HORMONE REPLACEMENT THERAPY & VENOUS THROMBOEMBOLISM

Week 87

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Reading Assignment:
ACOG Committee Opinion # 556, April 2013, Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism
LEARNING OBJECTIVES

• Review basics of menopause and commonly reported menopausal symptoms
• Review hormone replacement therapy and types of offered
• Understand the risks of VTE for those taking HRT and become comfortable counseling your patients regarding these risks
CASE VIGNETTE

• Ms. A is a 55 yo postmenopausal G2 P0111 woman who presents for a well woman visit. She reports worsening hot flushes and dyspareunia over the past several months.
What elements of this patient’s history are most relevant?

- **POBH:** 1x PTD @ 28 weeks, 1x EPF
- **PGYNH:** LMP 13 months ago; hx of reg cycles; denies STIs/fibroids/cysts/abnormal paps
- **PMH:** DVT @ 20 years old, in the setting of OCP use
- **PSH:** denies
- **MEDS:** Multivitamin, fish oil
- **ALL:** NKDA
- **SOC:** no toxic habits; married; denies IPV; works in accounting
- **FH:** denies
PERTINENT PHYSICAL EXAM FINDINGS

What elements of this patient’s physical exam are most relevant?

• VS: HR 80, BP 96/60, T 37.0, BMI 20 kg/m²
  • Gen: NAD
  • Chest: CTAB
  • CVS: RRR
• Abd: soft, NT, ND, no r/g/masses
• GU: NEFG, no CMT, no adnexal/uterine tenderness; uterus 6 wk size, antevorted; no masses; atrophic vaginal epithelium
• Ext: WWP
MENOPAUSE: REVIEW

• What is menopause?
  • The permanent cessation of menstruation that occurs after the loss of ovarian activity

• How do you diagnose menopause?
  • Cessation of menstruation x 1 year

• What are the symptoms most closely associated with the hormonal changes of the menopausal transition?
  • Vasomotor symptoms
  • Vaginal symptoms
MENOPAUSE: REVIEW

- What are vasomotor symptoms?
  - Sudden sensation of extreme heat in the upper body, lasting 1-5 minutes; symptoms include perspiration, chills, clamminess, anxiety, palpitations
  - Can cause sleep disturbances
  - 87% experience daily symptoms; 33% > 10 per day
  - Last usually between 6 months – 2 years (median durations 4-10.2 years also reported)

- What is the pathophysiology of vasomotor symptoms?
  - Decreased estrogen and elevated FSH levels
  - Thermoregulatory zone narrowing

- What are vaginal symptoms?
  - Vaginal atrophy; symptoms include vaginal/vulvar dryness, discharge, itching, dyspareunia
  - 10-40% of menopausal women

- What is the pathophysiology of vaginal symptoms?
  - Loss of superficial epithelial cells in the genitourinary tract leads to tissue thinning, loss of elasticity, shortening of vagina
  - Loss of subcutaneous fat in labia majora, leading to introital narrowing, labia minor fusion, shrinking of the clitoral prepuce and urethra
  - Vaginal pH is more alkaline, increasing risk of altered vaginal flora and thus infections
HORMONE REPLACEMENT THERAPY

What are the hormonal medications used in treating vasomotor symptoms?

Table 1. Treatment Options for Menopausal Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage/Regimen</th>
<th>Evidence of Benefit</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen-alone or combined with progestin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Standard Dose</td>
<td>Conjugated estrogen 0.625 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Micronized estradiol-17β 1 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Transdermal estradiol-17β 0.0375-0.05 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• Low Dose</td>
<td>Conjugated estrogen 0.3–0.45 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Micronized estradiol-17β 0.5 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Transdermal estradiol-17β 0.025 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• Ultra-Low Dose</td>
<td>Micronized estradiol-17β 0.25 mg/d</td>
<td>Mixed</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Transdermal estradiol-17β 0.014 mg/d</td>
<td>Mixed</td>
<td>No</td>
</tr>
<tr>
<td>Estrogen combined with estrogen agonist/antagonist</td>
<td>Conjugated estrogen 0.45 mg/d and bazedoxifene 20 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Progestin</td>
<td>Depot medroxyprogesterone acetate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Trazodone</td>
<td>25 mg/d</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Compounded bioidentical hormones</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

HRT use can alleviate weekly hot flash frequency by 75% and symptom severity by 87%.
HORMONE REPLACEMENT THERAPY

What are the hormonal medications used in treating vaginal symptoms?

Table 2. Treatment Options for Menopausal Vaginal Symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Evidence of Benefit*</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Estrogen Systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Standard Dose</td>
<td>Conjugated estrogen 0.625 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Micronized estradiol-17β 1 mg/d</td>
<td>Yes</td>
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<td>• Ultra-Low Dose</td>
<td>Micronized estradiol-17β 0.25 mg/d</td>
<td>Mixed</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Transdermal estradiol-17β 0.014 mg/d</td>
<td>Mixed</td>
<td>No</td>
</tr>
<tr>
<td><strong>Vaginal/Local</strong></td>
<td>Estradiol-17β ring 7.5 micrograms/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Estradiol vaginal tablet 25 micrograms/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Estradiol ring 0.05 mg/d</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estradiol-17β cream 2 g/d</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conjugated estrogen cream 0.5-2 g/d</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

- Low doses are effective (both oral and transdermal formulations)
- Systemic absorption is negligible in terms of risks of endometrial hyperplasia
- Ospemifene is the only FDA approved estrogen agonist/antagonist for treatment of severe dyspareunia in postmenopausal women
HRT AND VTE

• What is the absolute risk of VTE?
  • Age dependent risk:
    • Age 40s 54/100,000 per yr
    • Age 50s 62-122/100,000 per yr
    • Age 70-80 300-400/100,000 per yr
    • Age 80s 700/100,000 per yr

• What are some preexisting risk factors for developing VTE?
  • Coronary vascular disease, congenital thrombophilic disorders, obesity, immobilization, fracture
  • WHI emphasizes Factor V Leiden as the main thrombophilia associated with developing VTE
HRT AND VTE

Women’s Health Initiative
- EP use:
  - VTE rate 3.5/1000 py
  - HR 2.06
  - In women with a prior VTE: HR 3.9
- E only
  - VTE rate 3.0/1000 py
  - HR 1.32 (CI 0.99-1.75)

Heart and Estrogen/Progestin Replacement Trials
- EP use
  - HR 2.89 (34 participants out of 1380)

Estrogen and Thromboembolism Risk Study
- E only
  - Oral E: OR 4.2
  - Transdermal E: OR 0.9
    - When stratified by weight and presence of thrombophilia, transdermal E was not associated with increased risk of VTE compared to nonusers
HRT AND VTE

• Why does estradiol (E) and estradiol-progestin (EP) therapy increase risk of VTE?
  • Increase in activated protein C resistance
  • Prothrombotic effect of estrogen through hepatic induction--> high concentrations of estrogen in the liver due to the “first pass” effect

• Why is transdermally administered estrogen associated with no increased risk of VTE?
  • Avoids first-pass effect, suppressive effect on tissue plasminogen activator antigen and plasminogen activator inhibitor activity, beneficial effect on proinflammatory markers

• Does the type or dose of estrogen affect VTE risk?
  • Conjugated estrogens (not esterified estrogens): VTE risk increased, OR 1.7, compared to non-users
  • Addition of progestin increases risk of VTE (see prior slide)
  • Higher doses of estrogen may increase risk of VTE (i.e. OCP dosage vs HRT dosage)

• However, despite increased risk of VTE, absolute risk is LOW
CASE, CONTINUED

• How do you counsel the patient in the case?
  • Patient’s history is significant for a VTE provoked by contraception use, making her a less favorable candidate for estrogen-containing HRT due to her risk factors
  • She can be offered other alternative methods for her symptoms, including vaginal lubricants/moisturizers, and SSRIs/SSNRIs for vasomotor symptoms

• What if the patient only had a history of being heterozygous for Factor V Leiden?
  • You can offer transdermal estrogen after counseling
  • Shared decision making should be undertaken with the patient
SOCIAL DETERMINANTS OF HEALTH

• Education plays a role in the patient experience of menopause; those with less education report more severe symptoms and are less likely to seek treatment

• Homemakers may have more menopausal symptoms and poorer quality of life compared to employed women, likely due to lack of access to health care resources

• Lower socio-economic status is associated with early menopause; those with lower SES tend to have less access to health care and thus have more comorbidities that can exacerbate their menopause experience

The menopausal transition is a complex time in your patient’s life, where physiologic symptoms significantly impact their quality of life in all spheres. Utilize all resources available to optimize your patient’s health outcomes.
Description: HRT and VTE risk counseling

The risks, benefits, and alternatives to the initiation of estrogen-containing hormone replacement therapy was discussed with the patient. The benefits of estrogen-containing HRT for management of vasomotor symptoms and vaginal symptoms were discussed in detail. The risks of VTE were reviewed, including an increased risk of VTE in those women taking oral formulations of estrogen compared to transdermal estrogen.
CODING AND BILLING

• **N95.1**, Menopausal and female climacteric states
• **N95.2**, Postmenopausal atrophic vaginitis
EVIDENCE


Lobo R. Where are we 10 years after the Women’s Health Initiative? The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 5, 1 May 2013, Pages 1771–1780, https://doi.org/10.1210/jc.2012-4070
