



Menopause & Postmenopausal Bleeding

429 OB/GYN Team

Sources: Lecture ppt., BRS Obstetrics & Gynecology (Sakala), Hacker & Moore, and Toronto Notes 2011

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Menopause

Definitions

- **MENOPAUSE** is the permanent cessation of menstruation resulting from loss of ovarian follicular activity. Average age of onset is 51 years (50-55 yrs). Natural menopause is recognized to have occurred after **12 consecutive months of amenorrhoea**.
- **PERIMENOPAUSE** includes the period beginning with the first clinical, biological and endocrinological features of the approaching menopause (e.g. vasomotor symptoms, menstrual irregularity) and ending 12 months after the last menstrual period.
- **CLIMACTERIC** is the phase in the ageing of women marking the transition from the reproductive to the non-reproductive state.
- **POST-MENOPAUSE** dates from the final menstrual period and it's determined after a period of 12 months of spontaneous menstruation.
- **PREMATURE MENOPAUSE** is defined as menopause that occurs before the arbitrary cut off age of **40 years**. Mostly, it's idiopathic. It can be caused by abnormal karyotype involving the X chromosome, the carrier state of the fragile X syndrome, galactosemia, or autoimmune disorders
- **INDUCED MENOPAUSE** is the cessation of menstruation that follows either **surgical** removal of both ovaries or iatrogenic **ablation** of ovarian function (e.g. chemotherapy or radiotherapy).

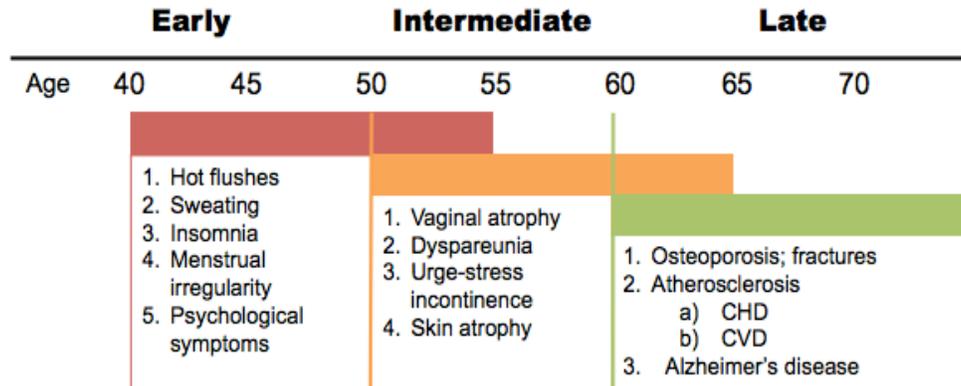
Investigations

- Increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
- Decreased levels of estradiol (later)

Menopause occurs earlier in smokers than in non-smokers. It also occurs early in women with Down's syndrome, and in women who live at high altitudes.

| REPRODUCTIVE STAGE | GERM CELL NUMBER | OVULATION STATUS | MENSTRUAL LEVEL | ESTROGEN LEVEL | GONADOTROPIN LEVEL |
|--|--|---|--|---|---|
| Fetal life | Rapid mitotic increase to 6-7 million oogonia by 20 weeks and then rapid depletion to 1.5 million at birth | NA | NA | ↑ Levels from maternal/placental source | ↑ Rapidly to adult levels by 20 weeks then gradually fall to term |
| Childhood (birth to 8 years) | Further gradual depletion of follicles | NA | NA | ↓ level from ovarian follicles | ↓ to low basal levels |
| Puberty (9 to 14) | Follicle number has declined to 350,000 | Irregular ovulation initially but becoming more regular | Anovulatory cycles initially but becoming ovulatory | Gradually increase to adult levels | |
| Reproductive years (15 to 45 years) | For every follicle that ovulate, 1000 become atretic | Regular ovulation with cycle | Ovulatory from regular follicle maturation | Normal cycles variation with menstrual cycles | |
| Perimenopause (45 to 55) | Only a few thousand less responsive follicle remain | Irregular ovulation becomes increasing frequent | Anovulatory cycles initially but becoming increasingly frequent followed by oligomenorrhea | Fluctuating; as follicles sensitivity varies | |
| Menopause (average age 51 years) | No functional follicles remain | Ovulation ceases | Menstrual cycles cease | ↓ levels from peripheral aromatization of androgens | ↑ levels from loss of estrogen feedback |

Effects of Menopause



1. Vasomotor Symptoms:

- **Hot flushes and night sweats** are episodes of inappropriate heat loss and its classic evidence of ↓ estrogen, experienced by 75% of women
- A sensation of heat begins in the **face, neck and chest** followed by profuse **sweating** in the upper body that **lasts about 4 minutes**
- The duration of symptom is 1-5 years
- Physically: cutaneous vasodilatation, ↓ body core temperature, and ↑ HR with pulses of LH
- They can occur at anytime and at night **disturb sleep** (adversely affect rapid eye movement (REM) sleep)
- Chronically disturbed sleep → insomnia, irritability and difficulties with short-term memory and concentration

2. Mood Disorders:

- The mood disorders that have been associated with the menopause include **depression, anxiety, irritability, mood swings, lethargy and lack of energy**
- The mechanism is thought to be decrease levels of central neurotransmitters and endogenous opioids

3. Urogenital Atrophy:

- Embryologically, the female genital tract and urinary systems develop in close proximity, both arising from the primitive urogenital sinus
- Urogenital complaints e.g. **vaginal discomfort, dysuria, dyspareunia, recurrent lower urinary tract infections and urinary incontinence** are more common in post-menopausal women
- **More than 50%** of post menopausal women suffer from at least one of these symptoms as a result of urothelium atrophy
- The vaginal mucosa often becomes thin, with flattening of rugae, ↑ in PH and ↓ in lubrication
- Premenopausally, the vaginal mucosa is colonized by **lactobacilli**, which provides protection against gram-negative bacteria. After the menopause the vagina is colonized by **fecal flora**.

4. Sexual dysfunction:

Interest in sexual activities declines in both men and women with increasing age and this change appears to be more pronounced in women.

5. Osteoporosis:

- This is a disease characterized by **low bone mass** (↓ density) and micro-architectural deterioration of bone tissue, leading to **enhanced bone fragility** (that is asymptomatic) and a consequent **increase in fracture risk**
- One in three post-menopausal women has osteoporosis
- Osteoporosis affects both sexes, but in general men have fewer fractures than women
- Following menopause, there is an accelerated period of bone loss, which lasts for 6-10 years
 - Peak bone mass is reached during 20s. After age 40, resorption exceeds formation by 0.5% /year (-ve balance). After menopause, trabecular bone loss reaches 5% per year.
- **The main clinical manifestations of osteoporosis are fractures of the wrist, hip and vertebrae**
- In clinical practice, the most important **risk factors** are **early ovarian deficiency** and **corticosteroid use**. Other risk factors include:
 - Ethnicity: white
 - Positive family history
 - Lifestyle:
 - Smoking
 - ↑ caffeine, alcohol or protein intake
 - ↓ calcium and vitamin D intake

Types

1. **Type I** affect **trabecular** bone primarily, with the **vertebral** bodies being most involved
 - a. Postmenopausal **women** are most often affected
2. **Type II** affect both **trabecular and cortical** bone, with the **hip** being most involved
 - a. Both men and women are affected with advancing age

Diagnosis

1. **Current bone density**: best assessed by DEXA (dual-energy x-ray absorptiometry) scanning
2. **Rate of bone loss**: best assessed by 24-hour urinary hydroxyproline or deoxypyridoline → measure changes in osteoclastic activity

Prevention & Treatment

1. Prevention → Lifestyle:
 - a. Vitamin D (400-600 U/day), calcium (1500 mg/day)
 - b. Weight-bearing exercise
 - c. Smoking & alcohol should be eliminated
2. Medications:
 - a. Estrogen: first-line → ↓ fracture rate
 - b. Alendronate (fosamax): bisphosphonate → inhibits osteoclastic activity → prevent & treat
 - i. Less side effects if taken properly (to avoid GI side effects)
 - c. Raloxifene: selective estrogen receptor modulator (SERM) → ↓ vertebral fracture rate
 - i. Antagonist in endometrium & breast ≠ estradiol
 - d. Calcitonin & parathyroid hormone: 2nd line adjunctives → line inhibits osteoclastic activity

6. Cardiovascular Disease

Cardiovascular disease is the number one cause of death in women older than 60.

- The primary end points of cardiovascular disease are myocardial infarction and stroke
- The incidence of coronary heart disease (CHD) increases after the menopause

Treatment Options

- The three main options available are estrogen based hormone replacement therapy (HRT), biphosphonates or selective estrogen receptor modulators (SERMs).
- The benefits of HRT include relief of vasomotor symptoms, prevention of osteoporosis, reducing the risks of cardiovascular disease and coronary heart disease.

Hormone Replacement Therapy

Estrogen is combined with a progestogen to reduce the risk of endometrial neoplasia in women whose uterus is intact. Can be given orally, transdermally, subcutaneously, vaginally & intranasally.

Benefits:

1. **Vagina:** estrogen thickens and cornifies the epithelium, which decreases dyspareunia. It also produces an acid pH, which decreases infectious vaginitis.
2. **Urinary tract:** estrogen decreases atrophy of the urothelium, enhancing normal bladder function
3. **Osteoporosis:** loss of bone density can be halted with stabilization of trabecular bone formation. Fractures can be reduced by more than 50%.
4. **Cardiovascular disease:** estrogen can decrease the risk of a heart attack by 50% (if taken early)
 - The mechanism which the estrogen decreases cardiovascular risk are as following:
 - Estrogen ↑ (HDL) fraction and ↓ (LDL) fraction
 - Estrogen ↓ atherogenic plaque formation by direct action on vascular epithelium
5. **Skin:** estrogen may halt the loss of collagen, which stabilizes elasticity
6. Reduction in the rate of **colorectal cancer** (30%)

Risks:

1. Increased risk of **breast cancer** especially in those who take estrogen progestin
2. Increased risk of **endometrial cancer** in those who still have a uterus and do not take progestin
3. Increased risk of venous **thrombo-embolic disease**
4. Increased risk of **gallbladder disease** (ERT increases plasma triglycerides and total cholesterol → gallstone formation)

Contraindications:

1. Undiagnosed **vaginal bleeding**
2. Acute or chronic **liver disease**
3. Acute **vascular thrombosis**
4. Hormonally dependent **carcinoma**

From Hacker & Moore 5ed - 2009:

"[HRT] was found to increase the risks for coronary artery disease events (by 29%), stroke (by 41%), thromboses (by 100%), and breast cancer (by 26%).

Additional analysis of WHI data has failed to confirm increased coronary artery events in subjects who began therapy less than 10 years after the menopause"

From RCT in Denmark – 2012:

"After 10 years of randomised treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of

Lifestyle Changes

- The most important change overall to increase longevity, reduce heart disease, and reduce calcium loss from bone is **to stop smoking**.
- Controlling weight, engaging in regular exercise, and eating a healthier, low-fat, and balanced diet should be strongly recommended
- The statin drugs are especially important for postmenopausal women with unfavorable lipid profiles, as they significantly reduce the risk of cardiovascular disease and protect against osteoporosis.

Post-Menopausal Bleeding

- Can be caused by simple or pathological conditions including cervical **polyps**, **cystic hyperplasia**, **endometrial hyperplasia**, **cervical dysplasia**, cervical, endometrial and ovarian **carcinomas** or even tubal carcinoma.
- **The older the patient and the more frequent the episodes of bleeding**, the more likely there is to be an underlying endometrial malignancy
- **Endometrial cancer is the most common gynecological malignancy**

Clinical Examination:

- Enlarged **lymph nodes** in the groin or supra clavicular fossa.
- Metastatic focus in the **vagina**
- **Enlarged uterus**
- **Breasts** – for possible secondaries from uterus or ovaries

Investigations

1. **Transvaginal ultrasound or hysterosonography** – endometrial malignancy is unlikely if the **endometrial thickness is less than 5 mm**
2. **Cervical smear**
3. **Colposcopy and cervical biopsy**
4. **Pipelle sampling for endometrial biopsy**
5. **Hysteroscopy**
6. **MRI**
7. **Fractional D&C**

Treatment

1. Local oestrogen preparations for
 - a. Atrophic vaginitis
 - b. Cervicitis
 - c. Endometritis
2. Malignant cervical, uterine, or ovarian pathology will require specific treatment