



# Lecture 6

## HORMONE REPLACEMENT THERAPY

### Objectives:

- ★ 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
- Additional Notes
  - **Important**
  - Explanation –Extra-

# Introduction

- **Menopause:**

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

- **Hormonal changes in menopause:**

- ❖ ↓ Estrogen & progesterone
- ❖ ↓ Androgen
- ❖ ↓ FSH & LH
- ❖ ↑ Insulin resistance

- ❖ **Hormonal Replacement Therapy (HRT) :**

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

	Immediate	Intermediate	Long term
<b>Menopausal Symptoms</b> (mainly due to low estrogen level)	<ul style="list-style-type: none"><li>★ Hot Flashes / Night sweat ( Vasomotor Symptoms )</li><li>★ Insomnia, Anxiety, Irritability</li><li>★ Mood disturbance</li><li>★ Reduction in sexuality &amp; libido</li><li>★ Poor concentration / Memory loss</li></ul>	<ul style="list-style-type: none"><li>★ Dyspareunia &amp; vaginal dryness</li><li>★ Urethral Syndrome ( dysuria, urgency , frequency )</li><li>★ Incontinence, difficulty in voiding</li><li>★ Increased bruising</li><li>★ Generalized aches and pains</li></ul>	<ul style="list-style-type: none"><li>★ Osteoporosis</li><li>★ CVS Risks : ↑ LDL / HDL ratio, CHD, Stroke</li><li>★ CNS deficits : Alzheimer's , dementia</li></ul>

# Hormonal Replacement Therapy

## 1-Estrogen:

- **With Progesterone:** in case of existing uterus\*
- **Without progesterone :** in case of Hysterectomy

## 2-Progesterone

## 3-Selective ER-Modulators[SERMs]

## 4-Phytoestrogens (from plant)

## 5-Androgens :

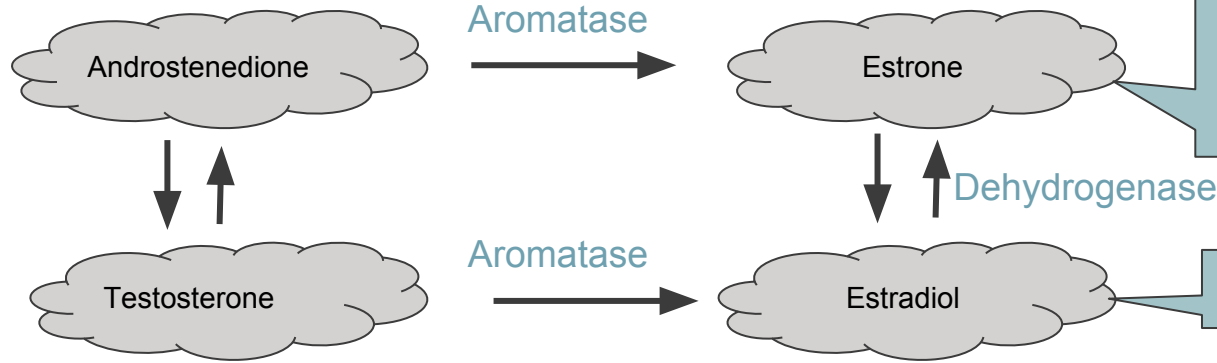
- For promotion of sexual desire
- Given only if there is **loss of libido & orgasm**

## ❏ 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
- Long term use was only indicated in osteoporosis & CVS protection , But now because better drugs are available , it is Not preferred any more

\* because estrogen has effect on endometrium , may cause endometrial carcinoma

# In Nature



## 1- Estrogen

- **In pre-menopausal** : produced by ovaries & Adrenals
- **In menopause** : produced by Adrenals only

- **in pre-menopause** :Produced by ovaries

# As Therapy

## 1- Estradiol :

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

## 2- Conjugated estrogen :

mixture of Na salts of **sulfate esters of estrone & equilin**(estrogen from horses)

## 3- Esterified estrogen

### Types of estrogen receptors:

#### 1- ER alpha :

##### Mediates female hormonal function:

Endometrium , breast , ovaries , hypothalamus

#### 2- ER beta :

##### Mediates other hormonal functions:

Brain, bone, heart, lungs, kidney, bladder, intestinal mucosa , endothelial cells

# 1-Estrogen

## Indication (in menopause)

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

## Notes

**\*Not given unless presence of symptoms;**

- Alone only after hysterectomy
- With progestin as HRT in the other conditions
- When given never exceed 5 years administration

## Other uses of estrogen

- ◆ Contraception
- ◆ Primary ovarian failure
- ◆ Amenorrhea & hirsutism caused by excess androgens

# 1-Estrogen

## Administration

- ❑ Oral :  
**Conjugated equine Estradiol valerate**  
**Estradiol succinate**
- ❑ Transdermal (estradiol) :
  - **Patches** : 24 hours twice weekly
  - **Gel** : 24 hours daily
- ❑ **Subcutaneous implant (estradiol)** : 6 monthly
- ❑ **Vaginal cream** as such or as ring pessaries

## ADRs

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

## Contraindications

- **Absolute :**
- ◆ Undiagnosed vaginal bleeding
- ◆ Severe liver disease
- ◆ Thromboembolic manifestation
- ◆ Cancer , endometrial, breast (hormone sensitive), ovarian

## Interactions

- **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.
- **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. (we can use it orally)
- Progestin preparations; as in contraceptive pills.

### What does progesterone do?

#### **Binds to its receptors:**

-Two types of progesterone receptors [PR] **PR-A & PR-B**

- They could exist in:
  - 1-cytoplasmic → mediating genomic long term effects.
  - 2-membranous → mediating non-genomic rapid effects.

# Indications

## A. In Menopause

- As HRT, usually given in combination with **estrogen** Some use it alone in risk of cancer (ex: endometrial carcinoma) but does not ↓ all menopausal symptoms.
- Protects against possibility of estrogen induced endometrial cancer **HOW?**

**Estrogen** causes cell growth. If unopposed endometrial cell lining can show (atypical hyperplasia)  
**With 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**(doubtful protection). Mammography recommended every 6ms.

- ❖ Confers neuroprotection, mild effect
- ❖ Controls insomnia & depression little effect
- ❖ Counteract osteoporosis, directly **+ve osteoblasts** (it's better to use with estrogen to give more protective effect)

## B. Other Uses

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



<b>Administration</b>	<ul style="list-style-type: none"> <li>❖ <b>Oral</b>; Micronized progesterone or progestins.</li> <li>❖ <b>IU(intrauterine)</b>; as Levonorgestrel or Progestasert.</li> <li>❖ <b>Vaginal</b> - natural progesterone (<b>gel / pessary</b>).</li> <li>❖ <b>Transdermal</b> - (sequential / continuous patch).</li> </ul>
<b>ADRs</b>	<ul style="list-style-type: none"> <li>-<b>Mood changes</b>, as anxiety, irritability</li> <li>-<b>Headache</b>, dizziness or drowsiness</li> <li>-Nausea, vomiting, abdominal pain or bloating (distention).</li> <li>-<b>Hirsutism , masculinization</b> (Not with new preparations)</li> </ul>

**Benefits and Risks of HRT**

<b>Definite benefits</b>	<b>Definite risks</b>	<b>Uncertain benefits</b>
<ul style="list-style-type: none"> <li>-<b>Alleviates symptoms of menopause</b> (vasomotor, genitourinary)(mostly estrogen)</li> <li>-<b>Osteoporosis</b> (Definite increase in bone mineral density; probable decrease in risk of fractures) (estrogen+progesterone)</li> </ul>	<ul style="list-style-type: none"> <li>-Endometrial cancer (<b>estrogen only</b>)</li> <li>-Venous thromboembolism (<b>long term</b>)</li> <li>-Breast cancer (<b>long term 5 yrs</b>)</li> </ul>	<p style="text-align: center;">Cognitive functions</p>

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

# 3-SERMs

**Raloxifen:** antagonist in breast and uterus and agonist in bone  
**Tamoxifen:** Antagonist in breast and partial agonist in bone and uterus (endometrium).  
 (Both of them are oral and non-hormonal)

**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.

**Tamoxifen** risk of venous thrombosis & tends to precipitate vaginal atrophy & **hot flashes**.

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

	brain	uterus	vagina	breast	bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERMs	++	-	++	-	++	++
tamoxifen	-	+	-	-	+	+
raloxifene	-	-	-	-	++	+

+ = agonist  
 - = antagonist  
 Tamoxifen & raloxifene are not ideal SERMs

## 4-Phytoestrogens

- **supplements from plants**; containing isoflavones (soybeans, flaxseeds) or lignans (whole grains). **Avoid in estrogen dependent breast cancer**
- They mimic action of estrogen on **ER-b** alleviate symptoms related to hot flashes, mood swings, cognitive functions & possess CVS protective actions. (data limited on their efficacy)
- They block actions mediated by **ER-a** in some target tissues lower risks of developing endometrial & breast cancer.

## 5-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** (anti-convulsant) 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.

## The Women's Health Initiative (WHI) and HRT

- 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.

# MCQs

**Q1 : Which of estrogen receptors works on endometrium & breast?**

- A) ER alpha
- B) ER beta
- C) Both of them

**Q2: An ideal SERMs should be antagonistic in?**

- A)breast & uterus.
- B)liver.
- C)bone & brain.

**Q2 : In which one of the following conditions is estrogen absolutely contraindicated ?**

- A) Amenorrhea
- B) Undiagnosed vaginal bleeding
- C) Poly cystic ovaries

**Q4 : Which of the these HRT is recommended for women who have had their uterus and ovaries removed by hysterectomy ?**

- A) Estrogen only
- B) Progesterone only
- C) Combined of both

**Q5: which one of the following is a synthetic steroid drug with estrogenic, progestogenic, and weak androgenic actions?**

- A)phytoestrogen.
- B)tibolone.
- c)fluoxitene

**Q6: Which one of the following therapy is given to a menopausal women in whom their menopausal symptoms are focused on lack of sexual arousal?**

- A)Levonorgestrel
- B)Clonidine
- C)androgens

# Good luck!

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