• Review physiology of female reproduction
• Menarche, menopause and the reproductive life span
• Factors which affect menarche, menopause and reproductive life span
• Menstrual cycle, conception and pregnancy loss
• Hypothalamic Gonadotrophin Releasing Hormone (GnRH) stimulates release of pituitary follicular stimulating hormone (FSH) and luteinizing hormone (LH)

• Hypothalamic positive and negative feedback in menstrual cycle
Menstrual cycle ovarian physiology

• FSH → follicular development during the follicular phase of the cycle → estrogen production → endometrial growth

• LH & estrogen → ovulation → corpus luteum → estrogen + progesterone → endometrial maturation

• **No pregnancy:** Degeneration of corpus luteum → decline in estrogen and progesterone → endometrial shedding and menses
Menstrual cycle

(Average values. Durations and values may differ between different females or different cycles.)
Fertilization

• Ovulation releases ovum into the fallopian tube ~ day 14 after LMP

• Fertilization ~ day 14-17

• Tubal transport ~ day 14-19

• Implantation ~ days 20-24
Implantation and pregnancy

- Implantation → human chorionic gonadotrophin (hCG) maintains corpus luteum and estrogen and progesterone production

- Estrogen promotes breast growth,

- Prolactin (hPrL) → milk production.

- Estrogen suppresses hPrL and thus inhibits milk production during pregnancy
Natural Fertility

The pattern of fertility observed in non-contracepting populations:

- No attempt to control fertility or limit the number of children born
- Spacing of births largely dependent on lactational amenorrhea
Natural Fertility

Data Source: NCHS age-specific fertility 4-year average (2000-2003)
Menarche and Puberty

**Definition**

*Menarche* (onset of first menses) is a late event in puberty (preceded by growth spurt, breast development, and pubic hair growth)
Before puberty, ovarian estrogen and progesterone inhibit hypothalamic GnRH center (negative feedback).

Early in puberty, GnRH released during sleep \( \rightarrow \) FH and FSH production with reduction of negative feedback.

Development of pulsatile GnRH release with positive steroid feedback initiates ovulation in girls and spermatogenesis in boys.
Number of oocytes decline with age, especially $> 40$


Data are adapted from Faddy et al. (Hum Reprod 1992;7:1342-1346)
Mechanism of menarche and puberty

- Mechanism unknown, but is linked to GPR54 gene on chromosome 19 which is needed for GnRH activity.
- Mutations lead to sexual infantilism, pubertal delay which can be corrected by GnRH treatment
Female Hormones at Puberty

![Graph showing the changes in FSH, LH, and Estradiol levels during puberty.](image)

- **FSH** (Light green line)
- **LH** (Dark green line)
- **Estradiol** (Yellow line)

*Graph legend*

**Y-axis:** ug%

**X-axis:** Age (years)

The graph illustrates the increase in hormone levels over time, particularly the rise in Estradiol levels.
Mean Age of Menarche and secular trends

- ~ 12 - 13 years in developed countries
- has declined by ~ 3 years per decade until 1960’s.
- Probable improved health and nutrition
Factors associated with age of menarche

- Delayed menarche associated with physical, nutritional, or psychosocial stress
  - Studies in athletes, ballet dancers, poorly nourished populations
Stress and Menarche

- Stress $\rightarrow$ cognitive response $\rightarrow$ hypothalmic corticol releasing hormone (CRH) $\rightarrow$ $\beta$-endorphin release $\rightarrow$ GnRH pulse inhibition $\rightarrow$ LH/FSH pulse suppression

- Stress before menarche causes delays in onset (e.g., ballet dancers, athletes)
Fertility and Menarche

- Fertility is low for 5-7 years following menarche

- **Adolescent subfertility** is due to anovulation and luteal phase inadequacy

- Menarche is not indicative of ovulation and the frequency of ovulatory cycles is lower for 5-7 years after menarche
Diet and sex hormones in adolescence

- Randomized trial of low fat diet in girls with lipid abnormalities
- 5 year evaluation
  - Low fat reduced estrogens and progesterone and increased testosterone
  - Moderate changes in diet result in important changes in hypothalamic-ovarian axis

Dorgan *JNCI* 2003;95:132
Menopause

**Definition**

- **Menopause**: Cessation of ovulation and menstruation lasting > 9-12 months

- **Perimenopausal period**: Period of increasing menstrual cycle length and variability preceding the menopause

- **Postmenopause**: Amenorrhea > 12 months
Primary ovarian failure (programmed senescence or “apoptosis” of oocytes).

Using hormonal stimulation and ovum donation from younger women, postmenopausal women can conceive and bear children.
Estrone and estradiol are synthesized from androstenedione and testosterone in adipose tissues after the menopause.

Decreased serum hormone binding globulin (SHBG) increases bioavailability of steroids.

Thus, obesity is associated with higher estrogen levels in postmenopausal women.
Age at Menopause

• Median age ~ 50 years. Little variation between populations (range of mean ages 48.8-51.5. Earliest mean age at menopause 44 years in malnourished populations),

• Early menopause associated with:
  – Smoking (↑ metabolism of estrogen)
  – Low body weight (lower estrogen production)
  – Poor nutrition / chronic infection (lower estrogen production)
FIGURE 2. Mean (standard error) age at natural menopause by birth cohort among women aged 60 or more years living in Massachusetts, New Hampshire, or Wisconsin in 1988–2001. Means are adjusted for state of residence, cigarette smoking, education, parity, age at last birth, height, and body mass index. Analysis was restricted to never users of postmenopausal hormone therapy.

Late menopause associated with:

- Obesity (possibly due to estradiol/estrone synthesis from androstedione/testosterone in adipose tissue)

- Diabetes (same mechanism)

- Endometrial and breast cancer (obesity and abnormal bleeding with endometrial cancer)
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>4.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.9</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>1.8</td>
</tr>
<tr>
<td>Live Birth</td>
<td>0.7</td>
</tr>
<tr>
<td>&lt; High School Education</td>
<td>1.19</td>
</tr>
</tbody>
</table>
Non-Reproductive Effects of Estrogen

• Bone growth and prevention of calcium resorption from cortical bone

• Decreased hepatic lipase activity (increases high HDL-cholesterol, reduces LDL-cholesterol)

• Maintain mucosa and connective tissue

• Endogenous estrogens (estradiol, estriol, and estrone)
• Due to estrogen deficiency
• Symptoms and health effects:
  – Vasomotor: Hot flashes and perspiration
  – Psychological: Mood lability, insomnia, depression
  – Musculoskeletal: Joint pains & stiffness
  – Mucosal atrophy (vaginal and bladder) and skin changes
  – Osteoporosis (calcium depletion due to estrogen deficiency)
Treatment of Postmenopausal Syndrome

- Estrogen replacement reduces symptoms

- Stopping estrogen may cause resurgence of symptoms (Ockene et al JAMA 2005;294:183)

- Randomized trial of estrogen/progesterone vs placebo.

- After stopping treatment
  - Flashes/sweats E/P 21%, placebo 4.8% (RR = 5.8)
## Efficacy of estrogen replacement

(Data Source: Grady NEJM 2006;355:2338)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Percent Reduction in Frequency of HotFlushes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral conjugated equine estrogens</strong></td>
<td></td>
</tr>
<tr>
<td>0.625 mg</td>
<td>94</td>
</tr>
<tr>
<td>0.45 mg</td>
<td>78</td>
</tr>
<tr>
<td>0.30 mg</td>
<td>78</td>
</tr>
<tr>
<td>Placebo</td>
<td>44</td>
</tr>
<tr>
<td><strong>Oral 17β-estradiol</strong></td>
<td></td>
</tr>
<tr>
<td>2 mg</td>
<td>96</td>
</tr>
<tr>
<td>1 mg</td>
<td>89</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>79</td>
</tr>
<tr>
<td>0.25 mg</td>
<td>59</td>
</tr>
<tr>
<td>Placebo</td>
<td>55</td>
</tr>
<tr>
<td><strong>Transdermal 17 β -estradiol</strong></td>
<td></td>
</tr>
<tr>
<td>0.1 mg</td>
<td>96</td>
</tr>
<tr>
<td>0.05 mg</td>
<td>96</td>
</tr>
<tr>
<td>0.025 mg</td>
<td>86</td>
</tr>
<tr>
<td>Placebo</td>
<td>45</td>
</tr>
</tbody>
</table>

Efficacy for prevention of hot flushes is greater with higher dose estrogen.
In developed countries

- Median age at menarche ~ 12-13 years
- Median age at menopause ~ 50 years
- Length of reproductive life in females ~ 37-38 years
Reproductive Life Span

In less developed countries

- Menarche often delayed (Latest menarche 18 years)
- Menopause generally ~ 50 years
- Shortest reproductive life span ~ 26 years
Mean reproductive life span by birth cohort

Epidemiology of the menstrual cycle

- Epidemiology of the menstrual cycle parameters (follicular and luteal phases, ovulation and menses)

- Epidemiology and endocrinology of menstrual cycle disorders and toxic shock syndrome (TSS)
Menstrual Cycle Length

- Mean cycle length: ~29 days,
- mode 28 days, 5th - 95th centiles 23-29 days
  - Variability increased in young and older women (< 20 and > 35 years)
  - Variability maximum 2-5 years after menarche and before menopause
Menstrual Cycle

- **Mean Follicular Phase**
  - 15 days (90th centiles 10.5 - 19 days)

- **Mean Luteal Phase**
  - 13.5 days (90th centiles 8.7 - 17.2 days)
  - Short luteal phase < 9 days.
• Cycle variability increased with emotional, nutritional, and physical stress
• Common CNS pathway (corticol releasing hormone (CRH) $\rightarrow$ $\beta$-endorphin release $\rightarrow$ GnRH pulse inhibition $\rightarrow$ LH/FSH pulse suppression
## RRs of Prolonged Cycles (> 43 days)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of long cycles</td>
<td>3.4 (1.6-7.1)</td>
</tr>
<tr>
<td>Start college</td>
<td>2.3</td>
</tr>
<tr>
<td>Stress &gt; median</td>
<td>3.1 (1.3-7.4)</td>
</tr>
<tr>
<td>Activity &gt; median</td>
<td>1.5 (1.0-2.3)</td>
</tr>
</tbody>
</table>

Dysmenorrhea

• **Definition:**
  Pain, cramping associated with menstruation (back ache, nausea)

• **Biology:** Due to prostaglandin production at menses
Dysmenorrhea

- **Frequency:**
  - 30-60% of women report symptoms
  - 7-15% interfere with daily activities
  - More frequent among < 25 years (67-72%)

- Decreases after pregnancy and with use of oral contraceptives

- Treatment: anti-prostaglandins oral contraception
Premenstrual Syndrome (PMS)

• Definition
  – Recurring psychological and/or somatic symptoms during the luteal phase of the cycle, relieved by onset of menstruation

• Frequency
  – 95% of women report mild symptoms
  – 5% severe symptoms disrupting normal life

• Etiology
  – Unclear, appears to be an abnormal response to hormones, rather than disturbed hormonal milieu.
  – Abnormal serotonin levels? Treated with selective serotonin-reuptake inhibitors (SSRIs)
Randomized trials of PMS treatment

- All trials show marked placebo effects

- 15 Cross-over trials of selective serotonin re-uptake inhibitors (SSRIs, i.e., antidepressents) show benefit in psychological and physical symptoms

- OR of improvement ~ 6.9

  - Dimmock Lancet 2000;356:1131
Toxic Shock Syndrome

• **Definition:**
  Shock, rash, peeling skin, multiple organ failure, potentially fatal

• **Biology:** Staphylococcus infection of menstrual blood releases toxin causing extreme shock

• Recognized in 1970’s; epidemic in 1980’s associated with tampon use (partly surveillance and detection bias)
Toxic Shock Syndrome

- Risk increased with retention of menstrual products (e.g., use of highly absorbent tampons, diaphragm)

- Risk decreased with reduced menstrual loss (e.g., oral contraceptive use)

- Treatment: antibiotics