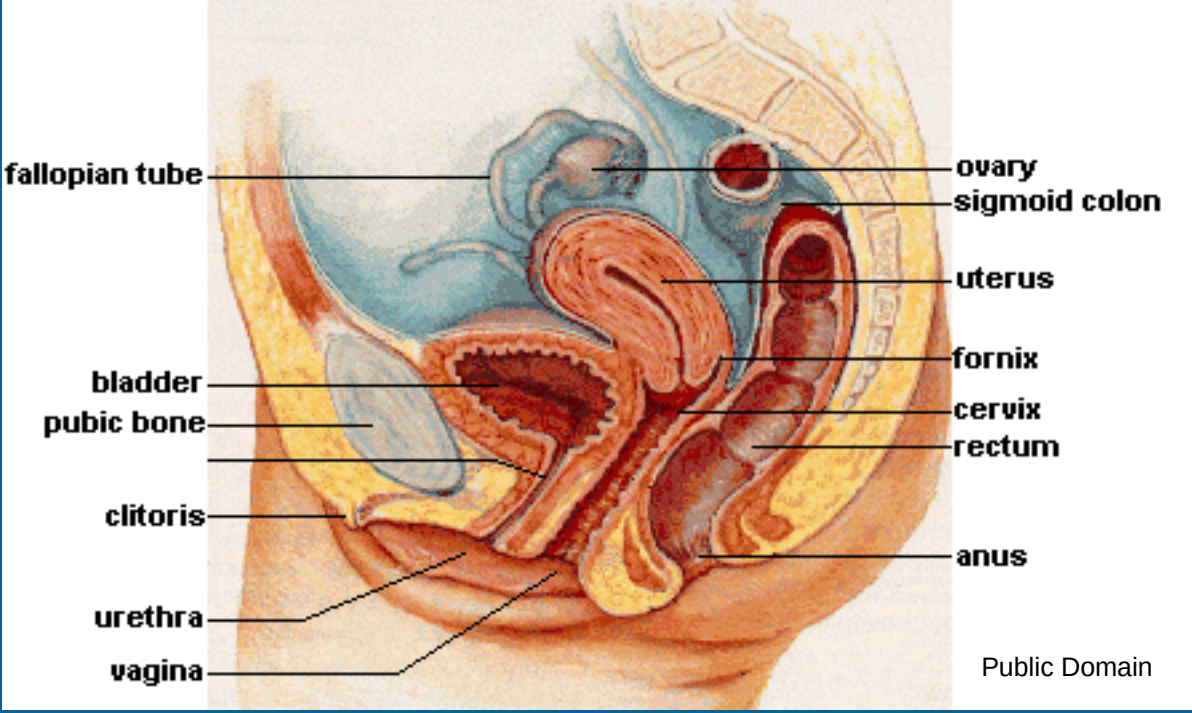
# Epidemiology of Reproductive Physiology

- 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

# Female Reproductive Tract



# Physiology Hypothalamus

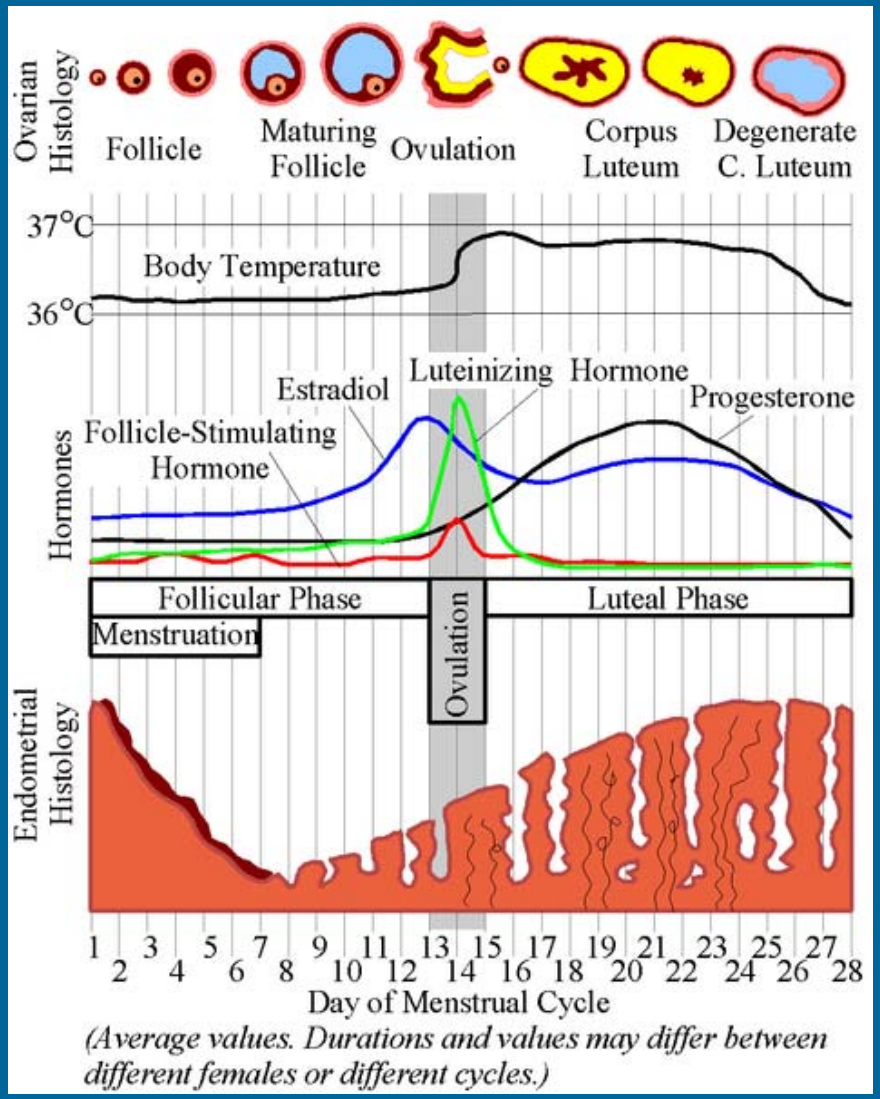
- Hypothalamic Gonadotrophin Releasing Hormone (GnRH) stimulates release of pituitary follicular stimulating hormone (FSH) and luteinizing hormone (LH)

- 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



# 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

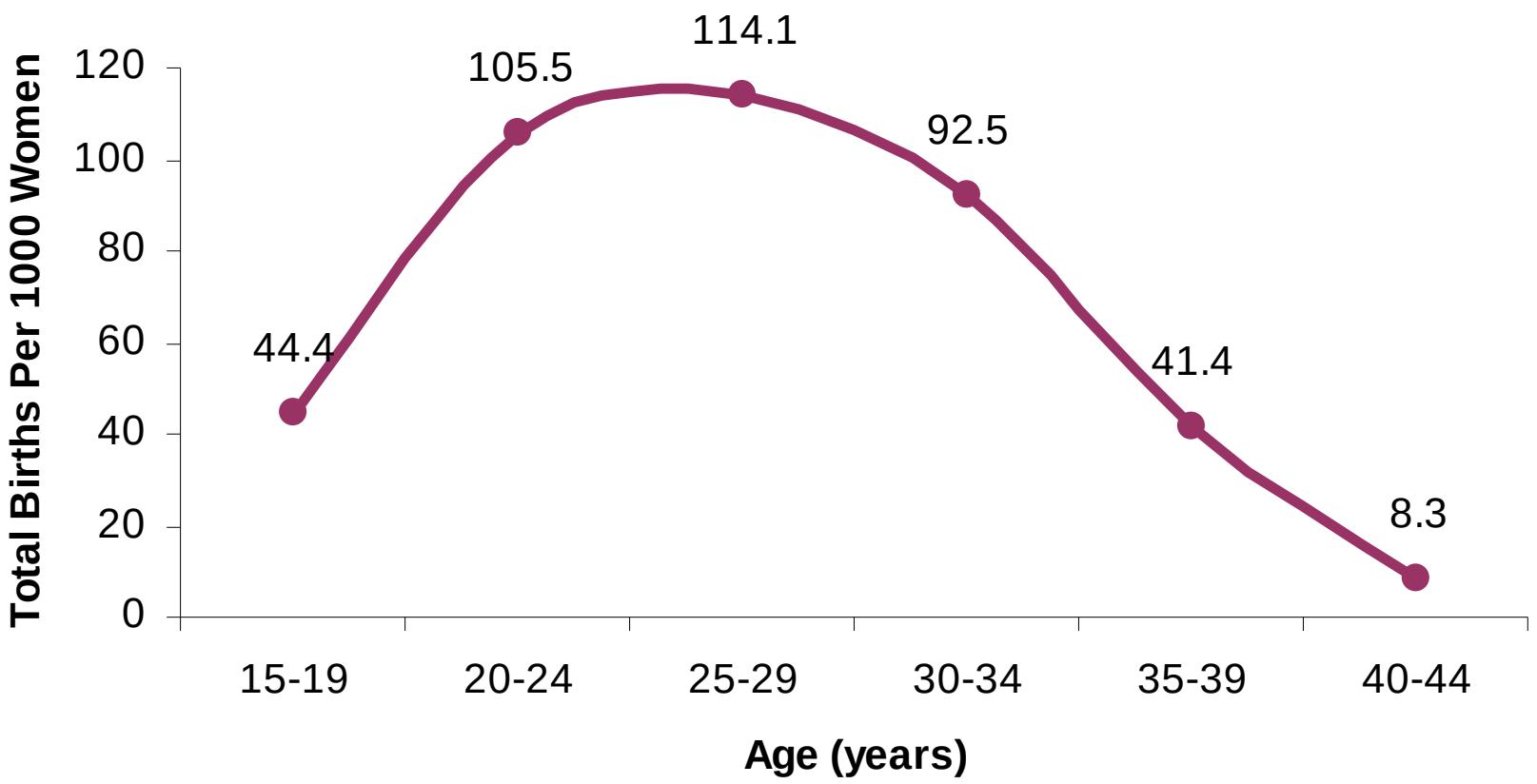
- Implantation $\rightarrow$ human chorionic gonadotrophin (hCG) maintains corpus luteum and estrogen and progesterone production
- Estrogen promotes breast growth,
- Prolactin (hPrL) $\rightarrow$ milk production.
- 
- Estrogen suppresses hPrL and thus inhibits milk production during pregnancy

# 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)

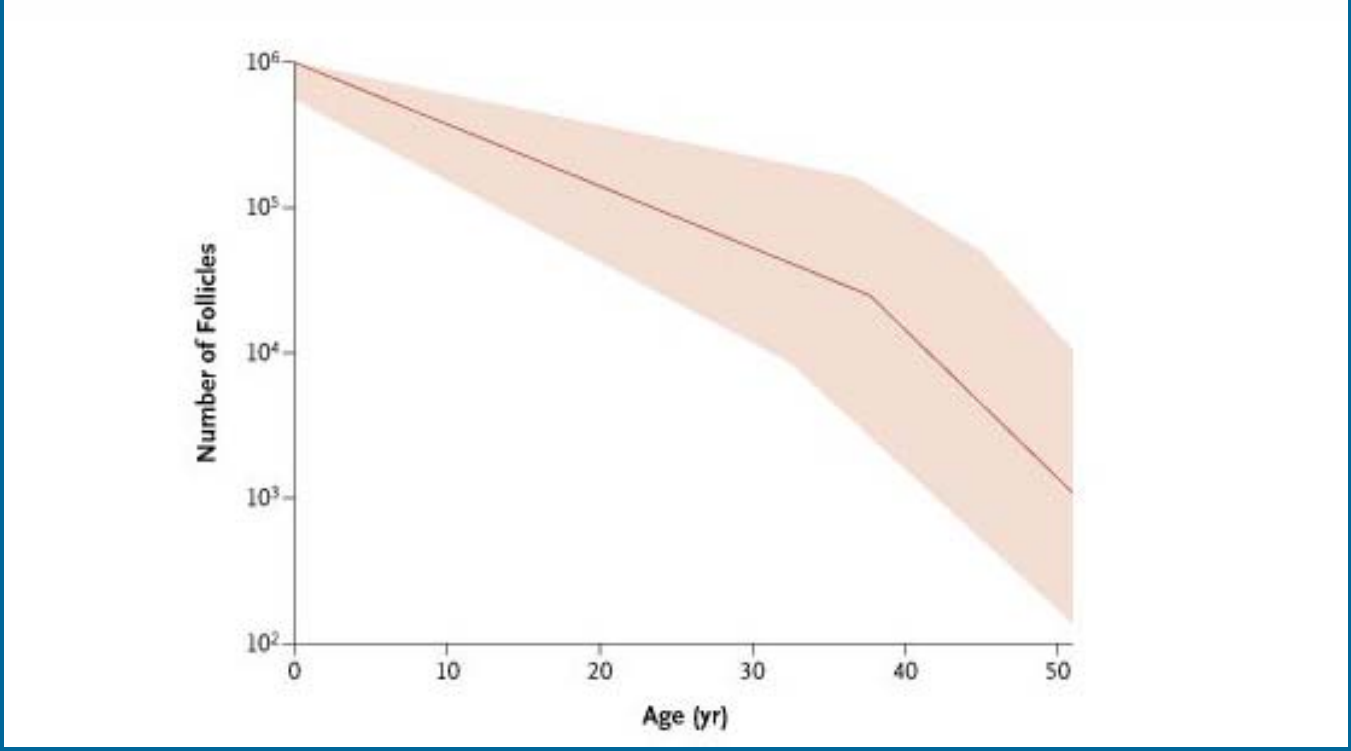
# Biology of Menarche and Puberty

Before puberty, ovarian estrogen and progesterone inhibit hypothalmic 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



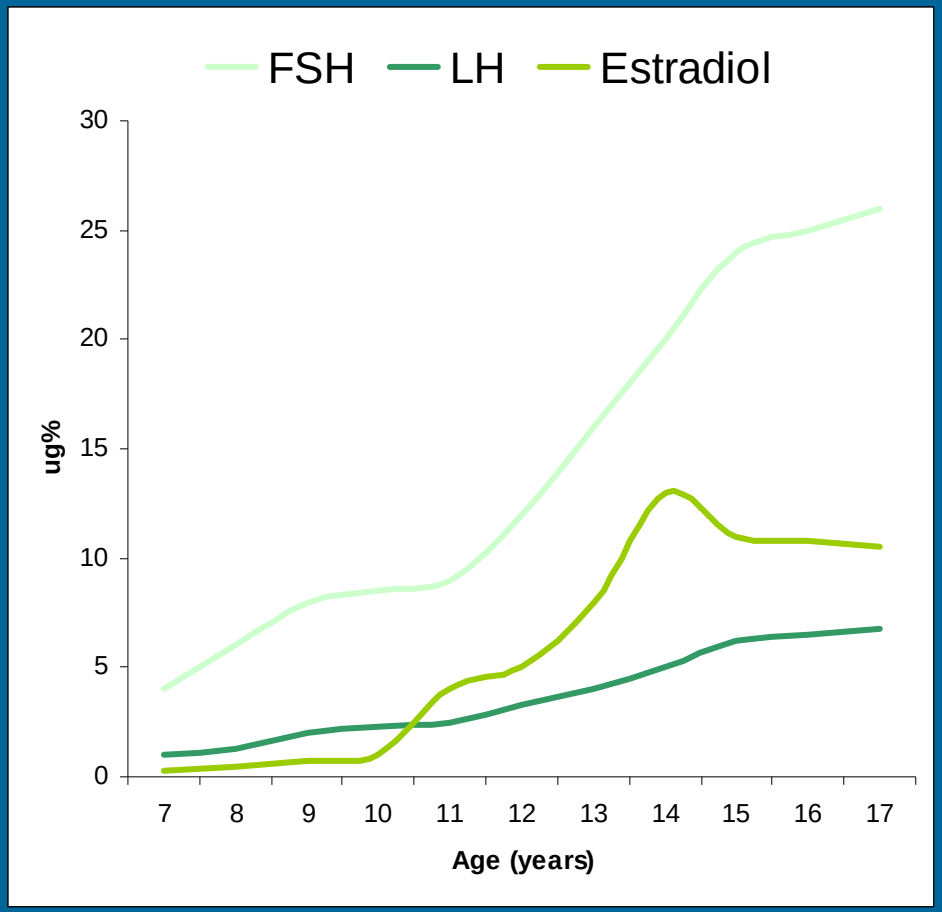

Source: Lobo RA. Potential options for preservation of fertility in women. N Engl J Med. 2005 Jul 7;353(1):64-73. Copyright © 2005 Massachusetts Medical Society. All Rights Reserved.

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



# 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

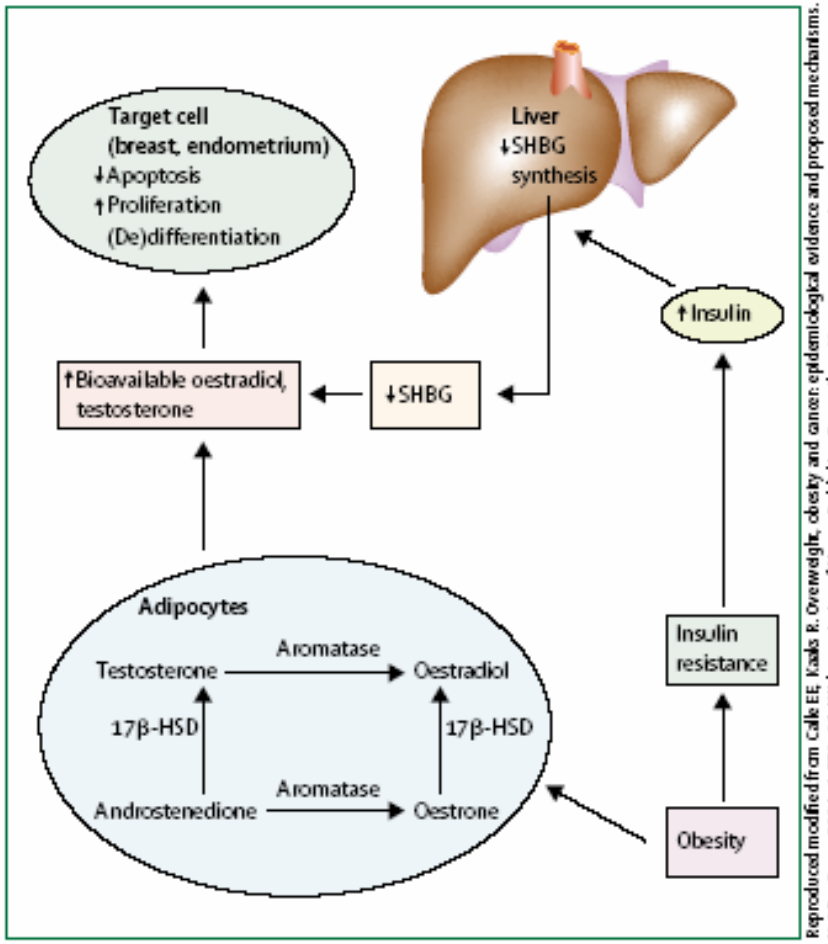
- ***Postmenopause*:** Amenorrhea > 12 months

# Biology of Menopause

Primary ovarian failure (programmed senesence or “apoptosis” of oocytes).

Using hormonal stimulation and ovum donation from younger women, postmenopausal women can conceive and bear children.

# Estrogen derived from adipose tissues in the postmenopausal state




Reproduced modified from Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004; 4: 579–91. With permission of Nature Publishing Group (http://www.nature.com)

*Figure 5:* Relation in postmenopausal women between hormones and obesity affecting endometrial growth
SHBG=sex-hormone binding globulin; 17β-HSD=17β-hydroxysteroid dehydrogenase.

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

# Age at menopause by birth cohort

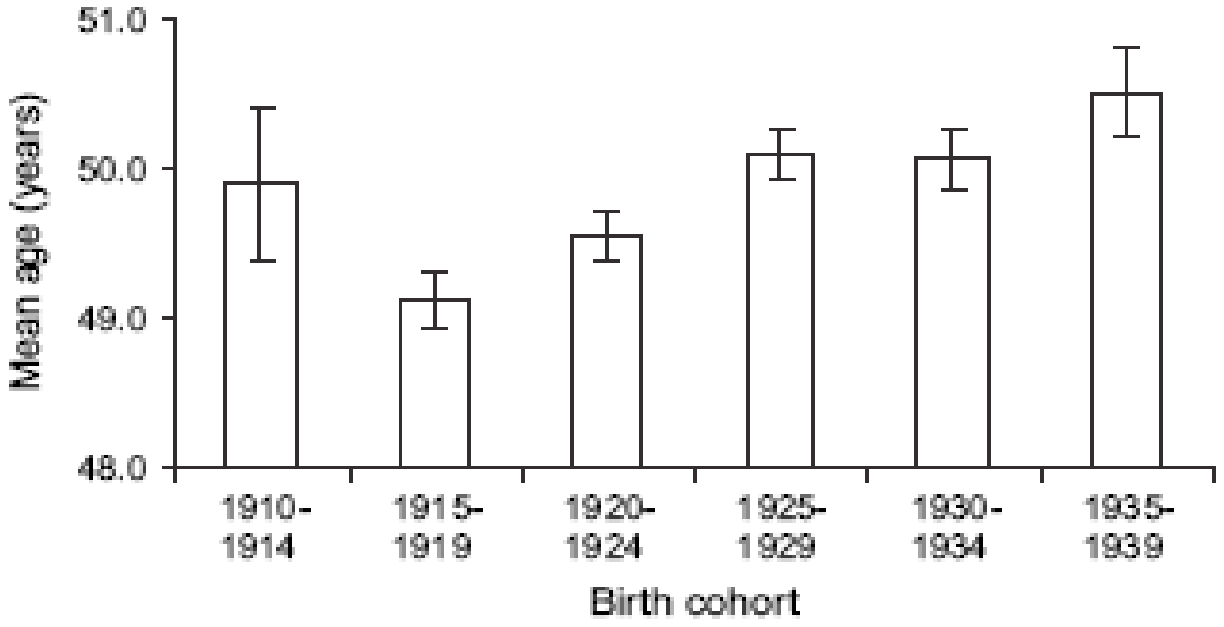



**FIGURE 2.** Mean (standard error) age at natural menopause by birth cohort among women aged 60 or more years living in Massachusetts, New Hampshire, or Wisconsin in 1988–2001. Means are adjusted for state of residence, cigarette smoking, education, parity, age at last birth, height, and body mass index. Analysis was restricted to never users of postmenopausal hormone therapy.

Nichols HB, et al. From Menarche to Menopause: Trends among US Women Born from 1912 to 1969. Am J Epidemiol 2006;1604:1003-1011. By permission of Johns Hopkins Bloomberg School of Public Health. 

# Age at Menopause

- **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)

# Risk Factors for Early Menopause < 50 yrs

| **Risk Factor** | **RR** |
|---|---|
| African-American | 4.3 |
| Smoking | 1.9 |
| Weight Loss | 1.8 |
| Live Birth | 0.7 |
| < High School Education | 1.19 |

# Non-Reproductive Effects of Estrogen

- Bone growth and prevention of calcium re-sorption 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)

# Postmenopausal Syndrome

- 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)

| Study Group | Percent Reduction in Frequency of Hot Flushes |
|---|---|
| *Oral conjugated equine estrogens* | |
| 0.625 mg | 94 |
| 0.45 mg | 78 |
| 0.30 mg | 78 |
| Placebo | 44 |
| *Oral 17β-estradiol* | |
| 2 mg | 96 |
| 1 mg | 89 |
| 0.5 mg | 79 |
| 0.25 mg | 59 |
| Placebo | 55 |
| *Transdermal 17 β -estradiol* | |
| 0.1 mg | 96 |
| 0.05 mg | 96 |
| 0.025 mg | 86 |
| Placebo | 45 |

Efficacy for prevention of hot flushes is greater with higher dose estrogen

# Reproductive Life Span

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

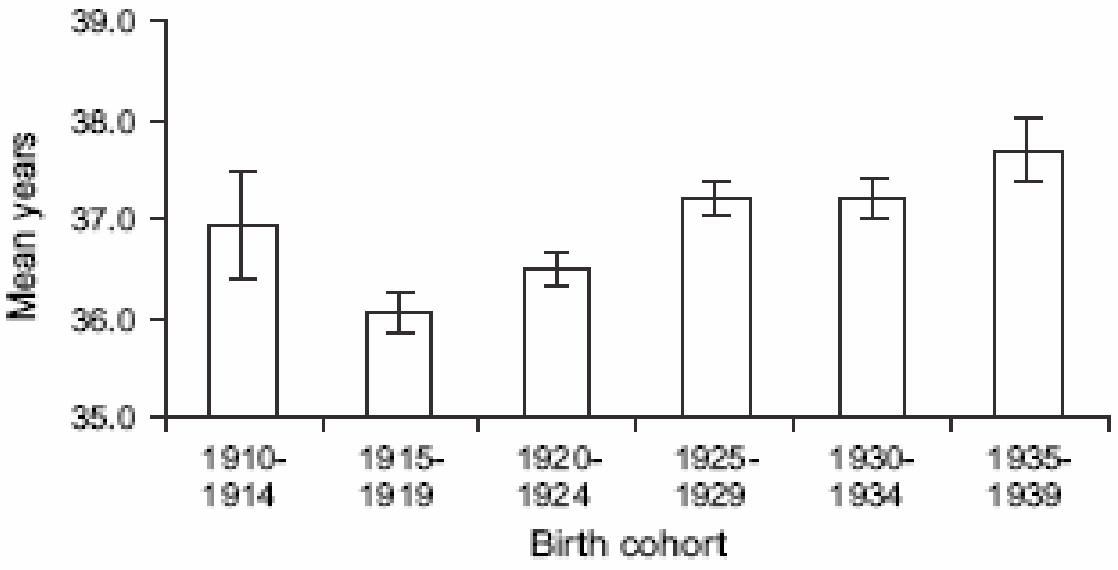



FIGURE 3. Mean (standard error) length of reproductive life span among women aged 60 or more years living in Massachusetts, New Hampshire, or Wisconsin in 1988–2001. Means are adjusted for state, cigarette smoking, education, parity, age at last birth, height, and body mass index. Analysis was restricted to never users of postmenopausal hormone therapy.

Nichols HB, et al. From Menarche to Menopause: Trends among US Women Born from 1912 to 1969. Am J Epidemiol 2006;1604:1003-1011.

# 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.

# Stress and the Menstrual Cycle

- 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)

| Risk Factor | Relative Risk (95% CI) |
|---|---|
| History of long cycles | 3.4 (1.6-7.1) |
| Start college | 2.3 |
| Stress > median | 3.1 (1.3-7.4) |
| Activity > median | 1.5 (1.0-2.3) |

*Harlow and Matanoski. Am J Epidemiol 1991;133:38.*

# 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 seretonin re-uptake inhibitors (SSRIs, i.e., antidepresentents) 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