

Alliance Members

Alan M. Altman, MD

Assistant Clinical Professor
Obstetrics, Gynecology, and Reproductive Biology
Harvard Medical School
Boston, MA

Mary K. Beard, MD, FACOG

Adjunct Clinical Professor
Department of Obstetrics and Gynecology
University of Utah
Salt Lake City, UT

Sarah L. Berga, MD

James Robert McCord Professor and Chair
Department of Gynecology and Obstetrics
Emory University School of Medicine
Atlanta, GA

J. Christopher Gallagher, MD

Professor of Endocrinology
Director, Bone Metabolism Unit
Creighton University Medical Center
Omaha, NE

Steven R. Goldstein, MD

Professor, New York University School of Medicine
Co-Director of Gynecologic Ultrasound
Co-Director, Bone Densitometry
New York University Medical Center
New York, NY

Andrew M. Kaunitz, MD

Professor and Assistant Chairman
Obstetrics and Gynecology Department
University of Florida Health Science Center
Director, Menopause and Gynecology Services
Medicus Women's Diagnosis Center
Jacksonville, FL

James Liu, MD

Chairman, Department of Obstetrics and Gynecology
University MacDonal Women's Hospital
Department of Reproductive Biology
Case School of Medicine
Cleveland, OH

Anne Moore, MSN, RNC, FAANP

Women's Health Nurse Practitioner
Professor of Nursing
Vanderbilt University
Nashville, TN

Lila E. Nachtigall, MD

Professor of Obstetrics and Gynecology
New York University School of Medicine
New York, NY

Philip Sarrel, MD

Emeritus Professor
Obstetrics and Gynecology, and Psychiatry
Yale University School of Medicine
New Haven, CT

James A. Simon, MD

Clinical Professor
George Washington University
Washington, DC

One of our goals as members of the Alliance for Healthy Women in Menopause, an educational board of menopause experts, is to share important information about hormone therapy and provide guidance for opinion leaders on how to implement this information in clinical menopause management strategies. This bulletin is designed to provide useful information that can be incorporated into lectures and discussions with colleagues regarding trends in menopause management.

In this issue of the Bulletin, we will discuss a recent publication and suggest ways for you to use this information in your practice and your lectures. The paper presents the results of a multicenter case-controlled study of postmenopausal women, in particular those who have a prothrombotic mutation.¹ The study examined their risk of venous thromboembolism (VTE) to determine whether route of administration of estrogen therapy (ET) affected that risk.

Differences in VTE Risk With Transdermal and Oral Estrogen

VTE risk with estrogen use is a concern for gynecologists. Morbidity and mortality associated with VTE is high: approximately 6% of people who experience deep vein thrombosis (DVT) will die within a month of the event; 1/3 of those who develop VTE will have recurrence within 10 years.²

The EStrogen and THromboEmbolic Risk (ESTHER) trial, a multicenter case-control study, was designed to determine the effect of the route of estrogen administration on the risk of VTE. Published in 2003, the initial findings showed that transdermal ET was not associated with a higher risk of VTE in postmenopausal women, while oral ET showed a 3-fold elevated risk.³

Several inherited conditions associated with coagulation problems increase the individual risk of blood clots. Factor V

Leiden and prothrombin gene mutations are two of the most common genetic defects associated with an increased risk for VTE. The study highlighted in this issue discusses the risk of VTE among postmenopausal women who have one of these two prothrombotic mutations.¹

The ESTHER researchers proposed that genetic defects in coagulation and prothrombin may impact the relationship between VTE and hormone therapy. The largest randomized trial to demonstrate this relationship was the Women's Health Initiative (WHI), which found that women with factor V Leiden who used oral combination HT had a 6.7-fold increased risk of VTE (95% CI, 3.1–14.5) compared with women in the control group who did not have factor V Leiden.⁴ Recognizing that the WHI results applied only to combined oral HT and are not necessarily relevant to other hormone regimens and delivery routes, the ESTHER study tested the impact of the route of estrogen administration on the association between prothrombotic mutations and VTE.

Certain factors that increase the risk of VTE include the following:

- Age >40 years
- Obesity
- Previous VTE
- Prolonged bed rest or prolonged immobility, as in lengthy air travel
- Surgery
- Pregnancy and childbirth, due to added pressure on the veins of the pelvis
- Exogenous estrogen, as in contraceptives and hormone therapy
- Existing circulatory or heart problems
- Genetic defects predisposing to thrombosis

BUPA Health Information Team. Deep vein thrombosis fact sheet. Available at: http://hcd2.bupa.co.uk/fact_sheets/deep_vein_thrombosis.htm. Accessed March 21, 2006.

The ESTHER trial comprised postmenopausal women between 45 and 70 years of age; the average age of the cohort was 61 years. Patients and controls were identified without knowledge of estrogen use; the diagnosis of VTE was confirmed by standard imaging procedures. VTE was defined as a first documented episode of idiopathic VTE—pulmonary embolism (PE) and DVT. The population included 235 cases (128 with PE, 107 with DVT) and 554 controls; the total population was genotyped for factor V Leiden and G20210A mutation, the genetic defect of prothrombin.

About 20% of cases and <10% of controls were current users of oral estrogen, and about 25% of cases and 33% of controls were current users of transdermal estrogen. Approximately 50% of the cohort had a history of varicose veins; 30% of the cases and 25% of the controls had at least one risk factor for VTE.

With nonusers of ET as a reference point, the OR for VTE was significantly increased in current users of oral estrogen (OR: 3.2, CI 2.0–5.0), but not in current users of transdermal estrogen (OR: 1.0, CI 0.7–1.4) (see Table). The ESTHER researchers concluded that users of transdermal ET seemed to have a lower risk of VTE compared to users of oral ET, especially among women carrying a prothrombotic mutation.

Implications of the Findings: What They Mean for Clinicians

The conclusion that oral but not transdermal ET increases thrombotic risk is biologically plausible. Although the effects of estrogen on coagulation and fibrinolysis are complex, several studies have alluded to the fact that transdermal ET has little or no effect due to its avoidance of first-pass hepatic metabolism. Some of the biomarkers of coagulation and fibrinolysis that have been studied in patients receiving oral or transdermal ET are:

- Plasminogen activator inhibitor-1 (PAI-1)
- C-reactive protein (CRP)
- Fibrinogen
- Factor VII coagulant activity

Small randomized, controlled studies⁵⁻⁷ have found that oral ET induces activated protein C resistance, activates blood coagulation, increases fibrinogen, and promotes a tendency toward hypercoagu-

| Results | Odds Ratio | Confidence Interval |
|-----------------------------------|------------|---------------------|
| No Prothrombotic Mutation | | |
| Oral ET | 4.1 | 2.4–7.1 |
| Transdermal ET | 1.2 | 0.8–1.8 |
| One Prothrombotic Mutation | | |
| Nonusers | 4.1 | 2.3–7.4 |
| Oral ET | 25.5 | 6.9–95.0 |
| Transdermal ET | 4.4 | 2.0–9.9 |
| Factor V Leiden | | |
| Nonusers | 2.6 | 1.3–5.4 |
| Oral ET | 16.4 | 4.3–62.2 |
| Transdermal ET | 4.6 | 1.6–13.8 |

Straczek C, et al. *Circulation*. 2005;112:3495-3500.

lability, whereas transdermal estrogen decreases fibrinogen and tends to have a neutral effect on the parameters that lead to thrombosis.

Key Points About ET Route of Administration and VTE

- Oral ET is associated with a high risk for VTE in women with a genetic predisposition to VTE
- Postmenopausal women who use transdermal ET have approximately the same risk for VTE as those who do not use ET at all
- Current data provide a biologic rationale for transdermal estrogen as first-line therapy
- More studies need to be undertaken

References

1. Straczek C, Oger E, Yon de Jonage-Canonica MB, et al. Prothrombotic mutation, hormone therapy, and venous thromboembolism among postmenopausal women. Impact of the route of estrogen administration. *Circulation*. 2005;112:3495-3500.
2. American Heart Association. Venous Thromboembolism—Statistics. Available at: Americanheart.org/downloadable/heart/1136823273598/VenousThromb06.pdf. 2004. Accessed March 21, 2006.
3. Scarabin PY, Oger E, Plu-Bureau G; Estrogen and THromboEmbolic Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet*. 2003;362:428-432.
4. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004;292:1573-1580.
5. Vehkavaara S, Silveira A, Hakala-Ala-Pietila T, et al. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost*. 2001;85:619-625.
6. Zegura B, Keber I, Sebestjen M, Koenig W. Double blind, randomized study of estradiol replacement therapy on markers of inflammation, coagulation and fibrinolysis. *Atherosclerosis*. 2003;168:123-129.
7. Oger E, Alhenc-Gelas M, Lacut K, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women. A randomized trial. *Arterioscler Thromb Vasc Biol*. 2003;23:1671-1676.

Practical Application of the Findings: What They Mean for Your Patients

Although additional studies are necessary, the evidence would seem to favor the use of transdermal estrogen in patients who are at risk of VTE. This presents a viable option for patients who have menopausal symptoms and understand that transdermal estrogen provides relief equivalent to oral estrogen. Below is a case study of a patient in whom transdermal estrogen would be beneficial:

Patient is 53 years old; recently had a vaginal hysterectomy for uterine fibroids. She is suffering multiple symptoms, including hot flushes, insomnia, and lack of concentration. In addition, she claims that for the first time in her married life, she is experiencing pain with intercourse. She is willing to try ET, but has concerns about safety. Her mother developed DVT after surgery and the patient thinks her risk is increased as well. You screen for factor V Leiden; the patient is negative. She took oral contraceptives for 15 years and never had problems with circulation.

Based on recent evidence, you should feel comfortable offering this patient a transdermal estrogen patch. You can also monitor her serum estradiol level to titrate the dose. If she still experiences dyspareunia, you may also consider adding vaginal estrogen.

The complete article of the ESTHER study update cited in this bulletin is enclosed. We hope you find it useful, and welcome your comments about it and other topics relating to transdermal ET.

The risks of VTE were reported as odds ratios (OR) according to the following factors:

- The absence of prothrombotic mutations in oral estrogen users and transdermal estrogen users compared with nonusers of ET
- The presence of factor V Leiden in oral estrogen users and transdermal estrogen users compared with nonusers of ET
- The presence of prothrombotic genetic mutation in oral estrogen users and transdermal estrogen users compared with nonusers of ET
- The presence of one or more genetic mutations in oral estrogen users and transdermal estrogen users compared with nonusers of ET