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

HORMONE THERAPY IN WOMEN (HRT)

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PERIMENOPAUSE AND MENOPAUSE

Perimenopause:

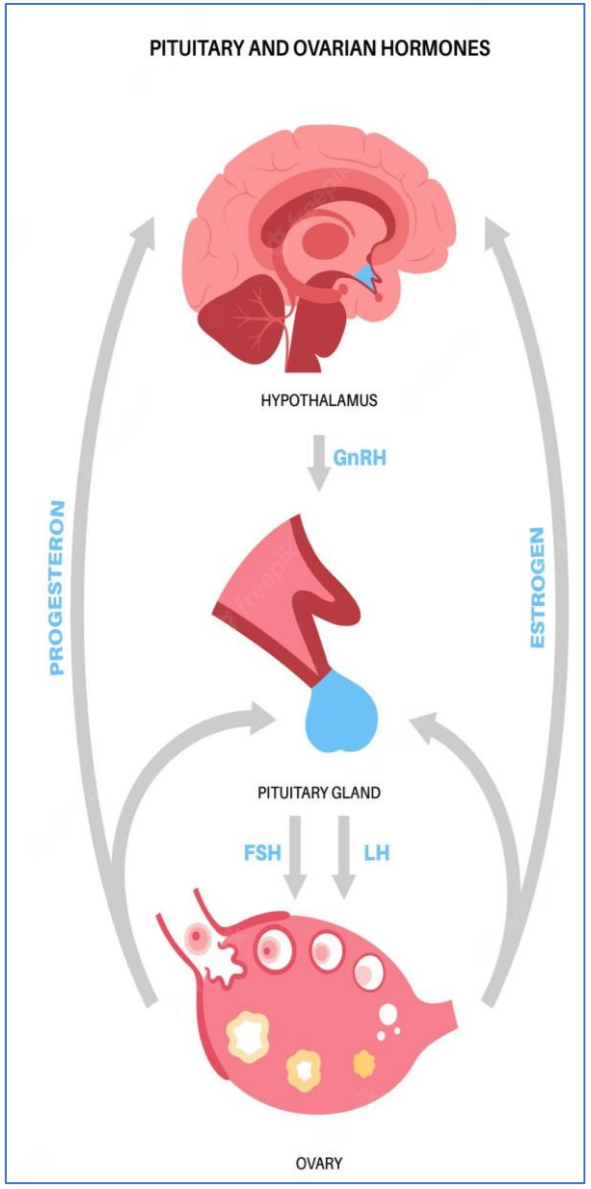
- **Perimenopause** begins with the onset of **menstrual irregularity** and ends **12** months after the **last** menstrual period, which **marks the beginning of menopause**.

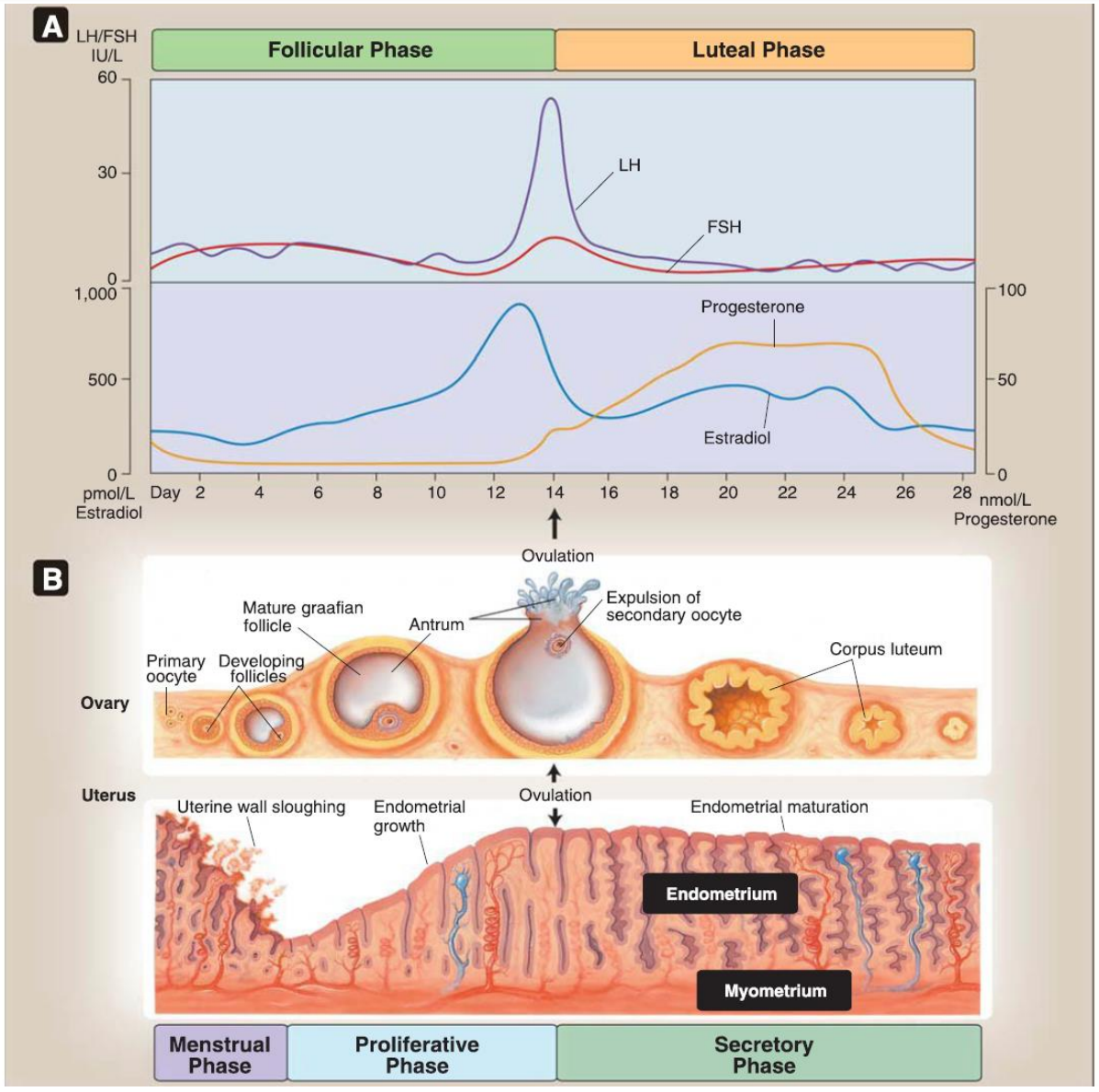
Menopause:

- **Menopause** is the **permanent cessation** of menses caused by the **loss** of **ovarian follicular activity**.
- Women spend about **40%** of their lives in postmenopause.

PHYSIOLOGY

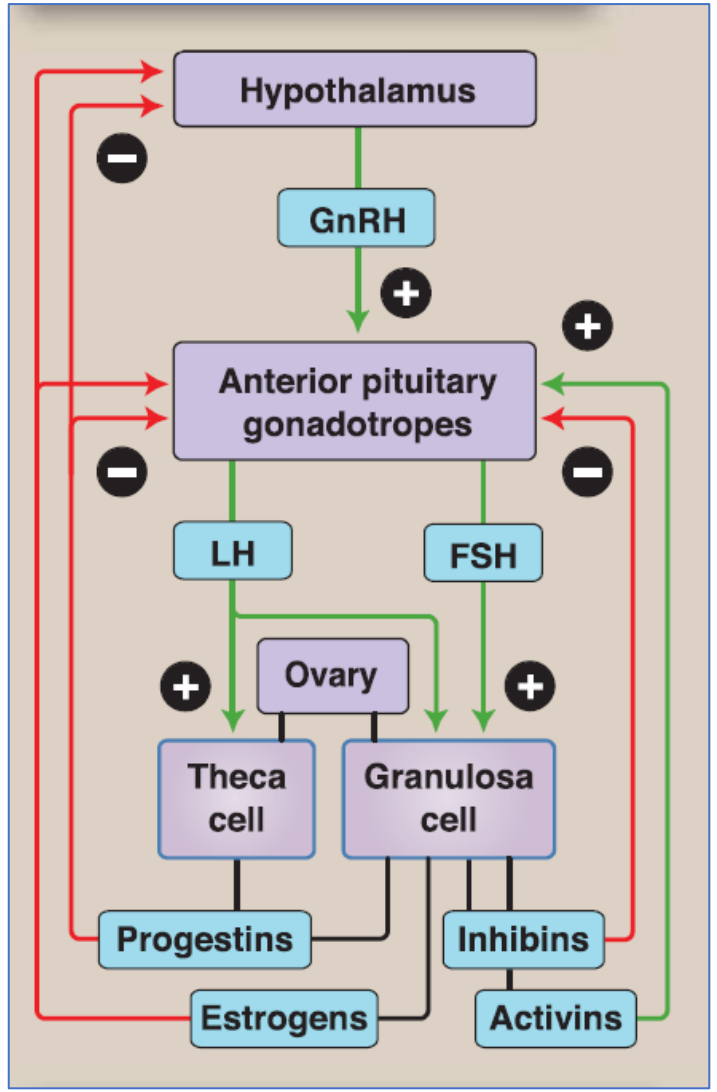
HPO axis and Physiology of Ovarian and endometrial cycle





PHYSIOLOGY

- 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.



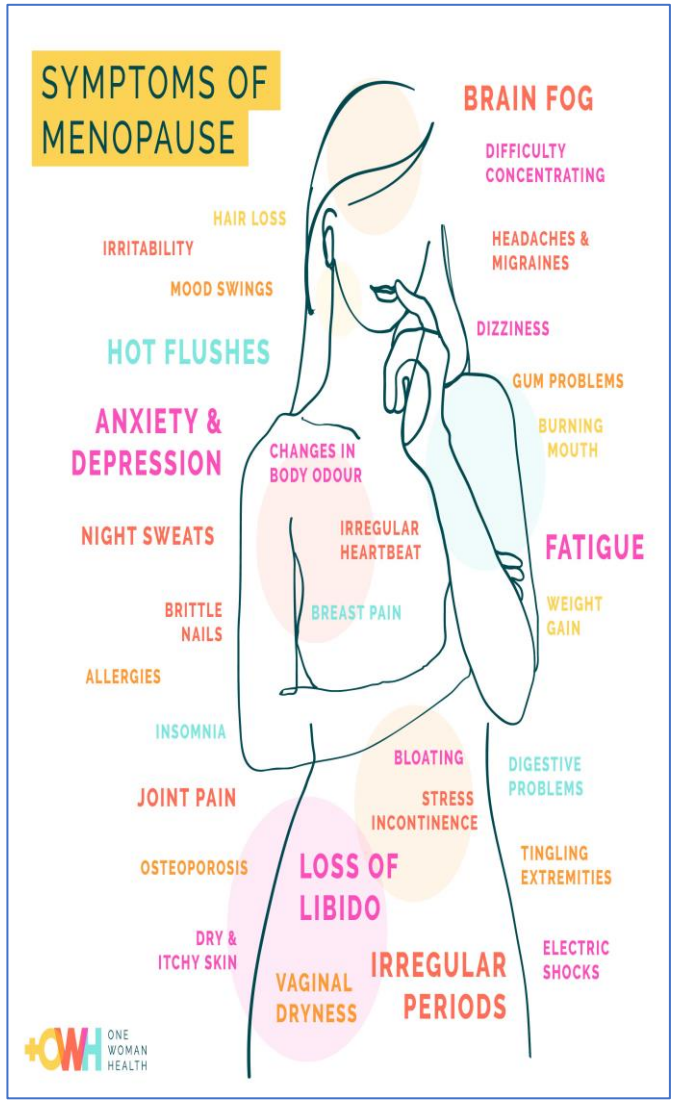
CLINICAL PRESENTATION

Symptoms of perimenopause and menopause include:

- Vasomotor symptoms (hot flushes and night sweats), sleep disturbances, depression, anxiety, poor concentration and memory, vaginal dryness and dyspareunia, headache, sexual dysfunction, and arthralgia.

Signs include:

- Urogenital atrophy in menopause and dysfunctional uterine bleeding in perimenopause [**Note:** Other potential causes of dysfunctional uterine bleeding should be ruled out].
- **Additionally**, loss of estrogen production results in **metabolic changes**; an 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** of menopause should include a **comprehensive medical history and physical examination, complete blood count, and measurement of serum FSH**.
- When the ovarian function has ceased, **serum FSH** concentrations **exceed 40 IU/L**.
- Altered **thyroid function** and **pregnancy** must be **excluded**.

TREATMENT

Goals of Treatment:

- The goals are to:
  - ✓**Relieve** symptoms
  - ✓**Improve** quality of life
  - ✓**Minimize** medication adverse effects.

NONPHARMACOLOGIC THERAPY

- **Mild vasomotor and/or vaginal symptoms** can often be alleviated by:
  - ✓Lowering the room temperature
  - ✓Decreasing the intake of caffeine, spicy foods, and hot beverages
  - ✓Smoking cessation
  - ✓Exercise
  - ✓Healthy diet
- **Mild vaginal dryness** can sometimes be relieved by **non-estrogenic vaginal creams**, but **significant vaginal dryness** often requires **local or systemic estrogen therapy**.

PHARMACOLOGIC THERAPY

1.Hormonal Therapy:

- HT can be prescribed as **local** (creams, pessaries, rings) or **systemi**c therapy (oral drugs, transdermal patches, gels, and implants), which may contain the following ingredients:

✓Estrogen alone

✓Combined estrogen and progestogen

✓Selective estrogen receptor modulator (SERM)

✓Gonadomimetics, such as tibolone, which contains estrogen, progestogen, and an androgen

✓Others (CBHT, Testosterone, SERM, …etc

2.Non-Hormonal Therapy

✓SSRIs, SNRIs, Clonidine, Gabapentin, … etc.

3.Complementary and Alternative Therapy

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.
- **Combined hormonal contraceptives** (CHCs) provide **contraception** and **vasomotor symptom relief** but should **not be used in perimenopausal women if** they smoke or have a history of estrogen-dependent cancer, cardiovascular or cerebrovascular disease, hypertension, diabetes with vascular disease, or risk factors for thromboembolism, liver disease, or migraine headaches.
- **MHT** remains the **most effective** treatment for **moderate** and **severe** vasomotor symptoms, impaired sleep quality, and vulvovaginal symptoms of menopause.
- **MHT** is effective and appropriate for the prevention of **osteoporosis-related fractures** in **recently** menopausal women at risk.

PHARMACOLOGIC THERAPY

- 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 (1) **minimizes systemic absorption** and is (2) **more effective** for vaginal symptoms than oral therapy. [Note: **Ospemifene**, a SERM, is **another option**.]
- Intravaginal estrogen (3) **reduces the risk** of recurrent UTIs and may (4) **improve** urge incontinence and overactive bladder.
- **Estrogen-only therapy** may (5) **decrease** heart disease and all-cause mortality in 50-59 year-old women with a history of hysterectomy.

PHARMACOLOGIC THERAPY

INTACT UTERUS CASE:

- In women with an **intact uterus**, **MHT consists** of **estrogen plus a progestogen** or **estrogen agonist/antagonist** eg, bazedoxifene (SERM).

HYSTERECTOMY CASE:

- In women who have undergone **hysterectomy**, **estrogen therapy is given** unopposed by a progestogen.
- **Concomitant progestogen** therapy is **unnecessary** when low-dose vaginal estrogen is used.
- **Women with vasomotor symptoms** taking **MHT have better mental health and fewer depressive symptoms** compared with those taking a placebo.
- **But** hormone therapy may **worsen the quality of life** in women **without** vasomotor symptoms.

ESTROGENS

- The **oral** and **transdermal routes** of estrogen products are used most **frequently** and are considered **equally effective**.

1.Conjugated equine estrogens:

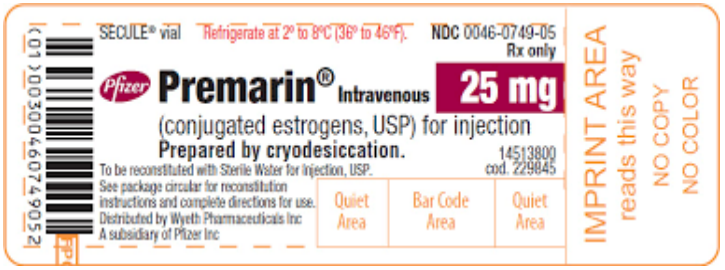
- They are composed of **estrone sulfate (50%–60%)** and **other** estrogens such as **equilin** and **17α-dihydroequilin**.

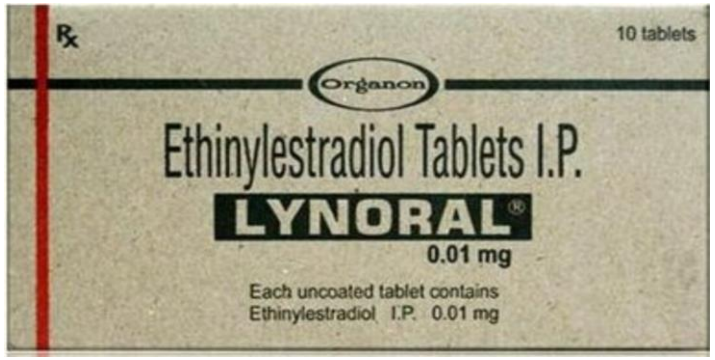
2.Estradiol:

- It is the **predominant** and **most active** form of endogenous estrogens.
- Given **orally**, it is **metabolized** by the intestinal mucosa and liver, and resultant **estrone** (less potent) with conc. are 3-6 times those of estradiol.

3.Ethinyl estradiol:

- It is a **semisynthetic** estrogen that has similar activity following **oral** or **parenteral** administration.





ESTROGENS

- **Non-Oral estrogens**, including **transdermal, intranasal, and vaginal products:**

1. **Avoid first-pass** metabolism
2. Result in **more physiologic estradiol: estrone ratio** (ie, estradiol conc. > estrone conc.).

- **Transdermal estrogen** is also **less likely** to increase sex hormone–binding globulin, triglycerides, blood pressure, or C-reactive protein levels and may also have a **lower risk** for deep vein thrombosis, stroke, and myocardial infarction.
- **Variability** in **absorption** is common with **percutaneous preparations** (gels, creams, and emulsions).
- **Estradiol pellets** (unavailable in the United States) **contain** pure crystalline 17β-estradiol and are placed **subcutaneously** (abdomen or buttock), and they are **difficult to remove**.

ESTROGENS

Estradiol pellets

ESTROGENS

- **Vaginal** creams, tablets, and rings are used for the treatment of **urogenital atrophy**.
- Most tablets and rings provide **local estrogen**, but **Femring** (Estradiol acetate vaginal ring)is designed to achieve **systemic estrogen conc.** 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.
- Low-dose estrogen regimens **include 0.3–0.45 mg conjugated estrogens**, **0.5 mg micronized 17β-estradiol**, and **0.014–0.0375 mg transdermal 17β-estradiol patch**.
- **Topical** gels, creams, and sprays are also available in **low doses**.

ESTROGENS

- **Lower doses** typically have **fewer adverse effects** and may have **better benefit to risk profiles** than standard doses, the **lowest effective** dose should be used.
- **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 gall bladder disease**.
- **Transdermal** estrogen is **less** likely to cause **breast tenderness, gallbladder disease, and deep vein thrombosis**.

ESTROGENS

- The Women's Health Initiative (**WHI**) trial showed an **overall increase** in the risk of **CHD** in healthy postmenopausal women ages 50–79 years taking **estrogen-progestogen therapy compared to placebo**. The **estrogen-alone** arm showed **no effect** (either increase or decrease) in the risk of **CHD**.
- The more recent Early versus Late Intervention Trial with Estradiol (**ELITE**) trial **suggests** that the **benefits** of hormone therapy are **dependent on the timing of initiation** and hormone therapy may be **cardioprotective** if started around the **time of menopause** (within 6 years) and therapy may be **harmful** when initiated in **late postmenopausal** women (after 10 years).
- MHT **should not be** initiated or continued **solely** for the prevention of cardiovascular disease.

ESTROGENS

- **Risk** of VTE and stroke **increases** with **oral MHT containing estrogen**, but the **absolute risk** is **low** in women **below 60 years** of age.
- **Transdermal** MHT and **low-dose oral** estrogen therapy appear to have a l**ower risk of VTE and stroke** compared to standard-dose oral estrogen regimens.
- The **norpregnane progestogens** also appear to be **thrombogenic**.
- **MHT** should be **avoided** in women at high risk for **thromboembolic** events (eg, those with Factor V Leiden mutation, obesity, or a history of previous thromboembolic events).
- **MHT** is **contraindicated** in women with a personal history of **breast cancer**.
- In the WHI, the **risk** of MHT-related breast cancer appears to be **associated** with the **addition of a progestogen** to estrogen **after 3 years** of combined use.

ESTROGENS

- The WHI trial **suggests** that **combined** oral MHT does **not increase endometrial cancer risk** compared with placebo, but **estrogen-alone given** to women with an intact uterus significantly **increases uterine cancer** risk.
- While the WHI trial **suggested** that **oral combined** MHT does **not increase the risk of ovarian cancer**, more **recent** research now suggests that MHTs are **associated** with an increased risk of ovarian cancer regardless of the type or the regimen used (More research is needed).
- The WHI study found that **postmenopausal** women 65 years or older **taking estrogen plus progestogen therapy** had **twice** the rate of **dementia**, including Alzheimer's disease, than those taking a placebo.
- **Combined** therapy did **not prevent** mild cognitive impairment, also the **estrogen-alone** arm showed **similar findings**.

PROGESTOGENS

- In women who have **not undergone hysterectomy**, a **progestogen** or **tissue selective estrogen complex** (estrogen/bazedoxifene) should **be added for endometrial protection**.
- **Several** progestogen regimens to prevent **endometrial hyperplasia**.
- **Adverse effects** of progestogens include irritability, headache, mood swings, fluid retention, and sleep disturbance.
- **Current progestogens preparation may include**:
  - ✓Medroxyprogesterone acetate (DEPO-PROVERA®)
  - ✓Micronized progesterone (DPROGEST ®)
  - ✓Norethindrone acetate (Primolut-N ®)

Methods of administration include the following:

1. Continuous-cyclic estrogen-progestogen (sequential):

- **Estrogen** typically is administered continuously (**daily**), and **progestogen** is coadministered with the estrogen for at least **12 to 14** days of a 28-day cycle.
- It results in scheduled vaginal withdrawal bleeding (1-2 days after the last progestogen dose) in approximately 90% of women.

2. Continuous-combined estrogen-progestogen:

- It causes endometrial atrophy but prevents monthly bleeding. It may initially cause unpredictable spotting or bleeding.
- Use of conjugated equine estrogens [0.625 mg/day] plus medroxyprogesterone acetate [2.5 mg/day]) lead to a decreased risk of endometrial cancer in the WHI study.
- This combination offers the **best protection** against **endometrial hyperplasia and cancer**.

Methods of administration include the following:

3. Continuous long-cycle estrogen-progestogen (cyclic withdrawal).

- Estrogen is given daily, and progestogen is given six times yearly (every other month) for 12–14 days, resulting in six periods per year.
- Bleeding may be heavier and last for more days than with **sequential use**.

4. 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 side 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 and several major medical **organizations** have released **statements against this practice**.

NON-HORMONAL TREATMENTS

- For women with **contraindications** to or who **cannot** tolerate estrogens and/or progestogens, other treatment options for hot flushes can be considered.
- Some clinicians consider **SSRIs**(eg, paroxetine, fluoxetine, citalopram, escitalopram) or **SNRIs** (eg, venlafaxine and desvenlafaxine) to be **first-line agents**.
- **Clonidine** can be **effective**, but side effects are often **problematic** (eg, sedation, dry mouth, hypotension).
- **Gabapentin** has beneficial effects for **reducing the frequency and severity** of vasomotor symptoms but **side effects** may limit dosing.
- **Gabapentin** may be a reasonable **option** for women with **disrupted sleep and hot flashes** when administered in the evening.

ANDROGENS

- **Testosterone** use in women, although **controversial**, is becoming more common, even in the absence of androgen deficiency.
- Testosterone, with or without estrogen, **may improve** the quality of the sexual experience in postmenopausal women.
- **Absolute contraindications** to androgen therapy include **pregnancy** or **lactation** and known or suspected **androgen-dependent neoplasia**.
- Evidence on the efficacy and safety of testosterone in women is **lacking**, and its use is currently **not recommended**.
- **Adverse effects** include virilization, fluid retention, and potentially adverse lipoprotein lipid effects, which are more likely with **oral** administration.
- 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** at a dose of 6.5 mg once daily at bedtime, which does **not appear** to convey the same **systemic risks** seen from other oral hormonal products.

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 the **breast** through high **affinity binding** to the estrogen receptor.
- 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**.

1. **Tamoxifen** is an **antagonist** in breast tissue and an **agonist** in the bone and endometrium.

2. Raloxifene is **approved** for the **prevention** and **treatment** of **postmenopausal osteoporosis** and **reduction** in risk of **invasive breast cancer,** in a **60 mg once** daily dose.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

3. 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**.

- **Side effects of bazedoxifene** include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain.

4. Ospemifene is approved for **moderate-to-severe dyspareunia** from menopausal vulvar and vaginal atrophy.

- It has a **boxed warning** for increased risk of **endometrial cancer** in women with a uterus who use ospemifene (an estrogen agonist in the endometrium) **without a progestogen** to reduce endometrial hyperplasia.
- It also has a boxed warning about the possible **risk of stroke and VTE**.
- **Adverse effects of ospemifene** include hot flashes, vaginal discharge, muscle spasms, genital discharge, and hyperhidrosis.

Tibolone

- **Tibolone** (unavailable in the United States) has **combined estrogenic, progestogenic, and androgenic activity** and **improves** mood, libido, menopausal symptoms, and vaginal atrophy.
- It **protects** against **bone loss** and reduces the risk of vertebral fractures.
- It **reduces total cholesterol** and **triglycerides** but may **decrease HDL** concentrations.
- It **decreases** the risk of **breast and colon cancer** in women ages 60–85 years.
- **Adverse effects** include weight gain and bloating, increased risk of stroke in older women, and possible breast cancer recurrence.
- It may increase **endometrial cancer risk**.

COMPLEMENTARY AND ALTERNATIVE AGENTS

Phytoestrogens:

- Phytoestrogens are **plant compounds** with **estrogen-like** biologic activity and relatively **weak estrogen receptor-binding properties**, resulting in **physiologic effects** in humans.
- Although some **data support their use**, **clarity regarding**, dosing, biological activity, safety, and efficacy is **needed** before they can be considered as an alternative to MHT in postmenopausal women.
- Common **adverse effects** include constipation, bloating, and nausea.

Others

- Other herbals and alternative treatments that may be used by women include **black cohosh, dong quai, red clover leaf** (which contains phytoestrogens), and **ginseng**.
- Complementary and alternative therapies should **not be recommended** to treat menopausal symptoms as their **efficacy and safety have not been completely established**.

EVALUATION OF THERAPEUTIC OUTCOMES

- In order to **adequately assess treatment effect**, women should be **encouraged** to continue their MHT regimen for at **least 1 month with dosages being modified** to balance adverse effects and efficacy.
- Women receiving MHT should be seen **annually for monitoring**.
- **Many** women have **no difficulty stopping MHT**, while **some** develop **vasomotor symptoms after discontinuation**, regardless of discontinuation rate (ie, gradual or sudden withdrawal).

THANK YOU FOR YOUR ATTENTION