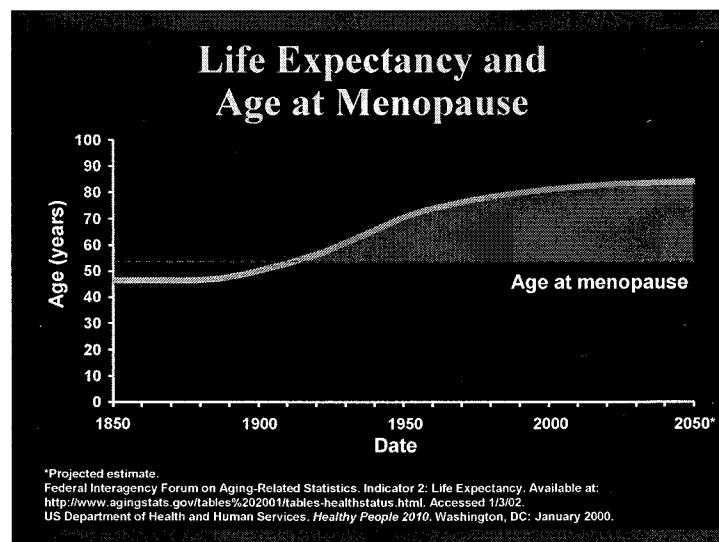


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Perimenopause and Menopause

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Department of Obstetrics and Gynecology
Oregon Health and Sciences University

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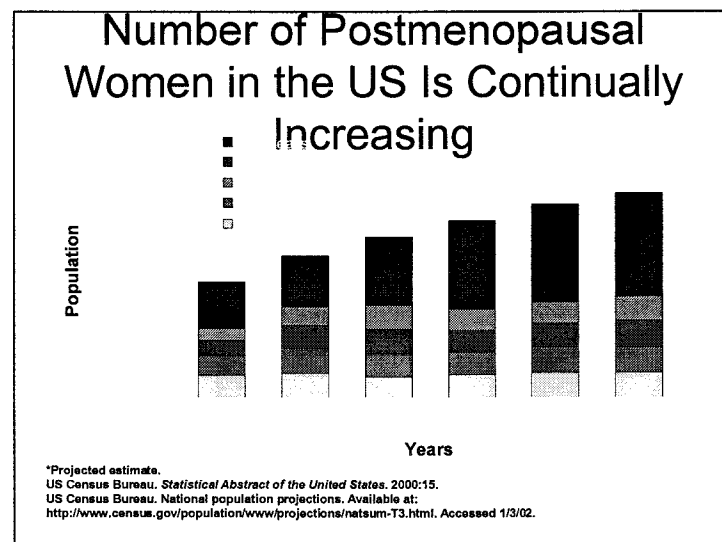
Menopause Facts

Most women spend at least one third of their lifetime in postmenopause

- 30 million women entered menopause during 2000
- This population will impact every area of medicine

North American Menopause Society, *Menopause Core Curriculum Study Guide*, Section A, June 2000.

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Perimenopause

- From the onset of menstrual cycle changes until 12 months after the last menstrual period
- Average duration is 4 years
- Range varies from 1 to 10 years

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Menopause

- No menstrual period for one year
 - A consequence of follicular depletion or removal of ovaries
 - Average age in the US is 51
 - Rare to still be ovulating by age 55
-

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Diagnosis of Perimenopause

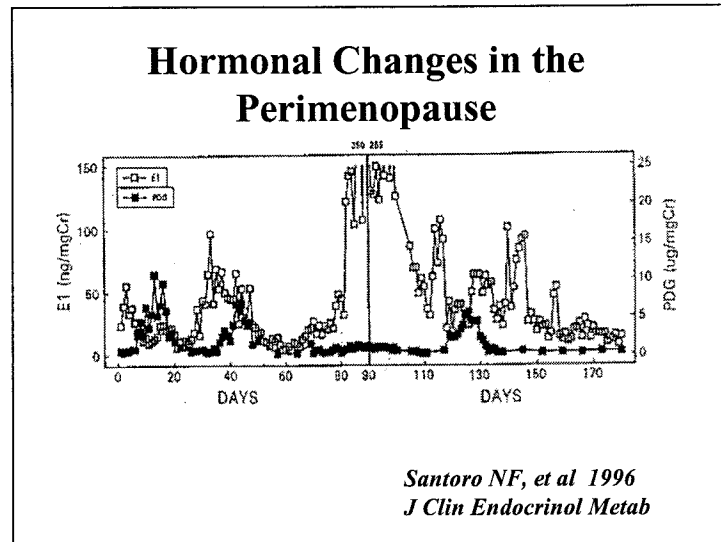
- This is a clinical diagnosis
- ***There are no reliable lab tests to determine perimenopause***
- Diagnosis based on symptoms
- Maintain a high index of clinical suspicion

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Symptoms of Perimenopause

- Variation in menstrual cycles
 - Change in quality of bleeding
 - Erratic hormone production due to:
 - Decline in oocyte number and quality
 - Resistance to pituitary gonadotropins
-

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Physiology of Menopause

- Estrogen levels decline due to depletion of ovarian granulosa cells

 - FSH levels increase

 - FSH levels above 20 IU/l generally indicate menopause
-

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Hot Flashes

- Early symptom of declining estrogen levels
- Recurrent, transient episodes of perspiration, flushing
- 75% of American women experience these in perimenopause and menopause

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Hot flushes

- Can occur at night (night sweats)
 - Contribute to fatigue, sleep disturbance, irritability
 - Can be followed by chills
 - Core body temp, skin temp increase
-

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Symptoms of Perimenopause

- Hot flashes
- Night sweats
- Sleep disturbance (due to intrinsic estrogen effect or night sweats???)

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Symptoms of Perimenopause

Psychological disturbance

- Menopause does not CAUSE depression
- Women with a history of depression more likely to manifest depressive symptoms in perimenopause and menopause

Cognitive effects?

Symptoms of Perimenopause

Changes in sexuality

- Many life stressors occur at this time
- Declining estrogen levels affect vaginal tissue
- Is changing libido due to external or internal events?

Symptoms of Perimenopause

- Other somatic symptoms
 - Breast tenderness, bloating
 - Worsening of preexisting medical problems?
 - Skin dryness
-

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Management of Perimenopause and Menopause

- Complete medical history and physical exam
- Rule out other possible causes of symptoms (thyroid, medication side effects, etc)
- FSH levels above 20 IU/l generally indicative of complete menopause
- Individualize interventions (nonpharmacologic and pharmacologic)

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Management

- Goal is symptom relief and maximization of long term health
 - Initiate preventative care (obtain pap, mammogram, lipid screening, thyroid, fasting glucose, complete blood count, flexible sigmoidoscopy and DEXA if appropriate)
 - This is a great opportunity for intervention re: lifestyle factors
-

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Nonpharmacologic Management

- Decrease saturated fat, caffeine, alcohol
- Increase whole grains, fruit, vegetables
- Exercise
- Manage weight
- Stop smoking!!!
- Calcium 1000-1500mg/day
- Vitamin D 800 IU/day

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Pharmacologic Treatments

- Hormone replacement therapy (HRT) indicated for postmenopausal women
 - HRT not usually effective in perimenopause because these women need CYCLE CONTROL
 - HRT dosages are about $\frac{1}{4}$ the strength of the lowest dose oral contraceptive (not enough to control irregular bleeding)
-

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Cycle Control in Perimenopause

- Primary need is to regulate bleeding
- Other symptoms are variable
- If bleeding is unpredictable—endometrial biopsy first

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Cycle Control in Perimenopause

- Perimenopausal hormone imbalances can cause endometrial changes
 - Endometrium progresses from *proliferative* to *hyperplastic* to *cancer* under the influence of estrogen
 - Endometrial biopsy to rule out pathologic changes if bleeding is unpredictable
-

Cycle Control in Perimenopause

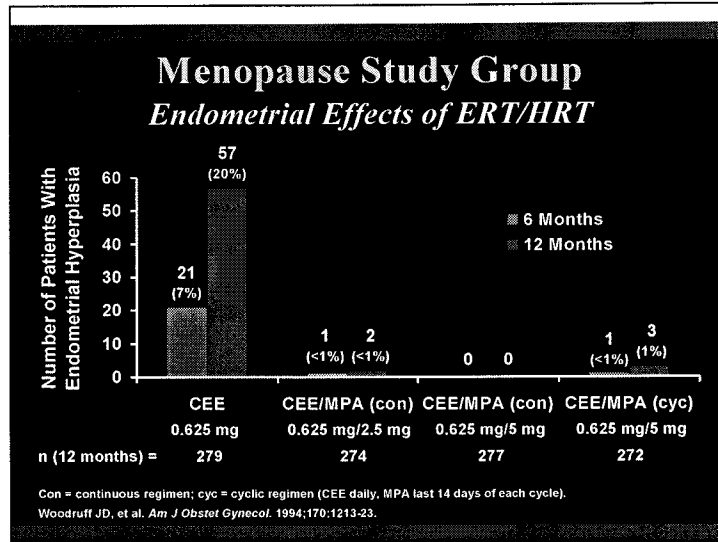
Options:

- Low dose oral contraceptives (provide contraception as well—poor choice for smokers)
- Cyclic progesterone (Provera 10 mg or Prometrium 200 mg days 1-10 each month)
- Mirena IUD

Pharmacologic Management of Menopause--HRT

- All HRT regimens should contain an estrogen and a progestin
 - Estrogen-only regimens limited to hysterectomized women due to estrogen's stimulatory effect on the endometrium
 - Unopposed estrogen causes endometrial cancer
-

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- ### Types of HRT Products
- Combination products:
 - Continuous combined (Prempro, Activella, FemHRT)
 - Cyclic in one tablet (Premphase, Prefest)
 - Combipatch (skin patch)

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Types of HRT Products

- Progestins
Oral: Provera, Prometrium,
compounded micronized progesterone
Intravaginal: gel, IUD
Injectible: Depo-provera
Topical: creams

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Types of HRT Products

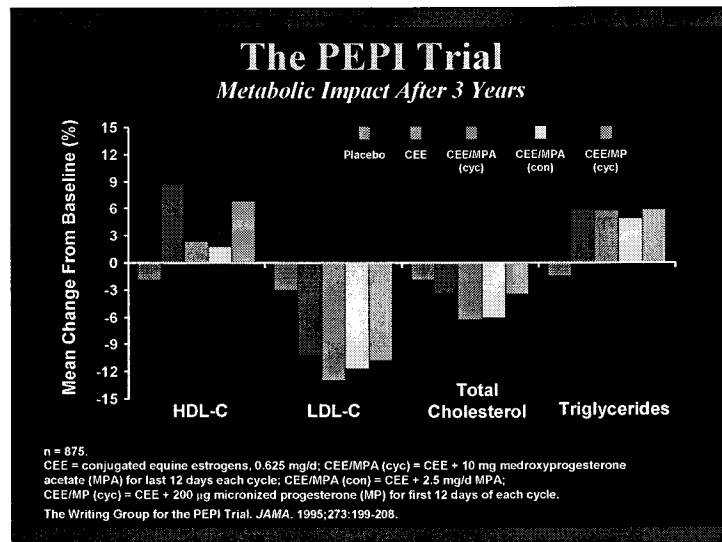
- Estrogens
Oral: Premarin, Estrace, Ogen, estradiol
Intravaginal: Vagifem tablets (one tablet
qhs times 2 weeks, then 2x weekly
thereafter)
-

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Pharmacologic Management of Menopause--HRT

- Use of HRT has become more controversial since release of the Women's Health Initiative data in summer 2002
- Old thinking: HRT prevented heart disease, osteoporosis, and did not increase risk of breast cancer

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Women's Health Initiative

- Trial designed in 1991
 - Total of 161,809 women
 - 16,608 in the randomized trial of E+P
 - 10,739 s/p hysterectomy in E only arm
 - Most expensive trial in US history (\$600 million plus)
-

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<i>Health Event</i>	<i>Relative Risk vs Placebo at 5.2 Years</i>	<i>Increased Absolute Risk per 10,000 Women/Yr</i>	<i>Increased Absolute Benefit per 10,000 Women/Yr</i>
Heart attacks	1.29	7	
Strokes	1.41	8	
Breast cancer	1.26	8	
VTEs	2.11	18	
Colorectal cancer	0.63		6
Hip fractures	0.66		5

Writing Group for the Women's Health Initiative Investigators. JAMA. 2002;288:321-33.

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WHI
Study Considerations

– WHI did not evaluate symptom relief, and therefore symptom relief was not included in the global index

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Estrogen-only arm of the WHI

- 10,739 postmenopausal women
- Aged 50 to 79 years
- Previously undergone hysterectomy

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Estrogen-only arm of the WHI

- Average followup of 6.8 years
 - Increased risk of stroke (12 cases/10,000 women each year compared to placebo)
 - No decrease in coronary heart disease risk
 - Reduced risk of hip and other fractures
 - No increase in breast or colon cancer risk
-

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What we don't know (or know yet) from the WHI

- Implications for other brands, doses
- Impact for recently postmenopausal woman
- Quality of life benefits/risks
- Impact on other conditions (e.g., ovarian cancer, Alzheimer's Disease, cholelithiasis)

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Short-Term Risks

- **venous thromboembolism**
 - **cholelithiasis**
 - **bloating**
 - **breast tenderness**
 - **headaches**
-

WHI
NIH Recommendations

- HRT should not be continued or started to prevent heart disease
- Women should consult their doctor about other methods of CVD prevention, such as lifestyle changes and cholesterol- and blood pressure-lowering drugs
- For osteoporosis prevention, women should consult their doctor and weigh the benefits against their personal risks for heart attack, stroke, blood clots, and breast cancer; alternate treatments are available to prevent osteoporosis and fractures

National Heart, Lung, and Blood Institute, National Institutes of Health. New facts about: estrogen/progestin hormone therapy. Available at: http://www.nhlbi.nih.gov/whi/hrtup/ep_facts.htm. Accessed August 19, 2002.

Nonprescription Remedies

- Evidence is generally lacking regarding efficacy and long term safety
- Most categorized as dietary supplements, therefore not regulated as drugs by the FDA
- Variability in production and content of active ingredients

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Nonprescription Remedies

- Interactions between various herbs and botanicals and with prescription medications not always known
- Patients can wrongly assume "If it's natural, it must be safe"

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Alternative Treatments

- Soy isoflavones
 - Black cohosh (Remifemin)
 - Red clover (Promensil)
 - Women's formula botanical combinations
 - Evening primrose oil (EPO)
 - Dong quai
 - Ginseng
-

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Isoflavones

- Plant-derived diphenolic compounds that exhibit both hormonal and nonhormonal properties
- Often called “phytoestrogens” because they bind to estrogen receptors
- Greater affinity to beta than to alpha estrogen receptor
- Exhibit both estrogen agonist and antagonist properties

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Isoflavones

- Found in whole foods, supplements, and fortified foods
 - Common sources:
 - Soy
 - Red clover
 - No toxicity has been found for whole foods except allergies
-

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Soy-derived Isoflavones

- 14 studies evaluating soy isoflavones and hot flashes to date
- 4 show a significant improvement, 10 show no improvement
- Comparing studies difficult due to differing products and amounts of isoflavones used
- Symptom indices used to measure outcomes also different

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Soy-derived Isoflavones

- Most studies used 40-80 mg/day of isoflavones
 - Food equivalents:
 - 1 cup tofu/day
 - 1 cup soy milk/day
 - ¼ cup soy nuts/day
 - The potential for adverse effects from isoflavones and soy foods in these amounts seems minimal
-

Alternatives for Hot Flashes

- Some evidence for efficacy of black cohosh in four RCTs, but longterm safety not established
- No reliable evidence of efficacy of red clover
- Single trials show no benefit of EPO, ginseng, dong quai, or other Chinese herbs

Alternatives for Hot Flashes: Adverse Effects

- No serious side effects reported for red clover, EPO
 - Dong quai can increase bleeding risk when combined with warfarin
 - Licorice may cause hypokalemia
 - Ginseng can cause postmenopausal bleeding
 - Black cohosh can cause hepatic insufficiency
-

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Topical Progesterone

- “Natural progesterone”
- Synthesized commercially using plants such as wild yam and soybeans
- Diosgenin, the precursor to progesterone found in these plants, cannot be converted to progesterone in the body

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Topical Progesterone

- Commercial preparations vary widely in dosages, formulations, additional ingredients
 - “Wild yam cream” often contains only precursors
 - Some may have progesterone mixed with them
-

Topical Progesterone

- 1-year, randomized, double-blind, placebo-controlled study of Pro-Gest cream (topical progesterone mixed with aloe vera and vitamin E)
- 102 women used 20 mg/day
- Hot flashes reduced 83% in treatment group, 19% in placebo group

Leonetti HB *Obstet Gynecol* 1999;94:225-228

Nonhormonal Prescription Therapies—Antidepressants

- Venlafaxine 37.5 or 75 mg/day
 - Paroxetine 12.5 or 25 mg/day
 - Fluoxetine 20 mg/day

 - Have all been shown to be more effective than placebo for hot flashes in randomized double-blind controlled trials

 - Effect is rapid, generally in 1-2 weeks
-

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Nonhormonal Prescription Therapies—Antidepressants

- 229 women with at least 14 hot flashes per week
- Randomized to placebo or one of three doses of venlafaxine

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Nonhormonal Prescription Therapies—Antidepressants

– 37.5 mg	37% reduction
– 75 mg	60% reduction
– 150 mg	60% reduction
– Placebo	27% reduction

Loprinzi CL *Lancet* 2000;356:2059-2063

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Side Effects of Antidepressants

- Dry mouth
- Decreased appetite
- Somnolence
- Dizziness
- Constipation
- Sexual dysfunction

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Drug Interactions

- Venlafaxine has dose-related risk of HTN
 - Venlafaxine, paroxetine, and fluoxetine contraindicated with MAO inhibitors
 - Paroxetine and fluoxetine contraindicated with warfarin
-

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Nonhormonal Prescription Therapies—Other Alternatives

- Gabapentin (300mg TID)
- Clonidine (0.05 mg po BID, may need 0.1 mg BID; patch 0.1 mg/day)
- Methyldopa (500-1000 mg/day)
- Bellergal spacetabs (phenobarbital, ergotamine, and belladonna)

Gabapentin well tolerated, others have side effects that make them less attractive

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Other Options

- Bisphosphonates
 - Lipid-lowering drugs
 - Antihypertensives
-

Current Management of Osteoporosis: A Review

Therapy*	Decreases Vertebral Fracture Rates	Decreases Hip Fracture Rates	Approximate Increases in BMD (%)†	Most Common Side Effect
ERT/HRT	Yes‡	Yes§	5 - 6	Breakthrough bleeding
Alendronate	Yes‡	Yes¶	5 - 8	Gastric ulceration
Risedronate	Yes	Yes	5 - 6	Upper GI symptoms
Raloxifene	Yes	No	1 - 2	Hot flushes
Calcitonin	Yes	No	1 - 2	Nasal irritation

*All therapies include calcium supplementation; †treatment time is 2 to 3 years; ‡dose effect; §retrospective; ¶long-term safety (>7 years) is unknown; ¶with pre-existing spine fractures.
American Association of Clinical Endocrinologists. *Endocr Pract.* 2001;7:293-312.
Torgerson DJ, Bell-Seyer SEM. *BMC Musculoskelet Disord.* 2001;2:7-10.
Actonel® (risedronate sodium tablets), Prescribing Information.
Chesnut CH III, et al. *Am J Med.* 2000;109:267-76.

- ### Counseling Topics for Patients Considering ERT/HRT
- Evaluate patient goals (symptom relief? Treatment of a condition?)
 - Review the risks and benefits of ERT/HRT
 - Review potential side effects
 - Discuss possible alternatives

