

IN SUMMARY  
OVARIAN FAILURE

**OVARIAN FAILURE**

Possible Menstrual Changes During the Perimenopause

- *Cycle shorter than 28 days*
- *Bleeding for more days than usual*
- *Bleeding for fewer days than usual*
- *Heavier bleeding*
- *Lighter bleeding*
- *Skipped periods*

**Causes of Ovarian failure**

**Genetic factors** □ - e.g. micro deletions X-chromosome, mosaic  
45X0/46XX  
- e.g. mutation in FSH receptor gene

**Viral factors** - e.g. mumps

**Iatrogenic factors** - surgery (e.g. oophorectomy, hysterectomy)  
- chemotherapy (e.g. for breast cancer, lymphoma)  
- *radiotherapy (e.g. for cervix cancer, Hodgkin's)*

**Life style factors** - e.g. cigarette smoking, vegetarian diet

**Other factors** - e.g. autoimmune diseases (myasthenia gravis)  
e.g. low body weight

Menopause

**Three phases over about 10 years**

-□ *Perimenopause (mid forties)*

- *Irregular cycles*
- *Hot flushes*
- *Mood changes*
- *Sleep disturbance*

-□ *Menopause*

- *2 months without a period*
- *Not pregnant*
- *Age 48-55*

-□ *Postmenopause*

- No periods
  
- Onset of menopause determined by the ovary
- Other functional body changes secondary
- Loss of the capacity of the ovary to sustain ovulation
- Nearly complete loss of ovarian follicles
- Minimum 1000 follicles has to be present for ovulation
- Birth - a few million primordial follicles are present
- Menarche - around 250,000 follicles

- 500 will reach the stage of a Graafian follicle
- Process of apoptosis and atresia
- 38 years - disappearance of follicles becomes accelerated
- Mid-thirties - the duration of the menstrual cycle gradually declines
- 4 to 6 years before menopause - women start to notice changes in their menstrual cycle
- Accompanied by
  - night sweats
  - hot flushes
  - vaginal dryness
  
- Ovulatory cycle remains intact until the mid-forties,
- 5 years before menopause - three-quarters of all women, mean cycle length Gradually increases from 28 days (range 26 - 32 days) to 60 days (range 35 - >100 days)
- Hormone levels may fluctuate - highly variable between cycles
- Estradiol tends to stay within the normal fertile range (400 - 600 pmol/L)
- Levels below 200 pmol/L at one year after menopause
  
- Postmenopausally - non-ovarian tissues
  - fat
  - liver
  - kidney
  
- Peripheral conversion of androgens
- Obese postmenopausal women
  - Higher circulating estradiol
  - Less oestrogen bound to SHBG
  
- Estrone may rise
- Secretion of androgen by the ovary is reduced
- Decline of peripheral androgen levels by 20 - 40 percent
- Increased androgen to estrogen ratio
  - Androgen-associated facial hair pattern
  - Deepening of the voice

#### The hypothalamic-pituitary-ovarian axis

- Growing hypothalamic-pituitary stimulation
- Early follicular phase FSH levels (cycle day 3 FSH)
  - Rise typically 10 years before the menopause
  
- Ovaries become also progressively less responsive to exogenous  gonadotrophins
- Refractory to stimulation with exogenous gonadotrophins

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HST 071

- Secretion of FSH is influenced
  - Estradiol
  - Inhibin
    - Products of the ovarian granulosa cells
- Both suppress the pituitary secretion of FSH
- LH serum levels remain unchanged

### **Symptoms of Menopause**

- *Hot flush*
  - *30-80 percent of postmenopausal women*
  - *Sudden sensation of heat rising to the top of one's body*
  - *Shiver at conclusion*
  - *Disruptive to sleep patterns*
  - *Cross-cultural differences*

*May last from 1 month to 7 years*

What's Hot Flush Really About ?

- *75% of women experience hot flushes*
- *10-15% seek physician help for this*
- *Highest during first 2 years*
- *85% for more than 1 year*
- *20-50% for up to 5 years*
- *Oophorectomy flashes are more severe and frequent*
- *2/3 premenopausal women*
- *May continue to have periods*

### **Description of Hot Flush**

- *Visible redness of upper chest, neck, face*
  - *Perspiration in that area*
  - *Finger temperature rises up to 6 degrees C.*
  - *Temperature drops after sweating*
  - *Night sweats*
    - *More severe*
    - *Awaken from sleep*
      - *Fatigue, irritability, inability to concentrate, impaired memory*
- Awakened before temperature changes

### **Ovarian function reduced**

- *6AM to 8 AM & 6 PM to 10 PM*
- *Most women have one a day*
- *Some have many or a few as one weekly*
- *Triggers*
  - o  *Stress*
  - o  *Warm weather*
  - o  *Hot drinks, alcohol*
  - o  *Aura*
    - *Anxiety attack*
    - *Uniformity of Experience But not Frequency*

Treatment

- *Evaluate severity - keep a chart*
- *Pinpoint triggers*
- *Evaluate therapy*
- **ESTROGEN WITHDRAWAL IS TRIGGER**
- *90+% effective*
  - *Pills*
  - *Patches*
  - *Creams*
  - *May take up to four weeks*
- *Other Causes*
  - *Thyroid*
  - *Carcinoid*
  - *Diabetes*
  - *Alcoholism*

Vaginal Dryness

- *Gradual process*
  - *May take years to develop*
- *Estrogen replacement*
  - *Systemic*
  - *Local*
- *Topical lubricants*
- *Uncomfortable*

**Linked to “decline” in sexual functioning**

Menopausal Therapeutics

- *35%-40% of women ever start conventional ERT*
- **Conventional ERT Benefits**
  - *Osteoporosis risk reduced 50%*
  - *Cardiovascular disease reduced ???*
  - *Reduced menopausal symptoms*
  - *Memory loss*
  - *Alzheimer’s disease*
  - *Tooth loss*
  - *Colon cancer reduction*
- **Conventional ERT Risks**
  - *Breast cancer*
  - *Vaginal bleeding*
  - *Endometrial cancer (negated by progesterone)*

### **Bone Density Evaluation**

- \*□ *DXA (Dual Energy X-ray Absorptiometry) measures the spine, hip or total body;*
- \*□ *pDXA (Peripheral Dual Energy X-ray Absorptiometry) measures the wrist, heel or finger;*
- \*□ *SXA (single Energy X-ray Absorptiometry) measures the wrist or heel;*
- \*□ *QUS (Quantitative Ultrasound) uses sound waves to measure density at the heel, shin bone and kneecap.*
- \*□ *QCT (Quantitative Computed Tomography) most commonly used to measure the spine, but can be used at other sites;*
- \*□ *pQCT (Peripheral Quantitative Computed Tomography) measures the wrist;*
- \*□ *RA (Radiographic Absorptiometry) uses an X-ray of the hand and a small metal wedge to calculate bone density;*
- \*□ *DPA (Dual Photon Absorptiometry) measures the spine, hip or total body (used infrequently);*
- \*□ *SPA (Single Photon Absorptiometry) measures the wrist (used infrequently);*

### **Estrogen Replacement Therapy (ERT) and Hormone Replacement Therapy (HRT)**

- *Estrogen replacement therapy (ERT) is approved for the prevention and management of osteoporosis. ERT has been shown to reduce bone loss, increase bone density in both the spine and hip, and reduce the risk of hip and spinal fractures in postmenopausal women.*
- **Alendronate Sodium (brand name Fosamax®)**
  - *Alendronate is a medication from the class of drugs called bisphosphonates.*
- **Risedronate Sodium (brand name Actonel®)**
  - *Risedronate is also from the bisphosphonate family. Taken daily, 5 mg of risedronate slows bone loss, increases bone density and reduces the risk of spine and non-spine fractures.*
- **Raloxifene (brand name Evista®)**
  - *Raloxifene, 60 mg a day, is approved for the prevention and treatment of osteoporosis. It is from a new class of drugs called Selective Estrogen Receptor Modulators (SERMs) that prevent bone loss at the spine, hip, and total body. Raloxifene produces increases in bone mass.*
- **Calcitonin (brand name Miacalcin®)**
  - *Calcitonin is a naturally occurring hormone involved in calcium regulation and bone metabolism. In women who are at least 5 years beyond menopause, calcitonin slows bone loss, increases spinal bone density,*

### Osteoporosis Detection

- *Ultrasound measures the heel*
- *DEXA (Dual Energy X-ray Absorptiometry) measures the spine, hip or total body*
- *SXA (single Energy X-ray Absorptiometry) measures the wrist or heel*
- *PDXA (Peripheral Dual Energy X-ray Absorptiometry) measures the wrist, heel or finger*
- *RA (Radiographic Absorptiometry) uses an X-ray of the hand and a small metal wedge to calculate bone density*
- *DPA (Dual Photon Absorptiometry) measures the spine, hip or total body*
- *SPA (Single Photon Absorptiometry) measures the wrist*
- *QCT (Quantitative Computed Tomography) measures spine or hip*

### Women's Health Initiative

- 7.7% of the study participants reported having had cardiovascular disease at enrollment.
- Not intended to measure the effect of HT on vasomotor symptoms
- Women were discouraged from participating in the study if they reported moderate or severe Menopausal symptoms during a 3-month period prior to the study
- Only approximately 500 women aged 50-54 with moderate -to -severe symptoms at study entry were included in the WHI
- Women randomized to the use of estrogen plus progestin were significantly more likely than women randomized to placebo to report a reduction in hot flashes and night sweats.
- Likewise had an improvement in sleep disturbances but no other benefit in terms of the other quality-of-life outcomes reported.
- Continuous conjugated equine estrogen (0.625 mg/d) and □ medroxyprogesterone acetate (2.5 mg/d) (Prempro®) □
- Women aged 50-79 years at enrollment,
- Similar numbers of women in each age category (50-59 years, 60-69 years, and 70-79 years)
- Mean age of study participants was 63 years,
- Most women experience natural menopause around age 50.
- HT is primarily prescribed to women aged 50-59 years,
- 33% of study participants were aged 50-59 years
- Absolute risks for women taking HT starting at age 50 are substantially lower than the comparable risks for women starting use at age 65

### Cardiovascular Disease

- No benefit for the prevention of coronary heart disease
- 22% increased risk of cardiovascular disease
- 29% increased risk of coronary heart disease
- 7 more coronary heart disease events (37 versus 30) per 10,000 women per year, and this risk is cumulative over time

### **Breast Cancer**

- Confirm an observed trend reported in previous research
- Increased risk of breast cancer with HT use
- 26% increased risk of invasive breast cancer
- 8 additional new cases (38 versus 30) per 10,000 women per year
- Breast cancer takes several years to develop
- Became clinically apparent at four years
- Survival rates are higher in women diagnosed with breast cancer who have taken hormone therapy than those who have not

### **Stroke and Pulmonary Embolism**

- 41% increased risk of
- 8 additional cases of stroke (29 versus 21)
- 8 additional cases of pulmonary embolism (16 versus 8) per 10,000
- Risk is cumulative
- Elevated risk of stroke appears in the second year - continues through year five

### **Fractures**

- Support previous research - decreased risk of vertebral and other osteoporotic fractures
- Hip fracture were reduced by 34%
- 5 per 10,000 women per year (10 versus 15)

### **Colon Cancer**

- Suggest a benefit in the prevention of colorectal cancer
- Reduced by 37%
- 6 fewer cases (10 versus 16) per 10,000 women per year

### **Cognitive Function**

- Subset of 4532 women aged 65 years or older
- Higher incidence of probable dementia - (66% versus 34%)
- Increase of 23 cases per 10,000 women
- Not helpful in preventing mild cognitive impairment

### **Recommendations For Hormone Replacement Therapy Use**

- Encouraged to take it for as short a time as needed
- Lowest effective dose.
- Long-term use should be counseled about the risks and benefits
- Talk about available alternatives.
- Women who want to continue taking HT
- May do so provided they understand the potential risks

***HT has been shown to be the most effective treatment for symptomatic relief of vasomotor symptoms including hot flashes***

*Nonhormonal alternatives such as selective serotonin reuptake inhibitors, may be helpful for this indication*

*Combined continuous estrogen and progestin therapy is no longer recommended for the prevention of cardiovascular disease*

*Alternatives for improved cardiovascular health, including lifestyle modifications such as exercise, smoking cessation, and weight loss, should be encouraged for all women. The use of cholesterol-lowering medications such as statins and the need for treatment of hypertension should be evaluated for each individual patient.*

Figures removed due to copyright restrictions. □  
[Kaplan-Meier Estimates of Cumulative Hazards for Breast Cancer; □  
Kaplan-Meier Estimates of Cumulative Hazards for CHD; □  
Disease rates for women as shown by WHI study results]□

Figures removed due to copyright restrictions. □  
[Kaplan-Meier Estimates of Cumulative Hazards for Hip Fracture; □  
Kaplan-Meier Estimates of Cumulative Hazards for Total CVD; □  
Kaplan-Meier Estimates of Cumulative Hazards for the Global Index]□

## FUNDAMENTAL QUESTIONS

1. □ Define menopause. What is the average age for natural menopause?
2. □ What happens to the number of viable oocytes as a woman ages?
3. □ Describe 7 physiologic changes seen in women during the menopausal period.
4. □ What happens to estradiol, FSH, LH and androgens as the ovaries age?
5. □ What is osteoporosis and how is it measured? Describe the techniques?
6. □ Why are some older women “hairy”?
7. □ How can one treat the vasomotor symptoms other than with estrogen?
8. □ What hormones are frequently used as HRT?
9. □ What are the proven benefits of HRT?
10. How do bisphosphanates work?
11. What are the risks of combined HRT?
12. What are the risks of estrogen only HRT in women with a uterus? Without a uterus?
13. What are the alternative therapies available to treat
  - a. □ Hot flushes
  - b. □ Vaginal dryness
  - c. □ Skin changes
14. What advice would you give women who insist on HRT because her menopausal symptoms make it impossible to function normally?

