Al-Mustaqbal University College
Department of Pharmacy
5th Stage
Applied therapeutics II
Lecture: 6

Hormone Replacement Therapy

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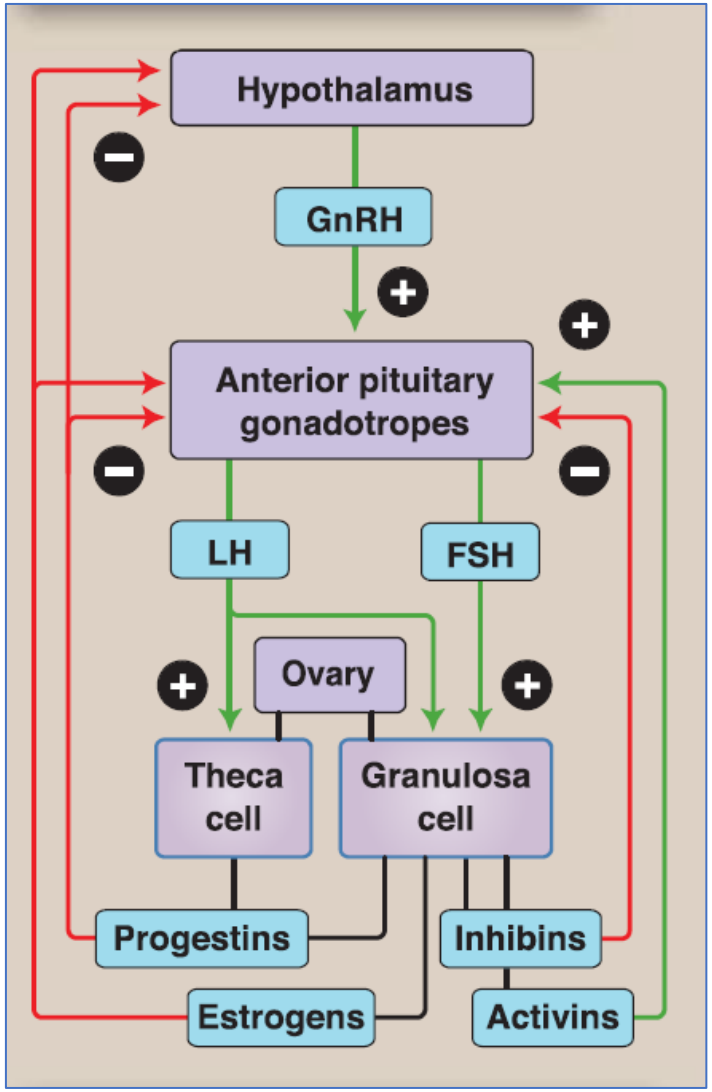
INTRODUCTION

- **Perimenopause begins** with the **onset of menstrual irregularity** and **ends 12 months after the last menstrual period**, which marks the **beginning of menopause**.
- **Menopause** is the **permanent cessation** of menses caused by the **loss of ovarian follicular activity**.
- Females spend about **40% of their lives** in **postmenopause**.

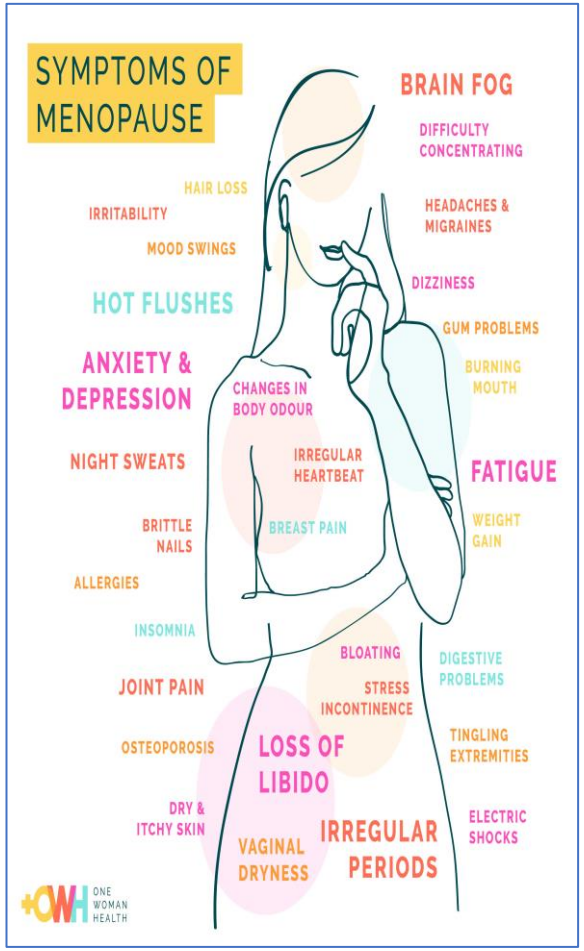
PATHOPHYSIOLOGY

- The **hypothalamic–pituitary–ovarian axis (HPO)** controls **reproductive physiology**.
- **FSH** and **LH**, produced by the **pituitary** in response to **GnRH** from the **hypothalamus**, regulate **ovarian function**.
- **Gonadotropins** are also influenced by **negative feedback** from the **sex steroids** estradiol (produced by the **dominant follicle**) and progesterone (produced by the **corpus luteum**).
- **Other sex steroids** are androgens, primarily testosterone and androstenedione, secreted by the **ovarian stroma**.
- As women **age**, circulating **FSH progressively rises**, and **ovarian inhibin-B** and **anti-Mullerian** hormone **declines**.
- In **menopause**, there is a **10-15 fold increase** in circulating **FSH**, a **4-5 fold increase** in **LH**, and a greater than **90% decrease** in circulating **estradiol** concentrations.



Clinical Presentation

- **Vasomotor symptoms** (hot flushes and night sweats), sleep disturbances, depression, anxiety, poor concentration and memory, vaginal dryness and dyspareunia, headache, sexual dysfunction, and arthralgia.
- Individuals of **different races/ethnicity** experience vasomotor **symptoms differently**.
- **Signs** include **urogenital atrophy** in **menopause** and **dysfunctional uterine bleeding** in **perimenopause**.
- **Additionally**, **loss of estrogen production** results in metabolic changes; increase in central abdominal fat; and effects on lipids, vascular function, and bone metabolism.



DIAGNOSIS

- **Menopause** is determined **retrospectively after 12 consecutive months of amenorrhea**.
- **FSH on day 2 or 3** of the menstrual cycle **greater than 10–12 IU/L** indicates **diminished ovarian reserve**.
- The diagnosis should include a **comprehensive** medical history and physical examination, complete blood count, and measurement of serum FSH.
- **Altered thyroid function** and **pregnancy** must be **excluded**.

TREATMENT

- The goals are to **relieve** symptoms, **improve** quality of life, and **minimize** medication adverse effects.

NONPHARMACOLOGIC THERAPY

- **Mild vasomotor and/or vaginal symptoms** can often be **alleviated by** lowering the room temperature; decreasing intake of caffeine, spicy foods, and hot beverages; smoking cessation; exercise; and a healthy diet.
- **Mild vulvovaginal symptoms** may be adequately **managed** with nonhormonal lubricants and moisturizers.

PHARMACOLOGIC THERAPY

- The **decision** to **use** menopausal hormone therapy (**MHT**) and the **type of formulation** used must be **individualized** based on several factors, including personal preference, age, menopause onset, the severity of menopausal symptoms, and MHT associated risks.
- MHT remains the **most effective** treatment for **moderate and severe** vasomotor symptoms, impaired sleep quality, and vulvovaginal symptoms of menopause.
- When **urogenital symptoms**, such as vaginal dryness and dyspareunia, are **the only menopausal complaint**, intravaginal estrogen cream, tablet, or ring **should be considered before oral therapy**.
- **Intravaginal** estrogen **minimizes systemic absorption** and is **more effective for vaginal symptoms** than **oral therapy**.
- Intravaginal estrogen **reduces the risk** of recurrent urinary tract infections and may **improve urge incontinence** and **overactive bladder**.
- **Ospemifene**, a **selective estrogen receptor modulator**, is another option.

PHARMACOLOGIC THERAPY

TABLE 31-1 FDA-Approved Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins

Indications	
For systemic use	Treatment of moderate-to-severe vasomotor symptoms (ie, moderate-to-severe hot flashes)
For intravaginal use (low systemic exposure)	Treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy (ie, moderate-to-severe vaginal dryness, dyspareunia, and atrophic vaginitis)
Contraindications	
Absolute contraindications	Undiagnosed abnormal genital bleeding
	Known, suspected, or history of cancer of the breast
	Known or suspected estrogen- or progesterone-dependent neoplasia
	Active deep vein thrombosis, pulmonary embolism, or a history of these conditions
	Active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction)
	Liver dysfunction or disease

PHARMACOLOGIC THERAPY

TABLE 31-1 FDA-Approved Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins

Relative contraindications	Elevated blood pressure
	Hypertriglyceridemia
	Impaired liver function and past history of cholestatic jaundice
	Hypothyroidism
	Fluid retention
	Severe hypocalcemia
	Ovarian cancer
	Exacerbation of endometriosis
	Exacerbation of asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, and hepatic hemangioma

PHARMACOLOGIC THERAPY

- **Estrogen only** therapy may **decrease heart disease** and all-cause **mortality** in **50-59 year old** females with a history of **hysterectomy**.
- **MHT** is **effective and appropriate** for prevention of **osteoporosis related fractures** in recently menopausal individuals at risk.
- In patients with an **intact uterus**, MHT consists of an **estrogen plus a progestogen** or **estrogen agonist/antagonist** (e.g. **bazedoxifene**).
- In patients who have undergone **hysterectomy**, **estrogen** therapy is given **unopposed by a progestogen**.
- **Concomitant progestogen** therapy is **unnecessary** when **low dose vaginal estrogen** is used.
- Individuals with **vasomotor symptoms** taking **MHT** have **better mental health and fewer depressive symptoms** compared with those receiving placebo, **but MHT** may **worsen the quality of life** in individuals **without vasomotor symptoms**.

Estrogens

- The **oral and transdermal routes** are used most **frequently** and are considered **equally effective**.
- **Conjugated equine estrogens** are composed of estrone sulfate (50%–60%) and other estrogens such as equilin and 17α-dihydroequilin.
- **Estradiol** is the **predominant** and **most active form** of **endogenous** estrogens.
- Given **orally**, it is **metabolized** by the intestinal mucosa and liver, and resultant **estrone** concentrations are **3-6 times** those of **estradiol**.
- **Ethinyl estradiol** is a **semisynthetic** estrogen that has **similar activity** following **oral** or **parenteral** administration.
- **Nonoral estrogens**, including transdermal, intranasal, and vaginal products, to **avoid first pass** metabolism and result in a **more physiologic estradiol : estrone ratio**.
- **Transdermal estrogen** is also **less** likely to **increase** sex hormone–binding globulin, triglycerides, blood pressure, or C reactive protein levels.

Estrogens

- **Transdermal** dosage forms may also have a **lower risk** for deep vein thrombosis, stroke, and myocardial infarction.
- **Variability** in absorption is **common** with **percutaneous preparations** (ie, gels, creams, and emulsions).
- **Vaginal creams, tablets, and rings** are used for treatment of **urogenital atrophy**.
- **Most** tablets and rings provide **local estrogen**, but **Femring** is designed to **achieve systemic estrogen** concentrations and is indicated for **moderate to severe vasomotor symptoms**.
- New evidence indicates that **lower doses of estrogens** are effective in **controlling** postmenopausal symptoms and reducing bone loss.
- Topical gels, creams, and sprays are also available in **low doses**.
- The **lowest effective dose** should be used.

Estrogens

- **Adverse effects** of estrogen include nausea, headache, **breast tenderness**, and heavy bleeding.
- More **serious adverse effects** include increased risk for **stroke, venous thromboembolism (VTE), and gallbladder disease**.
- **Transdermal** estrogen is **less likely** to cause **breast tenderness, gallbladder disease, and deep vein thrombosis**.
- **Risk** of VTE and stroke **increases** with **oral MHT** containing **estrogen**, **but** the absolute risk is **low below 60 years** of age.
- **Transdermal** MHT and **low dose oral** estrogen therapy appear to have a **lower risk** of VTE and stroke compared to standard dose oral estrogen regimens.
- **MHT** is **contraindicated** in individuals with a personal **history of breast cancer**.

Estrogens

- The **risk of MHT related breast cancer** appears to be **associated** with the **addition of progestogen** to **estrogen** after **3 years** of combined use.
- **Combined oral MHT** does **not increase endometrial cancer risk** compared with placebo.
- **But estrogen alone** given to individuals with an **intact uterus** significantly **increases uterine cancer risk**.
- **Postmenopausal** individuals **65 years or older** taking **estrogen plus progestogen** therapy had **twice the rate of dementia**, including Alzheimer disease, than those taking placebo.
- **Combined** therapy **did not prevent** mild cognitive impairment.
- The **estrogen alone** arm showed **similar findings**.

Progestogens

- In individuals who have **not undergone hysterectomy**, a **progestogen or tissue selective estrogen complex** (estrogen/bazedoxifene) **should be added** for endometrial protection.
- **Medroxyprogesterone acetate, Micronized progesterone and Norethindrone acetate** are progestogens **approved** for menopausal symptom treatment.
- **Adverse effects** of progestogens include irritability, headache, mood swings, fluid retention, and sleep disturbance.

Methods of Administration

- **Methods of administration include the following:**

1. Cyclic (Sequential) estrogen progestogen:

- It results in scheduled vaginal withdrawal **bleeding** in approximately **80%–90% of patients**.
- The **progestogen** is administered **12–14 days** of the 28day cycle.

2. Continuous combined estrogen progestogen:

- Itcauses **endometrial atrophy** but **prevents monthly bleeding**, which is **preferable**, although it may **initially** cause **unpredictable** spotting or bleeding.
- Use of **conjugated estrogens** (0.625 mg/day) plus **medroxyprogesterone acetate** (2.5 mg/day) lead to a **decreased risk of endometrial cancer**.

Methods of Administration

3. Intermittent combined estrogen progestogen (continuous pulsed)

- It consists **of 3 days of estrogen** therapy **alone**, followed by **3 days of combined estrogen** and **progestogen**, repeated **without interruption**.
- It causes **fewer adverse effects** than regimens with higher progestogen doses and **lowers the incidence** of **uterine bleeding**.

Compounded Bioidentical Hormone Therapy (CBHT)

- CBHTs are **hormone therapy formulations custom prepared** (ie, compounded) for individual patients, often involving the **use of measuring and monitoring hormone** levels in **blood** and/or other body fluids such as **saliva**.
- **Hormones commonly used** in CBHT include estrone, estradiol, estriol, progesterone, testosterone, DHEA, and thyroid hormone.
- Bioidentical hormones appear to **carry the same risks** as traditional hormone therapy products.
- Use is **recommended only** when there is a **medical need** for an unusual dosing regimen or ingredients or when **patients have allergies** to FDA approved therapies.

Estrogen Alternatives for the Treatment of Hot Flashes

- Some clinicians consider **selective serotonin reuptake inhibitors** (eg, paroxetine, fluoxetine, citalopram, escitalopram) or **serotonin norepinephrine reuptake inhibitors** (eg, venlafaxine and desvenlafaxine) to be **first line agents**.
- **Clonidine** can be **effective**, but **adverse effects** are often problematic (eg, sedation, dry mouth, hypotension).
- **Gabapentin** has beneficial effects for **reducing the frequency and severity** of vasomotor symptoms but **adverse effects** may limit dosing.
- It may be a **reasonable option** for those with **disrupted sleep** and **hot flashes** when administered in the **evening**.

Androgens

- **Testosterone** use is **controversial**, but use with or without estrogen, may **improve** the quality of the **sexual experience** in postmenopausal individuals.
- **Absolute contraindications** to androgen therapy include **pregnancy or lactation** and known or suspected **androgen dependent neoplasia**.
- **Adverse effects** include virilization, fluid retention, and adverse lipoprotein lipid effects, which are more likely with **oral administration**.
- **Evidence** on the **efficacy and safety** of **testosterone** in **females is lacking**.
- **Dehydroepiandrosterone (DHEA)** is a **precursor hormone** in the synthesis of estrone, estradiol, and testosterone.
- **Intravaginal DHEA (Prasterone)** has **FDA approval** for the treatment of **moderate to severe dyspareunia**.

Selective Estrogen Receptor Modulators (SERMs)

- SERMs are **nonsteroidal compounds** that act as **estrogen agonists** in some tissues such as **bone** and as **estrogen antagonists** in other tissues such as **breast** through **high affinity** binding to the **estrogen receptor**.
- **Tamoxifen** is an **antagonist** in **breast tissue** and an **agonist** on the **bone and endometrium**.
- **Raloxifene** is approved for **prevention and treatment of postmenopausal osteoporosis** and **reduction in risk of invasive breast cancer**.
- The **third generation** SERM, **bazedoxifene**, is used in **conjunction with conjugated estrogen**, and is FDA approved for **moderate to severe vasomotor symptoms** and **prevention of osteoporosis**.
- **Ospemifene** is approved for **dyspareunia** from menopausal vulvar and vaginal atrophy.

Selective Estrogen Receptor Modulators (SERMs)

- It has a boxed warning for **increased risk of endometrial cancer** in patients with a uterus who use **ospemifene without a progestogen** to reduce endometrial hyperplasia.
- Depending on tissue selectively, the **SERMs are associated with hot flashes and leg cramps**.
- They can also **increase the risk of VTE** and **stroke** similar to oral estrogen, but the degree of risk is agent specific.
- **Additional adverse effects** of **bazedoxifene** include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain.

Complementary and Alternative Agents

- **Phytoestrogens** are **plant compounds** with **estrogen like biologic activity** and relatively **weak estrogen receptor binding properties**, resulting in physiologic effects in humans.
- Although **clarity regarding**, dosing, biological activity, safety, and efficacy is needed before they can be considered as an alternative to MHT.
- Other herbals and alternative treatments that may be used include **black cohosh, dong quai, red clover leaf** (contains phytoestrogens), and **ginseng**.

EVALUATION OF THERAPEUTIC OUTCOMES

- In order to adequately **assess treatment** effect, individuals should be **encouraged to continue their MHT regimen for at least 1** month with **dosages being modified** to **balance adverse** effects and **efficacy**.
- Those receiving MHT should be seen **annually for monitoring**.

THANK YOU FOR YOUR ATTENTION