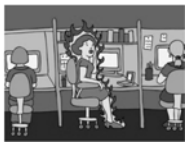
Pre-test question



Case

- 48 year old woman with hot flashes
- Menstrual periods have become irregular: now every one to three months
- Pelvic exam is normal

Pre-test question

How would you evaluate her?

1. Ask about menstrual cycles, hot flashes, mood changes, sleep disturbance
2. Ask about symptoms and check FSH, TSH, prolactin
3. Ask about symptoms and check FSH, TSH, prolactin and pelvic ultrasound
4. Pregnancy test is not necessary

Issues for the peri-menopausal woman

- Hot flashes
- Irregular bleeding
  - MORE (more frequent, more days of bleeding per cycle, heavier bleeding) MUST be evaluated: pregnancy test, pelvic USG, endometrial biopsy
  - LESS (less frequent, fewer days, lighter) doesn't need additional evaluation in woman older than 45
- Still needs contraception

Is FSH testing helpful in diagnosing perimenopause?

- Serum FSH levels are very variable
- NOT required to make diagnosis
- If normal, may be misleading
- If amenorrhea of $\geq$ 60 days and no other symptoms, FSH > 25 can be reassuring that amenorrhea is due to perimenopause and nothing else

Best treatment

- Low-dose oral contraceptive (OC) pill:
  - will control the bleeding
  - will treat the hot flashes
  - will provide contraception
- Use pill with 10-20 mcg of ethinyl estradiol plus a progestin

N Engl J Med 2008; 358:1262

Contraindications to low dose OC use in perimenopause

- Obesity: greater risk for thromboembolic complications
- Smoking
- Hypertension
- Migraines
- Other contraindications to systemic estrogen

How long to continue the estrogen-containing pill

- Stop by age 50-51
- Taper by 1 active pill a week
- Patient should then use condoms for 12 months
- If no menstrual bleeding for 12 months after stopping the pill:
  - she is officially in menopause and contraception is no longer needed
  - can then assess re whether treatment is needed for menopause symptoms

Case

- 52 year old woman with no menstrual periods for 1 year and hot flashes that have been disturbing her for six months
- She wants to know if she could take hormone therapy (HT) for her symptoms.

How do you assess your patient's risk for hormone treatment?

1. Check if she is free of contraindications to hormone therapy and calculate her cardiovascular risk
2. Take her blood pressure
3. Measure her cholesterol
4. Assess her risk for breast cancer

Contraindications to hormone therapy (HT)

- Breast cancer
- Coronary heart disease (CHD)
- Hx of venous thromboembolic event (VTE)
- Hx of stroke
- Active liver disease
- High risk for these complications

J Clin Endocrinol Metab 2015;100:3975

Helpful tool: **MenoPro** App

- Evidence-based free mobile app created by the North American Menopause Society to guide decision making about therapies for menopause symptoms
- Downloadable to mobile iPhone/iPad
- Designed for women ≥ 45 years old and for clinicians

Menopause 2015;22(3):254

MenoPro: how it works

- Asks questions
  - How severe are your symptoms?
  - Free from traditional contraindications to hormone therapy (HT)?
  - What is your CV risk: calculates using ACC/AHA ASCVD Risk Estimator
- Recommends lifestyle modifications for symptoms for at least 3 months

Recommendations about hormone therapy are based on patient's 10 year CV risk

- **Low (< 5%)** and less then 10 yrs since menopause: oral or transdermal therapy
- **Moderate (5-10%)** and less than 10 yrs since menopause: transdermal estrogen: less adverse effects on clotting factors, triglycerides, inflammation factors
- **High (>10%):** avoid systemic hormone therapy

Menopause 2015;22(3):254

Current thinking about hormone therapy (HT)

- **Efficacy:** Estrogen is the most effective treatment for relief of menopausal symptoms
  - combine with a progestin in women with a uterus
  - alone in women with hysterectomy
- **Risks:** Low in women ages 50-59

Cochrane Database Syst Rev 2004; :CD002978

Combined estrogen-progestin therapy: number of cases per 1000 women per 5 years of hormone use compared to placebo

- **Coronary heart disease (CHD):** 2.5 additional cases
- **Invasive breast cancer:** 3 additional cases
- Stroke: 2.5 additional cases
- Pulmonary embolism: 3 additional cases
- Colorectal cancer: 0.5 fewer cases
- Endometrial cancer: no difference
- Hip fracture: 1.5 fewer cases
- All-cause mortality: 5 fewer events

Stuenkel CA et al. J Clin Endocrinol Metab 2015

Estrogen-alone therapy: number of cases per 1000 women per 5 years of hormone use compared with placebo

- **CHD:** 5.5 fewer cases
- **Invasive breast cancer:** 2.5 fewer cases
- Stroke: 0.5 fewer cases
- Pulmonary embolism: 1.5 additional cases
- Colorectal cancer: 0.5 fewer cases
- Hip fracture: 1.5 additional cases
- All-cause mortality: 5.5 fewer events

Stuenkel CA et al. J Clin Endocrinol Metab 2015

Current conclusions about risks of hormone therapy (HT)

- **Risks** in younger postmenopausal women (ages 50-59) are significantly lower than in women in their 60s (the women studied in the WHI)
  - Due to lower baseline risk of CHD, stroke, VTE and breast cancer in younger women
- **Combined estrogen-progestin therapy** is associated with higher risk of CHD and breast cancer than unopposed estrogen

JAMA 2013; 310:1353

Options for our patient

- Decide about type of estrogen, the route, the need for progestin, most appropriate progestin regimen

Oral estrogens: Side effects

- Increase serum triglycerides
- Increase risk of venous thromboembolism (VTE) and stroke more than transdermal estrogen
  - Risk is very low in healthy, young postmenopausal women so oral estrogen can be used if patient prefers it
- Preparations include 17-beta estradiol and conjugated equine estrogen (CEE)

My recommendation: Transdermal 17-beta estradiol

- Transdermal: advantages over oral
  - Does not increase triglycerides
  - Less risk of venous thromboembolism and stroke
- 17-beta estradiol: main estrogen the ovary produces prior to menopause

Estrogen dose

- **Start low, titrate up if necessary**
- Start with transdermal estradiol 0.025 mg patch, or oral estradiol 0.5 mg/day
- If hot flashes not relieved after 1 month, increase transdermal to 0.0375 mg, oral to 0.75 mg, reassess after 1 month
- If symptoms persist, increase to 0.05 mg transdermal, 1 mg oral

Am J Med 2005; 118 Suppl 12B:74

Adding a progestin

- All women with intact uterus need a progestin in addition to estrogen to prevent endometrial hyperplasia
- Women who have had hysterectomy do not need a progestin

Progestin options

- **Medroxyprogesterone acetate**
  - Used in the Women's Health Initiative (WHI)
  - Associated with increased risk of coronary heart disease, breast cancer when given with conjugated estrogen in the WHI
- **Micronized progesterone**
  - Thought to be safer for heart and breast: benefits not yet proven

My recommendation: Micronized progesterone

- **For newly menopausal woman:**
  - Estrogen daily
  - Cyclic progestin 200 mg for 12 days/month
  - Decreases likelihood of irregular, unscheduled bleeding
- **≥ 2-3 years post menopause:** continuous dose
  - Less risk of irregular bleeding
  - Estrogen plus progestin 100 mg daily

Progestin side effects

- Mood symptoms
- Bloating
- Worse with cyclic dosing
- What to do: switch to continuous

Options for women who can't tolerate any oral progestin

- **Levonorgestrel IUD:** off-label use
  - High intrauterine but low systemic levels of levonorgestrel
- **New combination pill:** conjugated estrogen + bazedoxifene, a selective estrogen receptor modulator (SERM): CE 0.45 mg/BZA 20 mg qd)
  - Prevents endometrial hyperplasia
  - Associated with increased risk for venous thromboembolic events

Obstet Gynecol 2013;121:959

Endocrine Society Scientific Statement: Don't use bioidentical hormone therapy

- Custom-compounded, multi-hormone regimens: pills, gels, sublingual tablets, suppositories
- No randomized trials show efficacy or safety
- No regulatory oversight
- When tested, potencies and patterns of absorption have been highly variable

J Clin Endocrinol Metab 2016 Apr;101(4):1318-43

When to stop hormone therapy

- After 5 years or less of use
- Observational studies: 65-75% of women stop within 2 years

J Clin Endocrinol Metab 2008; 93:4567
Am J Med 2005;118 Suppl 12B:163

Should systemic hormone therapy ever be continued after age 65?

1. Yes
2. No

Continuing hormone therapy (HT) after age 65

- North American Menopause Society (NMAS): New position statement
- Continuing HT past age 65 is acceptable IF
  - The woman has been advised of increased risks after age 60
  - She continues to have bothersome symptoms
  - Unable to use any other appropriate medication
  - Her clinician has determined that benefits outweigh risks

Menopause 2015 Jul; 22:693

How to stop

- WHI: 55% will have recurrent hot flashes if hormone therapy stopped abruptly
- Discuss options of taper vs. stop with patient
- My recommendation: taper
  - Decrease estrogen by 1 pill every 2-4 weeks: e.g. 6 pills per week x 2-4 weeks, then 5 pills, etc.
  - Transdermal: gradual dose reduction
  - Decrease progestin on same schedule
  - If severe recurrent symptoms, taper more slowly

JAMA 2005;294:183

What if symptoms recur?

- Try non-estrogen alternative: SSRI or gabapentin
- If ineffective, restart estrogen at lowest dose if benefits outweigh risks

J Clin Endocrinol Metab 2010;95:257

Case

?

- 52 yo woman with breast cancer, on tamoxifen, with no menstrual periods for one year and severe hot flashes occurring throughout the day and night
- She would like to take non-hormonal therapy for her symptoms.

What is her best option?

1. Paroxetine
2. Venlafaxine
3. Fluoxetine
4. Gabapentin

Non-hormonal therapy: SSRIs and SNRIs

- Venlafaxine, desvenlafaxine, paroxetine, citalopram, escitalopram appear to have similar benefit
  - No head to head trials available
- Efficacy demonstrated in multiple trials
- Clinical response is more rapid (days) than response for depression (weeks)
- Sertraline, fluoxetine: not effective

JAMA 2006; 295:2057. Obstet Gynecol 2007; 109:823

My recommendation: Venlafaxine sustained release

- 37.5 mg/day for 1 week, increasing to 75 mg/day after 1st week
- Side effect: nausea: less with use of sustained release and gradual dose increase
- Preferred in women taking tamoxifen: minimally blocks conversion of tamoxifen to active metabolites

JAMA Intern Med 2014; 174: 1058

Low-dose paroxetine (7.5 mg/day)

- Only agent approved by FDA for treatment of hot flashes
- Expensive, not covered by many insurers
- Cheaper options (off-label)
  - 10 or 20 mg pill/day
  - 12.5 or 25 mg controlled release pill/day
- Avoid in women taking tamoxifen: blocks conversion of tamoxifen to its active metabolites

Menopause 2013; 20:1027

Citalopram or escitalopram

- Off-label use
- Optimal dose: 20 mg
- Side effects minimal

J Clin Oncol 2010; 28:3278. JAMA 2011; 305:267

Anticonvulsant: Gabapentin

- May be better option for women whose hot flashes are mainly at night
- Start with 100 mg one hour before bedtime, increase by 100 mg every 3 nights until relief of hot flashes, side effects or maximum of 900 mg
- Higher doses, up to 2400 mg: more efficacy but more side effects: headache, dizzy

Lancet 2005; 366:818

Case

?

- 53 year old woman is having severe pain on intercourse
  - Has had no menstrual periods for one year
  - Is not troubled by hot flashes

What is the most appropriate treatment for this woman with severe pain on intercourse?

1. Vaginal moisturizer
2. Vaginal lubricant
3. Low dose vaginal estrogen
4. Ospemifene
5. Oral estrogen

Symptoms of vaginal atrophy

- Dryness, burning, pain on intercourse
- Urinary symptoms: urinary frequency, frequent bladder infections

First line treatment: vaginal moisturizers and lubricants

- Helpful for mild symptoms
- Use of moisturizer several times a week
- Use of lubricant before sexual activity
- All are OTC

Vaginal estrogen

- For moderate-severe symptoms
- More effective than systemic therapy
- Low dose recommended: minimizes systemic estrogen effects
- Creams, tablets, rings: similarly effective

Obstet Gynecol 1998; 92(4 Pt 2):722

Low dose preparations

- **Tablet:** 10 mcg estradiol, insert in vagina nightly x 2 weeks, then twice a week
- **Vaginal ring:** Releases 7.5 mcg estradiol daily into vagina for 90 days
- **Low dose of vaginal cream:**
  - 0.5 gm of conjugated estrogen = 0.3 mg CE
  - 0.5 gm of estradiol = 50 mcg estradiol
  - Daily x 2 weeks, then twice a week

Serum estradiol levels

- Average level for postmenopausal woman: 5 pg/ml
- 10 mcg estradiol tablet: 3-11 pg/ml
- Ring: 5-10 pg/ml
- Creams: hard to quantify
  - 0.5 gm of conjugated estrogens: made up of many compounds. Serum estradiol level doesn't reflect total absorption
  - 0.5 gm of estradiol: approx. 10 pg/ml

Climacteric 2010; 13(3):219

Use of progestin

- Not needed with the tablet or ring
- Low dose vaginal creams
  - Systemic absorption hard to quantify and scant data on risk of endometrial neoplasia
  - Most conservative approach: use progestin 12 days a month

How long to continue low dose vaginal estrogen

- Can be continued indefinitely due to low risk of adverse effects
- Safety data available only up to 1 year

Menopause 2010; 17(2):242

NEW: Ospemifene

- Selective estrogen receptor modulator (SERM)
  - Estrogen **agonist** in vagina: treats atrophy
  - No estrogen effect on breast or endometrium
- One 60 mg pill daily
- Good for women who can't or don't want to use a vaginal product
- Side effects
  - Hot flashes
  - Potential for thromboembolic events: no data yet

Menopause 2010 May; 17(3): 480

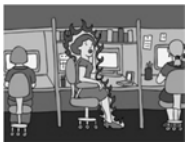
Take home points

1. Peri-menopausal women may need treatment for hot flashes, irregular bleeding and contraception. A low dose combined oral contraceptive pill is an effective choice.
2. MORE bleeding in peri-menopause (more frequent, more days/period, heavier bleeding) needs full evaluation
3. Many menopausal women who need treatment for hot flashes can be safely treated with hormonal therapy for up to 5 years
4. Non-hormonal therapy can effectively treat menopausal symptoms for years

Take home points, continued

5. Symptomatic vaginal atrophy can be treated for years with low dose vaginal estrogen or ospemifene
6. Try the MenoPro app: a useful tool for helping your patient with her menopause symptoms

Post-test question



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