44]

In the United States, menopausal hormone therapy is currently approved only for the treatment of moderate-to-severe vasomotor symptoms and vaginal atrophy and for the prevention (not treatment) of osteoporosis. It's contraindicated in women with breast cancer or a history of breast cancer, known or suspected estrogen-sensitive cancers, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, current or past VTE or pulmonary embolism, coronary artery disease, untreated hypertension, active liver disease, known hypersensitivity to hormone therapy, or porphyria cutanea tarda.[45]

In 2006 the American Association of Clinical Endocrinologists (AACE) published their menopause guidelines[45] and in 2010 the North American Menopause Society (NAMS) released their latest recommendations for the use of menopausal hormone therapy.[46] These groups agree that hormone therapy may be appropriate for selected women, based on their symptoms and risk-benefit profiles and in accordance with approved Food and Drug Administration (FDA) indications (treatment of moderate-to-severe vasomotor symptoms and vaginal atrophy, and prevention of osteoporosis). But, in all cases, *estrogen should be used at the lowest effective dose for the shortest period of time*. If a woman still has her uterus, to counteract an increased risk of endometrial cancer with systemic

Menopause Terminology

Menopause is one point in time, not a process that women "go through." It's defined as the time of a woman's final menstrual period. However, 12 months must pass without a menstrual cycle before it's determined that a woman's last period was the final one.

Menopausal transition is the correct term for the period of time from when a woman begins to have irregular menstrual cycles to her final period. This time is also referred to as *perimenopause* or the *climacteric*; although these two terms aren't considered appropriate medical terminology, you'll see them used in articles and books written for the general public and they're appropriate for use when talking to patients.

Postmenopause is the period of time after the final menstrual cycle. It's divided into two stages: the first five years is considered *early menopause* (an important distinction when talking about the timing of hormone therapy); from that time until death is *late menopause*.

Soules MR, et al. *J Womens Health Gend Based Med* 2001;10(9):843-8.

Five Myths About Bioidentical Custom-Compounded Hormones[46, 53, 55-57]

Myth 1
Bioidentical hormones are identical copies of the hormones your body makes, so they're safer than conventional hormones.

"Bioidentical" refers to a substance that has the same molecular structure as that made in the body. Many conventional hormones are bioidentical, such as 17β-estradiol and micronized progesterone.

Myth 2
Bioidentical hormones are "natural" products, so they're safer than conventional hormones.

"Bioidentical" and "natural" aren't the same, though the terms are often used interchangeably. Natural means that the substance comes from a source in nature. Bioidentical means that the substance is identical to that made by the body. Ironically, the only truly "natural" estrogen product is conjugated equine estrogen, which is extracted from horse urine and is often derided by proponents of natural estrogen products for that very reason. Numerous other conventional estrogen and progestogen products are derived from plant sources—the same sources (usually soy and yams) as those products marketed as "natural." Estrogen, in the form used by the body, isn't naturally part of yam or soy plants; it's synthesized from a substance in the plants called diosgenin.

Myth 3
Bioidentical hormones are safer and more effective than conventional hormones because the body is better able to absorb and metabolize them.

The body uses estrogen the same way, regardless of its origin. Differences in safety and efficacy may result based on the type of estrogen used, estradiol or estrone, or on the vehicle containing the estrogen or the route of administration. One of the problems with custom-compounded bioidentical hormones is the lack of consistency in their methods of delivery and absorption.

Myth 4
Bioidentical hormones are safer and more effective because they can be individualized for each woman.

There's currently no test that accurately determines the best hormone regimen for an individual woman. No evidence supports the use of salivary testing, and current salivary testing methods aren't consistently accurate. Treatment should be based on symptom relief, which for most women can be achieved with conventional hormones that have been rigorously tested and monitored for consistency.

Myth 5
Bioidentical hormones are a safe alternative when conventional hormones are contraindicated.

Estrogen is estrogen. The risks of exposure to hormones are the same for bioidentical hormones as for conventional hormones. Bioidentical hormones may actually be *more* risky than prescription hormones because the Food and Drug Administration doesn't regulate them, and there's no monitoring of consistency and purity.

estrogen, progestogen must be prescribed along with it; women without a uterus should *not* use progestogen. If a woman is 60 or older and has never taken hormone therapy, she shouldn't start unless there are unusually strong reasons for doing so—and if she does start, she should be closely monitored for CVD risks.[46]

Neither NAMS nor the AACE recommends the use of transdermal estrogen products over oral products.[45, 46] Although they acknowledge the advantages of transdermal delivery—such as no increase in triglycerides or changes in levels of C-reactive protein or blood pressure, along with the observational data about decreased risk of VTE—they argue that there's not enough strong evidence to support an increased safety profile for transdermal delivery over the oral route, especially at lower doses. However, the AACE does state that transdermal products should be "considered" in all women using systemic estrogen and that they're "preferred" in women with hypertension, hypertriglyceridemia, and increased risk of cholelithiasis.[45]

When using estrogen therapy only to treat vaginal symptoms, local administration is preferred.[45, 46] When local therapy is used in women with a uterus, it's not necessary to also add progestin. Local estrogen therapy for dyspareunia secondary to vaginal atrophy is effective and appropriate; however, hormone therapy for the treatment of sexual dysfunction due to decreased libido or other problems isn't recommended. Local estrogen therapy may also be helpful and is appropriate for the treatment of urge incontinence when vaginal atrophy is a factor.[46]

For women at risk for osteoporosis, hormone therapy isn't recommended as the first-line treatment; nonhormonal medications such as bisphosphonates (Fosamax and others), selective estrogen receptor modulators (for example, raloxifene [Evista]), or calcitonin (Miacalcin and others) should be tried first.[45] In women who can't tolerate these medications, hormone therapy is appropriate if there's an established loss of bone mass.[46]

Prevention of osteoporosis is the only indication where *long-term* use of hormone therapy is considered appropriate.[45, 46] Women should undergo baseline and periodic dual-energy X-ray absorptiometry scans to assess risk and monitor treatment efficacy. When considering hormone therapy for the prevention of osteoporosis, it's important to keep in mind that benefits of therapy aren't sustained once treatment ends.[46]

HORMONE THERAPY AND DISEASE PREVENTION

The results of KEEPS and future randomized controlled trials may provide further evidence to support the notion discussed earlier that hormone therapy may be cardioprotective in younger women when started in early menopause. However, for now the recommendation remains that hormone therapy should *not* be used for the prevention of CVD.[45, 46] On the other hand, available evidence indicates that short-term use of hormone therapy in women younger than 60 and within 10 years of menopause doesn't *increase* CVD risk.

There's some evidence that hormone therapy decreases the incidence of type 2 diabetes and improves insulin resistance, but this benefit is insufficient to offset the risks associated with long-term use.[47] Therefore hormone therapy is currently not recommended for the prevention of diabetes.[46] Although local vaginal estrogen may help to prevent recurrent urinary tract infections in women with vaginal atrophy, it isn't currently recommended or approved for this purpose.[46]

Hormone therapy is also not recommended for the prevention or treatment of dementia and depression.[45, 46, 48, 49] There are mixed results regarding the effect of hormone therapy on quality of life, with some evidence that it may improve quality of life in women with moderate-to-severe hot flashes.[46, 48, 50] There's also some evidence that hormone therapy reduces wrinkling of the skin in menopausal women[51, 52]; however, the risk-benefit profile doesn't justify its use solely for cosmetic enhancement and it's not recommended or approved for this use.

Use of bioidentical hormones. The use of bioidentical custom-compounded hormones isn't recommended by NAMS, the Endocrine Society, or the FDA.[46, 53, 54] There's no data to support claims that bioidentical hormones are a safer or more effective alternative to conventional hormone therapy. In fact, there's little data whatsoever on the safety or effectiveness of bioidentical hormones. In 2008, the FDA sent warning letters to seven pharmacy operations for misleading the public about the safety and effectiveness of their custom-compounded products. (See *Five Myths About Bioidentical Custom-Compounded Hormones*.[46, 53, 55-57])

NURSING IMPLICATIONS

So what do you advise Marcia and women like her? Our current knowledge indicates that *the benefits of hormone therapy outweigh the risks when it's used for the short-term treatment of moderate-to-severe vasomotor symptoms or vaginal atrophy, and to prevent osteoporosis in selected women younger than 60 and within 10 years of menopause*. Estrogen therapy can have numerous benefits in women during the menopausal transition and postmenopause. The relief of severe hot flashes such as those experienced by Marcia is one of the primary benefits.[58]

Decisions about treatment must be individualized. Your role is to work with women to reach a decision that will allow them to enjoy optimal health and well-being throughout this period in their life; this includes providing up-to-date information, conducting or directing women to get an individualized risk assessment, discussing treatment options, and arranging for appropriate ongoing monitoring if they decide to pursue hormone therapy.

Up-to-date information. Women like Marcia need to understand the implications of the WHI findings. Talking to them about what the results mean in real numbers and what follow-up studies have found will help them to put it in perspective. There's also a lot of information available on the Internet. Advise women to avoid Web sites that promote products or make dramatic claims and direct them to sites that are accurate and reliable (see *Resources*). Discuss the use of bioidentical hormones in particular, since these are being aggressively marketed on the Internet. If they do decide to use them, make sure they understand the risks and encourage them to get close follow-up.

Individualized risk assessment. Before starting hormone therapy, women need a physical exam, certain

Resources

American Association of Clinical Endocrinologists
www.aace.com/publications/guidelines

National Cancer Institute
www.cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use

National Institutes of Health
http://health.nih.gov/topic/Menopause

North American Menopause Society
www.menopause.org

Women's Health Initiative
www.nhlbi.nih.gov/whi

baseline tests, and to provide a complete history. Be sure the history includes information on risk of breast cancer, CVD, VTE, and osteoporosis. Tests to determine hormone levels aren't usually necessary unless a woman has had a hysterectomy and there's uncertainty about presenting symptoms or menopausal staging.[59] Many factors affect hormone levels, which can differ from one day to another and even within the same day. There's no evidence of any connection between serum hormone levels and menopausal symptoms or response to treatment.[46] All women should have had a mammogram within the previous 12 months.[46] The necessity of bone density testing should be based on individual history.[46]

Before performing a risk assessment, it's important to understand the woman's perception of risk and what she considers to be an acceptable risk-benefit balance. This is necessary to support women in reaching a decision they're most comfortable with.

Discussing treatment options. Treatment decisions should be individualized based on a woman's risk profile, goals of treatment, and personal preferences. For instance, if she complains of vaginal dryness and dyspareunia, then local estrogen is the best option; if her complaint is hot flashes, short-term oral or transdermal therapy should be considered. If she has a history of hypertension, transdermal administration is preferred over oral forms.

Before a final decision is made about therapy, make sure that the patient is aware of alternative strategies. Marcia and women like her should be told of alternative therapies for hot flashes, such as behavioral methods, other medications, phytoestrogens, certain dietary supplements, and acupuncture. There's some evidence to support limited efficacy of these strategies; however, you should advise these women to discuss any alternative therapy with their provider first. There's a lot of misleading information out there, especially on the Internet, and women can end up spending a lot of money on products that are useless and even dangerous.

Women taking estrogen plus progestin must also decide what type of progestin to use. There are a number of different options; the best for any woman is usually a personal choice based on the degree of withdrawal bleeding associated with each method.

Appropriate ongoing monitoring. Assessment and guidance doesn't end when a treatment decision is made. Women need to know that hormone therapy should be used at the lowest effective dose for the shortest period of time, preferably for no longer than five years. A woman's risk-benefit profile must be constantly reassessed and the drug dose decreased as she gets older.[45] Women should be encouraged to strictly adhere to current guidelines for health screening and to promptly follow up on any changes in their health status.

Ultimately, Marcia, like all women, will need to make her own decision about whether or not to use hormone therapy during this time in her life. As a nurse, you can provide the information and support she needs to make the best possible choice. ▼

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Karen Roush is a doctoral candidate at the New York University College of Nursing, New York City; the author of What Nurses Know . . . Menopause *(Demos Health; New York, 2011); and special editorial consultant to* AJN. *Contact author: kr792@nyu.edu.* *The author has disclosed no significant ties, financial or otherwise, to any company that might have an interest in the publication of this educational activity.*

REFERENCES

1. Centers for Disease Control and Prevention. *Women's reproductive health: menopause*. 2009. http://www.cdc.gov/ReproductiveHealth/WomensRH/Menopause.htm.
2. Wilson RA. The obsolete menopause. *Del Med J* 1964;36:20-1.
3. Wilson RA, et al. Specific procedures for the elimination of the menopause. *West J Surg Obstet Gynecol* 1963;71(1):110-21.
4. Wilson RA, Wilson TA. The fate of the nontreated postmenopausal woman: a plea for the maintenance of adequate estrogen from puberty to the grave. *J Am Geriatr Soc* 1963;11:347-62.
5. Kennedy DL, et al. Noncontraceptive estrogens and progestins: use patterns over time. *Obstet Gynecol* 1985;65(3):441-6.
6. Smith DC, et al. Association of exogenous estrogen and endometrial carcinoma. *N Engl J Med* 1975;293(23):1164-7.
7. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med* 1975;293(23):1167-70.
8. Gambrell RD, Jr. Hormones in the etiology and prevention of breast and endometrial cancer. *South Med J* 1984;77(12):1509-15.
9. Gambrell RD, Jr., et al. Reduced incidence of endometrial cancer among postmenopausal women treated with progestogens. *J Am Geriatr Soc* 1979;27(9):389-94.
10. Rossouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-33.
11. Simon JA, et al. The breast cancer "plunge" after initial publication of the WHI results: an alternative explanation. *Maturitas* 2010;66(3):277-84.
12. National Heart, Lung and Blood Institute. *Women's health initiative* [landing page]. National Institutes of Health. 2010. http://www.nhlbi.nih.gov/whi.
13. Anderson GL, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291(14):1701-12.
14. Alving B. NIH asks participants in Women's Health Initiative estrogen-alone study to stop study pills, begin follow-up phase. *South Med J* 2004;97(4):425-6.
15. Grady D, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117(12):1016-37.
16. Stampfer MJ, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991;325(11):756-62.

17. Colditz GA, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332(24):1589-93.
18. Gapstur SM, et al. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA* 1999;281(22):2091-7.
19. Magnusson C, et al. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999;81(3):339-44.
20. Hersh AL, et al. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004;291(1):47-53.
21. Heiss G, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299(9):1036-45.
22. Espeland MA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291(24):2959-68.
23. Rapp SR, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289(20):2663-72.
24. Manson JE, et al. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007;356(25):2591-602.
25. Manson JE, Bassuk SS. Invited commentary: hormone therapy and risk of coronary heart disease—why renew the focus on the early years of menopause? *Am J Epidemiol* 2007;166(5):511-7.
26. Matthews KA, et al. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol* 1996;143(10):971-8.
27. Barrett-Connor E. Hormones and heart disease in women: the timing hypothesis. *Am J Epidemiol* 2007;166(5):506-10.
28. Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297(13):1465-77.
29. Naftolin F, et al. The Women's Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. *Fertil Steril* 2004; 81(6):1498-501.
30. Rosano GM, et al. Hormone replacement therapy and cardioprotection: a new dawn? A statement of the Study Group on Cardiovascular Disease in Women of the Italian Society of Cardiology on hormone replacement therapy in postmenopausal women. *J Cardiovasc Med (Hagerstown)* 2009;10(1):85-92.
31. Herrington DM, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343(8):522-9.
32. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; 340(23):1801-11.
33. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res* 2002;53(3):605-19.
34. Banks E, Canfell K. Invited commentary: hormone therapy risks and benefits—the Women's Health Initiative findings and the postmenopausal estrogen timing hypothesis. *Am J Epidemiol* 2009;170(1):24-8.
35. Centers for Disease Control and Prevention, Division for Heart Disease and Stroke Prevention. *Women and heart disease fact sheet*. 2010. http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_women_heart.htm.
36. Manson JE, et al. Postmenopausal hormone therapy: new questions and the case for new clinical trials. *Menopause* 2006;13(1):139-47.
37. Centers for Disease Control and Prevention. *Breast cancer: rates of new cases and deaths*. 2010. http://www.cdc.gov/features/dsbreastcancertrends.
38. Alkjaersig N, et al. Blood coagulation in postmenopausal women given estrogen treatment: comparison of transdermal and oral administration. *J Lab Clin Med* 1988;111(2): 224-8.
39. Scarabin PY, et al. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17(11):3071-8.
40. Canonico M, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115(7):840-5.
41. Canonico M, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010; 30(2):340-5.
42. Renoux C, et al. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519.
43. Harman SM, et al. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8(1):3-12.
44. Hulley SB, Grady D. The WHI estrogen-alone trial—do things look any better? *JAMA* 2004;291(14):1769-71.
45. Cobin RH, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. *Endocr Pract* 2006; 12(3):315-37.
46. North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause* 2010;17(2):242-55.
47. Bonds DE, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia* 2006;49(3):459-68.
48. Hlatky MA, et al. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002;287(5):591-7.
49. Lethaby A, et al. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev* 2008(1):CD003122.
50. Hays J, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348(19):1839-54.
51. Sauerbronn AV, et al. The effects of systemic hormonal replacement therapy on the skin of postmenopausal women. *Int J Gynaecol Obstet* 2000;68(1):35-41.
52. Youn CS, et al. Effect of pregnancy and menopause on facial wrinkling in women. *Acta Derm Venereol* 2003;83(6):419-24.
53. Endocrine Society. *Position statement. Bioidentical hormones*. Chevy Chase, MD; 2006 Oct. http://www.menopause.org/bioidenticalHT_Endosoc.pdf.
54. U.S. Food and Drug Administration. *For consumers: bioidenticals: sorting myths from facts*. 2008. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049311.htm.
55. Borsage PM, Freeman S. Bioidentical hormones, compounding, and evidence-based medicine: what women's health practitioners need to know. *J Nurse Pract* 2009;5(6):421-7.
56. Cirigliano M. Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt)* 2007;16(5):600-31.
57. Patsner B. *Bioidentical hormone therapy: what's the harm?* Mayfield Heights, OH: North American Menopause Society; 2008. http://www.menopause.org/bioidentical.aspx.
58. Maclennan AH, et al. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2004(4):CD002978.
59. Nelson HD. Postmenopausal estrogen for treatment of hot flashes: clinical applications. *JAMA* 2004;291(13):1621-5.