Aging and the Female Reproductive System

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Why Menopause?

• Antagonistic Pleiotropy
  – Evolutionary value of an individual depends on its ability to produce surviving offspring
  – Selective pressures favor survival of young reproductively active individuals
  – Due to the increase in life span, women are living beyond a point where the reproductive system is designed to function
  – Menopause may be a pleiotropic effect of genes that had value earlier in life

• Menopause may carry advantage for survival of species
  – Beneficial to have non-reproducing species members to care for young
Terminology

- **Menopause**
  - Permanent Cessation of Menstruation Associated With Loss of Ovarian Follicular Activity

- **Perimenopause**
  - Period Immediately Prior to and at Least 1 Year After Menopause
  - Characterized by Physiological and Clinical Features of Altered Ovarian Function

- **Postmenopause**
  - Period of Life After Menopause

- **Premenopause**
  - The Reproductive Period Prior to the Menopause
Anatomy:
Female Reproductive Tract
Ovary Characteristics

- Ovaries
  - Contain germinal cells
  - Contain endocrine producing cells
    - Granulosa
    - Thecal
  - Determine secondary structures and sexual characteristics
Hypothalamo-Pituitary-Gonadal Axis (H-P-G)
Gonadotropin Action
Normal Female Hormone Patterns

<table>
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<tr>
<th>Gonadotrophic Hormone Levels</th>
<th>LH</th>
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<td>FSH</td>
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<th>Ovarian Cycle</th>
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<td>Follicular phase</td>
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<td>Estrogen</td>
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Hormone Patterns

Early to mid-follicular phase
- GnRH
- FSH
- LH
- Follicle
  - Granulosa cells
  - Thecal cells
- Estrogens
- Androgens
- Corpus luteum

Late follicular phase and ovulation
- GnRH
- FSH
- LH
- Follicle
  - Granulosa cells
  - Thecal cells
- High estrogen (inhibin)
- Small amount of progesterone
- Corpus luteum

Early to mid-luteal phase
- GnRH
- FSH
- LH
- Follicle
  - Granulosa cells
  - Thecal cells
- Estrogen
- Progesterone
- Inhibin

Luteal phase
- GnRH
- FSH
- LH
- Follicle
  - Granulosa cells
  - Thecal cells
- Progesterone
- Estrogen
- Corpus luteum
- New follicles begin to develop
- Corpus luteum dies

KEY
- Stimulus
- Integrating center
- Efferent pathway
- Tissue response

Feedback loop stops
Hormonal Changes From Aging

• Gonadotropins:
  – LH
    • Change occurs mid-follicular
    • Change to pulsatile pattern: ↑Duration, ↓Frequency
    • Possibly results in decreased responsiveness in feedback to estrogen
  – FSH
    • “Monotropic” FSH ↑
    • Evident during entire cycle
    • 1st Noticed prior to any change in cycle length

• Ovarian Steroidal Hormones
  – Estrone levels ↑ early in the cycle in older ovulatory women
    • Possible due to LH/FSH alterations
  – Luteal phase becomes shortened and Progesterone in insufficient to maintain corpus luteum
  – Eventually, H-P-G axis is unable to generate LH surge needed for ovulation
Fertility Changes and Perimenopause

- Fertility and Fecundity Decrease
  - Ovulatory cycle continues after onset of perimenopause
  - Cycle length becomes more variable
    - Shortening of follicular phase
    - No change in luteal phase
  - Peak fecundity occurs at 24, with a gradual decrease to 35, and a rapid decrease after 35
Ovarian Structural Changes

• Abnormalities in Older Oocyte
  – Change in microtubule and chromosome placement at the second metaphase of meiosis
  – May be linked to increased aneuploidy seen in offspring of older women

• Declining Follicular Reserve
  – 2 Million Primordial Follicles during fetal development
  – Declines to 1 million at birth and 250,000 by puberty
  – Primordial Follicles develop to primary and secondary follicles independent of hormone status
  – In the absence of LH/FSH, follicles undergo atresia
  – Once follicles are depleted, ovarian hormone production declines
Metaphase II

Chromosomes align on the metaphase plate.

Non-Disjunction during Meiosis II

Metaphase II

Non-Disjunction

Anaphase II
Menopause Symptoms

• Hot Flashes
  – Most common reported symptom
  – 70-80 % of women report signs of hot flashes
  – This rate increases in women with oopherectomy and thin women that smoke
  – Asian women have much lower rate
    • 10-25 % Reported
    • Possibly due to genetics, diet, lack of reporting
Physiological Characteristics of Hot Flashes

- Sweating
- Increased Skin Conductance
- Increased Core Body Temperature
- Increased Metabolic Rate
- Increased Skin Temperature
- Hot flashes appear to be the result of noradrenergic control independent of estrogen regulation
  - However, ERT alleviates the symptoms of hot flashes
Menopause Effects on the Reproductive Tract

- Reproductive targets for steroidal hormones experience atrophy following menopause
- In addition, these more specific changes are seen:
  - Vagina
    - Dryness
    - Decreased Vascularity
    - Decreased Secretions
    - Increased Risk of Infections
  - Ovaries
    - Become more fibrotic as follicles diminish
  - Uterus
    - Loses Weight and Volume
Effects on Non-Reproductive Steroidal Targets

• Skin
  – Thinning of epidermis
  – Atrophy of sebaceous glands
  – Increased sensitivity to temperature, humidity, and trauma

• Bladder
  – General Atrophy
    • Results in urinary incontinence

• Hair
  – Body hair undergoes redistribution
Menopause and Non-reproductive Targets

- **Skeletal System**
  - Osteoporosis (Lecture May 3)
    - Decreased bone mass following menopause that appears to be the result of declining estrogen level

- **Central Nervous System**
  - Psychological
    - Anxiety/Depression
  - Cognition/Memory

- **Cardiovascular System**

- All of these will be further discussed in the context of HRT during Wednesday’s Lecture