The art and science of managing perimenopause

By Mary Jane Minkin, MD

While managing menopausal patients can be difficult, the real challenge comes in treating perimenopause. This case-based approach offers several practical tips.

In the early days of daytime talk show television, Phil Donohue used to discuss menopause as if it were an overnight phenomenon: You go to bed premenopausal one night, and wake up the next morning postmenopausal. Unfortunately, it's not that easy. For many women, symptoms are the most annoying during those years surrounding the last menstrual period.

Adding insult to injury, patients often become frustrated because we can't even tell them they're perimenopausal. Menopause is itself a retrospective diagnosis. When a woman goes a year without a menstrual period, you can tell her she is now postmenopausal. Patients eagerly purchase home testing kits to check urinary or salivary FSH, and are disappointed when they find out that the test is meaningless: You don't need a significantly elevated FSH to say to a 53-year-old woman who hasn't had a period in 4 months and is having lots of hot flashes that she is perimenopausal. Similarly, elevated FSH will not tell her that she will have no more menstrual periods. Not until the STRAW study (Study of Reproductive Aging Workshop), in 2001, was an official nomenclature even established to define perimenopause. It was defined as the variable-length time frame during which menses become more erratic (greater than 7 days different from normal), and lasting through the 12 months of amenorrhea from the last menstrual period.[1]

As you may already realize, perimenopausal management is significantly more complicated than postmenopausal management. With that in mind, we'll consider three different patients presenting during this time frame, and discuss approaches to the management of each.

1 *Ms. Abrams, 40-years-old, used to bleed every 28 days, but is now bleeding every 21 days.*

Among the first questions I would ask this patient is, "Do you still plan to get pregnant?" Is her family complete, or is she just getting ready to start? I would also like to know for how long this menstrual pattern persisted, and is she charting her cycles? How heavy are the menses now, compared to her previous typical menses? Has she noted any other physical symptoms (fatigue, constipation, or hair loss) that might suggest other systemic disorders, such as hypothyroidism? Is she a high-risk candidate for endometrial cancer, i.e., is she obese, diabetic, hypertensive, or nulliparous?

My evaluation strategy is always based on Sutton's Law: Go where the money is.[2] After a thorough exam, I would check TSH levels to rule out hypothyroidism, and would check her endometrium to rule out pathol-

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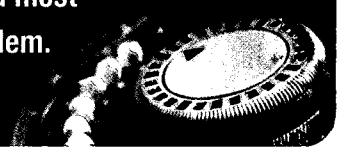
For many women, just the reassurance that they are normal is sufficient, and they will not want medical intervention (i.e., they are happier having 21-day cycles than taking medication). For women who are annoyed by their cycles, low-dose OCs are usually the best tolerated and most successful approach to this problem.



ogy. (This can be done by your procedure of choice: sonohysterography, simple ultrasound, or biopsy.) I would obtain a day 3 FSH level if Ms. Abrams were hoping to conceive. If the level were elevated, I would have her see a reproductive endocrinologist and if FSH weren't elevated, strongly encourage her to accelerate her childbearing plans. If this patient were done with her childbearing, I wouldn't check FSH. Although 40 years of age is certainly a bit early for perimenopausal changes, it's not unusual; at least 1% of women are menopausal by age 40. Lastly, it's wise to run a CBC to make sure that this more frequent flow has not rendered her anemic.

If Ms. Abrams has a normal endometrium and normal thyroid function—the likely scenario—the next thing to do is to reassure her that she is indeed normal, and to discuss the physiology of perimenopause. Explain that declining levels of progesterone most likely account for her changing menstrual pattern. You then need to explore what she would like. For many women, just the reassurance that they are normal is sufficient, and they will not want medical intervention (i.e., they are happier having 21-day cycles than taking medication). For women who are annoyed by their cycles, low-dose OCs are usually the best tolerated and most successful approach to this problem. Obviously, smokers and women with a history of thrombophlebitis and certain rarer medical conditions are not candidates. But for the typical healthy 40-year-old, OCs are your best bet.

[I usually start these women on a 30 µg pill; often with a 20 µg pill they will get breakthrough bleeding, which will only annoy them because you've failed to treat the problem they saw you for, namely bleeding. If they do well with 30 µg, step them down to 20 µg if you would like to.] And remember that women in their 40s are a very high-risk group for unintended pregnancies, so you are actually providing them with contraception as well as control of their menses.

Another approach is to insert a progesterone intrauterine system, such as Mirena. Although you won't be spacing out menses, these women will bleed much less during their periods, giving them a 1- or 2-day period, in general, so that they are less annoyed.

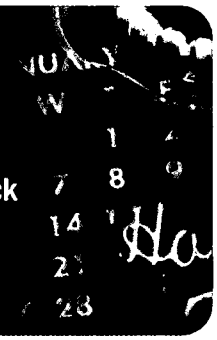
Another option would be cyclical progestins: Starting a progestin on the 14th or 15th day of the cycle, and administering it for 10 to 12 days, may prolong the cycle. In general, it's not as successful as OCs, and it is more difficult for the patient because she needs to time the medication with her cycle; but if the patient is not a candidate for the other options, she may want to try this option.

2 *Ms. Barcelli, 43-years-old, is waking up at 2 AM every morning.*

Many women find sleep disruptions the most annoying aspect of perimenopause. I ask every patient I see in her 40s, "How well do you sleep?" and the typical answer is, "Lousy, but why are you asking? You're my gynecologist." Patients often don't realize that sleep disruption is a common feature of perimenopause. Of course, sleep disruption is a common problem for many women. It's commonly associated with depression; but the sleep pattern associated with depression as well as exogenous stress is usually difficulty *falling* asleep. Perimenopausal women

Obtain day 3 FSH if patient wants to conceive . . . Rule out hypothyroidism . . . One approach: Insert a progesterone IUS . . . or prescribe cyclic progestins . . .

I find zaleplon helpful in perimenopausal women. It has a relatively short half-life, so that if a woman wakes up at 1 AM, she can still take this medication to help her get back to sleep quickly, and allow her to wake up and go to work at 6 AM.



classically pass out at 10 PM, but wake up spontaneously, or with a hot flash, at 2 AM. Many will turn to alcohol at this point in their lives, and alcohol can disrupt sleep.

Some women develop problems with fibromyalgia, or other pain syndromes, which can also manifest themselves as sleep disruption. And with the current epidemic of obesity, we are seeing more women with sleep apnea, which may present with awakening. You would obviously ask Ms. Barcelli about any other symptoms of menopause: irregular menses, hot flashes, and vaginal dryness particularly.

A medical history can be more helpful than lab tests in this situation. If this patient's only problem is sleep disruption, and you elicit a history of snoring, and she is obese, referral to a sleep evaluation center may be helpful and even life-saving. Histories suggestive of fibromyalgia or alcoholism obviously require further workup.

But if everything else is negative, you can approach the problem in several different ways. [Encourage some basic sleep hygiene. Joan Shaver, PhD, RN, refers to the basic tenets as the four Rs:[4] ***regularize***, ***ritualize***, ***relaxation***, and ***resist***.] She encourages patients to ***regularize*** their sleeping hours and keep them consistent from day to day, getting up at the same time every day. Patients should also establish a ***ritual*** as they prepare for sleep, and use the bedroom for sleep only. As far as the third R is concerned, you can suggest warm baths, ***relaxation*** techniques, and deep breathing. And finally patients will want to ***resist*** activities that interfere with sleep: caffeinated beverages, large meals, strenuous exercise, or intensive mental and emotional stimulation close to bedtime.

Sleeping medications are also an option but many patients will be concerned about habituation and you obviously don't want a patient to be dependent on sleeping medications every night. However, if Ms. Barcelli has had several poor nights of sleep in a row, medicating her with a hypnotic may be appropriate. I find zaleplon helpful in perimenopausal women. It has a relatively short half-life, so that if a woman wakes up at 1 AM, she can still take this medication to help her get back to sleep quickly, and allow her to wake up and go to work at 6 AM. Zolpidem, on the other hand, has a longer half-life, so it's best taken before bedtime. Some of the newer sleep medications, such as eszopiclone and ramelteon, are not related to benzodiazapines, and are supposedly less likely to be habit-forming—but they too require you to take them before going to sleep.

A less orthodox method is to assume that this patient's sleep disturbance is hormonal and experiment with a trial of estrogen. I offer patients a low dose of estrogen, such as a 0.05-mg patch. In these situations, the patient may do better with a patch, which provides stable steady-state levels of estradiol. I then ask her to chart her sleep over the next month or two. If she is clearly sleeping better, then you need to explore with her longer-term use of the estrogen. If she were still having regular menses, I probably would not add progestin therapy, but would ask her to monitor her menses, and have her check in with me in a few months.

3 *Ms. Cohen, 48-years-old, is still having regular periods but she can't sleep, has hot flashes at night, and an FSH of 20.*

Ms. Cohen is your classic perimenopausal patient. The most effective therapy here, if she is

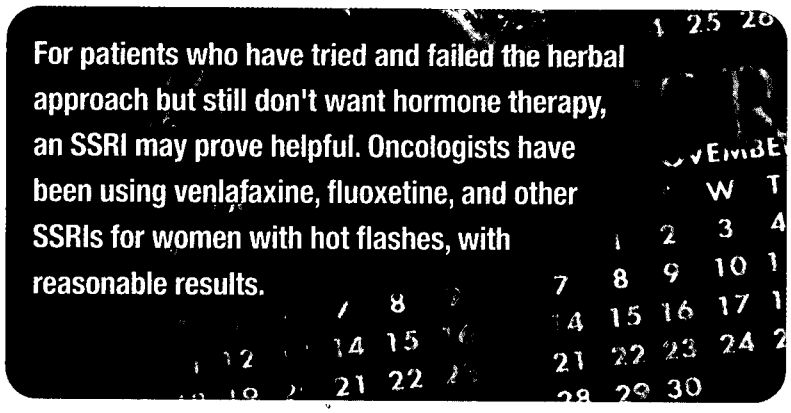
Fibromyalgia can manifest as sleep disruption . . . Urge patients to establish sleep ritual . . . Zolpidem best taken before bedtime . . . Some patients benefit from 0.05-mg estrogen patch . . .

an appropriate candidate, is a low-dose OC. In this patient, I would try 20 µg. And of the 20 µg pills available, she would be a very good candidate for a formulation that has 20 µg of ethinyl estradiol in the active pills, and 2 mg of 17 ß-estradiol in the last five of the "placebo" pills, which will keep her asymptomatic during the "placebo" week. Indeed, if any patient is symptomatic the week off standard pill therapy, you can always administer the pills in an uninterrupted sequence, or administer low-dose estrogen the week off of active pills.

Of course you can also use low-dose hormones—some experts would recommend no additional progesterone, some would advocate cycling (noncontinuous) therapy to match her menses.

If this patient prefers no hormonal intervention, she might find relief by adding soy products to her diet—there is no word for hot flash in Japanese, the country with the highest soy intake in the world. The efficacy data on soy supplements are a bit more controversial.[5] Another nonmedical approach would be black cohosh. Manufactured in Germany for 50 years as the product Remifemin, its efficacy and safety in some studies are documented, although the exact mechanism of action is not known.[6] Soy, of course, is a weak plant estrogen; cohosh is not. There are really very little data on any other herbal/botanical approach.

For the patient who has tried and failed the herbal approach, but still does not want (or is not a candidate for) hormonal therapy, you can use the SSRI (and SNRI) anti-depressant route. Oncologists have been using venlafaxine, fluoxetine, and other SSRIs for women with hot flashes, with reasonable results.[7] [One major concern with these medications is the loss of libido, which occurs in 30% to 60% of women.[8] Many perimenopausal women are already experiencing a decrease in libido, and they don't need further exacerbation of an already extant problem.] And a few women will experience weight gain with SSRIs, which for most is a very unwelcome side effect.



As we have already discussed, sleep medications may be used judiciously with any of these interventions. But the clinician and the patient will both want to avoid habituation to any sleep medication.

As you can see, the management of the perimenopausal patient is often more complex than managing a fully menopausal patient. But relieving the discomforts of a typical 40- to 50-year-old woman, who may well have a very demanding job, with the additional responsibilities of taking care of her children, parents, and extended family, and keeping her happy and healthy, can be quite gratifying. □

REFERENCES

1. Executive summary: Stages of Reproductive Aging Workshop (STRAW) Park City, Utah, July, 2001. *Menopause.* 2001;8:402-407.
2. Petersdorf R, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore).* 1961;40:1-30.
3. Coulam CB, Adamsen SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol.* 1986;67:604-606.
4. Eichling PS, Freedman R, Polo-Kantola P, et al. Clinicians Forum (menopausal impact on sleep). *Menopause Management.* 2005;14:25-29.
5. Albertazzi P, Pansini F, Bonaccorsi G, et al. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol.* 1998:91:6-11.
6. Osmers R, Friede M, Liske E, et al. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol.* 2005;105:1074-1083.
7. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol.* 2002;20:1578-1583.
8. Gregorian RS, Golden KA, Bahce A, et al. Antidepressant-induced sexual dysfunction. *Ann Pharmacother.* 2002;36:1577-1589.

Consider 20-µg OC in classical patient . . . Soy and black cohosh may help some women . . . Caution: SSRIs can cause weight gain.