OBJECTIVES

• To describe risks of HT by age and menopause onset
• To recommend specific HT regimen for women who undergo early menopause and who undergo menopause at the expected time

GLOSSARY

HT – Hormone therapy
ET – Estrogen only therapy
EPT – Estrogen-progestin therapy
CEE – Conjugated equine estrogen
MPA – Medroxyprogesterone acetate
MP – Micronized progesterone
PB is a 66-year-old G0 woman who underwent bilateral oophorectomy at age 40 after her sister was diagnosed with ovarian cancer. She was started on HRT for very bothersome hot flashes. She presents to discuss continuation of HRT. She is currently taking PO conjugated equine estrogen (CEE) and continuous medroxyprogesterone acetate (MPA).

### Consequences of Early Menopause and Primary Ovarian Insufficiency

- **Vasomotor symptoms**
- **Bone loss and osteoporosis**
- **Increased heart disease**
- **Dementia and cognitive decline**
- **Depression and anxiety related disorders**
- **Higher overall mortality**

### Management of Early Menopause

- Hormone replacement
- Exercise
- Healthy diet
- Adequate calcium and vitamin D intake
- Avoidance of smoking

**Estrogen therapy**
- Dosage higher than usual post-menopausal ET
- Monitoring estradiol levels
  - **NOT** recommended
- Progestin necessary if patient has intact uterus

### Indications for HT (FDA-Approved)

1. **Vasomotor symptoms**
2. **Prevention of bone loss**
3. **Hypoestrogenism**
4. **Genitourinary syndrome of menopause (GSM)** (or vulvo-vaginal atrophy)

(As modified by hypogonadism, hypertension, or PDD)
PB is 66yo G0 woman who underwent bilateral oophorectomy at age 40 after her sister was diagnosed with ovarian cancer. She was started on HRT for very bothersome hot flashes. She presents to discuss continuation of HRT. She is currently taking PO conjugated equine estrogen (CEE) and continuous medroxyprogesterone acetate (MPA).

**RECOMMENDED TREATMENTS**

**COMMON HT REGIMENS**

<table>
<thead>
<tr>
<th>Estrogen replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transdermal</strong> recommended (over oral)</td>
</tr>
<tr>
<td>Can also use vaginal ET</td>
</tr>
<tr>
<td>Lower risk of VTE</td>
</tr>
<tr>
<td>Rovinski D (2018): Oral HT was associated with increased risk of VTE, while non-oral HT was not</td>
</tr>
<tr>
<td>Lower risk of stroke</td>
</tr>
<tr>
<td>Lower risk of hypertriglyceridemia</td>
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</tbody>
</table>

**Bottom Line:** Start with transdermal estrogen patch (17-beta estradiol)
**BREAST & CV EFFECTS OF PROGESTINS**

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**CHOOSING WHICH REGIMEN TO PRESCRIBE**

- **Progestin therapy**
  - Recommendation for oral micronized progesterone (MP)
  - Sequential: 200mg/day x 12 days per month
  - Continuous: 100mg daily

**WHAT ABOUT LEVONORGESTEREL IUD?**

- Using LNG-IUS for endometrial protection would be considered an off-label use.
- Reasonable to consider in women who do not tolerate oral progestins.
- Can be utilized by women who desire ET at pro-progestogen levels and who are still at risk of pregnancy.
- Effective for endometrial protection for peri-menopausal and post-menopausal women using ET.

**WHAT ABOUT OCPS?**

- **Disadvantages**
  1. Higher dose of E+P therapy
  2. Inferior to higher dose HT in regards to BMD

- **Advantages**
  1. Easier to use, less stigma
  2. Offers contraception
PB is a 66-year-old G0 woman who underwent bilateral oophorectomy at age 40 after her sister was diagnosed with ovarian cancer. She was started on HRT for very bothersome hot flashes. She presents to discuss continuation of HRT. She is currently taking PO conjugated equine estrogen (CEE) and continuous medroxyprogesterone acetate (MPA).

**Should PB stop HT?**

1) Yes
2) No
3) It depends...

**WHEN TO STOP HORMONE REPLACEMENT?**

- Treatment for women with primary ovarian insufficiency/early menopause should continue until the average age of natural menopause (50–51 years).
- Treatment may continue past age 50–51 years if a woman has clinical symptoms or indications.
- Regardless of age, the decision to continue HT should be individualized and based on a woman's symptoms and the risk–benefit ratio.

**“LOWEST DOSE FOR THE SHORTEST PERIOD OF TIME” PRIOR GUIDING PRINCIPLE**

**“APPROPRIATE DOSE, DURATION, REGIMEN, AND ROUTE OF ADMINISTRATION” CURRENT GUIDING PRINCIPLES**

**WHEN TO STOP?**

Extended use may benefit women for relief of VMS, prevention of bone loss and fractures, and treatment/prevention of LDM.

Vasomotor symptoms occur in 50% of women.

Many of the benefits/risks of HT do not persist beyond 5 to 7 years.

- Elevated (but rare absolute risk) of breast cancer with CEE + MPA in median 13 yr follow-up.
- CVD risk became neutral.
- Bone protection rapidly dissipates after HT discontinuation.
- Significant reduction in breast cancer in CEE group in 13 year follow-up.
- All-cause mortality was neutral in CEE + MPA group in 13 year follow-up.

Data lacking on benefits/risks of longer duration and with discontinuation of HT.
OUR ADVICE FOR PB:
- Recommend discontinuation of HT
- If PB is hesitant to stop HT or has recurrent bothersome menopausal symptoms, would recommend:
  - Switching to transdermal estrogen
  - Switching to micronized progesterone
  - Lowering dose as tolerated
  - Reassessing HT on an annual basis

TG is a 64yo woman who underwent menopause at age 49. She has noticed increased joint stiffness and prolonged fatigue after exercising in the last 18 months. She was encouraged by her PCP to present to GYN to discuss initiating hormone replacement therapy for her symptoms. Her medical history is notable for hypertension and hyperlipidemia.

JOINT PAIN AND HT
- Evidence of estrogen binding to estrogen receptors on joint tissues
- Inconsistent evidence about effects of ET on osteoarthritis and arthralgia
- May be benefits of estrogen and SERMs on joint pain
- In WHI:
  - Women on CEE + MPA (vs placebo, 47.1% vs 38.4%) had less joint pain/stiffness, worse disease after stopping HT
  - Women on CEE had statistically significant less joint pain (vs placebo, 76.3% vs 74.2%)

Would you start TG on HT?
1) Yes
2) No
3) Maybe
SUMMARY OF HEALTH RISKS OF HT BY AGE AND/OR TIME FROM MENOPAUSE ONSET

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Age and/or Time from Menopause Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>Reduced risk of CHD</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Significant reduction in all-cause mortality</td>
</tr>
<tr>
<td>Stroke</td>
<td>Meta-analysis of RCTs: No increased risk of stroke</td>
</tr>
<tr>
<td>VTE</td>
<td>Rare risk but significantly increased with HT</td>
</tr>
</tbody>
</table>

CVD RISK AND TIME SINCE MENOPAUSE ONSET

NAMS ALGORITHM

CVD Risk and Time Since Menopause Onset

Manson JE, Menopause, 2015.

AASM ALGORITHM

Manson JE, JAMA 2013.
“For women who initiate HT more than 10 to 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of CHD, stroke, VTE, and dementia.”

2017 HT Position Statement of NAMS

BP is a 52yo woman who cannot sleep due to her hot flashes. Her last period was approximately 8 months ago. She is miserable. She is interested in exploring HT but worried specifically about risks of HT. In the past, she has had really bad experiences with progestin therapy.

TREATMENT OF VASOMOTOR SYMPTOMS
Most effective treatment: systemic hormone therapy (HT) with estrogen therapy

If uterus present...
- Estrogen + Progestin (EPT)

If uterus absent...
- Estrogen alone (ET)

INDICATIONS FOR HT (FDA-APPROVED)
1. Vasomotor symptoms
2. Prevention of bone loss
3. Hypoestrogenism (treated by HT otherwise, menopause, or PDS)
4. Genitourinary syndrome of menopause (GSM) (or vulvo-vaginal atrophy)
CONTRAINDICATIONS TO SYSTEMIC HT

- Unexplained vaginal bleeding
- Severe active liver disease
- Estrogen-sensitive breast or endometrial cancer
- Coronary heart disease
- Stroke
- Personal history or inherited high risk of venous thromboembolism

BP is a 52yo woman who cannot sleep due to her hot flashes. Her last period was approximately 8 months ago. She is miserable. She is interested in exploring HT but worried specifically about risks of HT. In the past, she has had really bad experiences with progestin therapy.

What type of estrogen therapy do you usually start with?

1) Oral CEE
2) Micronized oral 17-beta estradiol
3) Transdermal 17-beta estradiol
4) Oral CEE + bazedoxifene
**SYSTEMIC HORMONE THERAPY (HT) REGIMENS**


**TISSUE SELECTIVE ESTROGEN COMPLEX (TSEC)**

**CEE/BZA (0.45mg/20mg)**
- Estrogen present to treat vasomotor symptoms
- FDA approved for treatment of vasomotor symptoms and osteoporosis prevention
- SERM to block estrogen action in endometrium/uterus
- Progestin is NOT needed

BZA - Bazedoxifene

**TABLE 1**

<table>
<thead>
<tr>
<th>Target Tissue</th>
<th>TSEC</th>
<th>Oral HT (ET and EPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Improved BMD</td>
<td>Improved BMD, decreased fracture risk</td>
</tr>
<tr>
<td>Endometrial neoplasia</td>
<td>Neutral at 2y</td>
<td>Neutral with ET, increased with ET if uterus present</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Neutral at 2y</td>
<td>Increased in WHI trial 1/1000</td>
</tr>
<tr>
<td>VTE risk</td>
<td>2 fold risk with BZA, no additive risk with CEE/BZA</td>
<td>2 fold risk with oral ET &amp; EPT, potentially less with transdermal therapies</td>
</tr>
</tbody>
</table>

**TISSUE EFFECTS OF TSEC VS. TRADITIONAL HT**


BP was excited about CEE/BZA option but appreciated the lower risk of VTE with transdermal estrogen. In addition, she chose micronized progesterone for endometrial protection.

After this counseling, I don't desire hormonal treatment. Are there non-hormonal treatment options?
NON-HORMONAL TREATMENTS FOR VASOMOTOR SYMPTOMS

<table>
<thead>
<tr>
<th>Evidence of Benefit</th>
<th>FDA-approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHDRS and HAM-A</td>
<td>No</td>
</tr>
<tr>
<td>VAS</td>
<td>No</td>
</tr>
<tr>
<td>NDSS</td>
<td>Yes</td>
</tr>
<tr>
<td>VAS/OAS</td>
<td>Yes</td>
</tr>
<tr>
<td>OAS</td>
<td>Yes</td>
</tr>
</tbody>
</table>


KG is a 64yo P2 woman with no significant PMH who presents for her routine gynecologic visit. She reports dyspareunia despite lubrication. She declines vaginal estrogen, stating “she doesn’t want to try any hormonal medications as she doesn’t perceive them as safe.”

GENITOURINARY SYNDROME OF MENOPAUSE

...a collection of signs and symptoms associated with a decrease in collagen and other sex steroid hormones involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder.

SYMPTOMS AND SIGNS OF GSM

HORMONAL TREATMENT FOR GSM

Low dose vaginal estrogen preparations are generally safe

- Available in creams, tablets, rings
- Cochrane Review (2016): no difference in efficacy between the various intravaginal estrogen preparations

Estrogen therapy (ET) is the most effective treatment for GSM

Primary concern: Risk of endometrial cancer associated with unopposed estrogen

- Low dose vaginal ET produces very low serum levels of estrogen
- No evidence of increased endometrial proliferation or hyperplasia with low dose vaginal ET

SAFETY OF VAGINAL ET

SERUM LEVELS OF ESTROGEN (WITH LOW DOSE VAGINAL ET)

- Levels of E2 after administration of 10 mcg estradiol tablet on days 1, 14, and 83

WHAT ABOUT THE UTERUS WITH VAGINAL ET?

- Ulrich LS et al (Climacteric, 2010)
  - Prospective cohort study of postmenopausal women using 10 mcg vaginal estradiol tablet
  - Primary end point was endometrial hyperplasia/cancer at week 52
  - Outcomes
    - No cases of endometrial hyperplasia/cancer by week 52
    - Mean endometrial thickness was 1.96 mm at end of the study, compared to 2.26 mm at study start

CONCLUSION

Low doses of vaginal estrogen generally safe for endometrium
NON-ESTROGEN THERAPIES FOR GSM

OSPEMIFENE
- Only SERM approved in US for treatment of moderate to severe GSM
- Multiple RCTs comparing ospremifen to placebo demonstrated:
  - Improvement in vaginal maturation index
  - Vaginal pH
  - Vaginal dryness
  - Dyspareunia
  - Female sexual dysfunction

OSPEMIFENE - THE DETAILS

1. Dosage: 60 mg daily
2. Advantages:
   - Avoid use of vaginal product
3. Disadvantages:
   - Requires daily use
   - Systemic side effects (most common: hot flashes; theoretical risk of VTE)

INTRAVAGINAL DHEA (DEHYDROEPIANDROSTERONE)
- Also known as vaginal prasterone
- Requires daily administration
- Mechanism of action is likely aromatization of androstenedione and testosterone locally to estrone and estradiol
- Slight increase in serum levels of DHEA, testosterone, and estrone but levels remained within range of postmenopausal women
- No direct comparison to vaginal estrogen
OTHER TREATMENTS (NOT YET APPROVED)

**Testosterone**
- Data support the effect of testosterone on vaginal mucosa and symptom improvement of GSM
- Small studies showed improvement in vaginal maturation index, vaginal dryness, and dyspareunia
- Elevations in serum testosterone
- Vaginal testosterone not recommended at this time

**Vaginal laser**
- Lack of well-designed studies
- Overall appears to be safe and potential non-pharmacologic intervention for GSM
- Approved by FDA for treatment of GSM
- Requires further RCTs to evaluate safety and efficacy

CONCLUSIONS

- HT is most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause
- Benefits of systemic HT most likely outweigh the risks for symptomatic women who initiate HT < age 60 or who are < 10 years of menopause
- "Appropriate dose, duration, regimen, and route of administration"
- Be mindful of HT regimen to minimize risk to patient

THANK YOU