

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

Question: How do you manage the woman who is newly menopausal, suffering from disruptive vasomotor symptoms and night sweats, but suffered a severe deep venous thrombosis during her one and only pregnancy 20 years ago? What workup, therapy, and follow-up would you suggest?

Answers:

With documented deep venous thrombosis (DVT) related to pregnancy, it is my opinion that hormone therapy (HT) is not an option. That is, I would not prescribe any

HT, including low-dose systemic therapy via transdermal or cutaneous routes, or local vaginal estrogen therapy (ET). Also, I do not recommend progestogens, or selective estrogen-receptor modulators (SERMs, which may exacerbate vasomotor symptoms) in this group of women. Regarding workup, I would not order a coagulation evaluation as I do not need further proof that this woman is at high risk for another thrombosis with HT. If coagulation issues (other than those related to HT) are of concern, I would refer the woman to a hematologist.

How would I manage the woman in this scenario? I basically follow the algorithm of care that The North American Menopause Society (NAMS) suggests, with intervention based on severity of symptoms.¹ First and foremost, I would determine if the woman actually desires treatment. Although 85% of newly menopausal women report vasomotor symptoms, about half of them do not find their symptoms distressing. Many of my newly menopausal patients report vasomotor symptoms to me not because they want an intervention, but rather because they want me to validate that they are indeed menopausal.

In this group, as with women who report mild hot flashes and do want an intervention, I counsel them on lifestyle-related strategies.



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These include maintaining a cool core body temperature, engaging consistently in exercise, wearing loose fitting, layered clothing, and avoiding hot flash triggers, such as spicy foods, caffeine and hot soups. I also encourage the use of yoga-like techniques to promote relaxation. For one such technique—paced respiration—I instruct symptomatic women to

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— Gloria Bachmann, MD

start taking slow, deep breaths when they feel the sensation of a hot flash commencing. Staying in areas with good air circulation (or using a fan) and drinking/eating cold foods and beverages are also preventive strategies.

Some over-the-counter treatments may also be useful; while consistent efficacy has not been shown in the majority of clinical trials, no serious adverse events have been reported either. Therefore, soy foods, isoflavone supplements, black cohosh and vitamin E may also be suggested. I do not recommend supplement-type remedies such as dong quai, evening primrose oil, licorice and ginseng, which have shown little or no efficacy. Acupuncture and magnet therapy lack efficacy trials.

For women with moderate to severe symptoms, I prescribe an antidepressant, such as venlafaxine, paroxetine or fluoxetine. I start with the lowest dose suggested to treat depression. I also have found that if one antidepressant doesn't work, another may. With the use of antidepressants, a decline in mean hot flash composite score of up to 60% can be expected.² Recent data on the anticonvulsant gabapentin suggest that this intervention may be as efficacious as estrogen. In a report on a small cohort of women by Reddy et al,³ gabapentin titrated to 2,400 mg/d demonstrated a 71% reduction in hot flash composite score compared with a reduction of 72%

with 0.625mg/d of conjugated estrogens.³ I usually stay away from prescribing clonidine and methyldopa, two antihypertensive agents that have modest efficacy but a relatively high rate of adverse effects. Placebo alone reduces mean hot flash scores by up to 25%.⁴

Although no intervention has consistently been shown to equal ET in alleviating vasomotor symptoms, a combination of lifestyle modification, nonpharmacologic strategies and/or pharmacologic interventions usually will decrease the intensity and frequency of hot flashes for most women. One other important counseling point is that most women with vasomotor symptoms will note that they spontaneously resolve with time. Therefore, use of prescription and over-the-counter interventions should be evaluated on an annual basis to determine if continued intervention is necessary.

— Gloria Bachmann, MD

References

1. The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004;11:11-33.
2. Stearns V, Beebe KL, Iyengar M, et al. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003;289:2827-34.
3. Reddy SY, Warner H, Guttuso T Jr, et al. Gabapentin, estrogen, and placebo for treating hot flashes. *Obstet Gynecol* 2006;108:41-48.
4. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057-71.

Because of the history of a DVT during pregnancy, I would not prescribe conventional HT (estrogen plus progestin) for the treatment of vasomotor symptoms. In addition, I am also concerned that this woman may have a genetic predisposition to hypercoagulation. In the past I have referred such patients to a hematologist colleague, but at his recommendation I now obtain initial testing for lupus anticoagulant, factor V Leiden, prothrombin mutation, and methylenetetrahydrofolate reductase (MTHFR) mutations as well. (Variations in the MTHFR gene are associated with elevated homocysteine levels, leading to cardiovascular disease.)

In terms of actual therapy there are several nonhormonal options that one could suggest

and prescribe. I would remind the patient to take the following steps:¹

- Get regular exercise to promote better, more restorative sleep
- Keep cool by dressing in layers, using a fan and sleeping in a cool room
- Enhance relaxation with meditation, yoga, massage or a leisurely lukewarm bath
- Try using paced respiration when a hot flash starts (deep, slow abdominal breathing)
- Avoid hot flash triggers (hot drinks, caffeine and alcohol).

Additionally, there are double-blind, randomized, placebo-controlled trials showing that the antidepressants venlafaxine (37.5–75 mg/d), paroxetine (12.5–25 mg/d) or fluoxetine (20 mg/d) are options for such a woman.² It should be pointed out that some of the trials were performed on breast cancer patients receiving tamoxifen, so these findings may or may not be appropriate to extrapolate to the situation of our patient at-hand. Finally, a recent randomized, placebo-controlled trial showed gabapentin to be as effective as estrogen in reducing vasomotor symptoms.³ Reduction in the hot flash score was 72% for conjugated equine estrogens, 71% for gabapentin, and 54% for placebo. Other alpha-2 delta ligands (gabapentin is one) are in development, as are compounds metabolically similar to selective serotonin-reuptake inhibitors (SSRIs).

So far, this is easy and straightforward. However, what do you do if the patient is not getting adequate relief from these nonhormonal methods, and is still experiencing disruptive symptoms? If she has a genetic basis for thrombosis I would not use HT. I would suggest that her offspring—especially daughters—be tested before embarking on childbearing. If genetic testing is all

negative, and all other therapies fail, some physicians would give very low-dose HT with baby aspirin. I know of no data to support this, but if the symptoms are truly disruptive

enough, then perhaps this might be a reasonable approach on a case-by-case basis.

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References

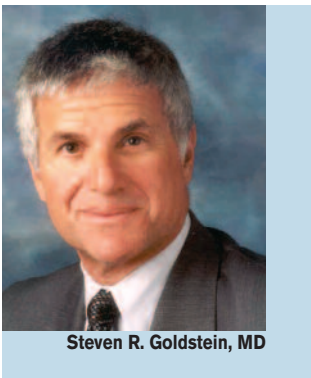
1. The North American Menopause Society. *Management strategies: menopause symptoms. Menopause practice: a clinician's guide*. Cleveland, Ohio: The North American Menopause Society, 2004:146-150.
2. The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004;11;11-33.
3. Reddy SY, Warner H, Guttuso T Jr, et al. Gabapentin, estrogen, and placebo for treating hot flashes. *Obstet Gynecol* 2006;108:41-48.

For a woman suffering from moderate to severe vasomotor instability (defined as 7–10 hot flashes per day or 50 per week), HT remains the gold standard for treatment. However, it is generally recommended that HT be prescribed with greater-than-usual caution in women at higher risk for venous thrombotic events (VTEs).^{1,2} Studies,³⁻¹¹ including the Women's Health Initiative (WHI),¹² show that HT raises the relative risk of VTE two- to four-fold, primarily within the first year of use, and in women with other risk factors for thrombosis. There is concern that women with more risk factors may be at clinically significant higher risk; there are no good data about whether this risk is additive or multiplicative. Factor V Leiden mutation has been associated with an additive risk of VTE.¹³

The absolute number of VTEs in this population of generally healthy postmenopausal women is small—unless the patient has an increased risk of VTE. In the WHI study of more than 16,000 women,¹² the incidence of thrombosis in those not taking HT was 16 cases/10,000 person-years; in HT users it was 32 cases/10,000 person-years. This risk was higher with more advanced age.

Evaluation for VTE Risk

In general, it is not believed to be cost-effective to screen for thrombophilia prior to initiating oral contraceptives or HT.¹ In this particular case, pregnancy itself increases the risk of DVT by 6%. Thrombosis is more likely to occur in women with preexisting risk factors, such as a positive family history, hypercoagulable state, prior VTEs,



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obesity, varicose veins, cancer, acute medical illness with restricted mobility, genetic predisposition to clotting, hospitalization, major surgery such as joint replacement, restricted mobility due to situations such as long-distance travel, medical conditions such as cardiovascular disease, congestive heart failure, inflammatory bowel disease, kidney failure and major trauma. An ultrasound of the affected extremity will show any post-DVT residual defects, which would also increase the patient's risk of recurrent DVT. However, in deciding whether to prescribe HT for a highly symptomatic woman with a prior DVT, I would evaluate her risk for recurrent VTE. If the workup is negative, I would discuss the pros and cons and risk and benefits of HT, with particular emphasis on the risk of VTE.

Is Transdermal Therapy Associated with a Lower VTE Risk?

It is not clear how HT increases the risk of VTE. There has been considerable discussion in the literature about whether transdermal HT is safer than oral HT with regard to VTE risk.⁷ However, there are no double-blind controlled trials comparing oral to transdermal HT in women at higher risk for VTEs. Because of its first pass through the liver, oral HT leads to increased production of procoagulants and may

affect the balance between procoagulant factors and antithrombotic mechanisms.¹³ In some studies transdermal HT appears to present less of a risk; at present, however, the data regarding the safety of transdermal over oral HT are not conclusive. The WHI² showed a smaller risk for VTE and pulmonary embolism in the estrogen-only group,¹⁵ while a 1996 UK study³ showed no significant difference.

toestrogens or relaxation techniques will provide sufficient relief for women with moderate to severe symptoms, alternative nonhormonal therapy should be considered in this patient. Nonhormonal options include the SSRIs, serotonin-norepinephrine reuptake inhibitors such as venlafaxine, and gabapentin. These therapies have shown benefit in small, pilot studies;¹⁴ none are FDA-approved for treatment of vasomotor symptoms. Of these, gabapentin and venlafaxine have been the most thoroughly studied, and could be discussed as off-label treatment options.

If the decision is made in favor of HT, using the lowest dose for the shortest period of time is recommended for all hormone users. Transdermal HT may be an option. Discontinuation of therapy for major surgery or long travel is prudent.

—JoAnn V. Pinkerton, MD

References

1. ACOG Task Force on Hormone Therapy. Venous thromboembolic disease. *Obstet Gynecol* 2004;104:118S-27S.
2. Warren MP. A comparative review of the risks and benefits of hormone replacement therapy regimens. *Am J Obstet Gynecol* 2004;190:1141-67.
3. Jick H, Derby LE, Myers MW, et al. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996;348:981-83.
4. Daly E, Vessey MP, Hawkins MM, et al. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 1996;348:977-80.
5. Greer IA, Walker ID. Hormone replacement therapy and venous thromboembolism. *Climacteric* 1999;2:224-31.
6. Heibraaten E, Abdelnoor M, Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism: a population-based case-control study. *Thrombosis Haemostasis* 1999;82:1218-21.
7. Scarabin PY, Oger E, Plu-Bureau G, on behalf of the Estrogen and Thromboembolism Risk (ESTHER) Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-32.
8. Varas-Lorenzo C, Garcia-Rodriguez LA, Cattaruzzi C. Hormone replacement therapy and the risk of hospitalization for venous thromboembolism: a population-based study in southern Europe. *Am J Epidemiol* 1998;147:387-90.
9. Grodstein F, Stampfer MJ, Goldhaber SZ, et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996;348:983-87.
10. Perez Gutthann S, Garcia Rodriguez LA, Castellsague J. Hormone replacement therapy and the risk of venous thromboembolism: population based control study. *BMJ* 1997;314:796-800.
11. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2002;32:689-96.
12. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
13. Rosendaal FR, et al. Hormone replacement therapy, prothrombotic mutations and the risk of venous thrombosis. *Br J Haematol* 2002;116:851-54.



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Should Women at Higher Risk Avoid HT?

There are no absolute answers to this question. Although it is unlikely that herbs, phy-

14. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057-71.

15. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.

I do not withhold the use of HT for the woman who has had an apparently provoked DVT remotely if she is symptomatic. I recommend first obtaining a factor V Leiden and prothrombin gene mutation test. These are done only once in a lifetime as they are genetic tests and the results will not change. I also obtain a homocysteine level; if it is elevated it can be treated with folic acid. If the woman is found to be heterozygous, or especially homozygous, for factor V Leiden, she is counseled that systemic HT is associated not just with an additive risk, but also with a multiplicative risk for DVT, and the route of administration is important.¹ If she is positive for a prothrombin gene mutation, I would advise her that there have been reports of increased risk of myocardial infarction in women taking HT.² If these tests are negative, the news is more reassuring; however, the woman is still counseled that she is at increased risk for DVT by virtue of her history.

In a woman who is symptomatic, needs HT, and has a history of DVT, I prefer to use non-oral HT formulations—such as the transdermal patch, topical gels or lotions and/or the estradiol acetate vaginal ring (Femring)—because of the theoretical (but

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not proven) advantage of causing less clotting activation. In 2003, The ESTHER case-control study concluded that transdermal ET may be safer in terms of less DVT risk compared with oral estrogen.³ If an endometrium/uterus is present, minimal but adequate progestin oppo-

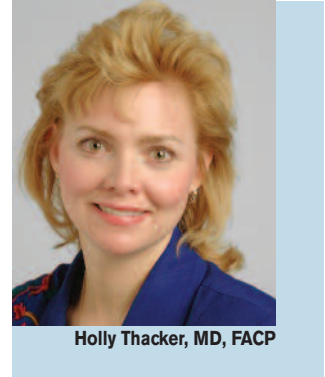
sition is used. I favor vaginal progesterone such as Prochieve progesterone gel or oral progesterone (Prometrium) with an extended cycle, and doing periodic checks of the endometrial stripe with transvaginal ultrasound. Based on the recent report from the WHI,⁴ it appears that medroxyprogesterone acetate is additive to oral estrogen in terms of thrombotic risk, so minimizing progestin exposure seems justified. If the woman does not have vasomotor symptoms, I prefer to treat her using the genitourinary-only route—with the estradiol vaginal ring (Estring)—and periodically monitor bone status. (It is important to note that Femring has local and systemic estrogen effects in contrast to the Estring vaginal ring, which has local genitourinary effects.)

In any menopausal woman, prior to embarking on any HT or SERM therapy, it seems prudent to control blood pressure, lipids and blood sugar, address smoking status, and counsel the patient regarding the other additive risks for DVT: inactivity, dehydration, immobilization, lower extremity injury, anesthesia and obesity. Even though aspirin does not reduce DVT risk, I begin discussing preventive daily baby aspirin use for stroke risk reduction in women by age 60–65 and in younger women with known cardiovascular disease or heart disease equivalents such as diabetes.

— Holly Thacker, MD, FACP

References

1. Straczek C, Oger E, Yon de Jonage-Canonico MB, et al for the ESTHER Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation* 2005;112:3495-3500.
2. Psalty BM, Smith NL, Lemaitre RN, et al. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. *JAMA* 2001;285:906-13.
3. Scarabin PY, Oger E, Plu-Bureau G, on behalf of the Estrogen and Thromboembolism Risk (ESTHER) Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-32.
4. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772-80.



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