Hormone Replacement Therapy
Therapeutics III
December 8, 2003
Alicia Forinash, Pharm.D.

Required Readings

Supplemental Readings


Writing group for the women’s health initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women principle results from the women’s health initiative randomized controlled trial. JAMA 2002:288;321-33. (WHI trial)


Content Questions:
1. Describe the changes in the hypothalamus-pituitary-ovary (HPO) axis in menopause
2. List symptoms present with menopause
3. List nonpharmacologic treatments for menopausal symptoms
4. List the goals for menopause treatment
5. Describe the difference between estrogen replacement therapy (ERT) and hormone replacement therapy (HRT)
6. Name the predominant form of estrogen in premenopausal and postmenopausal females
7. List common adverse effects from HRT. Describe ADRs that are less common in transdermal estrogen compared to oral
8. Define role for progestins in HRT
9. List the benefit of testosterone therapy in menopausal females. Explain why estrogen must be administered when giving testosterone therapy.
10. Explain the mechanism of action, benefits, and ADRs for selective estrogen receptor modulators (SERMs)
11. List the contraindications to HRT
12. List and explain the benefits and risk of HRT therapy
13. List important counseling points for HRT/ERT
14. List alternative treatments for vasomotor symptoms
1. **Introduction**
   Menopause: loss of ovarian function leading to a state of permanent amenorrhea
   - Occurs after 12 consecutive months of amenorrhea

   Climacteric or Perimenopausal →

   - At menarche, 380,000 oocytes are present within ovarian follicles
   - After age 35, the ovaries begin to decrease in weight and size and contain fewer oocytes and follicles; also a gradual decline in estrogen production
   - Series of irregular menstrual cycles with increased menstrual cycle length and variable intermenstrual intervals
   - Average age of menopause is 51 years old, usually between 49-53
   - Average life expectancy for a female is 79.7 years, so 1/3 of life is postmenopausal
   - Surgical menopause
   - Women who smoke typically undergo menopause approximately 2 years earlier likely due to alterations in steroid metabolism and gametotoxic effects of cigarette smoke

2. **Hormonal Changes**
   - Changes in the Hypothalamus-Pituitary-Ovarian (HPO) axis

   ![HPO axis diagram]

   - FSH levels increase 10-15x and LH increases 4-5x normal premenopausal levels; postmenopausal levels are >40mIU/mL
   - Lab tests
     - TSH
     - Urine HCG

3. **Menopausal symptoms and changes**
   - Vasomotor
   - Osteoporosis
   - Urogential atrophy
4. Estrogen Metabolism and Effects

- androstenedione -> aromatization -> Estrone (E1)
- testosterone -> aromatization -> 17β Estradiol (E2)

- Estrone (E1) is the predominant estrogen premenopausal females and is derived from developing follicles.
- 17β Estradiol (E2) is the predominant estrogen in postmenopausal females and is derived from adipose tissue. Adrenal glands and ovarian stroma cells produce the androgen androstenedione which is converted to estrone peripherally in the adipose and other tissues. This conversion is enhanced in obese women.

<table>
<thead>
<tr>
<th>Estrogens</th>
<th>Progestins</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ HDL and ↓ LDL*</td>
<td>↓ HDL and ↑ LDL **</td>
</tr>
<tr>
<td>↑ TG and VLDL</td>
<td>No effect on clotting factors</td>
</tr>
<tr>
<td>↑ factors VII and X</td>
<td></td>
</tr>
<tr>
<td>↓ antithrombin III activity</td>
<td></td>
</tr>
<tr>
<td>↑ Renin substrate*</td>
<td></td>
</tr>
<tr>
<td>↓ PAI-1</td>
<td></td>
</tr>
</tbody>
</table>

* May not be true for non-oral routes that avoid first-pass effect
** May not be as significant for micronized progesterone

- Progestosterone levels decrease.
- PEPI trial—involved 875 women to conjugated equine estrogens (CEE) 0.625mg/d, CEE 0.625mg + medroxyprogesterone (MPA) 2.5mg, CEE 0.625mg + MPA 10mg 12 days/mo, CEE 0.625mg + micronized progesterone (MP) 200mg/d for 12 days/mo, or placebo
  - CEE alone have the most beneficial effects on the lipid panel for increasing HDL. However, estrogen plus progestins still have beneficial effects on HDL
  - Patients with a uterus on CEE alone had significantly higher rates of endometrial hyperplasia
  - All treatment groups decreased LDL and increased TG without significant difference
Number one cause of death for females (not breast cancer)
Observational trials suggest 35-50% lower risk of coronary artery disease in women taking estrogen compared to nonusers. Effect is proposed to be from lipid effects
However, randomized trials have NOT supported observational trials

**Primary Prevention**

- Women’s Health Initiative—randomized trial 16,608 postmenopausal women
  
  **Results**
  
  In 10,000 women 50-79 years old that use HRT >1 year, HRT resulted in …
  
  - 7 more CHD events + 6 fewer cases of colon cancer
  - 8 more PE + 5 fewer hip fractures
  - 8 more cases of breast cancer

**Still has an arm of Estrogen alone versus placebo ongoing to evaluate 8 years of therapy. Expected conclusion in 2004.**

**Secondary Prevention**

- HERS—first randomized, double blind, controlled trial
  
  - Conjugated equine estrogens 0.625mg + medroxyprogesterone 2.5mg (Prempro) vs. placebo for four years with one year follow-up
  
  **Results**
  
  - Significantly increased risk during year one for the HRT group
  
  - No significant difference during years 2-4 but the data starting to trend in HRT’s favor

**American College of Cardiologists Recommendation:**

- “…does not support the initiation of conjugated equine estrogens combined with medroxyprogesterone acetate in older postmenopausal women with confirmed coronary disease.”

- “For women with CHD already on ERT for at least one year, it may be reasonable to continue therapy while awaiting the results of a HERS follow-up study”

- HERS II—2.7 years follow-up (total 6.8 years) to the HERS,
  
  - No significant difference in CAD events between HRT and placebo groups at years 5,6,7,8 or for, combined 6.8 years

* Professional Conclusions on HRT for CAD:

- United States Preventative Services Task Force (USPSTF)
  
  - “harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases, and the presence of menopausal symptoms.”

  - “Insufficient evidence to recommend for or against the use of unopposed estrogen for the prevention of chronic diseases in postmenopausal women with a hysterectomy.”

  - “…did not evaluate HRT for the management of menopausal symptoms.”

- North American Menopause Society (NAMS)
  
  - “Treatment of menopause symptoms are the primary indication for ERT and HRT.

  - “No HRT regimen should be used for CHD. …the effects of ERT on CHD is still unknown.”

  - “Use HRT/ERT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman”
Women should be informed of known risks

Questions still to be answered…
- Will ERT produce the same results?
- Do different formulations of HRT (i.e. Activella, FemHRT) produce different effects?
- Do different delivery routes (i.e. transdermal) have different results?
- Should different progestins be used? Dosed cyclically instead of QD?
- Many, many more

6. Benefits of HRT
   
   **Vasomotor Symptoms**
   - Most effective therapy for treatment
   - Higher doses often required to control vasomotor symptoms
   - Therapy continued for 1-2 years to control symptoms
   - Oral and transdermal preparations effective in treatment

   - Bone turnover increases with decrease in estrogen levels
   - Only for prevention, not treatment of osteoporosis
   - WHI found significant decrease of 34% of hip and vertebral fractures but HERS found no significant difference in vertebral and hip fractures
   - Oral and transdermal estrogens are effective
   - Is it worth the risk?

   **Urogential Symptoms**
   - Treatment of vaginal atrophy, dysparunea, vaginitis is successful with oral, transdermal, and vaginal preparation

   **Questionable Benefit**
   **CVA Prevention**
   - Epidemiologic data proposed that HRT would decrease risk of CVA.
   - Recent randomized, double-blind, secondary prevention trial noted no significant differences in CVA mortality or recurrence
   - WHI found significant increased risk of 41% and HERS found no significant difference

   **Cognitive Function and Alzheimer’s Disease**
   - Early observational trials suggested protection from cognitive decline.
   - However, randomized, controlled trials have failed to support this.
   - Proposed mechanism involves estrogen promote growth of cholinergic neurons, possess antioxidant effects, decrease apolipoprotein E levels, increase metabolism of amyloid precursor proteins, promote neurite growth, and increase cerebral blood flow

   **Colon Cancer**
   - Observational studies report a decreased risk of 8-33%
   - WHI found a significantly lower rate of 37%, the HERS II trial found no difference

   **Miscellaneous**
   - Prevention in tooth loss
   - Decreased risk of peripheral arterial disease

7. Risks of HRT
   **Thromboembolism**
   - ______________ can decrease with estrogen
   - ______________, ______________, and ______________ can increase with estrogen
   - Increases risk of DVT by 2-3.5, but the absolute risk if relatively small (20 per 100,000 cases)
Endometrial Cancer

- Estrogen stimulates endometrial cell mitosis and proliferation
- Unopposed estrogen (>1 year) increases the risk of endometrial cancer 8-10 times
- Endometrial hyperplasia is precursor
- Progestin therapy added to ERT decreases the risk
- Risk Factors: obesity, nulliparity, infertility, liver disease, and estrogen-secreting ovarian tumors

Breast Cancer

- ____________ lifetime risk for women in general with a greater incidence in those >60 years old
- No significant increase in the incidence of breast cancer for women who take HRT for LESS than 5 years. Reanalysis of data from 51 trials shows that breast cancer risk increases with long-term use of estrogen.
- 5 years after HRT has been discontinued, there is no longer an increased risk for breast cancer
- WHI was stopped early because of the higher rate of breast cancer in the HRT group. 15% higher rate for the first five years (nonsignificant) and 54% higher rate for greater than 5 years of use (significant)

Gallbladder dysfunction

- Observational trials report an increased risk of 2-3x.
- HERS trial had a 38% higher rate of gallbladder disease in those taking HRT
- Consider transdermal estrogen in high risk patients

8. Adverse Reactions

- Nausea (less likely with transdermal)
- GI discomfort
- Bloating, fluid retention
- Breast tenderness
- Headaches/Migraines (less likely with transdermal)
- Weight gain (cyclic) (from fluid retention)
- Decreased libido
- PMS-like symptoms from progestin
- Depression
- Spotting/breakthrough bleeding (BTB)

9. Contraindications

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>*</td>
<td>Uterine leiomyoma</td>
</tr>
<tr>
<td>*</td>
<td>History of migraines</td>
</tr>
<tr>
<td>*</td>
<td>History of cholelithiasis</td>
</tr>
<tr>
<td>*</td>
<td>History of thrombosis related to</td>
</tr>
<tr>
<td></td>
<td>pregnancy or oral contraceptives</td>
</tr>
<tr>
<td>*</td>
<td>Seizure disorder</td>
</tr>
<tr>
<td>*</td>
<td>HTN</td>
</tr>
<tr>
<td>*</td>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>CAD</td>
</tr>
</tbody>
</table>
10. **HRT Regimens and Products**
   - Not effective as contraceptives because regimens contain ~1/5 estrogen dose
   
   **Routes of Administration**

**ORAL**

- **Advantages:** Greater increase in effect on hepatic lipoproteins, ease of administration
- **Disadvantages:** Liver effects

**Continuous Estrogen and cyclic Progestin**

- Estrogen is given every day at a set dose
- Progestin is added for 10-12 days/month
- **Advantages:** no return of menopausal symptoms because estrogen is given each day
- **Disadvantages:** bleeding each month (usually begins 1-2 days after last progestin dose)

**Continuous Estrogen and Progestin**

- Thought to create an atrophic endometrium and induce amenorrhea
- Decreasing the estrogen dose or increasing the progestin dose can help induce amenorrhea
- **Advantages:** 75% of women have amenorrhea at one year
- **Disadvantages:** unpredictable spotting or BTB when beginning therapy

**Unopposed Estrogen**

- ONLY for women WITHOUT a uterus
- No progesterone given, so no bleeding

**TRANSDERMAL**

- Applied one (Climara) or two (Estraderm, Vivelle) times per week
- **Advantages:** Decreased or no liver effects, useful in patients with GI absorption problems, stable concentrations of estrogen
- **Disadvantages:** Skin irritation, less significant effects on lipids, still need to give progestins for women with an intact uterus
- COMBIPATCH is a combination patch of estradiol and norethindrone
  - 9cm² patch contains 0.62mg E2 and 2.7mg NETA (0.05/0.14mg/d)
  - 16cm² patch contains 0.51mg E2 and 4.8mg NETA (0.05/0.25mg/d)
  - Apply the patch to the abdomen twice a week

**VAGINAL**

- Cream Dosing – QD x1 week, QOD x1 week, then 1-2x/wk thereafter
- Vaginal rings (Estring, Femring) provides a sustained release of estrogen to treat vaginal atrophy
- **Advantages:** Useful for symptoms of vaginal atrophy
- **Disadvantages:** Erratic absorption, long-term use may cause endometrial hyperplasia

**PARENTERAL**

- Little information on hepatic effects
- Does not undergo hepatic first pass metabolism, so thought to not have much effect on lipids

**SUBCUTANEOUS PELLETS**

- Implanted into the anterior abdominal wall or buttock and contain crystalline 17β estradiol
- Pellets are difficult to remove and may continue to release estrogen for a long time after insertion; implanted every 6 months for osteoporosis protection
- Not popular in the U.S.

**PRODUCTS**

Start moderate doses and titrate therapy based upon ADRs. Goal is to keep patient symptom-free on lowest possible doses.
There is no evidence to suggest that one product is more effective than another.

<table>
<thead>
<tr>
<th>Product</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarin (conjugated estrogens)</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>Ogen (estropipate [piperazine estrone sulfate])</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>Estrace (micronized 17β estradiol)</td>
<td>1 mg</td>
</tr>
<tr>
<td>Estinyl (ethinyl estradiol)</td>
<td>0.02 mg</td>
</tr>
<tr>
<td>Estratab, Menest (esterified estrogen)</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>Estraderm, Vivelle (17β estradiol transdermal)</td>
<td>0.05 mg/d</td>
</tr>
</tbody>
</table>

Conjugated equine estrogen:
- 10 different estrogen components
- Most studied estrogen product
- Various components are being investigated for specific effects of lipids, breast tissue, antioxidant capabilities, and direct cardiovascular effects

Synthetic estrogen (ethinyl estradiol, quinestrol, DES)
- Most potent hepatic effects and extended half-life
- DES not commonly used for HRT

Micronized estradiol
- Rapid conversion to estrone when given orally

Estrone sulfate, estradiol valerate, equine estrogens:
- More potent hepatic effects than micronized estradiol when given at doses that reach similar serum estradiol levels

Estrogen/testosterone combinations
- Prescribed for women with decreased libido or sexual difficulties on estrogen
- May be most useful in surgically induced menopause because of severe symptoms after rapid declines in estrogen and testosterone levels
- Methyltestosterone available alone, but should not administer without estrogen
- Administer cautiously and use lowest dose for short periods of time
- ADRs: hirsutism, acne, potential hepatotoxicity, adverse lipid effects (↑TC, ↑LDL, ↑TG, ↓HDL), potential insulin resistance, fluid retention potential increased risk of breast cancer, potential for thromboembolic effects
- Testosterone Contraindications: pregnancy, lactation, known or suspected androgen-dependent tumor.
- Relative contraindications: moderate to severe acne, clinical hirsutism, and androgenic alopecia

PROGESTINS
Medroxyprogesterone (MPA)
- Progestin added to products for endometrial protection but must be taken for a minimum of 12-14 days per month to protect against endometrial hyperplasia
- Most used and studied progestin

Synthetic progestins (norethindrone, norgestimate, desogestrel)
- Newer products use these progestins in an effort to induce amenorrhea quicker and to ease the transition from OC to HRT
- Higher incidence of amenorrhea at one year which may be due to the higher binding affinity to the endometrium than MPA

11. Discontinuing HRT/ERT
- Abrupt discontinuation may result in vasomotor symptoms
- Tapering days—reduce the number of days/week the patient
- Tapering doses—reduce the dose of exposure

12. Monitoring
Before initiation of therapy
- Complete H&P (including medical and family history, BP, weight, breast and pelvic exams, PAP smear)
- Baseline mammogram
- Fasting lipid profile

Follow-Up
- Mammogram yearly
- Breast and pelvic exam yearly
- Fasting lipid profile

13. Nonpharmacologic treatments
Vasomotor
- Reduce or avoid the intake of hot beverages and caffeine
- Exercise
- Cool showers before bedtime
- Avoid turtlenecks
- Avoid spicy foods
- Relaxation/stress reduction (massage, meditation, yoga)
- Avoid wool or synthetic clothing
- Cool environment
- Cool beverages or ice chips

Other
- Calcium intake
- Vaginal lubricating gels, if needed
- Counseling for depression, if needed
- Vaccinations

14. Education
- Purpose(s)
- Proper use
  - Administration
  - Importance of compliance
  - Importance of communication
- Potential ADRs
  - Common ADRs
  - Potentially serious ADRs
- Decide together with the patient whether or not HRT is for her

15. Selective Estrogen Receptor Modulators (SERM)
- MOA: activates some estrogen receptors while blocking other estrogen receptors in the body
- Advantages: osteoporosis prevention, breast cancer prevention, lipid effects
- Disadvantages: hot flushes, leg cramps, thromboembolism risk
- Raloxifene (Evista) 60mg po QD
- Tamoxifen (Nolvadex) 10mg po QD

16. Alternative Treatments for Vasomotor Symptoms
- Many women cannot or do not want to take HRT for vasomotor symptoms for various reasons including CAD, breast cancer, ADRs, cost, etc.
- Poor or limited date on therapies; however, many patients will ask about or take these products

Antidepressants
- venlafaxine 75mg/d, fluoxetine 20mg/d, paroxetine 10-30mg/d, sertraline 25-50 mg/d
In small studies, 50-87% reductions in hot flushes

**Antihypertensive Agents**
- **Clonidine** has been studied as tablets and patches for reducing vasomotor symptoms. Adverse events limit its effectiveness
- **β-blockers** have also been shown effective in reducing hot flushing

**Bellergal-S**
- Contains belladonna 0.2 mg, phenobarbital 40 mg, ergotamine 0.6 mg)
- Has peripheral adrenergic and cholinergic antagonizing effects
- Double-blind, placebo controlled trial demonstrated 60% reduction in symptoms

**Others**
- Megesterol
- Gabapentin
- Mirtazapine

**Herbal Products**

<table>
<thead>
<tr>
<th>Herbal (Products)</th>
<th>F.Y.I.</th>
</tr>
</thead>
</table>
| **Black Cohosh** (Remifemin) | MOA: unknown  
- Uncontrolled, open-label trials demonstrated benefit over placebo  
- Limited to a maximum of 6 months of therapy in Germany  
- Usually takes >1 month of therapy to relieve symptoms  
- May cause intolerable GI effects. Not effective for osteoporosis  
- FDA statement |
| **Red Clover** (Promensil) | - Phytoestrogen with mild effects on vasomotor symptoms  
- No osteoporosis or lipid benefit  
- Should not use if patient has history of breast cancer |
| **Evening Primrose** | MOA: unknown  
- One small study found benefit over placebo but other studies do not support any benefit |
| **Don quai** | - Possess vasomotor and antispasmodic effects  
- No significant difference compared to placebo in a RCT  
- Chinese herbalists comment that don quai must be used in combination with other herbal to effectively relieve vasomotor symptoms  
- Be sure to avoid for patients on warfarin because of ↑ in the INR |
| **Soy, phytoestrogens** (Healthy woman 55mg/tab, Natrol for women 10mg/tab, etc) | - Metabolized in the GI tract to form structures that are similar to estrogens and can bind to the estrogen receptor and produce antioxidant effects  
- Active ingredients are Isoflavones, lignans, and coumestans  
- 37-100 mg/d of soy isoflavone or 20-60 mg/d soy protein given for effects  
- Has been shown to increase tumor growth in women with estrogen-receptor positive breast cancer and may interfere with tamoxifen  
- Small studies have demonstrated positive results in controlling hot flashes  
- Also proposed to prevent osteoporosis |

* Other products tried include flaxseed oil, fish oil, omega-3 fatty acids, red clover, ginseng, rice bran oil, wild yam, calcium, gotu kola, licorice root, sage, sarsaparilla, passion flower, chaste berry, ginkgo biloba, valerian root; however, no good evidence exists in the literature to support these products.

***Do not recommend these products because of little primary literature to support use. Be aware of drug interactions, adverse drug reactions. Also, FDA does not regulate contents of herbas because they are considered dietary supplements.