



Menopause & Postmenopausal Bleeding

429 OB/GYN Team

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

By: Afnan AlTamimi & Roa Alsajjan

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).

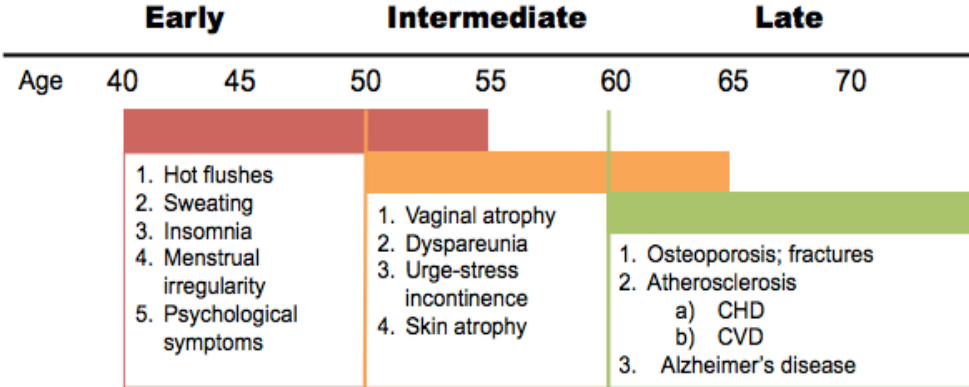
Investigations

- 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 declaim 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