Case

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

Issues for perimenopausal women

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

Is FSH helpful?

- Serum FSH levels are very variable
- NOT required to make diagnosis
- If normal, may be misleading

Best treatment

- Low-dose oral contraceptive (OC) will:
  - control the bleeding
  - treat hot flashes and other symptoms
  - provide contraception
- Use pill with 10-20 mcg of ethinyl estradiol
- Continuous pill use is the best approach

N Engl J Med 2008; 358:1262

Contraindications to low-dose OC use in perimenopause

- Hx of venous thromboembolism
- Hx of pulmonary embolism
- Smoking cigarettes
- Uncontrolled hypertension
- Heart attack
- Stroke
- Migraines with aura

How long to continue the OC?

- All the way to age 55
- 95% of women are menopausal by age 55
  - contraception is no longer needed
  - can then assess whether treatment is needed for menopause symptoms

Case

- 52 yo woman with no menstrual periods for 1 year and bothersome hot flashes for 6 months
- Should she could try hormone therapy?

Contraindications to hormone therapy

- Breast or uterine cancer
- Coronary heart disease
- Hx of venous thromboembolism
- Hx of stroke
- Active liver or gallbladder disease
- Unexplained vaginal bleeding

J Clin Endocrinol Metab 2015;100:3975

Calculating 10 year risk for atherosclerotic cardiovascular disease (ASCVD)

- New American College of Cardiology (ACC)-American Heart Association (AHA) online calculator:

  google: ACC cardiac risk
- ACC-AHA assessments of risk:
  - < 7.5% ten year risk: low
  - ≥ 7.5% ten year risk: moderate to high

Efficacy of hormone therapy

- **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

Cochrane Database Syst Rev 2004; :CD002978

Current estimates of risks of hormone therapy in women ages 50-59

Stuenkel CA, et al. Treatment of symptoms of the menopause: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015

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

- Coronary heart disease**:** 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 five 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

Conclusions about hormone therapy

- **Risks** in younger menopausal women (50-59) are significantly lower than in women in their 60s or 10 years beyond their LMP
  - lower baseline risk of CHD, stroke, VTE and breast cancer
- **Combined estrogen-progestin therapy** is associated with higher risk of CHD and breast cancer than estrogen alone

JAMA 2013; 310:1353

Helpful tool: **MenoPro** App

- Evidence-based and created by the North American Menopause Society to guide women through decision making about therapies for menopause symptoms
- Downloadable to mobile iPhone/iPad
- Designed for women > 45 years old with systemic and/or vaginal symptoms

Menopause 2015;22(3):254

MenoPro recommendations based on 10 year CV risk

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

Menopause 2015;22(3):254

Transdermal 17-beta estradiol

- Transdermal advantages vs oral
  - No increase in triglycerides
  - Less risk of venous thromboembolism and stroke
- 17-beta estradiol: main estrogen the ovary produces prior to menopause
- Bioidentical

Estrogen dose

- **Start low and titrate up**
- Transdermal estradiol 0.025 mg patch, or oral estradiol 0.5 mg/day
- If hot flashes not relieved after 6 weeks, increase transdermal to 0.0375 mg, oral to 0.75 mg, reassess after 6 weeks
- 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 a uterus need a progestin to prevent endometrial hyperplasia and cancer
- Women who have had hysterectomy do not need a progestin

Micronized progesterone

- **Choice #1**
  - Cyclic dosing
  - Micronized progesterone 200 mg days 1-14 of month
  - Decreases likelihood of irregular, unscheduled bleeding
- **Choice #2**
  - Continuous dosing
  - Leads to amenorrhea
  - Micronized progesterone 100 mg at bedtime

Progestin side effects

- Mood symptoms

Can't tolerate any oral progestin?

- Low dose levonorgestrel IUD
  - Contains 13.5 mg levonorgestrel
  - Releases 0.014 mg/day, with gradual decrease to 0.005 mg/day after 3 years
- Standard levonorgestrel IUD: 52 mg
- Off label and no data in menopause

NEW: Conjugated estrogen/bazedoxifene

- New class of drugs: tissue selective estrogen complex (TSEC)
  - Combination of conjugated estrogen (CE) and selective estrogen receptor modulator (SERM)
- FDA-approved for treatment of menopausal hot flashes and osteoporosis prevention

Obstet Gynecol 2013;121:959

Conjugated estrogen (CE)/Bazedoxifene (BZA)

- Estrogen **agonist** effects on bone, **antagonist** effects on endometrium, **neutral** effects on breast
- Dose: CE 0.45mg/BZA 20 mg daily
- Decreases hot flashes by 75%
- Increased risk of venous thromboembolism with BZA

Menopause 2009; 16:1116. J Bone Miner Res 2008; 23:1923

When to stop hormone therapy?

- Depends on who you ask!
- 75% of women stop within 2 years

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

Continuing hormone therapy after 65

- North American Menopause Society (NAMS): Position Statement on menopause.org
- HT past age 65 is acceptable when
  - Bothersome symptoms persist
  - Prevention of osteoporosis
  - Document increased risk discussion

Menopause 2015 Jul; 22:693

Best approach to discontinuing HT

- No data
- No formal recommendation
- Taper or stop cold turkey?

JAMA 2005;294:183

What if symptoms recur?

- Restart HT
- Try SSRI or gabapentin

J Clin Endocrinol Metab 2010;95:257

Case

?

- 52 yo menopausal woman with breast cancer, on tamoxifen, complaining of severe hot flashes day and night
- She wants to try non-hormonal therapy

Non-hormonal therapy: SSRIs and SNRIs

- Venlafaxine, desvenlafaxine, paroxetine have similar benefit
- Efficacy demonstrated in multiple trials
- Doses are lower than for depression

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

Venlafaxine sustained release

- 37.5 mg/day for 6 weeks
- Can increase to 75 mg/day if needed
- Side effects: minimal
- 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 FDA- approved non-hormonal treatment for hot flashes
- Expensive
- Generic Paxil 10 or 20 mg/day and 12.5 or 25 mg/day controlled release doses (off-label)
- Avoid in women taking tamoxifen: blocks conversion of tamoxifen to its active metabolites

Menopause 2013; 20:1027

Anticonvulsant: Gabapentin

- Better option for women whose hot flashes are only 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
- Side effects: drowsiness, dizziness, headache

Lancet 2005; 366:818

Case

- 53 yo woman with pain during intercourse
  - No menstrual cycles for one year
  - No hot flashes

Symptoms of vaginal atrophy

- Dryness, burning, irritation, pain with intercourse
- Urinary symptoms: frequency, urgency, bladder infections

Vaginal moisturizers and lubricants

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

Local vaginal estrogen

- For moderate-severe symptoms
- Local is not systemic estrogen

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

Local Estrogen Preparations

- **Tablet:** 10 mcg estradiol vaginally at bedtime for 2 weeks, then twice a week
- **Vaginal ring:** Releases 7.5 mcg estradiol daily into vagina for 90 days
- **Cream:**
  - Conjugated estrogen: 0.3 mg CE/0.5 g cream
  - Estradiol: 50 mcg estradiol/0.5 g cream

Serum estradiol levels

- Negligible and not clinically relevant

Climacteric 2010; 13(3):219

Use of progestin

- Not needed

How long can women continue local vaginal estrogen?

- Forever
- Safety data available only up to 1 year

Menopause 2010; 17(2):242

Ospemifene

- Selective estrogen receptor modulator (SERM)
  - Estrogen **agonist** in vagina
  - No estrogen effect on breast or endometrium
- 60 mg pill daily
- For women who can't/won't use local estrogen
- Side effects
  - Hot flashes
  - Potential for thromboembolic events

Menopause 2010 May; 17(3): 480

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