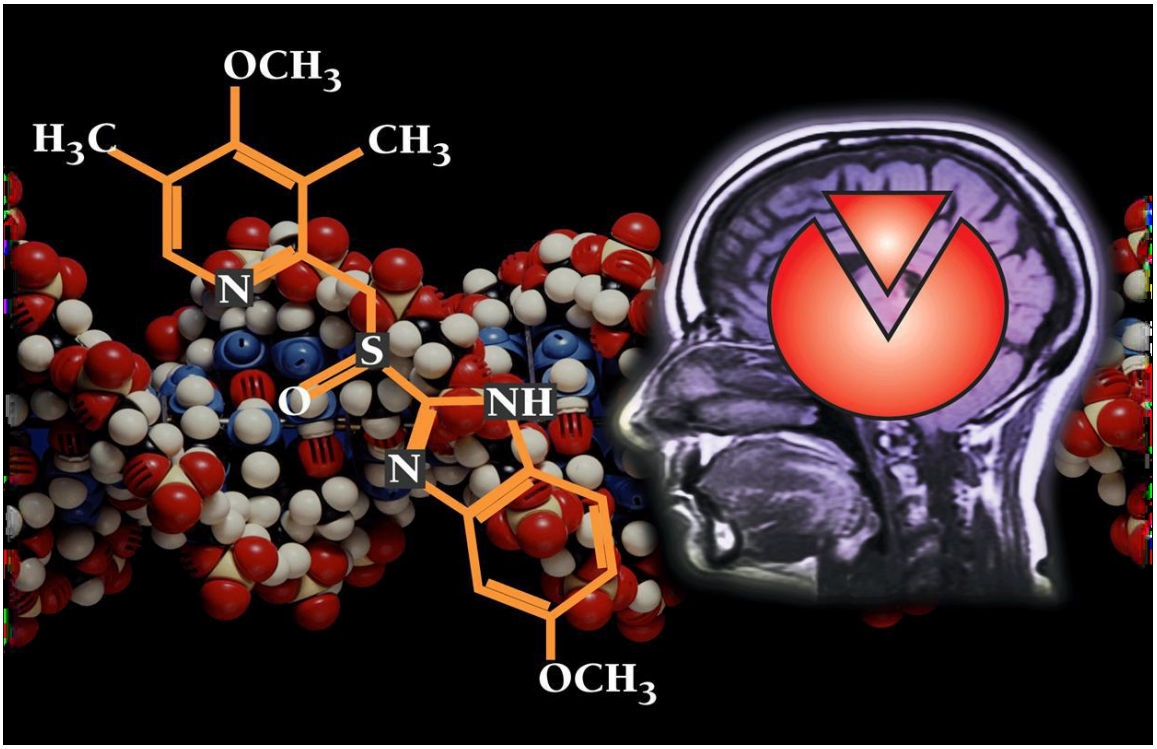
King Saud University
College Of Medicine
Pharmacology Team 430
Endocrine Block

# 07-Hormone Therapy




Note: Text in green is additional info, and text in red is important.

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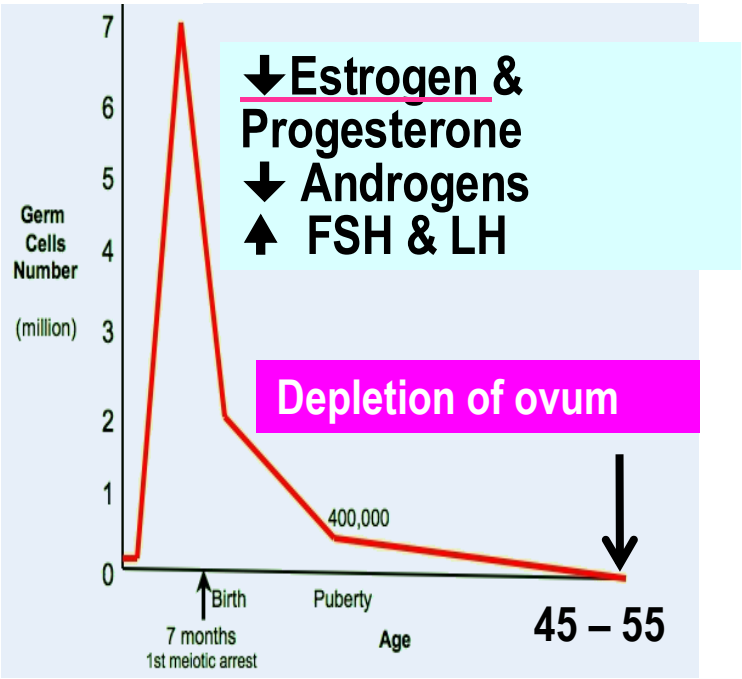
## Menopause:

- A complex physiological change that occurs at the time when the last period ends generally as women age and loss fertility
- It affects 1/3 of women population
- Obese women are more protected due to the increased concentrations of Esterone (peripherally formed by conversion of androgens secreted by the adrenals) and by the decrease in SHBG, which increases the ratio of free estrogen.
- Hormonal Changes are seen in the graph




## - Symptoms and Consequences of Menopause:

### Immediate Symptoms and consequences:

- Hot Flushes / Night Sweats

Hot flushes and sweats are a result of intense vasodilation and over activity of the sweat glands to lower body temperatures. The exact mechanisms of hot flushes is unknown, but it probably involves increased sympathetic stimulation, increased core body temperature, and decreased body tolerance to changing temperature

- Insomnia, Anxiety, Irritability
- Mood Disturbances
- Reduction In Sexuality & Libido (estrogens increase libido in humans)
- Poor Concentration / Memory Loss

### Intermediate Symptoms and consequences:

- Rapid loss of collagen. This maybe due to the loss of protein deposition properties that estrogen has on some tissues like the bones and reproductive system. This effect may also contribute to the production of osteoporosis.
- Dyspareunia (painful sexual intercourse) & vaginal dryness
- Urethral syndrome (non-specific urethritis, which are the presenting symptoms of urethritis without presence of an obvious pathogen) (dysuria, urgency & frequency)
- Incontinence, difficulty in voiding
- Increased bruising
- Generalized aches and pains

### Long Term Symptoms and Consequences:

- Osteoporosis, This is generally due to increased apoptosis of osteoclasts and decrease the resorbtion of bone by antagonizing PTH and other factors
- CVS Risks: LDL/HDL ratio, CHD, stroke
- C N S deficits: Alzheimer's, dementia

## Hormone replacement therapy:

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.

The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability and vaginal atrophy.

Hormone therapy should never exceed 5 years to control menopausal symptoms and to prevent estrogen induced malignant transformation.

Long-term administration was only indicated in osteoporosis & CVS protection, but is now not preferred because better drugs are available.

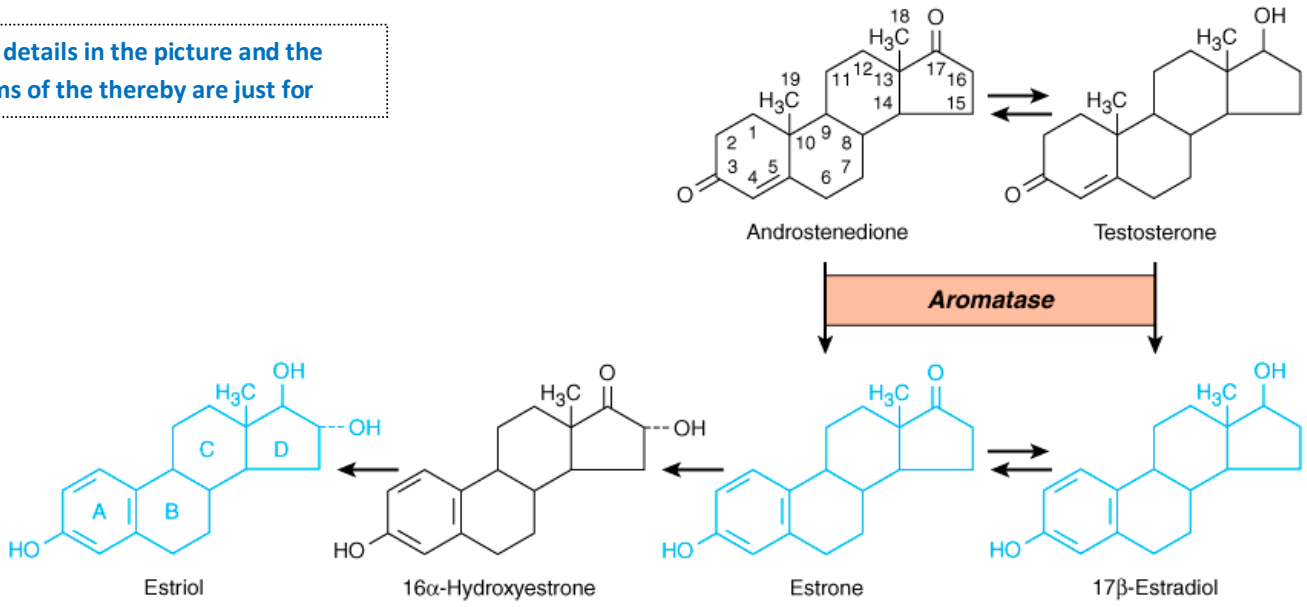
## Forms of replacement therapy:

1. Estrogen➔ Some undesirable side effects. Progesterone should be added but not if there is hysterectomy.
2. Selective ER-Modulators [SERMs]
3. Tibolone
4. Phytoestrogens (but it used for prevention more than for treatment-not powerful-)
5. Androgens: because they are *responsible for sexual arousal, are given only if there is loss of libido & orgasm.* (used carefully)

### 1. Estrogen Therapy:

Estrogen is naturally produced in the form:

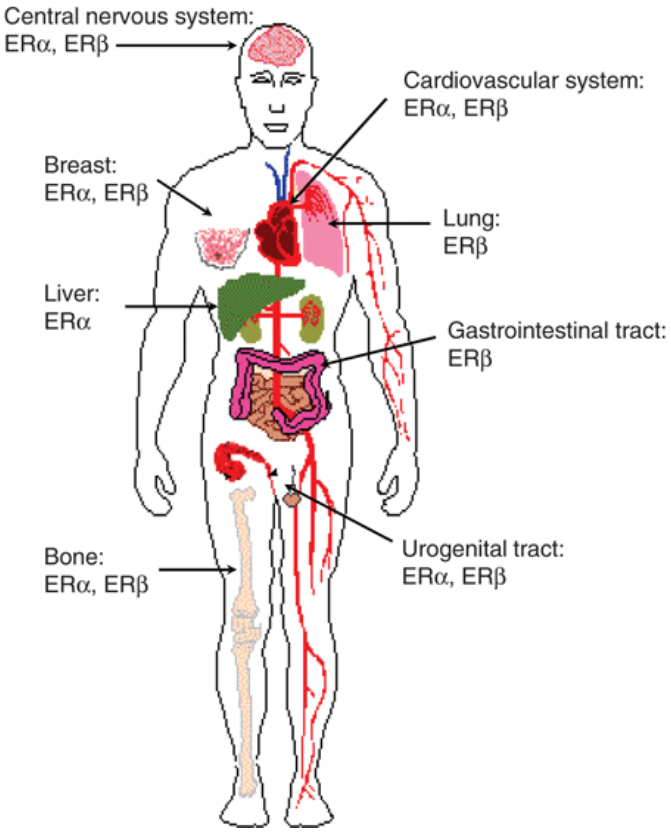
The details in the picture and the forms of the thereby are just for



As Estrogen therapy:

1. Estradiol; *Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, intradermal implant.*
2. Conjugated estrogens
3. Esterified estrogens

## Estrogen receptors and MOA




Types of Estrogen Receptors [ER]:

ER α➔ mediates female hormonal functions (in female sexual organ):

*Endometrium, breast, ovaries, and hypothalamus.*

ER β➔mediates other hormonal functions:

*brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, and endothelial cells.*

Estrogens bind to ER (αor β) that exist as either:

A. Cytoplasmic receptors (genomic effects):
Activate, translocate, dimerize on ERE of DNA ➔ Transcription & Translation of regulatory proteins

These genomic actions usually take hours and days. The produced protein cause developmental, neuro-endocrine, and metabolic effects of estrogen.

B. Membranous (non-genomic effect): binds to estrogen coupled G protein ➔2nd messenger ➔⬆Ca or cAMP. These effects mediate estrogen's non-genomic actions such as increased NO, neuro- transmitter production.

## Indications of Estrogen Therapy:

Just know the **indication** the **mechanism which is in black** will not be ask about them

### A- In menopause:

- **Improves hot flushes&night sweats** by acting on opiate, NE & 5HT regulating heat dissipation at hypothalamus.
- Controls **sleep disturbance&mood swings** by acting on NE, DA & 5HT at reticular formation, perioptic areas & hypothalamus.
- 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
- **Increases bone density** by:

1. ⬆osteoclast apoptosis & growth factors from osteoblasts
2. ⬇No. & depth of resorption cavities & release of cytokines
3. ⬆calcitonin release from thyroid

- Protects CVS: enhance vasodilatation via ↑ NO production, & cholesterol clearance via ↑ HDL &↓ LDL hepatic expression thus ↓ atherosclerosis & ischemic insults
  There has been a lot of dispute on the effect of estrogen and wehter it is benefitial or not, but generally speaking the cardiovascular risk depends on the degree of atherosclerosis at the onset of therapy.

- Improves insulin resistance & glycemic control in diabetics
- Improves cognitive function via ↑ expression of ER in brain & by ↓ amyloid deposition thus preventing Alzehimer 's.
- Delays parkinsonism by acting on DA system in midbrain

Daily therapy with low doses of conjugated equine estrogens and progesterone will eliminate cyclic bleeding, control vasomotor symptoms, prevent genital atrophy, maintain bone density, and show a favorable lipid profile with a small decrease in LDL and an increase in HDL concentrations.

**Menopausal Hormone Therapy Guidelines:**
- Not given unless presence of symptoms
- Alone only after hysterectomy
- With progestin as HRT in the rest of conditions
- When given never exceed 5 years administration

B- Other Uses (4 ur info):

- **Contraception (imp)**
- Primary ovarian failure
- Amenorrhea &Hirsutism caused by excess androgens
- Prostatic carcinoma in males: but cause feminizing characters so other drugs better given

## Administration:

Know them without details

- **Oral:**
- Conjugated equine estrogen (CEE); (EstroneSulphate + equilinsulphate+17 d dihydroequilin) from female horse
  Estradiol valerate
  Estrial succinate

  Some estrogen conjugates may be hydrolyzed in the intestine to active, reabsorbable compounds.Because significant amounts of estrogens and their active metabolites are excreted in the bile and reabsorbed from the intestine, the resulting enterohepatic circulation ensures that orally administered estrogens will have a high ratio of hepatic to peripheral effects. The hepatic effects are thought to be responsible for some undesirable actions such as synthesis of increased clotting factors and plasma renin substrate.

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

## Interactions:

*If given with:*

- SERMs➔ additive side effects for both drugs
- Aromatase inhibitors ➔↓ efficacy
- Corticosteroids ↑ side effects (they have the same ADRs )

## Contraindications:

**Absolute (very dangerous ):**

- Undiagnosed vaginal bleeding (Risk of cancer)
- Severe liver disease (Because estrogens are metabolized in the liver)
- Thromboembolic manifestations (because it increase the clotting factor)
- Cancer: endometrial, breast (hormone sensitive), ovarian

**Relative (should be more careful IN USING IT):**

- Headaches; specially migraine
- History of uterine fibroid or atypical ductal hyperplasia of breast
- Active gallbladder disease; cholangitis, cholecystitis

## 2-Progestins:

### Naturally:

Synthesis is induced by LH
Produced by: Adrenal glands, Gonads, Brain, and Placenta
Are precursor to estrogens, androgens, and adrenocortical steroids.

### Theraputically:

- Progesterone is natural form destructed 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

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:

1) As HRT, usually given in combination with estrogen. Some use it alone with paitents in risk of cancer, but progesterone does not alleviate all menopausal symptoms (eg; hot flushing , we use it more as contraceptive mini pill)

2) Protects against possibility of estrogen induced endometrial cancer:
   (a) Estrogen causes cell growth and proliferation of the endometrium, and If unopposed ➔endometrial cell lining can show (atypical hyperplasia)
   (b) Progesterone beneficially➔ matures endometrial cell lining (become differentiated) &↑ apoptosis of atypical cells by activation of p53.

3) Natural progesterone protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, BUT WITH SYNTHETIC PROGESTINS protection not confirmed ➔ so mamographyevery 6ms.
4) Confers neuroprotection, ↑ cognition &↓ incidence of Alzheimer's
5) Controls insomnia & depression ➔ precursor of melatonin & release 5HT
6) Contributes to CV protection ➔↑ NO & has anti-atherogenic actions
7) Counteract osteoporosis, directly +ve osteoblasts & indirectly blocking GC induced bone resorption

## Other indications:

### 1. Contraception

2. Dysmenorrhea
3. Infertility due to inadequate luteal phase

## Administration:

- Oral; Micronized progesterone or progestins ➔ see contraception
- IUS; as Levonorgestrel or Progestasert
- Vaginal - naturalprogesterone gel / pessary.
- Transdermal -sequential / continuous patch.

## 3-SERMS:

Selective estrogen-receptor modulators (SERMs) are a class of estrogen- related compounds that interact at estrogen receptors but have different effects depending on the tissues i.e. they display selective agonism or antagonism according to the tissue type).

SERMS are Classified according to how they bind to ER

- **Raloxifeneis Antiestrogens** that exhibits partial agonistic action;acting as an agonist in bone & an antagonist in breast.
- **Tamoxifen** competes with estrogen for binding to the estrogen receptor in breast tissue. It stabilizes ER in a conformation allowing transcription to occur on only certain ER-responsive genes(post receptor effect).
- **An ideal SERM for use as HRT should be agonistic in brain, bone, CV system, vagina & urinary system but antagonistic in breast & uterus**
- **Tamoxifen** ➔↑risk of venous thrombosis & tends to precipitate vaginal atrophy & hot flushes
- **Raloxifene** ➔ has no effect on hot flushes.

## 4-Tibilone

Tibilone is a synthetic steroid that is metabolized to many metabolites that **have estrogenic, androgenic &progestagenic properties**

**Tibolone is close to being ideal HRT, because:**

- It induces amenorrhoea
- Improves urogenital symptoms
- Enhances mood & libido.
- Protective on CVS system

- Prevents bone loss
- Protective on endometrium
- Least tendency of breast cancer

## Indications: (All in menopause):

- With history of endometriosis, fibroids, or treated breast cancer.
- In diabetics, hypertriglyceridemics
- In thromboembolic tendency
- In lack of sexual arousal

### 5-PHYTOESTROGENS:

Are supplements from plants; containing isoflavones (soya beans) or lignans (whole grains).

- They mimic action of estrogen on ER-b➔ alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions.
- They block actions mediated by ER-a 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, can be effective in some women ➔ has some androgen agonistic properties.*

**Imp:**

**As HRT we used:**

- **Estrogen with progestin**
- **SERMs:**
- **RALOXIFENE** best choice for bone (osteoporosis)
- **Tibilone** (is treatment of choice for obese ,lack of sexual arousal or other c.v.s problems

# Summary:

- Menopausal Hormone Therapy Guidelines:
- Not given unless presence of symptoms and when is given never exceed 5 years administration
- Alone only after hysterectomy and With progestin as HRT in the rest of conditions

- Types of Estrogen Receptors [ER]:
- ER α➔ mediates female hormonal functions (in female sexual organ): eg:Endometrium, breast and ovaries.
- ER β➔mediates other hormonal functions

- We use estrogen In menopause to :
- Improves hot flushes&night sweats ,Controls sleep disturbance&mood swings ,Improves urethral & urinary symptoms, Improves vaginal dryness ,Increases bone density
- Protects CVS, Improves insulin resistance & glycemic control in diabetics
- Improves cognitive function so preventing Alzehimer 's and Delays parkinsonism

- Estrogen is Contraindicated with:
- Undiagnosed vaginal bleeding , Severe liver disease
- Thromboembolic manifestations
- Cancer: endometrial, breast (hormone sensitive), ovarian

- We should be careful when using it with:
- Headaches; specially migraine
- History of uterine fibroid or atypical ductal hyperplasia of breast
- Active gallbladder disease; cholangitis, cholecystitis
- Drugs AS : SERMs , Aromatase inhibitors , Corticosteroids

- Progestins are **synthetic** HRT and Progesterone is **natural form** usually given in combination with estrogen. Some use it alone with patients in risk of cancer, but progesterone does not alleviate all menopausal symptoms we use it more as contraceptive mini pill

- **An ideal SERM for use as HRT should be agonistic in brain, bone, CV system, vagina & urinary system but antagonistic in breast & uterus**
- **Raloxifeneis is Antiestrogens** that exhibits partial agonistic action ;acting as an agonist in bone & an antagonist in breast.
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- **Tamoxifen➔↑**risk of venous thrombosis & tends to precipitate vaginal atrophy & hot flushes
- **Raloxifene➔** has no effect on hot flushes

- **Tibilone** has estrogenic, androgenic &progestagenic properties and it close to being ideal HRT

- Tibilone is treatment of choice With patient :
- history of endometriosis, fibroids, or treated breast cancer.
- In diabetics, hypertriglyceridemics
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- PHYTOESTROGENS Are supplements from plants; They mimic action of estrogen on ER-b and They block actions mediated by ER-a
- ANDROGENS:Testosterone is responsible for sexual arousal in females but Tibolone is better