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## Menopause

### Objectives:

- Define menopause and describe changes in the hypothalamic-pituitary-ovarian axis associated with perimenopause/menopause
  - Describe symptoms and physical exam findings related to perimenopause/menopause
  - Discuss management options for patients with perimenopause/menopausal symptoms
    - Counsel patients regarding the menopausal transition
    - Discuss long-term changes associated with menopause

References : **433 team , kaplan , hacker moore**

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# Menopause:

## Menopause

- Menopause is defined as 12 months of amenorrhea , associated with elevation of (FSH, LH)
- average age is 51.5 years. ( some women have their menopause before age of 40 )
- Menopause occurs due to the programmed loss of ovarian follicles .
- Women are born with between 1.5 and 2 million oocytes (primary ovarian follicles) and reach menarche (first menstruation) with about 400,000 potentially responsive eggs
- The perimenopause refers to the (several years of more gradually decreasing ovarian function that may be associated with the symptoms of reduced estrogen levels).
- The signs and symptoms of the perimenopause and menopause are related to progressively decreasing secretion of estrogen from the ovarian follicle .

## Premature menopause:

Occurs at 30-40 and is mostly idiopathic, but can also occur after radiation therapy or surgical oophorectomy.

## Premature ovarian failure:

Occurs at < 30 and may be associated with autoimmune disease or Y chromosome mosaicism.

## Pathophysiology

The hypothalamus produces GnRh which → stimulates the anterior pituitary to produce FSH and LH → this stimulates the ovary to produce estrogen .

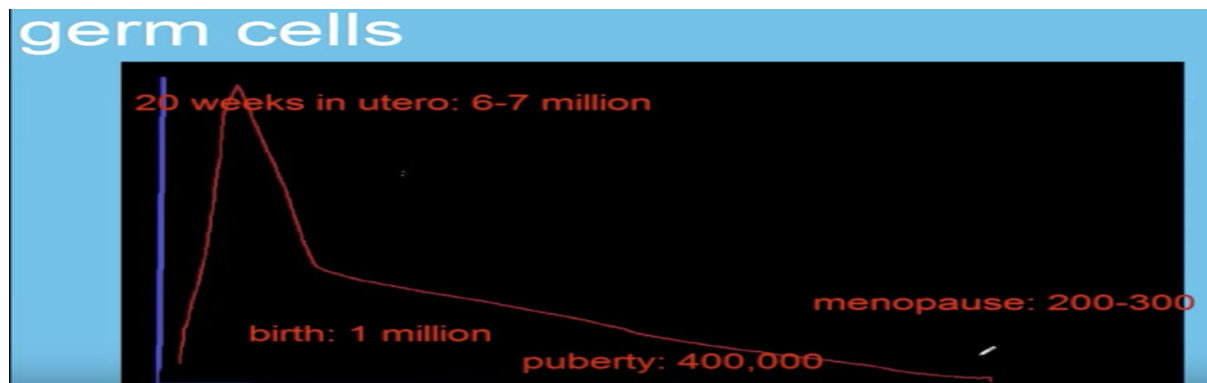
**With advancing age** as the oocyte number decline → estrogen levels decline .

The remaining oocytes become increasingly resistant to FSH and FSH plasma concentrations increase.

Both FSH and LH are very high in menopause but FSH increase first and thus it is a better marker and we can detect it earlier (important)

At the time of menopause FSH concentrations > 30 mIU/ml

## The number of the oocyte (germ cells)



## Hormonal changes

### Estrogen

Following menopause, estradiol (E2) values decline (to only 10 to 50 pg/mL), but estrone levels may increase. Estrone (E1) can be produced by peripheral conversion of androstenedione from the ovary and the adrenal gland.

### PROGESTERONE

With anovulation during the climacteric and ovarian failure after the menopause, the production of progesterone declines to low levels. The minimal progesterone present is insufficient to induce those cytoplasmic enzymes (estradiol dehydrogenase and estrone sulfuryltransferase) that convert estradiol to the less potent estrone sulfate and to reduce the levels of cellular estrogen receptors. Altogether, this may result in increased estrogen-induced mitosis in the endometrium. The absence of progesterone also prevents the secretory histologic transformation in the endometrium and its subsequent sloughing. As a consequence, perimenopause is often associated with irregular vaginal bleeding, endometrial hyperplasia and cellular atypia, and an increased incidence of endometrial cancer.

### Gonadotropin

When levels of estrogen are low, the arcuate nucleus and paraventricular nucleus in the hypothalamus are freed from negative feedback and are able to secrete increasing amounts of gonadotropin-releasing hormone (GnRH) into the pituitary portal circulation. This, in turn, stimulates an increased release of LH and FSH into the circulation

### Changes occur in the menstrual cycle (beginning at age 40) :

- Shortening or lengthening of menstrual cycle\*.
  - The luteal phase stays the same at 13-14 days.
  - Variation in cycle length is related to follicular phase.
  - women may notice that their cycle is now 21 days.

## Sign and Symptoms & complication of Menopause:

CONSEQUENCES OF LOSS OF ESTROGEN	
Symptoms (early)	Hot flushes (flashes) Insomnia Irritability Mood disturbances
Physical changes (intermediate)	Urogenital atrophy Stress (urinary) incontinence Skin collagen loss
Diseases (late)	Osteoporosis Dementia of the Alzheimer type (possible) Cardiovascular disease (unclear relationship) Cancers, for example, colon (unclear relationship)

### Amenorrhea:

The most common symptom is secondary amenorrhea. Menses typically become anovulatory and decrease during a period of 3–5 years known as perimenopause

## Hot flushes :

predictable profuse sweating and sensation of heat are experienced by 75% of menopausal women. This is probably mediated through the hypothalamic thermoregulatory center. Obese women are less likely to undergo hot flashes owing to peripheral conversion of androgens to estrone in their peripheral adipose tissues.

- Women describe the sudden sensation of extreme heat in the upper body particularly the face, neck, and chest .
- The episodes typically last for 1-5 minutes .
- For many women the hot flushes are tolerable and do not require any medical treatment .However 33% of women experience > 10 hot flushes/ day.
- the hot flushes can be associated with many significant adverse outcomes such as hampered
- job in productivity, and sleep deprivation.

## Management

Some women can simply use life style modifications , other women pursue medical therapy often based on the severity of their symptoms.

### Systemic Hormone therapy:

- It is the most effective treatment for hot flushes , it reduces the severity and frequency of hot flushes by 75%.
- If she has a uterus we give estrogen + progesterone (we don't give progesterone unless the patient has uterus to protect her from endometrial cancer)
- If she has no uterus we give estrogen only. *You give estrogen only unless the patient has a uterus we give progesterone to protect her from endometrial cancer*

*Hrt is the best therapy if the patient doesn't have any contraindication and they don't increase the risk of breast cancer the study that people afraid of has a lot of frauds and not longer in fashion, we give very low dose just keep screening the patient and follow her probably*

*Premature ovarian failure which comes in young age need a higher dose and to be fully estrogenized their bodies used to high estrogen & if we don't give higher dose they will have all of the risks with the dose for menopausal women which is low dose*

### Risks of Hormone therapy:

The women's health initiative was a large randomized placebo, control trail.

- Estrogen + Progesterone ↑ risk of ( coronary heart disease, breast cancer, stroke and Venous thromboembolic events).
- Estrogen + Progesterone ↓ risk of ( colon cancer, fractures).
- Estrogen only ↑ risk of (stroke and Venous thromboembolic events )

### Other treatment options

- SSRI/SNRI's:  
Reduce hot flushes by 50-62% .
- Herbal therapy:  
Have not been shown to be superior to placebo.

- Bio-identical hormones therapy:  
Limited evidence on their safety, potency and efficacy ,not preferred over traditional hormone therapy.

## Other Symptoms:

### Mood disturbance

Low estrogen leads to mood alteration, emotional lability, sleep disorders, and depression.

### Sleep disturbances

Decline in estrogen levels can induce a change in women’s sleep cycles independent of hot flushes.

Sleep disturbances are one of the most common and disabling effects of menopause

### Increased risk of osteoporosis:

Bone density decreases post-menopausally by 1-2% per year compared to 0.5% per year in peri-menopausal women

### Risk factors of osteoporosis

KNOWN RISK FACTORS FOR OSTEOPOROSIS IN WOMEN	
•	Family history of osteoporosis
•	Reduced ovarian function (decreased estrogen production)
•	Slender body composition
•	Caucasian and Asian ethnicity
•	Sedentary life style
•	Cigarette smoking
•	Thyroid excess
•	Use of corticosteroid or anticonvulsant medications

### screening

BOX 35-2 BONE DENSITY SCREENING BEFORE THE AGE OF 65 YEARS	
Recommended for women with any of the following risk factors:	
•	Body weight of <127 lb
•	History of fragility fracture
•	History of bone loss from medications or disease
•	Family history of hip fracture
•	Alcoholism
•	Current smoker
•	Rheumatoid arthritis

### How to manage osteoporosis

Lifestyle	Ca <sup>2+</sup> and vitamin D intake
	Weight-bearing exercise
	Stop cigarettes and alcohol
Medical	Historic gold standard for comparing therapies: estrogen replacement
	Inhibit osteoclasts: bisphosphonates (alendronate, risedronate)
	Increase bone density: SERMs (raloxifene)

### Pelvic organ prolapse and atrophic urethritis:

Occurs when the paravaginal tissue that supports the bladder and rectum becomes atrophic .

## Vaginal atrophy :

Low estrogen leads to decreased vaginal lubrication, increased vaginal pH, and increased vaginal infections.

40% of women will experience one or more symptoms of vaginal atrophy .

May present with ( itching and burning , loss of vaginal rugae and elasticity can cause narrowing and shortening of the vagina).

Vaginal atrophy and vaginal dryness can be symptomatic during intercourse and an cause significant dyspareunia.

Vaginal lubrication and vaginal estrogens can provide symptom relief.

## Cardiovascular disease. (from kaplan)

This is the most common cause of mortality (50%) in postmenopausal women, with prevalence rising rapidly after menopause.

# Case



**CASE:** A 53-year-old, G3P3 woman, whose last menstrual period was 4 months ago presents to the office with hot flushes, emotional lability, and insomnia. She experiences hot flushes 2-3 times per day and occasionally at night. She has been having trouble sleeping and is extremely fatigued. Since age 14, her periods have been regular until 2 years ago, when they began to space out to every 2-3 months. She is sexually active and recently has noted some dyspareunia. The patient rarely exercises. She smokes 2 packs of cigarettes a day and drinks alcohol socially. She recently started taking a soy supplement. She does not have any pertinent gynecological, medical or surgical history. Her family history is significant for her mother sustaining a hip fracture at age 60 and a sister with breast cancer and high cholesterol. On examination, she has normal vital signs. She is 5'4" tall and weighs 123 lbs. On pelvic examination, she has decreased vaginal rugae and a pale, small cervix. No masses or tenderness are palpated on bimanual exam.

### 1. What are the symptoms of perimenopause and menopause?

- Hypoestrogenism is the basis for the common changes of menopause.
- The common signs and symptoms of menopause include amenorrhea (of 12 months duration), hot flashes, memory changes, sleep difficulty, decreased libido, dyspareunia, urinary symptoms, breast changes

### 2. How do you make the diagnosis of menopause?

- Menopause is the permanent cessation of menses and usually occurs between the ages of 50 and 55, with an average of 50-52 years.
- The definition of menopause is the absence of menses for 12 consecutive months. It is, therefore, a retrospective diagnosis.
- Perimenopausal symptoms usually begin 3 to 5 years before amenorrhea or postmenopausal levels of hormones

### 3. What are the patient's risk factors for osteoporosis?

- This patient's risk factors include menopause, family history of osteoporosis, cigarette smoking, and sedentary lifestyle.
- Additional risk factors for discussion include age at menopause or oophorectomy, white or Asian origin, small body frame or low BMI, high risk for osteoporosis related fracture per FRAX tool, vitamin D3 deficiency, poor calcium intake, alcohol and caffeine intake, and corticosteroid use.

### 4. How do you diagnose and treat atrophic vaginitis?

- Patients commonly have vaginal dryness, vulvar irritation, pruritus, and dyspareunia.
- Associated urinary symptoms may be present.
- Examination shows vulvar erythema.
- Excoriation may be present. Loss of vaginal rugae, a pale vaginal mucosa, with patches of erythema and even superficial blood vessels are consistent with atrophy.
- The pale or yellow discharge has a pH of 5.5 or higher.
- Basal cells replace superficial vaginal epithelial cells and can be seen on a saline wet prep or Pap test.
- Treatment is topical estrogen (allow 4 to 6 weeks for symptomatic relief).

### 5. How do you counsel a patient regarding estrogen and alternative therapies?

- Risks and benefits of therapy should be reviewed (WHI and other studies).
- Contraindications should be discussed.
- Treatment options for menopausal symptoms and osteoporosis should be outlined.
- Bio-identical (compounded) hormones do not have an inherent advantage over standard therapies and may vary in their potencies.
- Micronized progesterone and estradiol are bio-identical by definition.
- Any patient on systemic HT with an intact uterus needs a progestogen.
- Transdermal estrogen administration is preferable due to a beneficial effect on lipid balance and thromboembolism risk.
- Lifestyle modifications including smoking cessation should be stressed.
- The importance of evaluating any postmenopausal bleeding should be discussed.
- Acknowledge frequent use of complementary and alternative treatments.
- SSRI antidepressants can be used as an alternative in women who are not candidates for HT.

### 6. What laboratory and diagnostic tests would you order for this patient?

Laboratory and diagnostic tests should focus on the patient's history and symptoms, as well as preventive screening. For example, a TSH and lipid panel is appropriate given her fatigue and family history.

General health maintenance/screening test guidelines (i.e. colonoscopy at age 50, bone density at age 65, etc.) should be discussed.

Tests include a mammogram, bone density (given patient's smoking and family history of fracture), colonoscopy.

Discuss new cervical cytology screening recommendations.

