Contraception and Hormone Therapy: Putting the Risk of Venous Thromboembolism into Perspective

Event Type
Live Online

ACPE Expiration Date
2/5/2016

Credits
1 Contact Hour

Target Audience
Nurses, Pharmacists, Pharmacy Technicians

Program Overview
Recent studies and FDA safety communications indicate that certain oral contraceptives may significantly increase the risk of deep vein thrombosis (DVT) or pulmonary embolism (PE). Likewise, prospective studies demonstrate an increased risk of DVT and PE in women using hormone therapy. However, women often need oral contraceptives to prevent pregnancy (or other non-contraceptive reasons) and hormone therapy for menopausal symptoms. So, how great is this risk? Through case studies and an evidence-based medicine approach, this webinar will present the benefits and evaluate the true risk of DVT and PE when women use these therapies.

Nurse Educational Objectives
- Describe the mechanism for which venous thromboembolism (VTE) occurs with estrogen-containing medications
- Compare and contrast various components of combined hormonal contraceptives and their potential risk for VTE
- Interpret current evidence that evaluates VTE risk for various contraceptives.
- Evaluate clinical trials that indicate increased risk of VTE in women using hormone therapy
- Given a specific patient situation, determine the benefits and risk of using an estrogen-containing medication
Pharmacist Educational Objectives

- Describe the mechanism for which venous thromboembolism (VTE) occurs with estrogen-containing medications
- Compare and contrast various components of combined hormonal contraceptives and their potential risk for VTE
- Interpret current evidence that evaluates VTE risk for various contraceptives.
- Evaluate clinical trials that indicate increased risk of VTE in women using hormone therapy
- Given a specific patient situation, determine the benefits and risk of using an estrogen-containing medication

Pharmacy Technician Educational Objectives

- List symptoms of venous thromboembolism
- List medications used to help treat thromboembolism

Activity Type
Knowledge

Accreditation

<table>
<thead>
<tr>
<th>Profession</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse</td>
<td>N-812</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>0798-0000-13-100-L01-P</td>
</tr>
<tr>
<td>Pharmacy Technician</td>
<td>0798-0000-13-100-L01-T</td>
</tr>
</tbody>
</table>

PharmCon, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

PharmCon, Inc. has been approved as a provider of continuing education for nurses by the Maryland Nurses Association which is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center’s Commission on Accreditation.

Faculty

Laura Borgelt, PharmD, FCCP, BCPS
Associate Professor, University of Colorado School of Pharmacy

Financial Support Received From
Pharmaceutical Education Consultants, Inc.
Disclaimer
PharmCon, Inc. does not view the existence of relationships as an implication of bias or that the value of the material is decreased. The content of the activity was planned to be balanced and objective. Occasionally, authors may express opinions that represent their own viewpoint. Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient or pharmacy management. Conclusions drawn by participants should be derived from objective analysis of scientific data presented from this activity and other unrelated sources.
Contraception and Hormone Therapy: Putting the Risk of Venous Thromboembolism into Perspective

LAURA BORGEET, PHARMD, FCCP, BCPS

CONTRACEPTION AND HORMONE THERAPY:
PUTTING THE RISK OF VENOUS THROMBOEMBOLISM INTO PERSPECTIVE
Contraception and Hormone Therapy: Putting the Risk of Venous Thromboembolism into Perspective

Accreditation
Pharmacists: 0798-0000-12-087-L01-P
Pharmacy Technicians: 0798-0000-12-087-L01-T
Nurses: N-807

CE Credit(s)
1.0 contact hour(s)

Faculty
Laura Borgelt
PharmD, FCCP, BCPS
Associate Professor,
University of Colorado School of Pharmacy

Faculty Disclosure
Dr. Borgelt has no actual or potential conflicts of interest in relation to this program.

Learning Objectives
• Describe the mechanism for which venous thromboembolism (VTE) occurs with estrogen-containing medications
• Compare and contrast various components of combined hormonal contraceptives and their potential risk for VTE
• Interpret current evidence that evaluates VTE risk for various contraceptives.
• Evaluate clinical trials that indicate increased risk of VTE in women using hormone therapy
• Given a specific patient situation, determine the benefits and risk of using an estrogen-containing medication

Legal Disclaimer
The material presented here does not necessarily reflect the views of Pharmaceutical Education Consultants (PharmCon) or the companies that support educational programming. A qualified healthcare professional should always be consulted before using any therapeutic product discussed. Participants should verify all information and data before treating patients or employing any therapies described in this educational activity.
Learning Objectives

• Describe the mechanism for which venous thromboembolism (VTE) occurs with estrogen-containing medications.
• Compare and contrast various components of combined hormonal contraceptives and their potential risk for VTE.
• Interpret current evidence that evaluates VTE risk for various contraceptives.
• Evaluate clinical trials that indicate increased risk of VTE in women using hormone therapy.
• Given a specific patient situation, determine the benefits and risks of using an estrogen-containing medication.
Personal Learning Objectives

Upon completion of this activity, I would like to be able to:

1. 

2. 

3.
Risk of Venous Thromboembolism (VTE) with Combined Hormonal Contraception (CHC)

• Patient case presentation
• Proposed mechanism of action
• Pro: There is an increased risk of VTE with CHC
• Con: There is not an increased risk of VTE with CHC
• Patient case discussion
Patient Case

KB is a 20 yr old female in clinic today for a co-consult with the medical resident and clinical pharmacists because she does not have normal periods. She has not had a normal period since she was 13 years old. She has moderate acne that she tries to cover with make up. She states the hair growth on her upper lip has been growing thicker the past few years, but she gets it waxed routinely. She has struggled with being overweight and finds it hard to lose weight. She has walked 5 days/week for 20 minutes for the past 6 months and lost 2 pounds. She smokes when she drinks which is almost every weekend.

She has a new boyfriend and they have been using condoms for STI and pregnancy prevention. The medical resident is asking you for a recommendation for a birth control pill to help her symptoms and provide more effective contraception.
Reflective Questions

• Which of the following hormonal contraceptives would you recommend for this patient?
  a. OC: Ethinyl estradiol + drospirenone
  b. OC: Ethinyl estradiol + desogestrel
  c. IUS: Levonorgestrel only
  d. POP: Norgestimate only
  e. Patch: ethinyl estradiol + norelgestromin

• T/F: I am concerned about a VTE in this patient.
Types of Progestins in CHCs

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd Generation</th>
<th>3rd Generation</th>
<th>4th Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethindrone</td>
<td>Levonorgestrel</td>
<td>Desogestrel (Etonogestrel)</td>
<td>Drospirenone</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>Norgestrel</td>
<td>Norgestimate (Norelgestromin)</td>
<td>Dienogest (possible 5th gen)</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Androgenic activity

Estrogenic activity
Proposed Mechanism for VTE Risk

- “Total estrogenicity” (estrogen + progestin)
  - Progestin component selected
  - Ethinyl estradiol vs estradiol valerate
- Presence of risk factors (genetic, acquired) that affect proteins involved in hemostasis
- Changes in coagulation
  - Increased fibrinogen, prothrombin, coagulation factors VII, VIII, and X; decreased factor V
  - More pronounced for desogestrel than levonorgestrel
- Changes in anticoagulation
  - Decreasing antithrombin and tissue plasma inhibitor
- Enhances fibrolytic activity
- Activated protein C resistance
  - Less resistance in users of 2nd generation than 3rd or 4th

[Thrombosis Research 2010;126:5–11]
PRO:
There is an increased risk of VTE with CHCs
### Increased risk of VTE for all CHCs

<table>
<thead>
<tr>
<th>CHC User</th>
<th>Nonuser</th>
</tr>
</thead>
<tbody>
<tr>
<td>(not pregnant,</td>
<td>(not taking hormones)</td>
</tr>
<tr>
<td>3-9/10,000 woman-years</td>
<td>1-5/10,000 woman years</td>
</tr>
</tbody>
</table>

FDA Safety Communication:
Updated information about the risk of blood clots in women taking birth control pills containing drospirenone
April 10, 2012

The U.S. Food and Drug Administration (FDA) has completed its review of recent observational (epidemiologic) studies...

...FDA has concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills.

The revised drug labels (Beyaz, Safyral, Yasmin and Yaz) will report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products. The labels also will include a summary of the previously released results of an FDA-funded study of the blood clot risk.

## The Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Thromboembolism: OR (95% CI) for VTE in drospirenone users vs. levonorgestrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinger, et al. Contraception 2007;75:344-54</td>
<td>1.0 (0.6-1.8) European prospective cohort study</td>
</tr>
<tr>
<td>Seeger, et al. Obstet Gynecol 2007;110:587-93</td>
<td>0.9 (0.5-1.6) US health insurance database</td>
</tr>
<tr>
<td>Lidegaard, et al. BMJ 2009;339:b2890</td>
<td>1.6 (1.3-2.1) Danish national registry cohort study</td>
</tr>
<tr>
<td>Van Hylckama, et al. BMJ 2009;339:b2921</td>
<td>1.7 (0.7-3.9) Netherlands case-control study</td>
</tr>
<tr>
<td>Dinger, et al. J Fam Plan Repro Health Care 2010;36(3):123-9</td>
<td>1.0 (0.6-1.6) German case-control study</td>
</tr>
<tr>
<td>Parkin, et al. BMJ 2011;340:d2139</td>
<td>3.2 (1.5-7.0) UK general practice research database</td>
</tr>
<tr>
<td>Jick, et al. BMJ 2011;340:d2151</td>
<td>2.3 (1.6-3.2) US claims data (PharMetrics)</td>
</tr>
<tr>
<td>Gronich, et al. CMAJ 2011;183(18):E1319-E1325</td>
<td>1.65 (1.02-2.65) Israel population-based cohort study</td>
</tr>
</tbody>
</table>
FDA Study:
CHCs and the Risk of Cardiovascular Disease Endpoints

- Retrospective cohort study evaluating data from four geographically diverse health plans
  - 835,826 women with 898,251 person-years
- Compared 3 new preparations with 4 older CHCs with similar low estrogen levels
- Primary outcomes measured
  - Atrial thrombotic events (AMI, ischemic stroke)
  - VTE events
  - Cardiovascular mortality
  - Total mortality

**FDA Study:**

**CHCs and the Risk of Cardiovascular Disease Endpoints**

<table>
<thead>
<tr>
<th>CHC – ALL USERS</th>
<th>Adjusted HR (95% CI) for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All comparators</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>1.74 (1.42-2.14)</td>
</tr>
<tr>
<td>(Oral contraceptive)</td>
<td></td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>1.55 (1.17-2.07)</td>
</tr>
<tr>
<td>(Patch)</td>
<td></td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>1.56 (1.02-2.37)</td>
</tr>
<tr>
<td>(Vaginal ring)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHC – NEW USERS</th>
<th>Adjusted HR (95% CI) for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All comparators</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>1.77 (1.33-2.35)</td>
</tr>
<tr>
<td>(Oral contraceptive)</td>
<td></td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>1.35 (0.90-2.02)</td>
</tr>
<tr>
<td>(Patch)</td>
<td></td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>1.09 (0.55-2.16)</td>
</tr>
<tr>
<td>(Vaginal ring)</td>
<td></td>
</tr>
</tbody>
</table>
The Prescription Labels

Based on presently available information on DRSP-containing COCs with 0.03 mg ethinyl estradiol (that is, Yasmin), DRSP-containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progestin levonorgestrel or some other progestins. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase. Before initiating use of Beyaz in a new COC user or a woman who is switching from a contraceptive that does not contain DRSP, consider the risks and benefits of a DRSP-containing COC in light of her risk of a VTE. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs.

...some data have suggested that use of drospirenone-containing pills has a higher risk of venous thromboembolism, this risk is still very low and is much lower than the risk of venous thromboembolism during pregnancy and the immediate postpartum period. When prescribing any oral contraceptive, clinicians should consider a woman’s risk factors for venous thromboembolism and refer to the U.S. Medical Eligibility Criteria for Contraceptive Use issued by the Centers for Disease Control and Prevention...
### U.S. Medical Eligibility Criteria for Contraceptive Use

<table>
<thead>
<tr>
<th>Subcondition</th>
<th>Category for CHC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deep vein thrombosis (DVT)/Pulmonary Embolism (PE)</strong></td>
<td></td>
</tr>
<tr>
<td>a) History of DVT/PE, not on anticoagulant therapy</td>
<td></td>
</tr>
<tr>
<td>i) Higher risk for recurrent DVT/PE</td>
<td>4</td>
</tr>
<tr>
<td>ii) Lower risk for recurrent DVT/PE</td>
<td>3</td>
</tr>
<tr>
<td>b) Acute DVT/PE</td>
<td>4</td>
</tr>
<tr>
<td>c) DVT/PE, established on anticoagulant therapy for ≥3 months</td>
<td></td>
</tr>
<tr>
<td>i) Higher risk for recurrent DVT/PE</td>
<td>4</td>
</tr>
<tr>
<td>ii) Lower risk for recurrent DVT/PE</td>
<td>3</td>
</tr>
<tr>
<td>d) Family history (first degree relatives)</td>
<td>2</td>
</tr>
<tr>
<td>e) Major surgery</td>
<td></td>
</tr>
<tr>
<td>i) With prolonged mobilization</td>
<td>4</td>
</tr>
<tr>
<td>ii) Without prolonged mobilization</td>
<td>2</td>
</tr>
<tr>
<td>f) Minor surgery without immobilization</td>
<td>1</td>
</tr>
</tbody>
</table>

Venous Thrombosis in Users of Non-oral Hormonal Contraception

- Denmark national registry 2001-2010
- Women aged 15-49 years
- Outcomes compared with non-users
  - Incidence rate of VTE in transdermal, vaginal, intrauterine, or subcutaneous hormonal contraception
  - Rate ratios of VTE in current users of non-oral products compared with standard reference oral contraceptive with levonorgestrel

BMJ 2012;344:e2990
### Venous Thrombosis in Users of Non-oral Hormonal Contraception

<table>
<thead>
<tr>
<th>Method</th>
<th>Relative Risk (95% CI) Compared with Non-Users</th>
<th>Incidence rate per 10,000 exposure years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal patch</td>
<td>7.9 (3.5-17.7)</td>
<td>9.7</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>6.5 (4.7-8.9)</td>
<td>7.8</td>
</tr>
<tr>
<td>Subcutaneous implants</td>
<td>1.4 (0.6-3.4)</td>
<td>1.7</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>0.6 (0.4-0.8)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Incidence rate of VTE for non-users was 2.1/10,000 women years

Compared with users of levonorgestrel-containing contraceptives:

- **Transdermal patches**: 2.3 (1.0-5.2) *p*=0.045
- **Vaginal ring**: 1.9 (1.3-2.7) *p*=0.001
- **Subcutaneous implants**: 0.4 (0.2-1.1) *p*=0.064
- **Intrauterine device**: 0.2 (0.1-0.3) *p*<0.001

*BMJ* 2012;344:e2990
Summary: VTE Risk Increases with CHCs

- Third and fourth generation progestins may have more VTE risk than second generation progestins
- Use of drospirenone is associated with an increased risk of VTE relative to the standard low-dose OCPs. Data are conflicting for the vaginal ring and contraceptive patch.
- New use (<3 months) of drospirenone has increased risk of VTE
- Levonorgestrel IUS or subcutaneous implant may have lowest VTE risk
- Decisions about contraceptives should take into account overall risk of VTE, patient preference, and available alternatives.
CON:
There is not an increased risk of VTE with CHCs
Estrogen Risks

COCs with 150 mcg of ethinyl estradiol (EE)

↓ Risk VTE by 17-32%

↓ Risk VTE by 18%

Rev Endocr Metab Disord 2011;12:77-84 Adapted from S. El-Ibiary, 2012 ACCP Annual Meeting
Kinetics Comparison

Data from van den Heuvel et al. Contraception 2005; 72:168-174 Adapted from S. El-Ibiary, 2012 ACCP Annual Meeting
## The Studies: Drospirenone

<table>
<thead>
<tr>
<th>Study</th>
<th>Thromboembolism: OR (95% CI) for VTE in drospirenone users vs. levonorgestrel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinger, et al. Contraception 2007;75:344-54</td>
<td>1.0 (0.6-1.8) European prospective cohort study</td>
<td></td>
</tr>
<tr>
<td>Seeger, et al. Obstet Gynecol 2007;110:587-93</td>
<td>0.9 (0.5-1.6) US health insurance database</td>
<td></td>
</tr>
<tr>
<td>Lidegaard, et al. BMJ 2009;339:b2890</td>
<td>1.6 (1.3-2.1) Danish national registry cohort study</td>
<td></td>
</tr>
<tr>
<td>Van Hylckama, et al. BMJ 2009;339:b2921</td>
<td>1.7 (0.7-3.9) Netherlands case-control study</td>
<td></td>
</tr>
<tr>
<td>Dinger, et al. J Fam Plan Repro Health Care 2010;36(3):123-9</td>
<td>1.0 (0.6-1.6) German case-control study</td>
<td></td>
</tr>
<tr>
<td>Parkin, et al. BMJ 2011;340:d2139</td>
<td>3.2 (1.5-7.0) UK general practice research database</td>
<td></td>
</tr>
<tr>
<td>Jick, et al. BMJ 2011;340:d2151</td>
<td>2.3 (1.6-3.2) US claims data (PharMetrics)</td>
<td></td>
</tr>
<tr>
<td>Gronich, et al. CMAJ 2011;183(18):E1319-E1325</td>
<td>1.65 (1.02-2.65) Israel population-based cohort study</td>
<td></td>
</tr>
</tbody>
</table>
American College of Obstetrics and Gynecology (ACOG) Committee Opinion

...some data have suggested that use of drospirenone-containing pills has a higher risk of venous thromboembolism, this risk is still very low and is much lower than the risk of venous thromboembolism during pregnancy and the immediate postpartum period. When prescribing any oral contraceptive, clinicians should consider a woman’s risk factors for venous thromboembolism and refer to the U.S. Medical Eligibility Criteria for Contraceptive Use issued by the Centers for Disease Control and Prevention. Patient education materials, including product labeling, should place information regarding oral contraceptive use and venous thromboembolism risks in context by also providing information about overall venous thromboembolism risks and venous thromboembolism risks during pregnancy and the postpartum period.

Obst Gynecol 2012;120(5):1239-42
Recent Use of CHCs and VTE Risk in New Users

- All VTEs and ATEs identified in 573,680 women aged 10-55 years from four healthcare programs
- New use of drospirenone, vaginal ring, patch compared with four low-dose estrogen comparators

<table>
<thead>
<tr>
<th></th>
<th>VTE HR (95% CI)</th>
<th>ATE HR (95% CI)</th>
<th>Total Mortality HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drospirenone</td>
<td>1.77 (1.33-2.35)</td>
<td>2.01 (1.06-3.81)</td>
<td>0.88 (0.52-1.53)</td>
</tr>
<tr>
<td>Ring</td>
<td>1.09 (0.55-2.16)</td>
<td>1.65 (0.38-7.12)</td>
<td>0.96 (0.29-3.14)</td>
</tr>
<tr>
<td>Patch</td>
<td>1.35 (0.90-2.02)</td>
<td>1.07 (0.36-3.23)</td>
<td>1.07 (0.56-2.05)</td>
</tr>
</tbody>
</table>
## The Studies: Transdermal Patch

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Adj OR or HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jick et al. Contraception 2010; 81:452-3</td>
<td>Nested case-control</td>
<td>1.2 (0.9-1.8)</td>
</tr>
<tr>
<td>Jick et al. Contraception 2010; 81:16-21</td>
<td>Nested case-control</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>Jick et al. Contraception 2010; 81:16-21</td>
<td>Nested case-control</td>
<td>2.0 (0.9-4.1)</td>
</tr>
<tr>
<td>Dore et al. Contraception 2010; 81:408-13</td>
<td>Nested case-control</td>
<td>2.0 (1.2-3.3)</td>
</tr>
</tbody>
</table>
Likelihood of Developing a Blood Clot

Risk of pregnancy without contraception in one year: 85%

Non-contraceptive Benefits

- Acne Treatment*
- Decreased risk of ovarian, uterine and colon cancer
- Hirsutism Treatment*
- Endometriosis
- Cycle regulation
- Dysmenorrhea
- Polycystic Ovarian Syndrome
- Premenstrual Dysphoric Disorder*
- *Indicates specific benefit with DRSP containing products
Summary:
VTE Risk is Not Increased with CHCs

- Data are conflicting for many CHCs
- Risk of VTE while taking CHCs much lower than risk of VTE while pregnant or post-partum
- CHCs offer significant non-contraceptive benefits which may outweigh any VTE risk
Summary Points: VTE Risk in Contraception

- Mechanism by which VTE occurs with CHC use is multifactorial; minimize risk when possible
- Conflicting data exist for various contraceptive options - make patient-specific recommendations
- Best “ranking” of hormonal contraceptives with the current data:
  - Progestin only IUS, implant, OC
  - Second generation OC
  - Vaginal ring
  - Third generation OC
  - Transdermal patch
  - Fourth generation OC

LEST RISK

VTE

MORE RISK
Reflective Questions

Back to the patient case...
20 year old woman with abnormal periods, acne, hirsutism, overweight. She exercises, smokes on the weekends and has a new boyfriend.

• Which of the following hormonal contraceptives would you recommend for this patient?
  A. Pill: Ethinyl estradiol + drospirenone
  B. Pill: Ethinyl estradiol + desogestrel
  C. IUS: Levonorgestrel only
  D. POP: Norgestimate only

• T/F: I am concerned about a VTE in this patient.
Speaker Perspectives: Patient Case

• In this case, I would recommend:
  • Low androgen combined hormonal contraceptive
    • Low-dose estrogen CHC with desogestrel or norgestimate
    • Vaginal ring
  • Smoking cessation
  • Continue diet and exercise
  • Additional supportive therapies as needed (e.g., topical agents for acne)
Risk of Venous Thromboembolism (VTE) with Hormone Therapy (HT)

- Patient case presentation
- Pro: There is an increased risk of VTE with HT
- Con: There is not an increased risk of VTE with HT
- Patient case discussion
Patient Presentation

MOM is a 57 year-old woman with a history of smoking (1 ppd x 35 years) and prehypertension (controlled with exercise and diet). She has been on estradiol 1 mg QD and norgestimate 0.09 mg (Ortho-Prefest) for 7 years. She previously took black cohosh, red clover and rose hips for hot flashes (12-15 per day) and night sweats (4-5 per night). She takes ASA 325 mg QD and a MVI QD.

PE: BP 110/65 HR 62
Bone mineral density (BMD) testing 2002: normal
Cholesterol 2003: TC=220 HDL=65 LDL=120 TG=175

PMH: Father died of colon cancer at age 83
Mother died of heart attack at age 89
Brother died of heart attack at age 57

Would you recommend continuation of hormone therapy?
Are you concerned about VTE?
PRO:
There is an increased risk of VTE with HT
Women’s Health Initiative (WHI)

- Prospective, randomized trial in 16,608 healthy postmenopausal women aged 50-79 years
- Prempro (CEE 0.625mg + MPA 2.5mg) vs. placebo
- Planned duration = 8.5 years
- 1° efficacy outcome = coronary heart disease
- 1° adverse outcome = invasive breast cancer

JAMA 2002;288:321-33
**WHI Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRT (n=8506)</th>
<th>Placebo (n=8102)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>164 (0.37)</td>
<td>122 (0.30)</td>
<td>1.29 (1.02-1.63)</td>
</tr>
<tr>
<td>Stroke</td>
<td>127 (0.29)</td>
<td>85 (0.21)</td>
<td>1.41 (1.07-1.85)</td>
</tr>
<tr>
<td>VTE*</td>
<td>151 (0.34)</td>
<td>67 (0.16)</td>
<td>2.11 (1.58-2.82)</td>
</tr>
<tr>
<td>Invasive Breast Ca</td>
<td>166 (0.38)</td>
<td>124 (0.30)</td>
<td>1.26 (1.00-1.59)</td>
</tr>
<tr>
<td>Colorectal Ca</td>
<td>45 (0.10)</td>
<td>67 (0.16)</td>
<td>0.63 (0.43-0.92)</td>
</tr>
<tr>
<td>Hip fracture*</td>
<td>44 (0.10)</td>
<td>62 (0.15)</td>
<td>0.66 (0.45-0.98)</td>
</tr>
<tr>
<td>Death</td>
<td>231 (0.52)</td>
<td>218 (0.53)</td>
<td>0.98 (0.82-1.18)</td>
</tr>
<tr>
<td>Global Index</td>
<td>751 (1.70)</td>
<td>623 (1.51)</td>
<td>1.15 (1.03-1.28)</td>
</tr>
</tbody>
</table>

*Fractures and venous thromboembolic disease were only outcomes to remain statistically significant after adjustment*

JAMA 2002;288:321-33
### WHI: Absolute Risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRT* (n=8506)</th>
<th>Placebo* (n=8102)</th>
<th>Absolute Difference*</th>
<th>Number Needed To Harm or Treat (NNH/NNT)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>37</td>
<td>30</td>
<td>7</td>
<td>1,429</td>
</tr>
<tr>
<td>Stroke</td>
<td>29</td>
<td>21</td>
<td>8</td>
<td>1,250</td>
</tr>
<tr>
<td>VTE</td>
<td>34</td>
<td>16</td>
<td>18</td>
<td>556</td>
</tr>
<tr>
<td>Invasive Breast Ca</td>
<td>38</td>
<td>30</td>
<td>8</td>
<td>1,250</td>
</tr>
<tr>
<td>Colorectal Ca</td>
<td>10</td>
<td>16</td>
<td>-6</td>
<td>1,667</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>10</td>
<td>15</td>
<td>-5</td>
<td>2,000</td>
</tr>
<tr>
<td>Global Index</td>
<td>170</td>
<td>151</td>
<td>19</td>
<td>526</td>
</tr>
</tbody>
</table>

* Based on 10,000 women treated for 1 yr  ** Based on treatment for 1 yr

JAMA 2002;288:321-33
WHI Issues: Regimen

• Only one HRT regimen (Prempro®) tested
• These results may/may not apply to:
  • Other doses, forms or routes of estrogen
  • Other doses or forms or routes of progesterone
  • Younger women in menopause
# Million Women Study

## STUDY METHODS
- 1,058,259 postmenopausal UK women (mean age: 56.7)
- Data collected through National Health Service
- HT use and risk of VTE examined using Cox regression analysis
- 3.3 million years of follow-up

## RESULTS
- 2200 women had VTE
- Diagnosed avg 1.5 yrs after last HT use
- Current vs never users by formulation
  - Oral HT: 2.07 [1.86-2.31]
  - Oral E only: 1.42 [1.21-1.66]
  - Transdermal E only: 0.82 [0.64-1.06]
  - Medroxyprogesterone preparations: 2.67 [2.25-3.17]
  - Other progestin preparations: 1.91 [1.69-2.17]

*J Thromb Haemost 2012;10:2277-86*
Million Women Study: Results

- Estrogen constituent and dose
  - Equine estrogen: RR 1.43 [95% CI 1.23-1.75]
    - Doses > or ≤ 0.625 mg statistically significantly increased for current users
  - Estradiol: RR 1.45 [95% CI 1.06-1.98]
    - Doses > or ≤ 1 mg statistically significantly increased for current users

- Twice the risk of VTE in first 2 years of initiation

- Over 5 years, those admitted to hospital (or died from) pulmonary embolism:
  - 1 in 660 never users of HT
  - 1 in 475 current users of estrogen-only
  - 1 in 390 current users of HT containing norethistrone/norgestrel
  - 1 in 250 current users of HT containing medroxyprogesterone acetate

Cochrane Review:
Long-term HT for Postmenopausal Women

- 23 studies involving 42,830 women (70% from WHI and HERS)
- Mean age in most studies was over 60 years

<table>
<thead>
<tr>
<th>Outcome – Continuous HT</th>
<th>Absolute risk per 1000 [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary event (after 1 yr)</td>
<td>4 [3-7]</td>
</tr>
<tr>
<td>VTE (after 1 yr)</td>
<td>7 [4-11]</td>
</tr>
<tr>
<td>Stroke (after 3 yrs)</td>
<td>18 [14-23]</td>
</tr>
<tr>
<td>Breast cancer (after 5.6 yrs)</td>
<td>23 [19-29]</td>
</tr>
<tr>
<td>Gallbladder disease (after 5.6 yrs)</td>
<td>27 [21-34]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome – Estrogen only</th>
<th>Absolute risk per 1000 [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE (after 1-2 yrs)</td>
<td>5 [2-10]</td>
</tr>
<tr>
<td>VTE (after 7 yrs)</td>
<td>21 [16-28]</td>
</tr>
<tr>
<td>Stroke (after 7 yrs)</td>
<td>32 [25-40]</td>
</tr>
<tr>
<td>Gallbladder disease (after 7 yrs)</td>
<td>45 [36-57]</td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub4
CON:
There is not an increased risk of VTE with HT
The Hot Flash

*Estrogens are the most effective treatment (80-90% reduction)
Kronos Early Estrogen Prevention Study (KEEPS)

STUDY METHODS
- 727 women aged 42-59 yrs (mean age 52) within 3 years after menopause
- Randomized to 0.45 mg/day Premarin conjugated estrogen (o-CEE), 50 mcg Climara estradiol patch (t-E2), or placebo for four years
- Women on estrogen received 200 mg micronized progesterone (Prometrium®) x 12 days/month

RESULTS (compared to placebo)
- HT reduced symptoms of menopause and had favorable effects on BMD
- HT caused improvements in lubrication and decreased pain with intercourse. Additionally, t-E2 group had improved arousal and desire; o-CEE group didn’t.
- Carotid ultrasound studies showed similar rates of progression of arterial wall thickness in all 3 treatment groups. Trend toward lower rate of coronary artery calcium with HT.
- o-CEE increased HDL, decreased LDL, and increased TG and CRP levels.
- T-E2 improved glucose levels and insulin sensitivity and had neutral effects on other biomarkers.
- No sig diff in rates of breast cancer, endometrial cancer, MI, TIA, stroke, or VTE between the 3 groups.

Summary: VTE Risk with HT

- Not indicated for primary or secondary prevention of coronary heart disease
- Data support the initiation of HT around the time of menopause to treat menopause-related symptoms
- Current use of oral HT in postmenopausal women increases the risk of VTE approximately 2-fold
- Risk of VTE varies by formulation
  - Transdermal appears to be safer than oral
  - Micronized progesterone or progestins appear safer than medroxyprogesterone acetate
Back to the Patient Case…

- Estrogen most effective, but patient now 57 years old
- Consider transdermal formulation with micronized progesterone if HT continued
  - Try to minimize use to 5 years
- Consider other options for hot flashes
  - Taper and discontinue HT; use non-pharmacologic measures
  - Antidepressants
    - Venlafaxine
    - Fluoxetine
    - Paroxetine
  - Gabapentin

Menopause 2011;18(10):1052-1059
Menopause 2012;19(3):257-271
Conclusions:
VTE Risk in Contraception and HT

• VTE risk due to both estrogen and progestogen contributions
• Need to evaluate VTE risk for individual patients
  • Acquired, transient risk (e.g., surgery, immobilization)
  • Smoking
  • Obesity
  • Personal and family history
• Studies can always be improved
• Discuss risks vs. benefits and tailor recommendations
• Educate patients to minimize risk and monitor for signs and symptoms
Were your personal objectives met?

laura.borgelt@ucdenver.edu
THANK YOU!!