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TEAM 443
PHARMACOLOGY

MED 443
King Saud University

Hormonal replacement therapy

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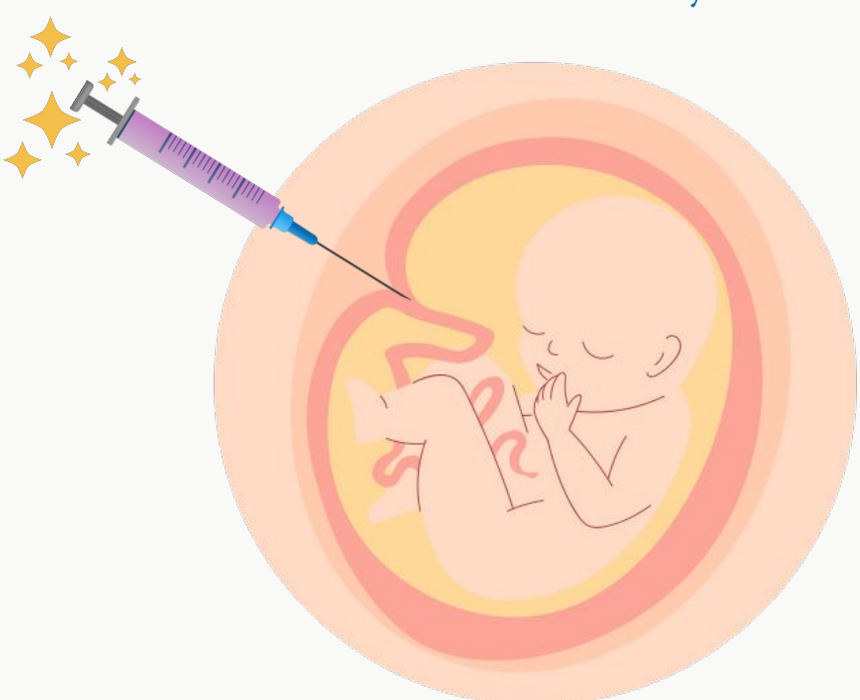


- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

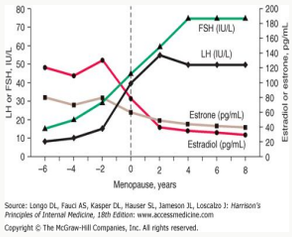
Objective

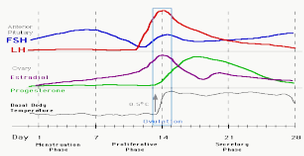
- Recognize menopausal symptoms & consequences
- Classify drugs used to alleviate such symptoms that are used as Hormonal Replacement Therapy [HRT]
- Expand on the mechanism of action, indications, preparations, side effects & contraindications of such agents.

Menopause

Definition & Characteristics

- **menos (month) pausis (cessation)**, so **<u>menopause</u>** means a complex physiological changes that occur at the time when the last period ends generally as women get older and lose fertility, usually in late 40s of age.
- Menopausal Symptoms *are mainly* due to ↓ **Estrogen**
- **hormonal imbalance :**
  - ↓ **Progesterone, Estrogen & Androgens**
  - ↑ **FSH & LH & ↑ insulin resistance**





Normal menstruation

Symptoms & Consequences of Menopause

Immediate

- Vasomotor symptoms: Hot flushes / Night sweats
- Insomnia, Anxiety, irritability
- Mood Disturbances
- Reduction in Sexuality & Libido
- Poor concentration / Memory loss

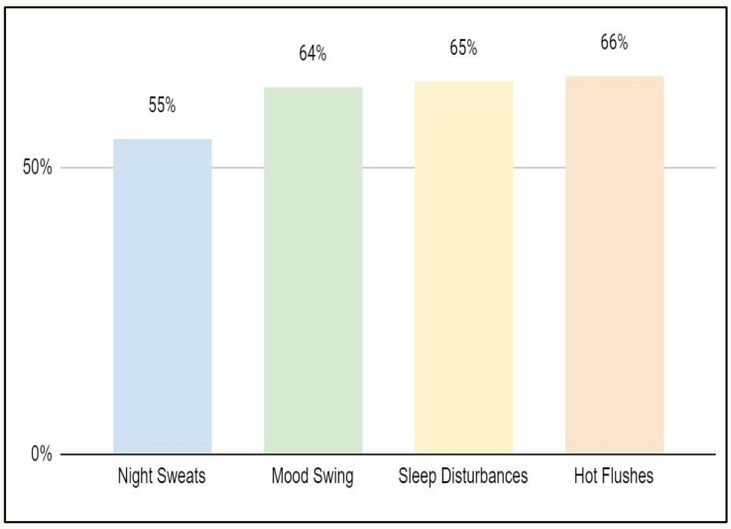
Intermediate

- Dyspareunia & Vaginal Dryness
- Urethral Syndrome (Dysuria, Urgency & Frequency)
- Incontinence, Difficulty in Voiding
- Increased Bruising
- Generalized Aches and Pains

Long term

Most Dangerous

- Osteoporosis
- CVS Risks: ↑ LDL/ HDL ratio, Coronary Heart Disease,Stroke
- CNS deficits: Alzheimer's, Dementia

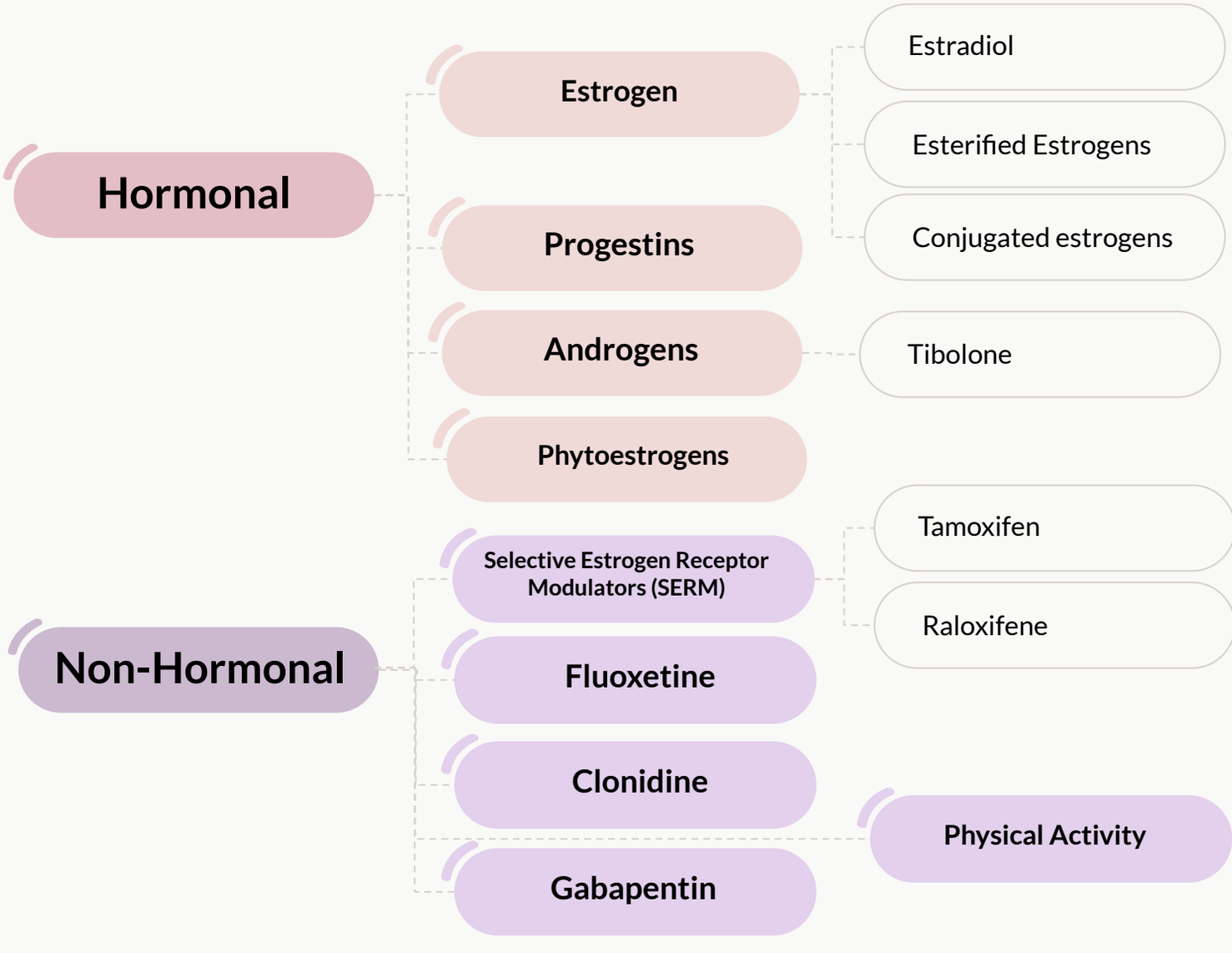


Symptoms Experienced Most During Menopause:
20% no symptoms | 60% some symptoms | 20% severe symptoms

Hormonal Replacement Therapy (HRT)

Definition	• Is a system of medical treatment that is designed to artificially boost female hormones, in hope to alleviate symptoms caused by decrease in their circulating levels. • This decrease in female hormones could be natural, pathological or induced. • HRT is used in 1/3rd of total female population (Perimenopause & Postmenopause).	
Administration	**Given for short term**	**Never exceed 5 years** to control menopausal symptoms without allowing ample time for **malignant transition** **that might be induced by estrogen**
	Long-term administration	No more preferred (many ADRs). Was only indicated in **osteoporosis** & **CVS protection** but now better drugs are available
Benefits & Risks of HRT	**Definite benefit**	• ↓ symptoms of **menopause** (vasomotor, genitourinary) • **osteoporosis** (definite ↑ in bone mineral density → probable ↓ in risk of fracture)
	Uncertain benefit:	• ↑ **cognitive** function. **Note:** The risk of CVS problems and breast cancer with HRT is more than their benefits
	Definite risks:	• Endometrial cancer (estrogen only). • **Venous thromboembolism (long term)** • breast cancer (long term 5 years)

Agents used in management of Menopausal Symptoms

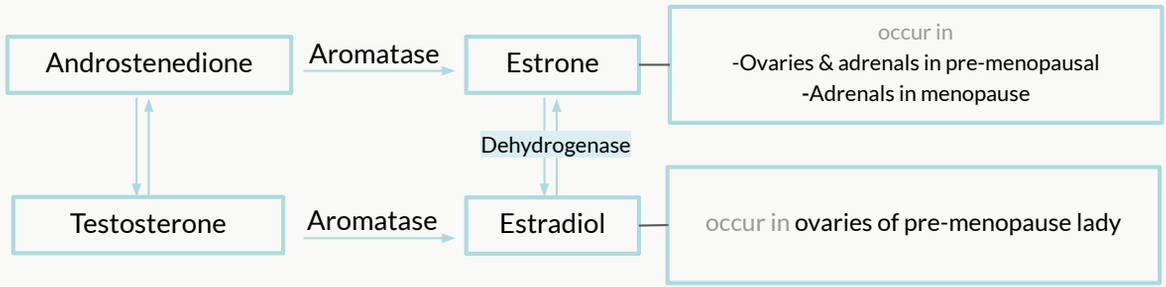


Management of Menopausal Symptoms (*HRT*)

Estrogen

General Info

❖ **In natural:**



❖ **As therapy:**

- **Estradiol:** Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, intradermal implant and subcutaneous implant.
- **Conjugated estrogens:** mixture of Na salts of sulfate esters of estrone & equilin.
- **Esterified estrogens**

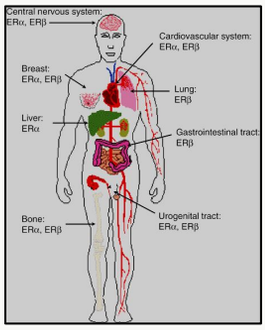
MOA

What does estrogen do? It binds with its receptors.

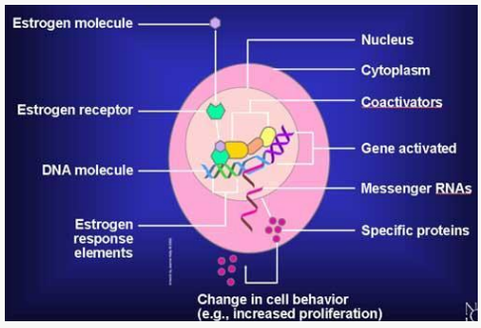
- **Types of estrogen receptors (ER):**
  1. **ER α :** mediates female hormonal functions. They are located in (Endometrium, breast, ovaries, hypothalamus).
  2. **ER β:** mediates other hormonal functions. They are located in (brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells).
- **Estrogens bind to ER (α or β) that exist either:**
  1. **Cytoplasmic:** mediates its genomic actions (hours to days time scale) and this kinds of receptors important for development, neuroendocrine, metabolism.
  2. **Membranous:** G protein estrogen receptors(GPER) → 2nd messenger → ↑ Ca or cAMP or ↑ mitogen activated protein (MAP) Kinase → mediates its non-genomic actions (seconds to minutes time scale). E.g. receptors of: nitric oxide, neurotransmitters, endometrium. (MAP kinase activate transcription factors to promote mitogenesis)

Administration

- **Oral:** Conjugated equine, Estradiol valerate, Estrial succinate.
- **(estradiol):**
  1. Transdermal Patches (24 hour twice weekly).
  2. Subcutaneous implant: 6 monthly
- **Subcutaneous implant (estradiol):** 6 monthly.
- Intravaginal "topical" :Vaginal cream as such or as rings pessaries



Distribution of ER



Genomic effects

Management of Menopausal Symptoms (*HRT*)

Estrogen

Indications

- In menopause: Not given unless presence of symptoms
  - Alone only after hysterectomy
  - In the presence of uterus, combined with progestin as HRT to avoid cancer (never exceed 5 years administration)
- Effects:
  - Improves hot flushes & night sweats.
  - Increases bone density by ↓ osteoclastic activity. Added Progestins act synergistic by blocking corticosteroid induced bone resorption (decrease incidence of hip fracture)
  - Controls sleep disturbance & mood swings by acting on norepinephrine, dopamine & serotonin at reticular formation.
  - Improves urethral & urinary symptoms by ↑ epithelial thickness, vascularity & collagen content at urethra & norepinephrine transmission that contract sphincters & relax detrusor muscles of the urinary bladder.
  - Improves vaginal dryness by ↑ epithelial thickness , vascularity & collagen content (topical and systemic estrogens preparation are effective).
  - Improves cognitive function via ↑ expression of estrogen receptor in brain & by ↓ amyloid deposition thus preventing Alzheimer's.
  - Delays parkinsonism by acting on dopamine system in midbrain
  - Improves insulin resistance & glycemic control in diabetics..
  - Short term HRT started at the beginning of menopause will prevent CVS problems
    Protects CVS by enhance vasodilatation via:
    - ↑ nitric oxide production & ↑ HDL
    - ↓ LDL thus ↓ atherosclerosis & ischemic insults

    However long term HRT increases cardiovascular problems and thromboembolism

- **Uses other** *than HRT for menopause:*
  - Contraception: Depends on dose
  - Primary ovarian failure.
  - Amenorrhea & Hirsutism caused by excess androgens

ADRs
Undesirable side effect

- **Patients discontinue HRT** at early stages [non-compliance] :
  - Irregular vaginal bleeding
  - Breast tenderness
- Nausea
- Vaginal discharge (Increased vascularity)
- Fluid retention, **Weight gain**
- Spotting or darkening of skin on face

C.I

- **Absolute:**
  - **Undiagnosed vaginal bleeding.**
  - Severe liver disease. (Metabolized by the liver)
  - **Thromboembolic manifestations** *since long term therapy ↑ CVS risks*
  - Cancer in: endometrial, **breast** **(hormone sensitive)**, ovarian.

Interactions

- See contraception *"similar to interactions of oral contraceptives "*
- *Special Interactions for HRT*
  - With SERM: additive side effects for both drugs.
  - With Aromatase inhibitors: ↓ efficacy. *(Will need a higher dose)*
  - With Corticosteroids: ↑ side effects.

Management of Menopausal Symptoms (*HRT)*

Drug	Progestins
General Info	● **<u>In nature:</u>** ○ Produced by Adrenal glands, Gonads, Brain, Placenta ○ The synthesis is induced by LH ○ Are precursor to estrogens, androgens, and adrenocortical steroids. Cholesterol → Pregnenolone → Progesterone ● **As therapy:** ○ Progesterone is degraded in GIT, so can be given only parentally ○ Progestins are synthetic progestogens that have progestinic effects similar to progesterone but are not degraded by GIT ○ Progestin preparations as in contraceptive pills:
MOA Same as Estrogen	**What does progesterone do?** Binds to its receptors. ● There are two types of progesterone receptors [PR]: PR-**α** & PR-**β** ● They could exist cytoplasmic to mediate genomic long term effects or exist membranous to mediate non-genomic rapid effects
Administration	● **Oral**: Micronized progesterone or progestins →see contraception ● **IntraUterine (IU):** as Levonorgestrel or Progestasert ● **Vaginal**: natural progesterone gel, pessary. ● **Transdermal**: sequential (replaced daily), continuous patch
Uses	● **In menopause:** **As HRT, usually given in combination with estrogen** Some use it alone in risk of cancer but does not ↓ all menopausal symptoms as estrogen. ○ **Protects against possibility of estrogen induced endometrial cancer** ■ Estrogen ↑ cell growth. If unopposed → endometrial cell lining can show atypical hyperplasia ■ Progesterone beneficially matures endometrial cell lining. Become differentiated & ↑ apoptosis of atypical cells by activation p53 ○ Progesterone (natural) **protects against breast cancer development by anti-inflammatory & apoptotic mechanisms**, ***but this effect is not as clear with synthetic progestin.*** Mammography recommended every 6 months. ○ **Counteract osteoporosis** by direct activation of osteoblast. ● **Other uses:** ○ Contraception (Estradiol + Progestins) ○ Dysmenorrhea ○ Menopausal symptoms : **Estradiol + Progestins, given together** if uterus is present
ADRs	● Mood changes e.g. anxiety, irritability ● Headache, dizziness or drowsiness ● Nausea, vomiting, abdominal pain or bloating (distention). ● Hirsutism, masculinization (Not with new preparations)

Other Types of HRT

Phytoestrogens

Source	Supplements from plants containing **isoflavones** (soya beans, flaxseeds) or lignans (whole grains).
Uses	• They mimic the action of estrogen on estrogen receptor-β: • **Alleviate symptoms related to hot flushes,** mood swings, cognitive functions & possess CVS protective actions. (data limited on their efficacy)
C.I (#)	**Avoid in estrogen dependent breast cancer.**

Androgen | Tibolone

Source	Testosterone is responsible for sexual arousal in females, given only if there is **loss of libido** & orgasm.
Uses	• Testosterone is given as sole therapy to menopausal women in whom their menopausal symptoms are focused on lack of sexual arousal. • It is given as adjuvant to combined estrogen & progestin if all other menopausal symptom exist. • **Tibolone**, can be effective in some women has some androgen agonistic properties. (androgens use is not approved by FDA in women)

The Women's Health Initiative (WHI) and HRT

- **Menopausal hormone therapy:**
  - For decades, hormone therapy widely used in menopausal symptoms.
  - Estrogen has been used alone in menopausal women who have had their uterus removed.
  - Progestin, the synthetic form of an estrogen-related hormone called progesterone, is combined with estrogen in menopausal women who still have their uterus.
  - The Women's Health Initiative (WHI), a 15-year research program launched in 1991, addressed the most common causes of death, disability, and poor quality of life in postmenopausal women.
  - The research program examined the effectiveness of hormone replacement therapy in women. In 2002, findings from two WHI clinical trials examined:
  - The use of estrogen plus progestin in women with a uterus
  - The use of estrogen only in women without a uterus.
  - In both studies, women were randomly assigned to receive either the hormone medication or placebo.
  - In both studies, when compared with placebo, the hormone medication (whether estrogen plus progestin or estrogen only) resulted in an increased risk of stroke and blood clots. In addition, the estrogen plus progestin medication resulted in an increased risk of heart attack and breast cancer.
  - These concerns are one reason that many women are turning to mind and body practices and natural products to help with menopausal symptoms.

Non-Hormonal management

Selective Estrogen Receptor Modulators (SERMS) (oral)

Drugs	Raloxifene	Tamoxifen
M.O.A	Antagonist in the breast and uterus Agonist in bone	Antagonist in the breast. Partial agonist endometrium & bone
Effects	• Has no effect on hot flushes. • Very effective preventing vertebral bone fracture. • Cardiovascular problems are less compared to Estrogen. • For osteoporosis use of bisphosphonate is better than SERMs.	• Increase the risk of venous thrombosis. • Tends to precipitate vaginal atrophy & hot flushes. • Not used for history of endometrial cancer

Selectivity

+ = agonist - = antagonist	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERM	++	-	++	-	++	++
Tamoxifen	-	+	-	-	+	+
Raloxifene	-	-	-	-	++	+

Not ideal

- An ideal **SERM** for use as **HRT** should be ***agonistic*** in brain, bone, cardiovascular system (not necessarily the liver), vagina & urinary system but ***antagonistic*** in breast & uterus

Non-hormonal Agents Used in management of menopausal symptoms

Fluoxetine	Selective Serotonin Reuptake Inhibitor (SSRI)
Clonidine	*Anti-adrenergic* Centrally acting antihypertensive
Gabapentin	Anticonvulsant.
Physical activity	Exercise, smoking cessation and relaxation of mind will improve symptoms of menopause (e.g.hot flushes) and fall prevention strategies prevents chances of fracture.

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