Treatment of Menopausal Vasomotor Symptoms with Hormone Therapy

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Financial Disclosures

- None
Disclaimers

- Will use “female”/”women” to describe individuals born with ovaries and a uterus at birth. I understand that those individuals may not identify as “female” or “woman” and this is not indicating that they should.
52-year-old G1P2 Postmenopausal Honduran woman

- CC: Hot flashes and accompanying sweats
- Wakes her up from her sleep nightly and stop her from going to social events
Past Medical History

- LMP was 3 years ago.
- She denies any postmenopausal bleeding or Hx of Hysterectomy.
- Prior to 45 yo her periods were regular.
- Menarche was at 10 yo.
- She had her twins at 36 yrs old.
- 10-yr ASCVD risk from her most recent annual physical was 4.5%.
- She denies personal of Family hx of cancer.
- Colonoscopy and Mammogram are normal.
- BMI is 26.
- No Hypertension
- No Diabetes
- She is a never smoker.
Objectives

1. REVIEW EPIDEMIOLOGY, CLINICAL PRESENTATION AND DIAGNOSIS OF MENOPAUSAL VASOMOTOR SYMPTOMS

2. REVIEW THERAPIES FOR MENOPAUSAL VASOMOTOR SYMPTOMS

3. DISCUSS SYSTEMIC APPROACH TO HORMONAL MENOPAUSAL TREATMENT
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Almost all females experience menopausal symptoms & Vasomotor Symptoms are the most common

- 85% report ≥1 symptom such as:
  - Vasomotor symptoms (79%): hot flashes, sweats (including night sweats)
  - Sleep disruption (43%)
  - Depressed Mood (34%) Have a life expectancy of at least 10 years,
  - Other: sexual dysfunction, cognitive symptoms, vaginal dryness, urinary incontinence, and somatic or bodily pain symptoms

- Symptoms are not specific to menopause
Diagnosis of Menopause is defined as 12 months of Amenorrhea

- 95% have final menstrual period between ages 45 - 55 years
- Excluded:
  - underlying anovulatory cycles
  - taking oral contraceptives
  - s/p Hysterectomy
  - s/p endometrial ablation
  - Age < 40 yo (Primary Ovarian Failure)
Vasomotor Symptoms are most common in the first 5 years pre- and post-menopause.

The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in females

<table>
<thead>
<tr>
<th>Stage</th>
<th>Terminology</th>
<th>Duration</th>
<th>PRINCIPAL CRITERIA</th>
<th>SUPPORTIVE CRITERIA</th>
<th>DESCRIPTIVE CHARACTERISTICS</th>
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</thead>
<tbody>
<tr>
<td>-5</td>
<td>REPRODUCTIVE</td>
<td>Variable</td>
<td>Menstrual cycle: Variable to regular</td>
<td>Endocrine FSH Low Low</td>
<td>Vasomotor symptoms likely</td>
</tr>
<tr>
<td>-4</td>
<td>Early</td>
<td></td>
<td></td>
<td>AMH Low Low Variable</td>
<td>Vasomotor symptoms most likely</td>
</tr>
<tr>
<td>-3b</td>
<td>Peak</td>
<td></td>
<td></td>
<td>Inhibin B Low Low Variable*</td>
<td>Increasing symptoms of urogenital atrophy</td>
</tr>
<tr>
<td>-3a</td>
<td>Late</td>
<td></td>
<td></td>
<td>Variable* ↑Variable↑</td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td>MENOPAUSAL TRANSITION</td>
<td>1-3 years</td>
<td>Subtle changes in flow/regular</td>
<td>↑25 international units/L↑ Variable</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Early</td>
<td></td>
<td>Variable length: Persistent ≥7-day difference in length of consecutive cycles</td>
<td>Variable Low Low</td>
<td></td>
</tr>
<tr>
<td>+1a</td>
<td>Late</td>
<td>2 years (1+1)</td>
<td>Interval of amenorrhea of ≥60 days</td>
<td>↑ Variable Low Stabilizes</td>
<td></td>
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<tr>
<td>+1b</td>
<td>Perimenopause</td>
<td>3-6 years</td>
<td></td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>+1c</td>
<td></td>
<td>Remaining lifespan</td>
<td></td>
<td>Very low</td>
<td></td>
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FMP: final menstrual period; FSH: follicle-stimulating hormone; AMH: anti-müllerian hormone; Arrow: elevated.

* Blood draw on cycle days 2 to 5.

† Approximate expected level based on assays using current international standards.
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<td>Stabilizes</td>
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† Approximate expected level based on assays using current international standards.
Providers and Patients are uncomfortable with medical management of menopausal symptoms

- 10% of Women seek out Healthcare Provider

- Medical Students and Residents receive little or no training in the management of menopausal women
  - 50-60% of residents in their final year of training could not identify optimal therapy for a 52-year-old menopausal woman with severe symptoms (and no contraindications to estrogen) or recommend appropriate treatment for an otherwise healthy, 39-year-old woman with primary ovarian insufficiency

- Women’s Health Initiative (WHI) study-induced hesitancy
  - 80% reduction in MHT prescriptions since the initial publication of the WHI results in 2002

- The North American Menopause Society has also changed recommendations
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Clinical presentation gives insight into possible laterality of location

- Hormonal therapy is the most effective intervention
- SSRIs/SNRIs are a safe alternative in those with contraindications
- Placebo effect is significant, found to be correlated with anxiety

Hot flash score changes from baseline for a series of eight randomized, placebo-controlled trials, plus a trial in which women were randomized to venlafaxine (75 mg/day) versus a single dose (400 mg) of intramuscular medroxyprogesterone acetate. Six week data shown for the latter trial.
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Estrogen is the “active ingredient” in treating menopausal vasomotor symptoms

- All estrogens are effective in treating vasomotor symptoms
- Resolution of symptoms in 80%
- Reduced severity and frequency in 20%
- 17-beta estradiol is most structurally similar to endogenous estradiol
- There is no standard dose: start at the lowest dose and titrate up as needed to get desired effect
Progestins are used to prevent endometrial hyperplasia

- Cyclic Dosing (mimics luteal phase of premenopausal women):
  - 200 mg/day for 12 days/month

- Continuous Regimen
  - 100 mg daily

- Some of its metabolites are associated with somnolence which may help with sleep disturbances of menopause (take at bedtime)

- Avoid MPA as it has increased risk of Coronary Heart Disease
Clinical Indications for MHT

1. Moderate-Severe Symptoms
   - negative impact on sleep
   - negative impact on quality of life
   - negative impact on ability to function at home and/or work

2. Final Menstrual Period < 10yrs ago

3. Age < 60 years old

4. Low (<1.67%) 5-yr risk of Breast Cancer

5. No contraindication to treatment
Contraindications to MHT: Significant risk/Hx of ASCVD

- Previous venous thromboembolic (VTE)
- Chronic Heart Disease
- History of Stroke
- History of Transient ischemic attack
- 10-yr ASCVD Risk > 10%:
  - NOTE: For women at moderate risk of cardiovascular disease (CVD; 5–10% 10-year risk), transdermal rather than oral estrogen is recommended
Contraindications to MHT: Hypercoagulable States

- Active liver disease
- Unexplained vaginal bleeding
- High-risk endometrial cancer
- History of breast cancer
- Moderate - High 5-yr risk of Breast Cancer
- Smoker
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Calculation of 5-year Risk of Breast Cancer

- Breast Cancer Risk Tool from NIH
- https://bcrisktool.cancer.gov
Your Answers

These results are based upon how you answered the following questions:

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) or has she received previous radiation therapy to the chest for treatment of Hodgkin lymphoma?</td>
<td>No</td>
</tr>
<tr>
<td>2. Does the woman have a mutation in either the BRCA1 or BRCA2 gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer?</td>
<td>No</td>
</tr>
<tr>
<td>3. What is the patient’s age?</td>
<td>52</td>
</tr>
<tr>
<td>4. What is the patient’s race/ethnicity?</td>
<td></td>
</tr>
<tr>
<td>Assessments for Hispanics/Latinas are subject to greater uncertainty than those for white and African American/black women. Researchers are conducting additional studies, including studies with minority populations, to gather more data and to increase the accuracy of the tool for women in these populations.</td>
<td></td>
</tr>
<tr>
<td>a. What is the sub race/ethnicity or place of birth?</td>
<td>Born outside the US</td>
</tr>
<tr>
<td>5. Has the patient ever had a breast biopsy with a benign (not cancer) diagnosis?</td>
<td>No</td>
</tr>
<tr>
<td>a. How many breast biopsies with a benign diagnosis has the patient had?</td>
<td>n/a</td>
</tr>
<tr>
<td>b. Has the patient ever had a breast biopsy with atypical hyperplasia?</td>
<td>n/a</td>
</tr>
<tr>
<td>6. What was the woman’s age at the time of her first menstrual period?</td>
<td>7 to 11</td>
</tr>
<tr>
<td>7. What was the woman’s age when she gave birth to her first child?</td>
<td>30 or older</td>
</tr>
<tr>
<td>8. How many of the woman’s first-degree relatives (mother, sisters, daughters) have had breast cancer?</td>
<td>None</td>
</tr>
</tbody>
</table>

5-Year Risk of Developing Breast Cancer
- Patient Risk: 1.5%
- Average Risk: 0.8%

Lifetime Risk of Developing Breast Cancer
- Patient Risk: 12.7%
- Average Risk: 6.8%
Calculation of 5-year Risk of Breast Cancer

- Breast Cancer Risk Tool from NIH
- [https://bcrisktool.cancer.gov](https://bcrisktool.cancer.gov)
- High Risk: > 3% 5-yr Risk of Breast Cancer, >30% lifetime risk of Breast Cancer
- Moderate risk: [>1.67 5-yr risk of Breast cancer], >17% lifetime risk of breast cancer
- **NOTE:** May 9 2023 USPSTF Draft Recommendation (B) switching breast cancer screening to every other year starting at age 40. Needs more data on if dense breast tissue will require increased frequency of screening.
Take Home Points

• Screen patients for menopausal symptoms
• Symptom severity matters
• Know the contraindications for estrogen
• Estrogen is most effective
• Progesterone for people with a uterus
• SSRI also effective
• Assess breast cancer risk (note
• Follow up in office in 3 months
• Treat for as long as patient has no contraindications
• Talk to the patient about the transition out of MHT
• Discontinuation Side effects should be limited with taper
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References

- UpToDate
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