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Issues in postmenopausal hormone therapy

Depression, endometrial health, and discontinuation

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DISCLOSURES

James H. Liu, MD, reports that he receives grants/research support from Procter & Gamble, Ferring Pharmaceuticals, Teva Pharmaceutical Industries Ltd, Barr-Duramed, Boehringer Ingelheim, and the World Health Organization; and serves as a consultant to Teva Pharmaceutical Industries Ltd and Barr-Duramed.

Veronica A. Ravnikar, MD, FACOG, reports that she serves on the advisory board for Barr-Duramed; is a member of the Cystic Fibrosis Therapeutic Development Network; and is a researcher for Altus Pharmaceuticals, Pharmaxis Ltd, Vertex Pharmaceuticals, and Gilead Pharmaceuticals.

Nanette F. Santoro, MD, reports that she serves as a consultant to QuatRx Pharmaceuticals.

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Introduction

In this case-based discussion, James H. Liu, MD, Nanette F. Santoro, MD, and Veronica A. Ravnikar, MD, FACOG, address evolving information about the role of hormone therapy during the menopausal transition.

In particular, these clinicians discuss the use of hormone therapy in the treatment of depressive symptoms, which many women experience for the first time during the menopausal transition. Emerging data regarding the interaction between the physical and physiologic changes of menopause are reviewed, such as the interplay between hot flashes, night sweats, sleep difficulties, and depression.

Physicians and patients continue to report being confused by conflicting reports of the efficacy and safety of hormone therapy. This panel considers the case of a woman with very typical concerns, and her case illustrates one approach to such patient conversations. Further, these experts offer their suggestions for monitoring endometrial health in patients using nonstandard hormone therapies.

Finally, results published from the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) study prompted one-third of postmenopausal women to discontinue use of hormone therapy. Yet best practices for discontinuation have not been established, and women may experience bothersome vasomotor and vaginal symptoms when attempting to stop hormone replacement therapies. The authors share their experience with discontinuation and review the available literature.

NEEDS ASSESSMENT

Background

American women on average spend one-third of their lifetimes in the postmenopausal period, characterized by diminution of ovarian function with consequent changes in metabolism and body composition. Physical and physiologic changes associated with the postmenopausal state range from annoying to life-threatening. These include hot flushes, night sweats, sleep difficulties, depression, incontinence, sexual dysfunction, osteopenia and osteoporosis, and cardiovascular disease. However, it has been difficult to distinguish changes in bodily composition and metabolism due to normal aging from those due to ovarian senescence. Problems appear to be most common during the menopausal transition, or perimenopause, although the prevalence varies with race, ethnicity, smoking, alcohol consumption, exercise, weight, and general physical condition. As the population of the United States as a whole has aged, with increasing numbers of women in the postmenopausal state, medical researchers have sought remedies for postmenopausal symptoms. For almost 50 years, physicians have recognized that administration of estrogen alleviates hot flushes in some women, although in some women administration of placebo appears also to mitigate the frequency and severity of these thermogenic vasomotor episodes.

Therapy for postmenopausal symptoms has focused on either (1) treating the underlying cause, ie, diminished production of ovarian hormones, or (2) treating the symptoms, ie, difficulty sleeping, bone loss, etc. Selection of hormonal versus nonhormonal treatments must be tailored to a woman's specific circumstances, such as presence of an intact uterus, family history of breast cancer or osteoporosis, individual history of cardiovascular problems, etc. In addition, standard medical practice requires that therapy be based on sound scientific evidence and not place women at undue risk of adverse events. The publications emanating from the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) study led to a one-third decline in the use of hormone therapy by postmenopausal women ages 50 to 74 due to apparent slight, but statistically significant, increases in certain metabolic diseases. Stratification and reanalysis of the data now suggest that in fact hormone therapy does not increase the incidence of either breast cancer or coronary heart disease. The lingering uncertainty regarding the safety of hormone therapy has driven many patients and physicians to consider nonhormonal alternatives that have not proven effective in randomized controlled trials. These include soy, isoflavones, black cohosh, vitamin E, dong quai, evening primrose oil, ginseng, licorice, and acupuncture. Some women with mild hot flushes gain relief with simple modifications of lifestyle.

A substantial proportion of women have resorted to "bioidentical" hormone preparations under the mistaken notion that a bioidentical hormone is better than a US Food and Drug Administration (FDA)-tested and approved preparation. Technically, a bioidentical hormone is one that is structurally identical to a naturally occurring hormone. The term *bioidentical* has come to be used to refer to mixtures of naturally occurring hormones prepared individually for patients by compounding pharmacists. These preparations vary with the person preparing the mixture. In January 2008, the FDA officially warned 7 pharmacy operations that their claims about the safety and efficacy of their so-called "bioidentical hormone replacement therapy" preparations were misleading and unsupported by medical evidence because the mixtures are not tested for purity, potency, efficacy, or safety.

Identification of the Practice Gap

Patients and physicians are confused by conflicting reports of the efficacy and safety of hormone therapy, both FDA-approved and non-FDA-approved bioidentical, as evidenced by the decline in women using hormone therapy despite their desire to continue therapy.^{1,2} A large percentage of postmenopausal women report being worried by news reports that the 2002 WHI report showed that hormone therapy is dangerous.³ Physicians report that the ambiguous and inconclusive results of the WHI reports sent mixed messages to physicians and patients that compromised physicians' ability to discuss hormone therapy with their postmenopausal patients.⁴ Regardless of the type of preparation used, use of hormone therapy must consider the varying formulations available, pharmacodynamics, and individual patient factors.

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of health professionals who care for women from adolescence to postmenopause.

ACGME COMPETENCIES

Patient Care; Interpersonal and Communication Skills

EDUCATIONAL OBJECTIVES

At the conclusion of the educational activity, participants should be able to:

- Identify postmenopausal patients who might benefit from therapy with estrogens, progestogens, and/or androgens, alone or in combination.
- Compare and contrast the benefits and risks of different hormone therapy preparations and regimens, with specific reference to randomized controlled trials such as the WHI.
- Translate reports on efficacy and safety of various hormone therapies into appropriate prescriptive decisions.
- Discuss the issues of concern to patients and approaches to counseling patients about alleviation of postmenopausal symptoms.

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STATEMENT OF SUPPORT

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CASE 1

HT and new-onset depression

Presented by Nanette F. Santoro, MD

Ms D is a 49-year-old woman who reports irregular menses and poor sleep. In the past 2 months, she has had unintentional weight loss of 5 pounds. Ms D says she feels sad most of the time and experiences bouts of crying and helplessness that are making it difficult for her to cope. She works as an executive secretary at a large real estate firm. Her job has become more hectic and stressful since the economic downturn, and she is having difficulty performing her work adequately. She also notes a complete loss of libido, which is causing marital difficulties. She asks whether hormones will help her situation.

Dr Liu: What is the prevalence of depression in middle-aged women?

Dr Santoro: Three recent studies have shown that the rate of new-onset depression during the menopausal transition is substantially higher than previously thought: As many as 25% of women may be at risk.¹⁻³ The risk of experiencing depressive symptoms doubles during perimenopause and increases nearly 3-fold among women who have hot flashes, compared with premenopause (**FIGURE 1**).² Given this surprising finding, clinicians should be alert to the possibility of depression among women who have never had this diagnosis before.

Dr Liu: How do you screen for depression among menopausal women?

Dr Ravnikar: I use a standard questionnaire to screen for depressive symptoms. When patients show signs of depression, I ask how their mood is affecting their quality of life and ability to function. I question them about any bad habits that have developed because of their depression and about thoughts of suicide. For patients already seeing a therapist, I ask about their medications.

When a patient denies changes in function or suicidal thoughts, I readdress the depressive symptoms at the next appointment. With new-onset depression, the patient often does not understand her mood changes because it is the first time in her life she is struggling with these issues.

Dr Liu: What has the Study of Women's Health Across the Nation (SWAN) revealed about the incidence of depression among perimenopausal women?

Dr Santoro: Depression increases in perimenopause. Data from SWAN are still being collected, but other studies have shown that depressive symptoms—measured by the Center

for Epidemiologic Studies Depression Scale (CES-D)—and even major depression increase during perimenopause.²⁻⁴ These mood changes seem to accelerate at the late transition, that is, they are worse when women have more than 3 months of amenorrhea. As women become postmenopausal, the prevalence of depressive symptoms goes down (**FIGURE 2**).^{5,6} Once more women in SWAN are past their final menses, we will be able to tell if the depressive symptoms return to baseline or even improve.

Dr Liu: How are these mood changes linked to hormonal changes?

Dr Santoro: The Penn Ovarian Aging Study showed that hormone fluctuations, rather than absolute hormone levels, are related to depressive symptoms (**TABLE**).⁴ It seems that the rapidly changing hormonal milieu of perimenopause may contribute to the problem.

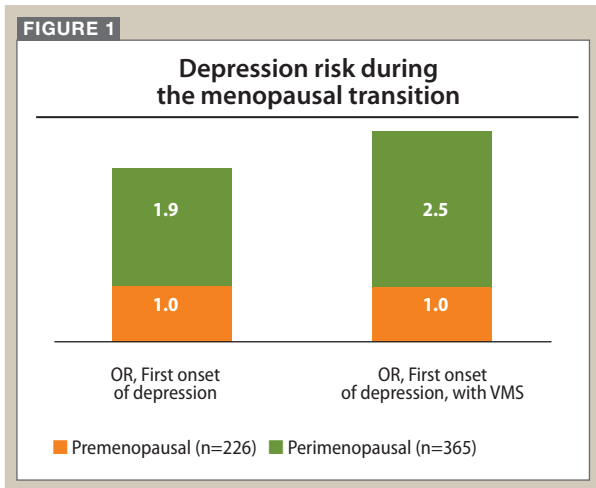
In general, as women become more estrogen deficient, depressive symptoms become more prevalent.⁷ This pattern provides the rationale for using estrogen to treat depression. Women seem to be more vulnerable to depression when estrogen declines most sharply; using a low-dose estrogen may smooth out fluctuations and provide a softer landing.

A number of factors beside hormones are associated with perimenopausal depression. Stressful life events are the strongest predictor of depression, but other risk factors include poor health, low socioeconomic status, cigarette smoking, and nulliparity.⁵

Dr Liu: Dr Santoro, how do you decide on a treatment approach for a patient like Ms D?

Dr Santoro: The first issue is determining how depressed she is. A person who is self-destructive, particularly someone with suicidal ideation and a suicidal plan, needs an immediate psychiatric referral. At that level of depression, it is unrealistic to think that hormones are going to have a major benefit. For such a patient, antidepressant therapy and even hospitalization are more appropriate.

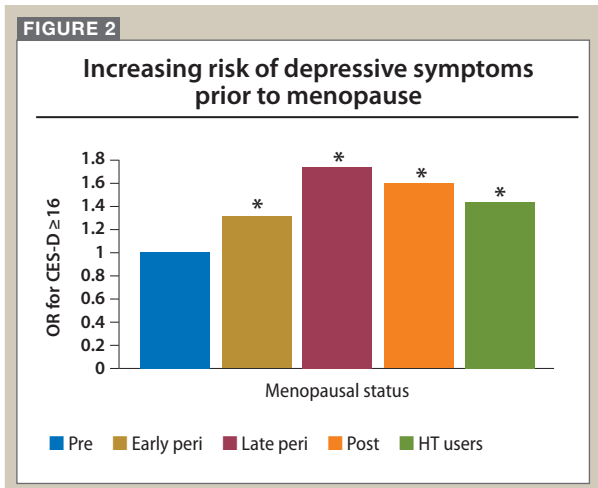
For mild to moderate depression, a trial of hormone therapy (HT) alone could be considered. Studies have shown that HT can produce a modest benefit regardless of whether antidepressants are used concomitantly.⁸ In particular, this may be an appropriate treatment approach if the patient is willing to go to counseling and is likely to come back for a follow-up appointment. It may be possible to make the psychiatric referral and initiate hormones at that same visit.



OR, odds ratio; VMS, vasomotor symptoms.

Risk of first onset of depression, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D), among perimenopausal and postmenopausal women with no lifetime history of major depression. VMS are associated with a greater prevalence of depression.

Cohen L, et al. Arch Gen Psychiatry. 2006;63:386-390.



CES-D, Center for Epidemiological Studies of Depression; CI, confidence interval; HT, hormone therapy.

Premenopause = reference group.

*95% CI does not include 1.

Bromberger JT, et al. J Affect Disord. 2007;103:267-272.

Dr Liu: What role do selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) play in your practice?

Dr Ravnikar: Treatment with SSRIs and SNRIs is complicated and not without risks. I am concerned about treating a potentially hypomanic depressive individual who may worsen on an SSRI. I have seen multiple mildly hypertensive patients who are taking SNRIs at the risk of worsening hypertension. The psychotherapeutic combinations that psychiatrists are using to maximize their well-being are becoming increasingly complex, making it challenging for non-mental health professionals to stay savvy.

I have started a few patients with vasomotor symptoms who were not candidates for estrogen on an SSRI or SNRI after ruling out major depression. For some women, these agents provide relief from vasomotor symptoms and perhaps mild depression. However, I usually refer more complex patients to a psychiatrist for antidepressant therapy.

Dr Liu: Do you prefer certain agents?

Dr Ravnikar: I use venlafaxine most often. I have not seen as many benefits in my patients with fluoxetine, which often acts as a stimulant. Interestingly, I have noticed that many primary care providers use the SSRIs and SNRIs interchangeably for hot flushes, although for many there is no evidence base for their use in treating vasomotor symptoms.

Dr Liu: Many people seem to be choosing venlafaxine and paroxetine because they are available generically.

Dr Santoro: Citalopram has been shown to be effective for vasomotor symptoms in some recent studies.⁹

Dr Liu: Dr Santoro, how did you ultimately treat and follow up with Ms D?

Dr Santoro: Ms D was willing to try a 6-week course of estrogen and begin counseling, but she was reluctant to take an antidepressant. The literature suggests starting patients at 50 to 100 mcg of transdermal estradiol.⁸ Assuming there are no bleeding abnormalities, I do not add a progestin initially because progestin has an effect on mood that may confound the effects of estrogen. If a patient does have irregular bleeding, I perform an ultrasound to check her endometrial thickness. If the thickness is less than 5 mm, I give her estrogen alone for up to 8 weeks and then assess for improved mood. If she feels better, I introduce the progestin for endometrial protection.

Ms D did better with estrogen, but at her follow-up visit she was more willing to go on an antidepressant. Although her mood had improved, it was not enough for her.

Dr Liu: Is 6 weeks of estrogen sufficient to see mood benefits?

Dr Santoro: It may take up to 12 weeks for some depressive symptoms to improve with treatment,¹⁰ but it is difficult for patients to wait for that long for an effect. Therapeutic agents that work more quickly may increase patients' satisfaction with their treatment. Estrogen's effects on mood may be seen a little sooner than with antidepressants, which is one advantage of this approach to therapy.

Dr Ravnikar: The data are controversial as to whether estrogen

alone is sufficient to treat severe depressive symptoms.⁹ Estrogen definitely treats vasomotor symptoms effectively. Is there any indication that estrogen augments the benefit of antidepressants?

Dr Santoro: Yes, when an antidepressant and estrogen are used concurrently, patients seem to do better.¹¹

Dr Ravnikar: I advise patients with depressive symptoms that they are not going to feel better right after starting estrogen. Although not everyone is receptive to this, I think it is important to emphasize that treatment is going to take up to 8 weeks to show benefit, and it may still be necessary to add an antidepressant.

Dr Liu: How did you treat Ms D's libido issues?

Dr Santoro: When treating with an antidepressant, the depression-related loss of libido is replaced with loss of libido due to the SSRI or SNRI. Conversely, estrogen is unlikely to cause loss of libido.

Some interesting research is under way to assess what it is about the menopausal transition that leads to depression¹²: Is it the symptoms of menopause? Is it sleep? Or does depression exacerbate the symptoms? And what predicts who will improve?

Based on this research, it appears that sleep improvement is the first sign of improved mood. For clinicians, asking about how a patient is sleeping may be useful as a barometer of treatment success. If the patient is sleeping

better, it may be worth continuing the current treatment.

Dr Ravnikar: Patterns of wakefulness may be helpful to assess ongoing problems. In sleep studies, the patients whose sleep is disturbed by hot flushes generally have trouble falling asleep or wake up early in their sleep.¹³ Conversely, early morning waking is a common sign of depression. ■

TABLE

Hormone	OR		95% CI	P value
	Unadjusted	Adjusted		
Estradiol				
Mean	1.10	1.06	(0.63-1.78)	.83
SD ^{a,b}	1.30	1.36	(1.02-1.80)	.03
FSH				
Mean	4.38	4.58	(2.03-10.35)	<.001
SD ^{a,b}	1.90	2.09	(1.70-3.41)	<.001
Inhibin B				
Mean	0.34	0.37	(0.20-0.66)	<.001
SD ^{a,b}	1.32	1.20	(0.89-1.60)	.21
LH				
Mean	2.98	3.00	(1.52-5.93)	.002
SD ^{a,b}	1.57	1.57	(1.18-2.22)	.005

CES-D, Center for Epidemiological Studies of Depression; CI, confidence interval; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OR, odds ratio; SD, standard deviation.

^aSD is the deviation of the hormone measures around the subjects' mean, calculated for each subject at each assessment period. ^bRefers to odds per 1 unit change in SD.

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CASE 2

Estrogen and endometrial health

Presented by Veronica A. Ravnikar, MD, FACOG

Mrs K is a 53-year-old woman with vasomotor symptoms. She was started on a daily combination of conjugate estrogen (CE), 0.3 mg, and medroxyprogesterone acetate (MPA), 1.5 mg. This regimen controls her hot flushes but is causing bothersome breakthrough bleeding. Mrs K also read about the Women's Health Initiative (WHI) on the Internet and is now reluctant to take CE+MPA. This is despite the fact that she is on

half the dose of hormones used in WHI. Her medical history is significant only for a previous cesarean delivery. Her paternal grandmother had breast cancer at age 80.

Dr Liu: How would you address Mrs K's concerns about her HT and the WHI?

Dr Ravnikar: I have written up a synopsis of the WHI data for my patients. In addition to describing the study drug doses and the risks reported in the initial publication, my handout highlights findings from subset analyses of the WHI showing that overall risk of cardiovascular disease is different in younger women.¹⁴ I emphasize that they are taking the hormone for an FDA-approved indication. It is important that these patients understand that they probably will not have to take hormones for the rest of their lives.

Dr Liu: Looking at the most recent WHI data, the 2 major risks really are (1) clotting, leading to a thromboembolic event or stroke, and (2) an association with increased breast cancer risk.¹⁵ Current data suggest that the cardiovascular risks in younger women are minimal, so I de-emphasize that as one of the risks.

Dr Ravnikar: Yes, the incidence of cardiovascular events is very low and was a consistent finding in the younger-aged women, between 50 and 59 years. In the entire WHI cohort from ages 50 to 79, the risks were increased for coronary heart disease (CHD), stroke, and invasive breast cancer. The dose of E+P used in WHI was 0.625 mg CE and 5 mg MPA. It is difficult to say whether these statistics apply to half the dose of the same EPT combination (0.3 mg CE and 1.5 mg MPA).¹⁶ In the WHI ancillary Coronary Artery Calcium Study, women who averaged 55 years of age, had surgical menopause 11 years before, and were on estrogen (no progestin use) for an average of 7.4 years had a 42% reduction in coronary calcifications and a 30% reduction in total mortality.¹⁷ Short-term use of estrogen therapy around the time of menopause will certainly benefit vasomotor symptoms, urogenital atrophy, and skeletal health, and likely has no deleterious effect on CHD and no increased risk for breast cancer.

Long-cycle progesterone therapy (LCPT) studies are difficult to compare, since most of the studies are open label, and they use different durations and dosages of progestin therapy. In general, either 5 or 10 mg of progestin for at least 14 days has been shown to be optimal for use either monthly or every 3 months.¹⁸ Women on lower doses of estrogen still need to be opposed by progestin periodically.¹⁹

Dr Santoro: The WHI data show that cardiovascular risk was not decreased overall, but they did not show an increase in cardiovascular disease risk in the combined data. Younger women are less likely to have a cardiovascular event, in any case.

The biggest concern for most of my patients is the risk of breast cancer, despite its being a small risk. I describe it to patients in terms of absolute risk over time and explain that with estrogen and progestin therapy, the risk only emerges after a number of years of treatment. However, there probably is no lower limit of exposure that causes absolutely no increase. Second, I explain that the magnitude of the

risk for every year of HT is similar to what a woman would have were she to experience menopause that number of years later. That puts the risk into a physiologic context for patients.

Dr Liu: What type of treatment did you recommend for Mrs K?

Dr Ravnikar: I explained to her that HT would be the best treatment for her symptoms. She was unwilling to continue CE, so I discussed the oral and transdermal alternatives. In this case, I changed her to oral 17-beta estradiol, 1 mg, with micronized progesterone, 200 mg, for days 1 to 15. I told her that she could take the progestin every 3 months. The literature indicates that the risk of taking the progestin every 3 months is minimal. A 5-year, Swedish study of 129 women taking CE, 0.625 mg/day, with MPA, 10 mg, for 14 days every 3 months, showed acceptable rates of bleeding, with 56% of women developing an atrophic endometrium.¹⁸ Withdrawal bleeding may be heavier, with a longer interval between progestin administration, but women generally find this less bothersome than unscheduled bleeding.

However, it has been shown that even low doses of estrogen must be opposed by progestin periodically. The HOPE trials studied both the bleeding and hyperplasia rates on lower estrogen doses (0.3 mg or 0.45 mg) with or without MPA (1.25 mg or 2.5 mg). The hyperplasia rates with unopposed, low-dose estrogen were low but not zero.¹⁹

Dr Liu: What factors do you consider when selecting a type and interval of progestin exposure?

Dr Ravnikar: Other than the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial,¹⁹ most of the data about using a progestin every 3 months come from studies using CE, 0.625 mg, and then MPA, 10 mg.¹⁸

Mrs K wanted to switch to a "natural" progesterone cream, for which there are no data. I suggested that she use micronized progesterone instead. The combination of transcutaneous estrogen and micronized progesterone is being used more commonly, although good supporting evidence is still lacking. We do have large cohort studies from Europe that showed no increase in breast cancer risk with micronized oral progesterone.²⁰⁻²² Since there is no evidence-based standard, I monitor my patients very closely.

I selected a dosage of 200 mg because when it is taken every 3 months, I think a slightly greater progesterone effect is necessary. The Postmenopausal Estrogen/Progestin Intervention (PEPI) study used monthly cyclical micronized progesterone at 200 mg.²³

Dr Santoro: Many of my patients dislike the progestin, and if I put them on a regimen of progestin every third month,

many will wait 4 or 5 months before taking it. In those cases, I try to bargain for every other month and figure they will probably take it every 3 months or so.

Monitoring is critical in the absence of a standard. A transvaginal ultrasound is sufficient for most patients. I am comfortable changing a hormone regimen as long as it is possible to continue endometrial monitoring.

Dr Liu: If the endometrial thickness is 5 mm or less, I feel that the progestin is adequately opposing the estrogenic effect. What measurement do you look for?

Dr Ravnikar: PEPI showed that for serious endometrial disease, endometrial thickness at a threshold of 5 mm had a poor positive predictive but a high negative predictive value.²⁴ Common consensus indicates that 5 mm or less is acceptable. I measure within the month after the patient takes the progesterone because a random measurement on estrogen may reveal a little bit of a proliferative lining that is easily opposed by progesterone.

Dr Santoro: Individuals with a stable endometrium are probably less likely to develop adverse effects of therapy. Serial monitoring that shows no change in thickness is reassuring, even if the endometrium is 4 to 5 mm. I perform a

biopsy on patients who have unscheduled bleeding.

Dr Liu: Returning to the case, you discover that Mrs K forgot to tell you she had a thermal ablation for menorrhagia when she was 48 years old. Does she still need progesterone? If so, how would you assess its effectiveness?

Dr Ravnikar: I tell all patients that they still need the progesterone even after ablation. The pockets of endometrium that remain after an ablation could still become hyperplastic if estrogen is unopposed. Mrs K was not amenorrheic, so I gave her progesterone on a scheduled basis.

Women who do not have a withdrawal bleed after taking progesterone also frequently ask if they need progesterone; I believe that they do.

Dr Liu: In my experience, the necessity of progesterone depends on the type of ablation they had. The thermal ablation does not seem to be as effective as some of the newer bipolar techniques that partially destroy myometrium. Some individuals do not have a true, organized endometrial stripe after an ablation, which makes it difficult to evaluate the efficacy of the progestin. In those cases, I assess them based on bleeding pattern and ensure that they do not have a hematometra. ■

CASE 3

Discontinuing HT

Presented by James H. Liu, MD

Ms J is a 55-year-old menopausal woman with no chronic medical conditions. At age 49, she began taking estradiol, 2 mg/d, and MPA, 2.5 mg/d, to treat severe vasomotor symptoms and vaginal dryness. This regimen successfully alleviated her symptoms. Her life situation has changed dramatically in the past 6 months due to divorce. She is no longer sexually active and now wants to stop HT.

Dr Liu: The data show that many women have discontinued HT in the past decade (**FIGURES 3 AND 4**).^{25,26} However, women who start HT for menopausal symptoms may experience flushing, sleep disturbances, or vaginal dryness again upon discontinuation.²⁷ The symptoms may last as little as a few months to more than a year. This effect seems to be less severe in women who are older than 55. How would you counsel a patient on stopping HT and the symptoms she should anticipate?

Dr Santoro: The effects of stopping hormones are very individual. I tell patients that they will not know how discontin-

uing HT is going to affect them until they try. Furthermore, if the weaning attempt fails, we know what benefits the hormones are providing and why therapy is still necessary.

Dr Ravnikar: People have tried day and dose tapers, but supporting studies are limited. I use the patch to wean patients, even with those on an oral therapy, because there are many dosages to work with. I encourage patients to try other ways of managing hot flashes: Experience shows that weight loss can help ease the transition for obese women and exercise decreases hot flashes for everyone.²⁸

I advise patients that there may be some bad days and breakthrough hot flashes. With a slow taper and plenty of encouragement, most patients can discontinue HT. Patients who are on very high estrogen doses have the most difficulty tapering, but this is becoming less common.

Dr Liu: Very little has been published about this topic. One small, randomized trial (N=70) ultimately showed no difference between the group that tapered and the one that stopped abruptly.²⁹

Dr Santoro: However, in that study, the patients who tapered felt a little better during the withdrawal.²⁹

Dr Liu: Cohort studies have shown the same thing.^{30,31}

Because Ms J was taking estrogen and the MPA separately, it may be possible to taper the estradiol orally first, while maintaining the MPA, and then tapering the MPA, which does have some effects on hot flashes.

Which patients have a particularly difficult time tapering hormones?

Dr Santoro: Women who have had a hysterectomy seem to have worse symptoms.³²

Dr Ravnikar: In the WHI, younger women seemed to have stranger symptoms when they stopped hormones abruptly.³³ This group had musculoskeletal joint symptoms and more neurologic symptoms.

Dr Liu: There probably is a very small group of women who cannot be tapered off due to severe vasomotor symptoms.³²

Dr Ravnikar: In my experience, many patients who stop estrogen do not respond to estrogen if they restart it. If a patient cannot completely stop estrogen, I encourage them to stay on a low dose, usually 0.375 mg of transcutaneous estrogen.

Dr Santoro: The literature suggests that 10% to 15% of women in their 60s remain symptomatic, and some cannot or will not stop HT; this prevalence declines among women in their 70s.^{27,34} For such women, I weigh the risks and benefits of continuing hormones. If it is still in an acceptable range, I continue to monitor them for another year and periodically recommend that they try an alternative. The toughest cases are those individuals with terrible vulvovaginal symptoms, because there is no alternative to estrogen for them.

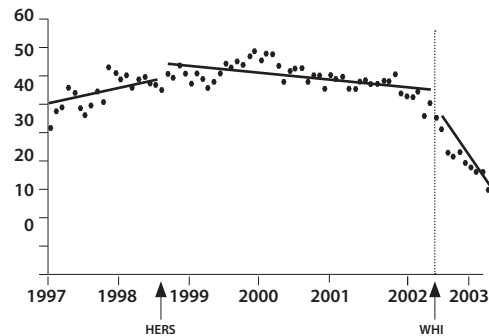
For women in whom the risk of hormones was too great to continue, I have had luck using SSRIs to manage their hot flashes. Low doses of gabapentin (100 to 300 mg) have also helped some women. Because gabapentin can make some women sleepy, I recommend starting it on a weekend.

Dr Ravnikar: I have used gabapentin successfully in patients who are very symptomatic after discontinuing estrogen or with very low doses of estrogen. Although the literature supports use of very high doses of gabapentin,³⁵ I also use much lower doses. I do not usually use gabapentin as a single agent or a first-line agent for vasomotor symptoms because of the somnolence and because I have to continually increase the dose.

Dr Liu: In sum, it seems that the side effects of discontinuing estrogen can be worse than the original symptoms. Managing the patient's expectations before they

FIGURE 3

Rates of hormone therapy use among postmenopausal women, 1997-2003



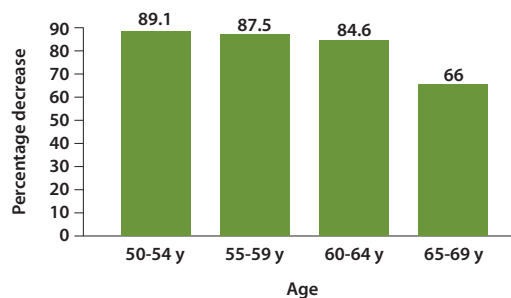
The first vertical line represents the publication date of the Heart and Estrogen/progestin Replacement Study (HERS) in August 1998. The second vertical line represents the publication date of the Women's Health Initiative (WHI) in July 2002. Circles represent unadjusted rates of current hormone therapy use for each month between January 1997 and May 2003. Lines represent the adjusted change in hormone therapy use for 3 time periods: before the publication of HERS, after the publication of HERS, and before and after the publications of the WHI.

Change in hormone therapy use is adjusted for age, race or ethnicity, history of childbirth, family history of breast cancer, history of breast biopsy, previous hysterectomy, and median income for the ZIP code of residence.

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FIGURE 4

Change in hormone use since WHI by 2007



WHI, Women's Health Initiative.

Barbaglia G, et al. *Menopause.* 2009;16:1061-1064.

stop taking HT is probably the most important aspect of discontinuing HT because, unfortunately, there is little evidence to guide tapering practices. Tapering estrogen to every other day may be a gentler approach to discontinuing hormones, although the literature shows no major difference between stopping abruptly or gradually. ■

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CME Questions

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1. At what age is the prevalence of depression the greatest for a woman?
 - A. 20
 - B. 30
 - C. 40
 - D. 50
 - E. 60
2. Improvement in which of the following menopause-related symptoms is most closely associated with improvement in depression?
 - A. Hot flushes
 - B. Vaginal dryness
 - C. Libido
 - D. Sleep
 - E. Urinary frequency
3. The nonhormonal factor best associated with depression during the menopausal transition is:
 - A. Prior history of depression
 - B. Obesity
 - C. Late menopause (after age 54)
 - D. Hysterectomy with ovarian conservation
 - E. Perceived stress
4. Ancillary studies in the Women's Health Initiative (WHI) have shown that in the younger menopausal female (age 50-59)
 - A. Coronary heart disease increases and VTE increases
 - B. Coronary heart disease decreases and VTE decreases
 - C. Coronary heart disease decreases and VTE increases
 - D. Coronary heart disease does not change and VTE increases
 - E. Coronary heart disease increases and VTE does not change
5. A patient with a balloon endometrial ablation can be treated with a combination estrogen-progesterone transcutaneous patch or
 - A. Estrogen therapy alone
 - B. Progesterone therapy alone
 - C. Long-cycle progesterone therapy
 - D. Progesterone cream
 - E. Sequential estrogen-progesterone therapy
6. Which of the following is likely to occur when estrogen is opposed with a progestogen every 3 months:
 - A. Transitory endometrial hyperplasia
 - B. Heavier withdrawal bleeding
 - C. Decreased compliance with therapy
 - D. Irregular bleeding patterns
 - E. Increased blood pressure
7. Which one of the following symptoms would not be expected upon stopping hormone therapy?
 - A. Sleep disturbances
 - B. Joint stiffness
 - C. Vaginal dryness
 - D. Loss of long-term memory
 - E. Headaches or migraine
8. In studies that have examined women who have stopped hormone therapy, the major reason for restarting hormones is:
 - A. Mood changes
 - B. Cognitive decline
 - C. Severe vasomotor symptoms
 - D. Vaginal dryness
 - E. Weight gain
9. Which one of the following strategies appears to lessen the discomfort of discontinuing hormone therapy?
 - A. Changing to transdermal estrogen
 - B. Starting a selective serotonin reuptake inhibitor
 - C. Adding a progestin
 - D. Starting black cohosh
 - E. Tapering the estrogen dose to every other day
10. In the HOPE trial, lower dosages of unopposed estrogen, ie, 0.3 mg/d and 0.45 mg/d, were associated with:
 - A. Increased vaginal bleeding
 - B. Lower incidence of endometrial hyperplasia
 - C. Increased breast tenderness
 - D. Persistent hot flushes
 - E. Increased headaches