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Video Case

Menopause

Objectives:

→ Define climacteric and menopause
→ Explain the hormonal changes in peri-menopause and menopause.
→ Describe the Clinical manifestations related to menopause
→ List the investigations related to menopause.
→ Discuss the management options for climacteric including lifestyle changes and alternate treatments.
→ Identify the relative risks associated with hormonal replacement therapy.
→ Define menopause and describe changes in the hypothalamic-pituitary-ovarian axis associated with perimeno- pause/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

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Menopause

What is menopause :

Menopause is a retrospective diagnosis and is defined as 12 months of amenorrhea, associated with elevation of (FSH, LH) and low estrogen levels.

- → The mean age is **51 years** is genetically determined and unaffected by pregnancies or use of steroid Contraception.
- → 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).**
- → **Smokers** experience menopause up to **two years earlier**.

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/m**

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.

Menopause

Clinical Findings

The majority of menopausal symptoms and signs are caused by **a lack of estrogen.**

Amenorrhea	**Menses typically become anovulatory and decrease during a period of 3-5 years known as perimenopause.** (most common symptom is secondary amenorrhea)
Hot flushes (75% of menopausal women)	• Unpredictable **profuse sweating** and **sensation of heat**, 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 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**.
Reproductive tract	• Low estrogen leads to: ○ ↓ **vaginal lubrication.** ○ ↑ **vaginal pH.** ○ ↑ **vaginal infections.** • 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, vaginal moisturizers and vaginal estrogens** can provide symptom relief.
Urinary tract	Low estrogen leads to increased **urgency**, **frequency**, **nocturia**, and **urge incontinence**. **Pelvic organ prolapse and atrophic urethritis:** Occurs when the paravaginal tissue that supports the bladder and rectum becomes atrophic .
Mental symptoms	Low estrogen leads to **mood alteration**/swings, **emotional lability, sleep disorders** (Decline in estrogen levels can induce a change in women's sleep cycle independent of hot flushes and is the most common disabling effects of menopause) and **depression**.
Cardiovascular disease (most common cause of mortality (50%) in postmenopausal women)	
Osteoporosis	• A disorder of decreased bone density, leads to pathologic fractures when density falls below fracture threshold. **Bone density ↓ postmenopausally** by 1-2% per year compared to 0.5% per year in peri-menopausal women **(Screening at age 65 y/o).** • The most common sites for fracture are : -**hip joint -wrist -vertebrae**

Menopause

Diagnosis

→ The laboratory diagnosis of menopause is made through serial identification of **elevated gonadotropin (FSH and LH) and low estrogen.**

Management

Benefits

→ Both **combined OCP** and **estrogen only** OCP, have ↓ **osteoporosis fracture and colorectal cancer rates.**

Risks

→ Postmenopausal women of more than 5 years or 10 are more prone to these risks than newly menopausal women.

→ The risk of **venous thromboembolism (VTE)** and **ischemic stroke** increases with **oral** MHT but the absolute risk is rare age <60.

→ **The estrogen only** ↑ risk of (**stroke and Venous thromboembolic events**)

→ **Estrogen + Progesterone** ↑ risk of (**coronary heart disease, breast cancer, stroke and Venous thromboembolic events**)

→ The risk of **breast cancer in women age >50** associated with the **addition of a progestin** to estrogen therapy (HT) and related to the **duration of use.**

Indications for use MHT :

01 Vasomotor symptoms

→ Most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for **symptomatic women age <60 or within 10 years after menopause.**

02 Vaginal dryness

→ **Local low-dose estrogen** therapy is preferred for women whose **symptoms are limited to vaginal dryness or associated discomfort with intercourse.**

03 Premature menopause

→ In women with premature ovarian insufficiency, systemic MHT is recommended at least until the average age of the natural menopause.

Menopause

Benefits of MHT but no indications for use

Osteoporosis

→ Effective and appropriate for the prevention of **osteoporosis** related **fractures in at-risk women age <60 or within 10 years after menopause.**

Coronary heart disease

Findings depends on the kind of MHT used :

→ **Estrogen-alone (ET) :** may decrease coronary heart disease and all-cause mortality in women age <60 and within 10 years of menopause.

→ **Estrogen plus progestin (HT):** in this age group shows a similar trend for decreased mortality but no significant increase or decrease in coronary heart disease has been found

Contraindications of MHT

→ **Personal history of an estrogen-sensitive cancer (breast** or endometrium)

→ **Active liver disease**

→ **Active thrombosis**

→ **Unexplained vaginal bleeding**

Administration of Menopausal Hormonal Therapy

→ **Estrogen** can be administered by **oral**, **transdermal, vaginal, or parenteral routes**.

→ The most common current regimen is oral estrogen and **progestin** given continuously.

Uterus present or absent

→ Estrogen as a single systemic agent (ET) is appropriate in women after **hysterectomy** because taking estrogen for a long time will thicken the endometrium then will go into endometrial hyperplasia and then endometrial cancer, but additional progestogen (HT) is required in the presence of a uterus to **protect her from endometrial cancer**

Individualized management

→ The option of MHT is an individual decision in terms of quality of life and **health priorities**, as well as **personal risk factors** such as age, time since menopause, and risk of venous thromboembolism, stroke, ischemic heart disease, and breast cancer.

Dose and duration

→ Dose and duration of MHT should be consistent with treatment goals and safety issues, and thus should be individualized.

Other treatment options for hot flashes

→ **Bioidentical hormones**: Limited evidence on their safety, potency and efficacy ,not preferred over traditional hormone therapy.

→ **SSRI/SNRI's**: Reduce hot flushes by 50-62% .

→ **Herbal therapy**: Have not been shown to be superior to placebo.

Menopause

Estrogen Alternatives

→ In patients with contraindications to estrogen-replacement therapy, **SERMs** can be used.
→ These are medications with estrogen agonist effects in some tissues and estrogen antagonist effects on others.
→ Although protective against the heart as well as bone, these medications do **not have** much effect on **hot flashes and sweats**.
→ **Tamoxifen is a SERM with endometrial and bone agonist effects, but breast antagonist effects.**
→ **Raloxifene has bone agonist effects, but endometrial antagonist effects**.

Teaching 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

Q1: 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.

Q2: 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.
→ Bleeding after a year or more of amenorrhea is called postmenopausal bleeding not menses.

Q3: 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**. Family Hx is a very imp, risk factor and previous personal Hx of fracture.
- 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**.
  - lack exposure to the sun

Q4: 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)**

Q5: How do you counsel a patient regarding estrogen and alternative therapies ?

- Risks, benefits and contraindications of therapy should be reviewed (WHI and other studies).
- For this patient, give combined estrogen and progesterone therapy because the uterus is intact. But, now she's at risk of breast cancer, Coronary heart disease, stroke, and VTE.
- For osteoporosis, put her on FRAX tool and see what she needs or maybe use DEXA scan, then give vitamin D and calcium as required.
- **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**.
- Herbal use counseling: "Have not been shown to be superior to placebo"

Teaching Case

Q6: What are the laboratory and diagnosis

Laboratory and diagnostic tests should focus on the **patient's history and symptoms**, as well as preventive screening. For example:

- → **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.

441 Doctor's Notes

- → **Why menopause is an important topic?**Because women spend 1/3 of their lives in the postmenopausal period. Menopause is associated with morbidity (economic and health issues) and mortality.
- → **What does menopause mean?** "Meno" means monthly, and "pause" means to cease or stop. The end of monthly menstruation (menstrual cycle). It is a life event that happens once in a lifetime.
- → **Premenopause** means "before menopause" **climacteric**" which proceeds menopause by 5-10 years.
- → **Perimenopause** means "during or around menopause"
- → **Postmenopause** means "after menopause" (6 or 12) months of secondary amenorrhea.
- → **Why do women have menopause?** Due to low estrogen levels resulting from decreased ovarian function.
- → **Are postmenopausal women totally estrogen deficient?** No, because estrogen comes from two other sources: adipose tissue and the adrenal glands. Adipose tissue peripheral conversion (converts androstenedione → estrogen).
- → In the past, when women were approaching menopause, they would begin to gain weight (to get estrogen) due to the lack of exogenous estrogen.

- → **Types of estrogen in females' lives:**
  - → **Estrone (E1) → high in menopause** (estrone is higher than estradiol in cases of obesity and PCOS)
  - → Estradiol (E2) → high in reproductive life
  - → Estriol (E3) → high in pregnancy "fetoplacental origin"
- → **What is the best and most effective type of estrogen?** Estradiol (E2)
- → **Why estrone (E1) is bad estrogen?** The Target organ for estrone is the endometrium → overgrowth → cystic and glandular hyperplasia → risk of developing cancer.

441 Doctor's Notes

- **What are the effects of deficient estrogen on the body?**
  - **Psychological:** memory changes, sleep difficulties, mood swings, depression, irritability, lack of concentration.
  - **Genitourinary:**
    - **Vulva:** atrophy, thinning of the skin epithelium (epidermis and dermis)
    - **Vagina:** Risk of infection: low estrogen → lactobacilli is depleted → decreased glycogen metabolism → ↑ pH (alkaline) → infections (weak pathogen).
      - (Vaginal PH of women of reproductive age is acidic because of the presence of lactobacilli).
      - The rigidity of the vulva and vagina are lost and can be a source of bleeding (may be misdiagnosed as cancer even though it's basically just an atrophic vagina)
    - **The urinary bladder:** urgency, frequency, dysuria. Sometimes there's bleeding, but it is not a UTI. This is called "urethral syndrome" related to postmenopausal due to estrogen deficiency.
    - **The uterus:** shrinks (myometrium cells are replaced by fibrous tissue).
    - **The ovaries:** The cortex shrinks and thins, the medulla becomes thick, and the color becomes silvery white fibrotic.
  - **Cardiovascular:** high risk of CVD because of ↑ cholesterol, ↓ HDL, ↑ LDL, ↑ triglycerides.
  - **Skeletal:** osteoporosis → The osteoclasts "bone resorption" is more than the osteoblasts "bone formation". Bone becomes porous and can fracture easily without trauma .

- **What are the most common sites of fractures in menopause?** Neck/head of femur, vertebrae, and wrist.
- **Postmenopausal bleeding approach:**
  - **Hx:** DDx: (hemorrhoids, fissures, urethral granulation tissue, urethral meatus injury, rupture of varicose vein on the vulva).
    - Medications: Anticoagulants or HRT.
  - **PE:**
  - **Inspection:** vulva, anus, urethra, vagina and cervix.
    - Inspect the vagina with a small and lubricated speculum (to prevent pain and laceration).
    - Inspect cervix + external os for ectropion or any pathology (ectropion is an overgrowth of columnar epithelium over ectocervix).
  - **Bimanual examination:** to check for uterine fibroid, adenomyosis, and endometriosis.
    - Check size, mobility, position (retroverted or anteverted), consistency (firm/soft) and tenderness.
    - Examine adnexa: (fallopian tube, broad ligament, and ovary).
  - **Investigation:** hysteroscopy (gold standard), US, karyopyknotic index, screening endometrial sampling, and directed biopsy.

- **What happened to bone density in postmenopausal?** Decrease, because of demineralization and depletion of estrogen
- **During menopause what happens to each of the following?**
  - **Vaginal acidity?** ↓ Decrease
  - **Estradiol?** ↓ Decrease
  - **Estrone?** ↑ Increase
  - **Plasma cortisol?** ↑ Increases
  - **Triglyceride?** ↑ Increase
  - **HDL?** ↓ Decrease **VLDL?** ↑Increase
- **Is it true that the uterine body shrinks greater than than the cervix in menopause?** Yes, it goes back to childhood proportion (The cervix is longer than the uterine body).
- **Which increases in postmenopause, FSH or LH?** FSH, FSH (10 to 20 folds higher) while LH (3 folds higher).
- Estrone has a 1/10 biological effect of estradiol.
- The average age of natural menopause is 51 years (in the West).
- Premature menopause: less than 40 years.

Female Students Presentation

- **The “climacteric” refers to a period of time when decreasing reproductive capacity occurs in both men and women. For women, this period in their lives is marked mostly by the last menstrual period or menopause and a variable time leading up to the last menses called the perimenopause.**

SMLE QBank:

- **A patient candidates for MHT underwent total hysterectomy with bilateral oophorectomy what to give her?**
  - A. Estrogen patch
  - B. lUD
  - C. OCP (Progesterone and estrogen)
  - D. Progesterone only pills

Explanation:

Surgical menopause — In women who have undergone a hysterectomy and who are candidates for MHT, unopposed estrogen is given. Progestins are only given to women with an intact uterus to prevent endometrial hyperplasia and cancer

Correct Answer: A

- **A postmenopausal patient, known to have DM, hypertension and morbid obesity, presenting with abnormal uterine bleeding, what is the most appropriate test to reach diagnosis?**
  - A. Pelvic US
  - B. Pelvic MRI
  - C. Pelvic CT
  - D. Endometrial biopsy

Explanation:

Postmenopausal patients with any uterine bleeding, regardless of volume (including spotting or staining), should undergo evaluation for endometrial hyperplasia or carcinoma via endometrial sampling, pelvic ultrasound is an alternative

Correct Answer: D

439 Doctor's Notes

- Average age of menopause (51y/o)
- In menopause there is:
  - decrease in(bone density + vaginal acidity + estradiol) and increased in (estrone)
  - FSH increases 3-10 folds while LH increases 2-3 folds
  - increase free testosterone (total unchanged)
  - plasma cholesterol (LDL increase while HDL decrease) +increase in triglyceride level.
  - Uterine body shrunken in relation to the cervix
- local absorption of estrogen = systemic absorption of estrogen but bypass the liver.
- Calcium supplements not as effective as giving estrogen.
- the endogenous estrogen sources are (adrenal gland- adipose tissue-ovaries)1 while the exogenous from (hormonal replacement therapy).
- estrogen produced excessively in case of > granulosa cell tumor
- one of the contraindications of estrogen therapy is > acute liver disease.
- menopausal symptoms not responding to estrogen therapy > vaginal relaxation.
- The biological activity of the estrone =1/10 biological activity of the estradiol.
- In case of osteoporosis (give estrogen no need to give progesterone has no role but you have to check if there is any contraindication regarding estrogen therapy) +encourage physical activity and give calcium and vit D.

Reference

As average life expectancy increases, in the United States and elsewhere (Table 35-1), women and men are often living well into their ninth decade of life. The preservation of their quality of life in terms of both physical and mental activity is a high priority for them. Many women will live for 30 to 40 years after reproductive function ends.

The "climacteric" refers to a period of time when decreasing reproductive capacity occurs in both men and women. For women, this period in their lives is marked mostly by the last menstrual period or menopause and a variable time leading up to the last menses called the perimenopause.

Menopause and Perimenopause

Menopause literally refers to the last menstrual period. The exact time of menopause is usually determined in retrospect; that is, 1 year without menses. **In most women, menopause occurs between the ages of 50 and 55 years, with an average age of 51.5 years,** but some have their menopause before the age of 40

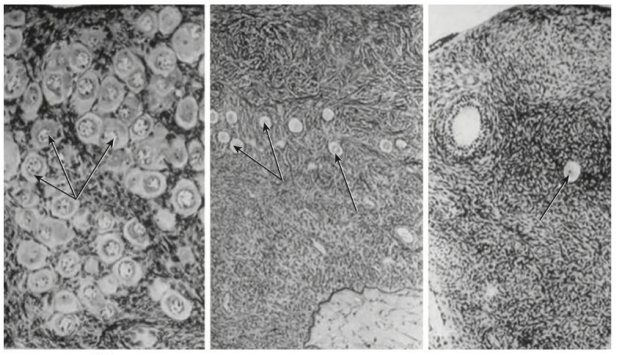

FIGURE 35-1 Histologic illustration of the density of oocytes *(arrows)* from birth to menopause. Note the abundance of eggs at birth and only an occasional one at or near menopause.

TABLE 35-1
INCREASING LIFE EXPECTANCY IN WOMEN, 1900-2015

Year	Age
1900	48 yr
1950	72 yr
2000	79 yr
2015	>80 yr

(premature menopause), whereas a few may menstruate until they are in their 60s.

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. Figure 35-1 illustrates the decreasing density of oocytes from birth until age 50 years. Most women ovulate about 400 times between menarche and menopause and during this time, nearly all other oocytes are lost through atresia. When the oocytes either have all ovulated or become atretic, the ovary becomes minimally responsive to pituitary gonadotropins, the ovarian production of estrogen and progesterone ends, and ovarian androgen production is reduced. These hormonal alterations often result in unpleasant and even harmful physical, psychological, and sexual changes in postmenopausal women, which can have a negative impact on their quality of life.

Menopause rarely occurs as a sudden loss of ovarian function. **For some years before menopause, the ovary begins to show signs of impending failure.** Anovulation becomes common, with resulting unopposed production of estrogen and irregular menstrual cycles. Occasionally, heavy menses, endometrial hyperplasia, and increasing mood and emotional changes may occur. In some women, hot flashes (or flushes) and night-sweats begin well before the last menses. **These perimenopausal symptoms may occur 3 to 5 years before there is complete loss of menses and postmenopausal levels of hormones are reached.**

Some women may suffer a more abrupt loss of estrogen. This usually occurs following a surgical intervention that removes or damages the ovaries or their blood supply or occasionally, following chemotherapy or radiotherapy for cancer. Women who are overweight may continue to produce estrogen indirectly in substantial amounts for many years after menopause. **Androstenedione from the ovary and the adrenal gland is converted in peripheral fat tissues to estrone, which is then capable of maintaining the vagina, skin,**

and bone in reasonable cellular tone and reducing the incidence of flashes. Although this unopposed estrogen may be beneficial to women in terms of symptom control, it is also responsible for the increased incidence of endometrial or breast cancer among obese women. It is important that all postmenopausal women have regular breast examinations and, if abnormal vaginal bleeding occurs, endometrial sampling.

PREMATURE MENOPAUSE

Women who reach menopause before the age of 40 years are said to have premature menopause or premature ovarian failure. Other causes of premature ovarian failure include abnormal karyotypes involving the X chromosome, the carrier state of the fragile X syndrome, galactosemia, and autoimmune disorders that may cause failure of a number of other endocrine organs.

Ovarian Senescence and Hormonal Changes

The ovary produces a sequence of hormones during a normal menstrual cycle. Under the influence of luteinizing hormone (LH), cholesterol from the liver is used to produce the androgens, androstenedione and testosterone, in the theca cells of the ovarian follicle. They, in turn, are converted in the granulosa cells immediately surrounding the oocytes into estrogen. Following ovulation, the luteal cells (luteinized granulosa cells) manufacture and secrete progesterone as well as estrogen. The synthesis of these sex hormones depends on the presence of viable follicles and ovarian stroma and the production of follicle-stimulating hormone (FSH) and LH in adequate amounts to induce their biosynthetic activity.

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. In some women, the amount of postmenopausal estrogen may be considerable.

ANDROGENS

Women normally produce significant quantities of androgens by the metabolic conversion of cholesterol to both androstenedione and testosterone. Although the major portion of androgen is aromatized to estrogen, some androgen circulates. After menopause, there is a decrease in the level of circulating androgens, with androstenedione falling to less than half that found in normal menstruating young women, whereas testosterone gradually diminishes over about 3 to 4 years. **Even though postmenopausal women produce less androgens, they tend to be more sensitive to them because of the lost opposition of estrogen.** This sometimes results in unwelcome changes such as excessive facial hair growth and decreased breast size.

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.

GONADOTROPINS

The two gonadotropins, LH and FSH, are produced in the anterior pituitary gland. **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. The higher central nervous system neurotransmissions responsible for the increased pulsatile release of GnRH (and subsequent gonadotropin release) are also thought to have parallel effects elsewhere in the hypothalamus, especially in the body temperature control region. This leads to the sudden induction of increased skin blood flow and perspiration, the hot flash, which is so characteristic of the menopause. Typical levels of FSH in postmenopausal women are greater than 40 IU/L.

Clinical Manifestations

Loss of estrogen is associated with urogenital atrophy and osteoporosis (Table 35-2). Although postmenopausal women have a higher incidence of heart disease and of cancer, the relationship between these adverse events and reduced endogenous estrogen production, as well as the effects of hormonal therapy on these adverse events, remains controversial.

GENERAL SYMPTOMS

About 85% of women experience hot flashes as they pass through the climacteric, but about half of these women are not seriously disturbed by them. For about

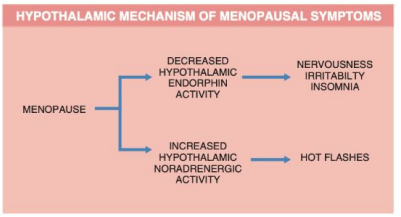

FIGURE 35-2 Combined effect of decreased endorphins and increased adrenergic activity at the time of decreasing estrogen (menopause and perimenopause). Although the exact mechanism of the menopausal (perimenopausal) hot flash is not known, evidence suggests that hypothalamic norepinephrine acts as a trigger for this temporary event that results in disordered thermoregulation. Core body temperature may actually decrease slightly at the time of the hot flash, with skin temperatures increasing from 2 to 10 degrees over a short period of time.

TABLE 35-2
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)

40% of affected women, the hot flash is a most distressing experience. Flashes may occur as frequently as every 30 to 40 minutes, but more often they occur about 8 to 15 times daily. There may be associated sweating, dizziness, and palpitations. Often, the hot flash may awaken the woman at night and impair the quality of her sleep. Although the exact mechanism that triggers a hot flash is not known, they are probably caused by excessive noradrenergic activity. Studies show a significant rise in plasma norepinephrine before most hot flashes. There is also a related decrease in endorphin levels. **As a consequence of frequent flashes at night, the woman may experience increased fatigue, and irritability.** Figure 35-2 illustrates the combined effect of decreasing endorphins and increasing adrenergic activity on sleep-depriving hot flashes and mood.

Women are often given sedatives, hypnotics, or psychotropic drugs in an attempt to relieve the symptoms caused by deficiency of estrogen. **Some complain of confusion, loss of memory, lethargy, and inability to cope, as well as mild depression.** In addition, the hypoestrogenic state may be associated with a **loss of the sense of balance,** possibly resulting in an increased risk of falls. Many of these symptoms improve considerably when appropriate hormonal therapy (estrogen and a progestin or estrogen alone) is initiated. **Severe or even sustained moderate depression should never be attributed solely to climacteric hormonal changes.**

UROGENITAL SYMPTOMS

The vagina is very sensitive to estrogen, and it responds to this hormone by producing a thick moist epithelium with an acidic secretion (pH of about 4.0). The absence of estrogen results in a thin, dry epithelium with an alkaline secretion (pH > 7.0). **The postmenopausal vagina shrinks in diameter and splits and tears easily.** Atrophic vaginitis may result in unpleasant dryness, discharge, and severe dyspareunia.

Because the bladder and vagina are derived from the same embryologic tissue, it is not surprising that **some postmenopausal women also complain of urinary symptoms such as frequency, urgency, nocturia, and urinary incontinence.** Hormonal therapy markedly improves atrophic vaginitis but cannot prevent or treat urinary incontinence.

Osteoporosis

Remodeling of bone continues throughout life, but with estrogen deprivation, osteoclastic activity far exceeds the osteoblasts' ability to lay down bone. Under these conditions, osteopenia and finally osteoporosis occur. Figure 35-3 compares normal bone and bone with severe osteopenia. An early clinical sign of osteoporosis is a loss of height greater than 1.5 inches because of vertebral compression fracture, which may

Reference

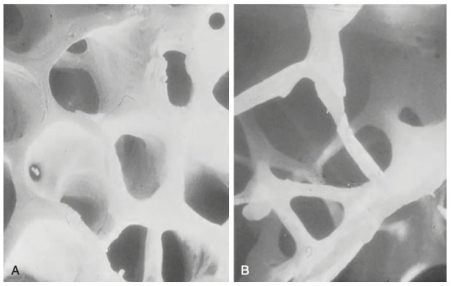

FIGURE 35-3 The appearance of normal bone (A) and bone with severe osteopenia (B) as seen on a dual-energy x-ray absorptiometry (DEXA) scan. Osteopenic bone is much more susceptible to fracture and deformity.

BOX 35-1

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

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

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be accompanied by acute and chronic back pain. Other important osteoporotic events include wrist and hip fractures. **Ten to 15 years after menopause, women begin to fracture their bones at a rate exceeding that of men by a factor of threefold to fivefold.** About 200,000 women break a hip each year in the United States, and the annual cost of osteoporotic fractures and their complications has been estimated to be in excess of $14 billion. The earlier women are deprived of estrogen in their lives, the earlier osteoporotic bone loss begins. **Most calcium is lost from trabecular bone, and as a consequence, the spinal column and femoral neck are the bones most commonly fractured.** Box 35-1 **lists the known risk factors for osteoporosis in women.**

The American College of Obstetricians and Gynecologists (ACOG) recommends bone mineral density screening for osteoporosis in women with risk factors (Box 35-2**) who are under the age of 65 years, and in women without risk factors who are 65 years or older.** The preferred screening modality is dual-energy x-ray absorptiometry measurements of the total hip and spine. The results of these studies are expressed in T scores, which are standard deviations (SDs) from the peak bone mineral density of normal young adults. Osteoporosis is defined as a T score of less than –2.5 SD. Drug therapy is recommended in postmenopausal women with a T score of less than –2.5 SD or a T score of –2.0 to –2.5 SD plus an additional risk factor for fracture. If bone mineral density measurements are used to monitor the effects of drug therapy, they should be repeated after at least 2 years of treatment.

Reducing the risk of osteoporotic fracture entails several changes of diet and lifestyle. **Postmenopausal women should consume 1200 to 1500 mg of calcium and 400 to 600 U of vitamin D daily, which are contained in two to three portions of dairy products.** Those who cannot or will not include dairy products in their meals should be encouraged to use calcium and vitamin D supplements. Excessive supplementation should be discouraged to avoid renal complications. **Walking and weight-bearing exercises both help to increase bone mineral mass and reduce the risk of fracture-causing falls.** The risk of falling can be reduced further by eliminating throw rugs in the home, placement of handrails in the bathroom, and minimizing the use of alcoholic beverages. **Smoking should be discouraged** for many other health reasons in addition to prevention of osteoporosis. Patients receiving replacement therapy for hypothyroidism should be tested to ensure that they are not receiving an excessive (and potentially bone density–depleting) dose.

Pharmacologic treatments for osteoporosis include estrogen (with or without a progestin), selective estrogen receptor modulators (SERMs), biphosphonates, calcitonin, and parathyroid hormone. Data from the Women's Health Initiative (WHI) study demonstrated that combined estrogen/progestin therapy reduced postmenopausal total fractures by 24% compared to controls, with a 34% reduction of hip fractures. This translates to a reduction of the hip fracture rate from 15 to 10 cases per 10,000 postmenopausal women per year. **SERMs, such as raloxifene, have been found to be beneficial for the prevention of vertebral fractures,** but data are lacking regarding the prevention of hip fracture. **Biphosphonates, such as alendronate, can effectively prevent and, at higher doses, treat osteoporosis** without requiring continued usage. In general, biphosphonates have few adverse side effects. However, they must be taken properly (empty stomach, upright position, and with a large glass of water) to minimize the risks of esophagitis and esophageal ulcers. **Both calcitonin and parathyroid hormone are second-line adjunctive treatments for osteoporosis.**

Ovarian Hormone Therapy

For over four decades, ovarian hormonal therapy (HT), called hormone replacement therapy (HRT) in the past, had been advocated for an expanding set of prophylactic indications. Initially, hormonal therapy was provided for the treatment of hot flashes and the symptoms of genitourinary atrophy. Later, increasing evidence revealed that prevention of osteoporosis was a specific benefit of ovarian hormonal therapy.

A number of large observational cohort and case–controlled studies had suggested ovarian hormonal therapy might prevent or delay the onset of arteriosclerotic heart disease and Alzheimer disease through a number of diverse mechanisms. On the other hand, observational studies had raised concerns about associated risks of venous thrombosis/pulmonary embolism and breast cancer.

Randomized controlled trials tend to minimize the biases of observational studies. However, they are difficult and time-consuming to do when the conditions being observed are relatively uncommon and all women who are studied are volunteers. In an attempt to control for most of the biases inherent in observational studies, the Women's Health Initiative (WHI) study was undertaken with a goal of sorting out the risks and benefits of ovarian hormonal therapy. Nearly 17,000 women were entered into one arm of the study comparing a combined preparation of conjugated estrogens and medroxyprogesterone acetate with placebo. There was also an estrogen only arm in the WHI study. After 5 years of follow-up, the combined ovarian hormonal arm was halted in July of 2002. **The previously reported protection from osteoporotic fracture was confirmed by the WHI study in all arms. In addition, a 37% reduction in the rate of colorectal cancer was found.** This would result in six fewer cases of colorectal cancer (10 vs. 16) per 10,000 women per year. **Combined ovarian hormone use, however, was found to increase the risks for coronary artery disease events (by 29%), stroke (by 41%), thromboses (by 100%), and breast cancer (by 26%).** Although most of the risks increased after 1 to 2 years of use, increased risk of breast cancer became apparent only after 4 years of use. **There was no significant increase in death rates between treatment and placebo groups.** Contrary to several previous studies, the WHI found an overall harmful rather than protective effect on cognitive decline and dementia.

In February 2004, the estrogen-only arm of the WHI was halted because of a significantly increased risk of stroke. It confirmed a protective effect against hip fracture, although none of the other significant findings in the combined arm were found to be present. **The risk of breast cancer was not increased in the estrogen-only arm of the WHI study.**

The WHI study has been widely criticized for examining women who, for the most part, were well past the age of menopause when they were entered into the study (average age 63). This was neither intentional nor desirable, but occurred because the study group was necessarily made up of those women who volunteered to participate in the study, and as a group they were older. Laboratory/animal studies have shown an atherosclerotic protective effect of estrogen after gonadectomy, when begun immediately. **Additional analyses of WHI data have failed to confirm increased coronary artery events in those subjects who began therapy less than ten years after the menopause.**

Although definite limitations of the WHI study have been identified, **the findings have had a significant effect on clinical practice, and the routine use of HT after the menopause is currently viewed with caution.**

The general consensus now is that combined ovarian hormonal therapy is indicated primarily for the relief of significant menopausal symptoms such as frequent hot flashes, genitourinary discomfort, and other quality-of-life issues. The length of treatment should be minimized, depending on the individual patient's clinical course and preference, and after informed consent. On the other hand, most experts recommend that younger hypoestrogenic women, such as those who undergo premature menopause or bilateral oophorectomy, should take HT.

A very large observational cohort study, the **Million Women Study (MWS)** also addressed the risks and benefits of hormonal therapy after menopause (age 50 years). Over one million women were enrolled in the United Kingdom, and long-term follow-up continues. After more than 4 years of follow-up, the MWS has also reported an increased breast cancer risk with hormonal therapy with and without progestin. Box 35-3 summarizes the goals and findings of the MWS.

The need for prevention and treatment of osteoporosis should be determined by bone densitometry studies rather than ovarian status, per se. **Biphosphonates or raloxifene should be regarded as the first line of treatment in the absence of concomitant significant menopausal symptoms.**

Management of Ovarian Hormonal Therapy

Women who still have a uterus should not be given unopposed estrogen for the treatment of menopausal symptoms because of the high risk of developing endometrial hyperplasia and endometrial adenocarcinoma. Concurrent progestin is protective for endometrial disease and may be given for 12 days per month or for 14 days per quarter with predictable uterine bleeding on withdrawal. **Patients who seek complete amenorrhea may use continuous combined estrogen/progestin** (e.g., conjugated estrogens, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg daily). This latter regimen is characterized by unpredictable breakthrough bleeding, with a majority of patients achieving amenorrhea within a year. The estrogen-only arm of the WHI study (with lower breast cancer risk) suggested that progestins may be the more important element of risk for breast cancer in patients receiving hormonal therapy, so thought should be given to minimizing exposure to progestins.

There has been a recent trend toward the use of so-called bio-identical medications for hormonal treatment after menopause. This can be accomplished using U.S. Food and Drug Administration–approved estrogen patches (bio-identical to 17-beta estradiol) with progesterone suppositories (bio-identical to progesterone) added for women who still have a uterus. This method also avoids the oral route of delivery that has been shown to increase potentially harmful hepatic effects such as coagulation abnormalities. The use of a progestin-releasing intrauterine device (Mirena) has been suggested as a way to control irregular bleeding and protect the endometrium from the effect of unopposed estrogen.

Severe continuous bleeding or intermittent bleeding after more than 4 months of hormonal therapy should prompt a search for uterine pathology. Optimization of menopausal symptom control, although reducing adverse side effects of therapy, may be accomplished by using the lowest effective dose and by substituting continuous transdermal estrogen for oral preparations of estrogen when symptoms are not adequately controlled. When the patient's main concerns are with genitourinary symptoms, vaginal estrogen cream, tablets, or rings may be used on an "as needed" basis without necessarily adding a progestin.

BOX 35-3

MILLION WOMEN STUDY

Study Goals

Recruit and study (with follow-up) at least one million women (aged 50 years and older) in the United Kingdom (UK) between 1993 and 2004, who are taking estrogens and progestogens with particular emphasis on breast cancer risk.

Study Design

Observational cohort study with 70% of those recruited participating in and completing the questionnaire and screening program.

Study Findings

Breast Cancer

Study included estrogen and progestogen in combination; estrogen only; and included oral, transdermal, and implanted hormones whether they were given continuously or sequentially.

Past users of hormones were not at increased breast cancer risk.

Current users of combination hormones (estrogen and progestogen) had a 2-fold increased risk of breast cancer.

Current users of estrogen only had a 1.3-fold increase in breast cancer risk.

Study authors estimated that 20,000 extra cases of breast cancer occurred between 1993 and 2004 in the UK because of hormone use.

Endometrial Cancer

Study confirmed that women with a uterus who used estrogen only had an increased risk of endometrial cancer and that the risk of endometrial cancer may be reduced in women taking estrogen and a progestogen in combination.

Ovarian Cancer

Study found no increased risk of ovarian cancer in former users of hormones. Current users have a 1.2-fold increase in ovarian cancer risk. Putting this risk into perspective, the study concluded that there would be one extra case of ovarian cancer for every 2500 women taking hormones and one extra death from ovarian cancer in 3300 hormone users over five years.

Selective Estrogen Receptor Modulators

The biologic effect of estrogenic substances is mediated by the translocation of a ligand-estrogen receptor complex into the nucleus, where various estrogen-responsive genes are activated or repressed. **At least two estrogen receptors, α and β, are presently known to exist.** They exert different biologic effects and exist in different proportions in different tissues. In addition, different ligands bound in a complex with the same receptor manifest different biologic activity. The use of SERMs attempts to take advantage of these facts to produce some, but not all of the biologic effects of native estradiol. SERMs in use today include clomiphene, tamoxifen, and raloxifene. Unlike estradiol and other SERMs in current use, **raloxifene does not stimulate endometrial or breast duct epithelial proliferation.** However, **raloxifene does seem to reduce osteoclastic activity and prevent osteoporosis (at least in the spine).** Hence, raloxifene has some of the bone-sparing effect of estradiol without incurring the risk of endometrial hyperplasia/carcinoma. It may actually prove to be protective against breast cancer in the same way as tamoxifen. However, **raloxifene appears to worsen rather than ameliorate vasomotor symptoms.** Perhaps new SERMs will be discovered in the future that will provide symptom relief as well as skeletal protection.

Lifestyle Changes and Alternative Treatments for the Climacteric

Increasingly, an emphasis is being placed on the importance of lifestyle changes as a strategy for decreasing the inevitable effects of the aging process. **The most important change that anyone can make 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,** especially in women with diabetes, hypertension, or significantly elevated blood lipids. All counseling about the effects of menopause should include a discussion of these issues, along with any possible medical therapies. In particular, **the statin drugs are important for postmenopausal women with an unfavorable lipid profile, as they significantly reduce the risk of cardiovascular disease and serendipitously protect against osteoporosis.**

Phytoestrogens (plant products that are functionally or structurally similar to estrogen) and herbal substances have been marketed to consumers as the "natural" alternative to traditional hormonal therapy for the symptoms of perimenopause and menopause. Women should be made aware that even placebos may decrease some of the symptoms, such as hot flashes, and that some herbal preparations have been shown to be ineffective or even harmful. Also, patients should be made aware of the less rigorous evaluation and regulation that these products undergo.

With proper counseling, appropriate screening, and professional care, the signs, symptoms, and sequelae of the climacteric can be managed successfully. Short-term use of hormonal therapy for symptom control, healthy lifestyle changes, appropriate monitoring, and medical or surgical interventions when necessary should provide a safe and effective level of care.

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Good Luck!

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