



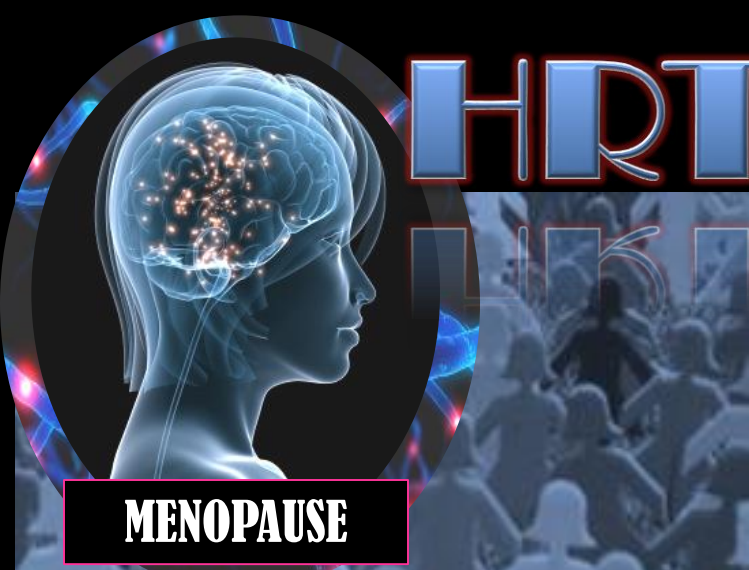
# HORMONE REPLACEMENT THERAPY

# ILOs

By the end of this lecture you will be able to:

- ✳ 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.



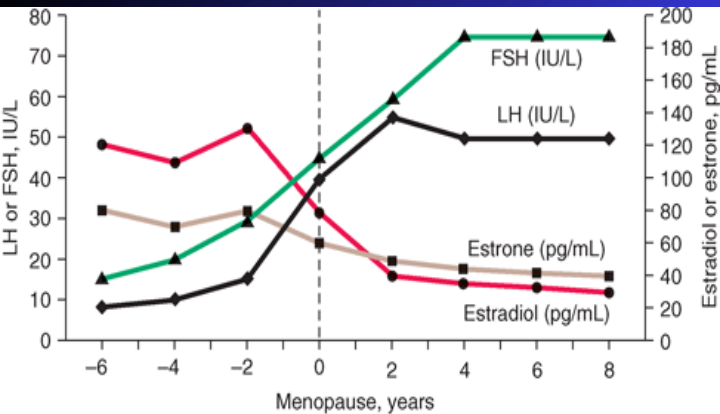


Is a system of medical treatment that is designed to artificially boost female hormones, in hope to alleviate symptoms caused by ↓ in their circulating levels

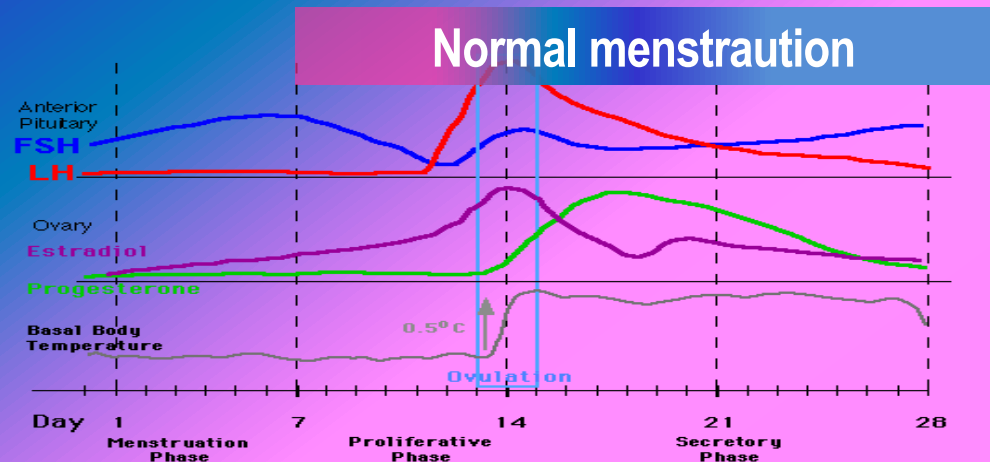
The physiological changes that occur at the time when the last period ends generally as women get older and lose fertility (age late 40s)

- ↓ Estrogen & Progesterone
- ↓ Androgens
- ↑ FSH & LH
- ↑ Insulin Resistance

'*menos*'( *month*)  
'*pausis*'(*cessation*)



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com  
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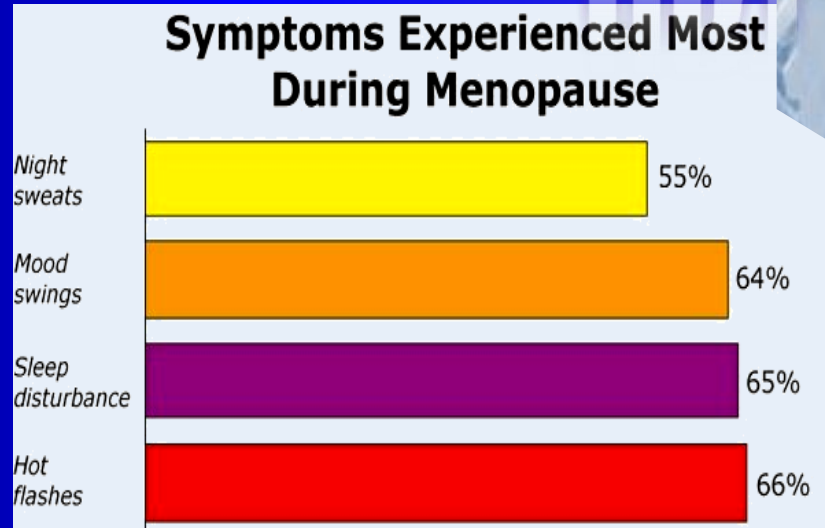


# SYMPTOMS & CONSEQUENCES of MENOPAUSE

# HRT



- Hot Flashes / Night Sweats (vasomotor symptoms)
- Insomnia, Anxiety, Irritability
- Mood Disturbances
- Reduction In Sexuality & Libido
- Poor Concentration / Memory Loss



20% no symptoms, 60% some symptoms, 20% severe symptoms

- Dyspareunia & vaginal dryness
- Urethral syndrome  
(dysuria, urgency & frequency)
- Incontinence, difficulty in voiding
- Increased bruising
- Generalized aches and pains

- Osteoporosis
- CVS Risks; ↑ LDL/HDL ratio, CHD, stroke,..
- CNS deficits; Alzheimer's, dementia



# Menopausal Symptoms

→ ↓ Estrogen

Replace the Estrogen ← Alleviate

Estrogen → Some undesirable side effects

↑  
add Progestins; *but not if there is hysterectomy*

Selective ER-Modulators [SERMs]

Phytoestrogens

Androgens → *responsible for sexual arousal* → *given only if there is loss of libido & orgasm*

## HRT

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

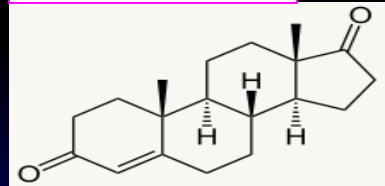
No more preferred

~~Long-term~~ administration was only indicated in osteoporosis & CVS protection but now better drugs are available

## HRT

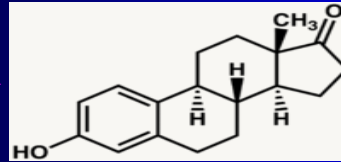
## 1. ESTROGEN

### In NATURE



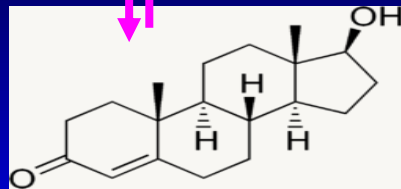
Androstenedione

Aromatase



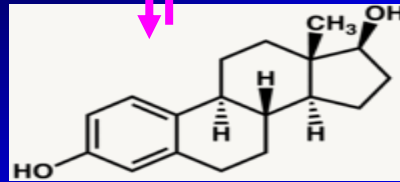
Estrone

Ovaries & adrenals pre-menopausal  
Adrenals in menopause



Testosterone

Aromatase



Estradiol

Dehydrogenase

Ovaries in pre-menopause

### As Therapy

**Estradiol**; Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, subcutaneous implant, ...

**Conjugated estrogens** → mixture of Na salts of sulfate esters of estrone & equilin.

**Esterified estrogens**



What does estrogen do  
It binds to its receptors



# ESTROGEN

## Distribution of ER

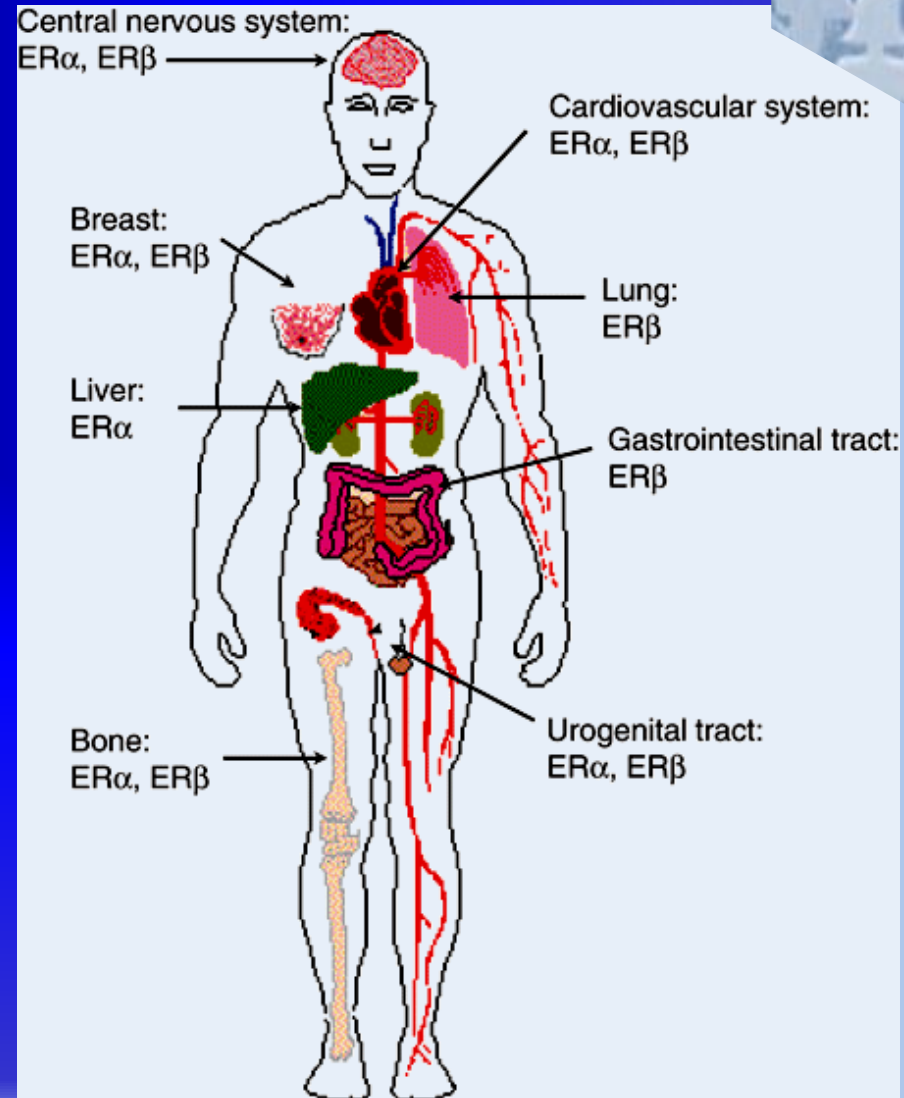
### Types of Estrogen Receptors [ER]

#### ER $\alpha$ $\rightarrow$

> mediates female hormonal functions  
*Endometrium, breast, ovaries, hypothalamus,...*

#### ER $\beta$ $\rightarrow$

> mediates other hormonal functions  
*brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells,....*





# INDICATIONS

# ESTROGEN

- A. In Menopause** Not given unless presence of symptoms; alone only after hysterectomy or with progestin as HRT (never exceed 5 yrs administration)
- Improves hot flushes & night sweats
  - Controls sleep disturbance & mood swings by acting on NE, DA & 5HT at reticular formation
  - Improves urethral & urinary symptoms by ↑ epithelial thickness & vascularity, collagen content at urethra & NE transmission that contract sphincters & relax detrusal muscles
  - Improves vaginal dryness by ↑ epithelial thickness & vascularity, collagen content (topical and systemic estrogens prep are effective)
  - Increases bone density by ↑ calcitonin release from thyroid to ↓ osteoclastic activity.
  - Progestins act synergistic by blocking cortico-steroid induced bone resorption. (Decrease incidence of hip fracture)



# ESTROGEN



- Protects CVS: enhance vasodilatation via  $\uparrow$  NO production, &  $\uparrow$  HDL &  $\downarrow$  LDL thus  $\downarrow$  atherosclerosis & ischemic insults (HRT started at the beginning of menopause will prevent CVS problems) **HRT increases CVs problems (long term)**
- Improves insulin resistance & glycaemic control in diabetics
- Improves cognitive function via  $\uparrow$  expression of ER in brain & by  $\downarrow$  amyloid deposition thus preventing Alzheimer 's.
- Delays parkinsonism by acting on DA system in midbrain



## B. Other Uses

- Contraception
- Primary ovarian failure
- Amenorrhea & Hirsutism caused by excess androgens

# Prescription of HRT: ROUTES

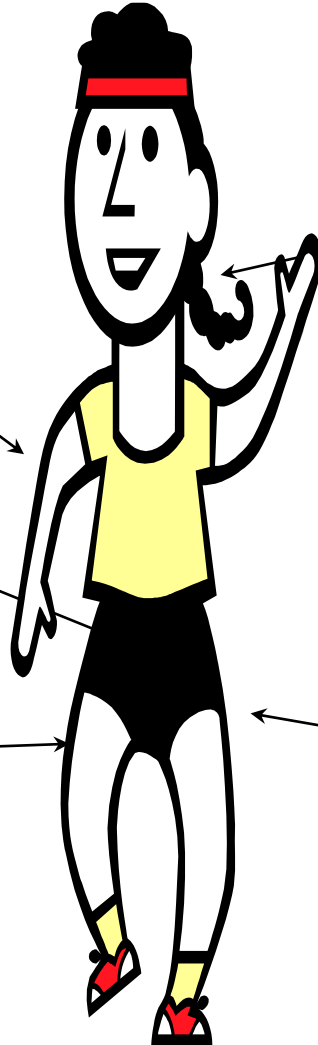
**Transdermal:  
patch or gel**

**Oral**

**Subcutaneous  
(implant)**

**Intramuscular  
(depot)**

**Intra-vaginal  
(pessaries, ring  
or cream)**



## Administration

Oral: -  
Conjugated equine

Estradiol valerate  
Estradiol succinate

- Transdermal (estradiol);  
Patches → 24 hour twice weekly.  
Gel → 24 hours daily.
- Subcutaneous implant (estradiol) → 6 monthly.
- Vaginal cream as such or as rings pessaries

## ADRs

- Irregular vaginal bleeding (**patients discontinue HRT**).
- Nausea.
- Vaginal discharge.
- Fluid retention, Weight gain.
- Breast tenderness (**patients discontinue HRT**)..
- Spotting or darkening of skin (on face)





## Contraindications

### Absolute:

- Undiagnosed vaginal bleeding
- Severe liver disease
- Thromboembolic manifestations
- Cancer; endometrial, breast (hormone sensitive), ovarian

## Interactions

- ⚠ See contraception
- ⚠ NB. If given with
  - Ⓢ SERMs → additive side effects for both drugs
  - Ⓢ Aromatase inhibitors → ↓ efficacy
  - Ⓢ Corticosteroids ↑ side effects



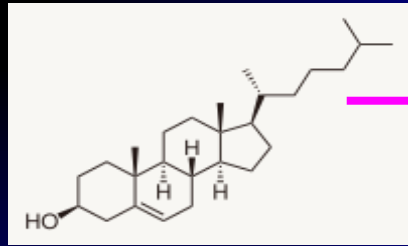


## 2. PROGESTINS

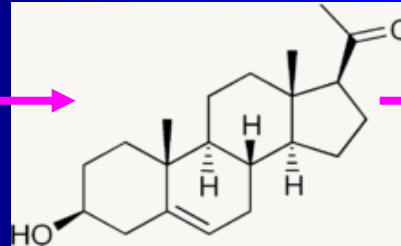
### In NATURE

Produced by; Adrenal glands, Gonads, Brain, Placenta

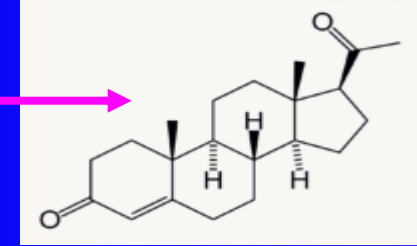
Synthesis;  
Induced by LH



Cholesterol



Pregnenolone



Progesterone

Are precursor to estrogens, androgens, and adrenocortical steroids.

### As Therapy

- ✚ Progesterone is degraded in GIT, so can be given only parentally
- ✚ Progestins are synthetic progestogens that have effects similar to progesterone but are **not degraded by GIT**.

Progestin preparations; as in contraceptive pills

Binds to its receptors

What does progesterone do?

- ↓ Two types of progesterone receptors [PR] → PR-A & PR-B
- They could exist cytoplasmic → mediating genomic long term effects
- or membranous → mediating non-genomic rapid effects

# INDICATIONS

# PROGESTIN

**A. In Menopause** As HRT, usually given in combination with estrogen. Some use it alone in risk of cancer but does not ↓ all menopausal symptoms

- **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.
- **Progesterone (natural) protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, but this effect is not as clear with synthetic progestins. Mammography recommended every 6ms.**
- **Confers neuroprotection, mild effect**
- **Controls insomnia & depression** → little effect
- **Counteract osteoporosis, directly +ve osteoblasts**

## B. Other Uses

1. Contraception (Estradiol + Progestins)
2. Dysmenorrhea
2. Menopausal symptoms (Estradiol + Progestins given together)

## Administration

- ⊗ Oral; Micronized progesterone or progestins
- ⊗ IU; as Levonorgestrel or Progestasert
- ⊗ Vaginal - natural progesterone gel / pessary.
- ⊗ Transdermal - sequential / continuous patch.

## ADRs

- Mood changes, as anxiety, irritability
- Headache, dizziness or drowsiness
- Nausea, vomiting, abdominal pain or bloating (distention).
- Hirsutism, masculinization (Not with new preparations)



# Benefits and Risks of HRT

## Definite benefits

- Alleviates symptoms of menopause (vasomotor, genitourinary)
- Osteoporosis (Definite increase in bone mineral density; probable decrease in risk of fractures)

## Definite risks

- Endometrial cancer (estrogen only)
- Venous thromboembolism (long term)
- Breast cancer (long term 5 yrs)

## Uncertain benefits

- Cognitive functions
- **Note: the risk of CVS problems and breast cancer with HRT is more than their benefits)**



## 3. SERMs Tamoxifen, Raloxifene (oral and non-hormonal)

- **Raloxifen** antagonist in breast and uterus and agonist in bone
- **Tamoxifen** Antagonist in breast and partial agonist in bone and endometrium.

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

		Brain	Uterus	Vagina	Breast	Bone	CVS
+ = agonist	Estradiol	++	++	++	++	++	++
- = antagonist	<u>Ideal SERM</u>	++	—	++	—	++	++
<b>Not Ideal</b>	Tamoxifen	—	+	—	—	+	+
	Raloxifene	—	—	—	—	++	+

Tamoxifen → ↑ risk of venous thrombosis & tends to precipitate vaginal atrophy & **hot flushes**

Raloxifene → has no effect on hot flushes or **increases hot flushes** (very effective preventing vertebral bone fracture and CVs problems less compared to Estrogen) for osteoporosis use of bisphosphonate is better than SERMs

## 5. PHYTOESTROGENS

supplements from plants; containing isoflavones (soya beans, flaxseeds) or lignans (whole grains). Avoid in estrogen dependent breast cancer

■ They mimic action of estrogen on ER- $\beta$  → alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions. (data limited on their efficacy)

■ They block actions mediated by ER- $\alpha$  in some target tissues → lower risks of developing endometrial & breast cancer.

## 6. ANDROGENS

■ **Testosterone** is responsible for sexual arousal in females. It is given as the 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.

N.B. *Tibolone*, is a synthetic steroid drug with estrogenic, progestogenic, and weak androgenic actions . (*androgens use is not approved by FDA in women*)

# Non-hormonal agents used in management of menopausal symptoms

- **Fluoxetine** (SSRI) reduces vasomotor symptoms
- **Clonidine** (centrally acting antihypertensive, alpha 2 agonist) helps with vasomotor symptoms.
- **Gabapentin** (anticonvulsant) reduces severity and frequency of hot flushes
- **Physical activity:** exercise, smoking cessation and relaxation of mind will improve symptoms of menopause (e.g. hot flushes) and fall preventing strategies prevents chances of fracture.