Obstetrics & Gynecology TEAM

Menopause & Postmenopausal Bleeding

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◆very important ◆mentioned by doctor ◆team notes ◆not important

Definitions

- The term **menopause** is derived from Greek "Meno" (months) and "pause" (cessation). The word means cessation of menstruation.
  (After 40 years of age, before that it's premature ovarian failure)

- **Climacteric**:
  The period of life when fertility and sexual activity decline (starts around 40 years)
  It is a wide term leading to:
  - Pre Menopause
  - Peri Menopause
  - Post Menopause

- **Perimenopause**:
  3-5 years period before menopause, with increase **frequent irregular** anovulatory bleeding, followed by **episodes of amenorrhea** and **intermittent** menopausal symptoms.

- **Menopause**:
  - The point in time at which menstrual cycles **permanently cease.**
  - It is a **retrospective diagnosis** after **12 months of amenorrhea** women **classified as being menopause**.
  - Mean age – 51 years.

Pathophysiology of Menopause

- The number of **primordial follicle** declines even before birth, but **declines dramatically just before menopause.**

- **Increase in FSH, LH** from about 10 years **before** menopause.
  (depleted follicles in ovaries → low progesterone & low/normal estrogen→ -ve feedback → ↑ FSH & LH)

- **Close to menopause**, there will be:
  - **Anovulation**
  - **Inadequate luteal phase** → decrease progesterone **but not estrogen level** → leading to **DUB** (dysfunctional uterine bleeding) & **endometrial hyperplasia** (heavy bleeding)

- **At menopause:**
  - Dramatic **decrease of estrogen** →menstruation ceases + symptoms of menopause start.
  - But still ovarian stroma produces small androstenedione and testosterone.
  - However, main **postmenopausal estrogen** is **estrone** produced by **peripheral fat** from adrenal androgen.

Symptoms of Menopause

- **Hot flushes** (cutaneous vasodilation), usually first symptom:
  - occur in **75% of women**
  - more severe after surgical menopause (removal of ovaries)
  - continue for 1 year
  - 25% continue more than 5 years

- **Urinary Symptoms**
  - UTI
  - urgency
  - frequency
  - nocturia

- **Psychological changes** (decreased level of central neurotransmitters):
  - Depression
  - Irritability
  - Anxiety
  - Insomnia
  - loss of concentration

So if patient after 40 and has psych. symptoms, suspect menopause and investigate it before referring her to psychiatry

- **Atrophic Changes [IMP]**

  - Vagina:
    - **vaginitis** due to thinning of epithelium. (causes bleeding)
    - ↑ PH and ↓ lubrication
    - dyspareunia to decrease vascularity and dryness

  - Decrease size of cervix and mucus
  - Retraction of squamocolumnar (SC) junction into the endocervical canal.
  - Decrease size of the uterus, shrinking of myoma (so if she has polyps, it will shrink with menopause, so don't treat if it is not causing problems like anemia)
  - Adenomyosis.
  - Decrease size of ovaries, become non palpable.
  - Pelvic floor relaxation → **prolapse** (procidentia)
  - **Urinary tract atrophy** →loss of urethral tone → **caruncle** (click here to read more)
    Also: Hypertonic Bladder - detrusor instability (incontinence)
  - Decrease size of breast
  - Breast benign cysts

- **Skin Collagen**
  ↓ collagen & thickness → ↓ elasticity of the skin

- **Reversal of premenstrual syndrome**

Late Effects of Menopause

- **Osteoporosis: [IMP]**

  - Bone mass reaches its peak at the end of 3rd decade of life
  - After 40 years, bone resorption exceeds bone formation by 0.5% per year.
  - This negative balance increases after menopause, to a loss of 5% of bone per year.
  - Predisposes to fractures by slight causes, eg: pelvic fracture → 50% may die
  - Considered a cause of death in old ladies

  - **Risk factors:**
    - Gender: more in women (male to female ratio is 1:3)
    - BMI (low BMI is more risky than obese)
    - Race:
      - High in white women
      - Moderate in Asian women
      - Lowest in Black women

- Family History +ve
- Life style: smoking, caffeine intake, alcohol, increase in protein diet, decrease in calcium and vit D intake
- Steroid Medication :
    - **Exogenous medication** (give prophylactic treatment with medication)
    - Cushing Syndrome

- **Diagnosis:**
  DEXA (Dual Energy X-ray Absorptiometry),
  for assessment of bone densemetry, to demonstrate if bone density is above or below fracture threshold.

- **Prevention:**
    - improve lifestyle
    - regular exercise
    - eliminate smoking & alcohol

- **Medication**:
    - ERT (Estrogen Replacement Therapy),
      controversial because may cause breast cancer. Not used routinely.
    - **Bisphosphonate** (Fosamax): inhibits osteoclastic activity & minimal side effects.
    - **Raloxifene** (Evista): selective estrogen receptors modulator [SERM]:
      (it's a good drug, drug of choice if breast cancer)
        - It binds with high affinity to estrogen receptors.
        - It has some **estrogen like effect** e.g. ↑ bone density, ↓LDL Cholesterol [cardioprotective]
        - Acts as **estrogen antagonist** on **endometrium and breast**.
    - Calcitonin: inhibit osteoclastic activity + analgesic effect of bone pain
    - Calcium Supplement & Vit D. [IMP]

- <u>**Cardiovascular Disease:**</u>

    - CVD is now the leading cause of death among post menopausal women:
        - **before menopause**: risk of heart attack is 1/3rd compared to men
        - **after menopause**: increase in women risk of heart attack, so it becomes equal to the risk of men at the age of 70 years

    - Because of effect of estrogen:
        - Before menopause:
            - Increase HDL
            - Decrease LDL
            - Decrease atherogenic plague formation by direct action on vascular endothelium.

    - After menopause:
        - HDL : LDL ratio become closer to male ratio

- Observational Studies:
  - HRT decreases mortality by 30%.
  - But **recent epidemiological studies** do not show a beneficial effect of HRT on CHD, but there is **increase number of breast cancer** when compared with non users of HRT.

- **Urogenital System:**

  - Embryologically, female genital tract & lower urinary system develop in close proximity from primitive urogenital sinus.
  - The **urethra** and **vagina** have a high **concentration of estrogen receptors**
  - There is significant evidence to support the **use of estrogen in treatment of urogenital symptoms** such as recurrent UTI, vaginitis and dyspareunia.

- **Alzheimer's Disease:**

  - Prevalence of dementia: as high as 50% by age of 85 years.
  - Alzheimer's disease accounts for 60-65% of cases.
  - Observation studies: decrease risk of Alzheimer's by 1/3 among women taking HRT.
  - HRT has beneficial effect on brain function, but no randomized studies to confirm observational data.

Diagnosis and Investigations

- **The triad of:**
  - Amenorrhea (12 months)
  - Hot flushes
  - increase FSH > 15 i.u./L (i.u. = international unit)
  - Above 40 years of age

- **Before starting treatment, the following should be performed:**
  - breast self examination (to ensure no masses before treating)
  - mammogram
  - pelvic exam (pap smear) (to check for any cancers, because HRT will promote their growth)
  - Measurement of: weight, blood pressure

- **No indication to perform**
  - Bone density
  - Endometrial Biopsy

  - However, **any bleeding** should be **investigated** before starting any treatment.

Treatment

- Estrogen:
  A minimum of 2mg of estradiol is needed to maintain bone mass and relieve symptoms of menopause.

- Women **with uterus** → add **progestin** in **last 10 days** to **prevent** endometrial **hyperplasia**

- Sequential Regimens → used in patient close to menopause
  (patient will have monthly bleeding, given if patient desires it so she can feel she's still young)
  - **Estrogen** in the **first half** of 28 day per pack
  - **Estrogen** & **progestin** in **2nd half** of 28 day pack

- Combined continuous therapy that has **progesterone** everyday:
  - Useful for women who are few years **past menopause**, and who do not have vaginal bleeding

- There is evidence of increased **risk of endometrial cancer** with **sequential regimens** for more than 5 years.
- However, **combined** continuous regimens **decrease** risk of **cancer**.

Hormonal Replacement Therapy (HRT)

- **Benefits:**

  - Vagina: ↑ vaginal thickness of epithelium → ↓ dyspareunia & vaginitis.
  - Urinary tract: enhancing normal bladder function.
  - Osteoporosis: decrease fractures by more than 50%
  - CVS: decrease by 30% by observation studies, but recent studies shows no benefits.
  - Colon Cancer: decrease up to 50%

- **Confirmed Risk:**

  - Endometrial cancer (and breast cancer) eliminated by:
    1. Adding progesterone
    2. or: Using selective estrogen receptors modulators (SERMS).
  - Gall Bladder Disease (with estrogen replacement therapy):
    - ↑ triglyceride
    - ↑total cholesterol
    - increase risk of gall stone, and liver disease, so be careful if +ve history.
  - **Breast cancer** risk with long term HRT adds:
    - 2/1000 after using it for 5 years – 6/1000 after 10years
    - 12/1000 after 15 years
    - background risk 45/1000 between the age of 50 and 70

- **Contraindications to HRT:**

  - Undiagnosed vaginal bleeding
  - Acute liver disease, or chronic impaired liver functions
  - Acute vascular thrombosis
  - Breast Cancer

Postmenopausal Bleeding

- **Definition:**
  Vaginal **bleeding** that occurs after **12 months of amenorrhea** in middle aged women who are **not receiving replacement therapy**.
  It can never be dysfunctional or anovulatory in nature (because with loss of functional ovarian follicle, bleeding from normal ovulatory cycle is impossible).

- **Causes:**

  - Upper reproductive tract causes:
    - Atrophic endometritis
    - Endometrial polyp, submucous fibroids
    - Endometrial hyperplasia
    - Endometrial cancer (important to be excluded)
    - Ovarian or tubal cancer

  - Lower reproductive tract causes:
    - Vaginits (most common along with atrophic endometritis)
    - Vaginal or vulvar tumors
    - Varicose veins (from vulva)
    - Cervical polyp or cervical tumors

  - GIT causes:
    - Hemorrhoids
    - Anal fissures
    - Colorectal cancer

  - Anticoagulant medications

Endometrial cancer (as a cause of Postmenopausal Bleeding)

- The most common gynecological malignancy.

- Endometrial neoplasia can progress from simple hyperplasia to invasive cancer caused by **unopposed estrogen**.

- The **mechanism** of many endometrial cancers is prolonged estrogen stimulation of the endometrium, unopposed by progesterone.

- The **source** of estrogen may be:
  - **Exogenous** estrogen (E2) (Estrogen Replacement Therapy: ERT), without taking progesterone
  - **Peripheral aromatization** of androstenedione to estrone, as in obesity or PCO
  - Estrogen (E2) producing **tumor**, like granulosa cell ovarian tumor
  - **Tamoxifen** stimulation of endometrium (tamoxifen is used for breast cancer)

- **Risk factors:**
  - No pregnancy
  - Prolonged reproductive life – late menopause
  - Unopposed estrogen
  - Triad of diabetes, hypertension & obesity
  - Tamoxifen (worst prognosis)

Diagnosis of Postmenopausal Bleeding

- **Upper Reproductive Tract Causes :**
  - Upper reproductive tract causes can be identified only by:
    tissue diagnosis obtained by endometrial evaluation .
    An ultrasound is done before that to check endometrial thickness
  - Endometrial Biopsy:
    Inaccurate for diagnosis of polyp, misses a sufficient number of hyperplasia.
  - **Hysterosonography**:
    - performed by infusion saline in the uterine cavity to identify endometrial **polyps.**
    - If endometrial thickness is more than10mm → indicates risk of hyperplasia→ **tissue** should be obtained for **histological studies**.
  - **Pipelle sampling** for endometrial biopsy (catheter that has suction and takes biopsy):
    - If +ve → refer to oncology (and perform hysterectomy)
    - If –ve → continue investigation (hysteroscopy) because it's a blind procedure
  - **Hysteroscopy [best facility, diagnostic]**:
    - performed at the time of D&C for polyp & operative resection.
  - Fractional dilation and curettage (D&C):
    - Done if no hysteroscopy
    - It's the good standard for evaluating post menopausal bleeding.
    - It is performed in 2 stages:
      1. Initially, **endocervical** canal is curetted obtaining the first specimen to rule out invasion of cervix by cancer.
      2. **Uterine cavity** is curetted; obtaining second specimen to assess endometrial neoplasia or malignancy.
    - If negative: still it's not diagnostic
  - Pap Smear:
    - has **poor sensitivity** for endometrial cancer. Only 40% cases are identified
  - MRI
- **Lower Reproductive Tract Causes :**
  - Pelvic Exam
  - Pap Smear & appropriate Biopsy
  - Colposcopy and cervical biopsy
- **GIT etiology:**
  - Rectal exam
  - Stool for occult blood
  - Proctosigmoidoscopy

Treatment of Postmenopausal Bleeding

1. Investigate the cause, exclude cancer... Treat the cause.
2. Atrophic vaginitis, cervicitis and endometritis may need only **local estrogen preparations**
3. Malignant cervical, uterine or ovarian pathology will require **specific treatment.**