

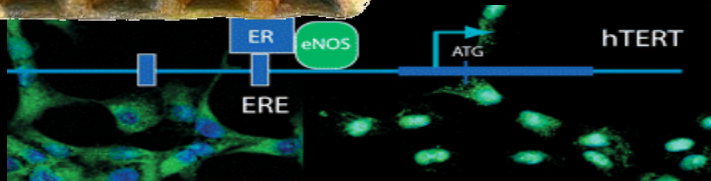


HORMONE REPLACEMENT THERAPY

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.





HRT

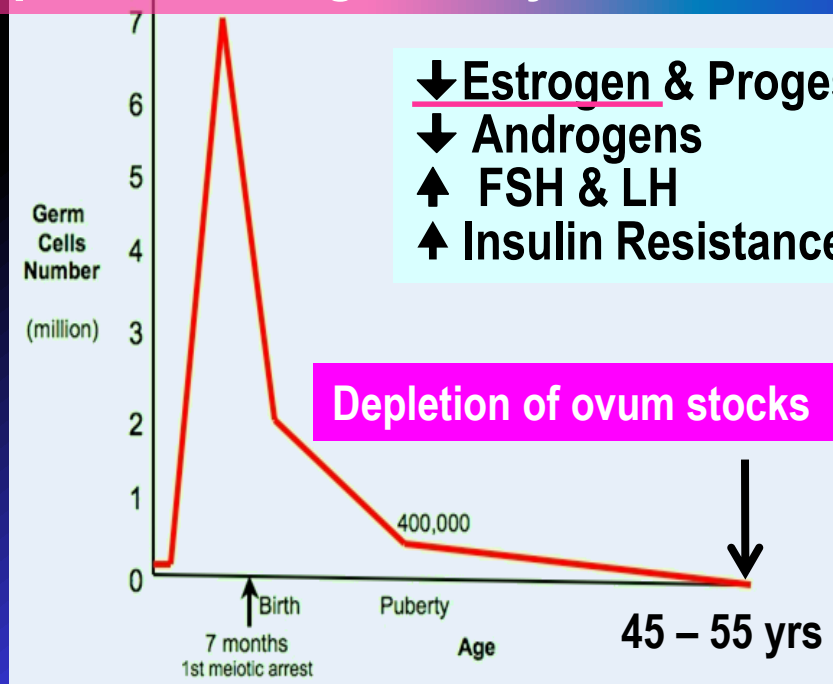
Is a system of medical treatment that is designed to artificially boost female hormones, in hope to alleviate symptoms caused by ↓ in their circulating levels

PERI & POSTMENOPAUSE

Natural, Pathological, Induced



A complex physiological change that occurs at the time when the last period ends generally as women age and loss fertility



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

1/3rd of total female population



Obese women are > protected →
 ↑ relative amounts of estrone & ↓ SHBG



SYMPTOMS & CONSEQUENCES of MENOPAUSE

HRT

➤ Immediate

➤ Intermediate

➤ Long Term

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

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

Symptoms Experienced Most During Menopause



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

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



Menopausal Symptoms → ↓ Estrogen

Replace the Estrogen ← Alleviate

■ Estrogen → Some undesirable side effects

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

■ Selective ER-Modulators [SERMs]

■ Phytoestrogens

Androgens → *responsible for promotion of sexual desires* → 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

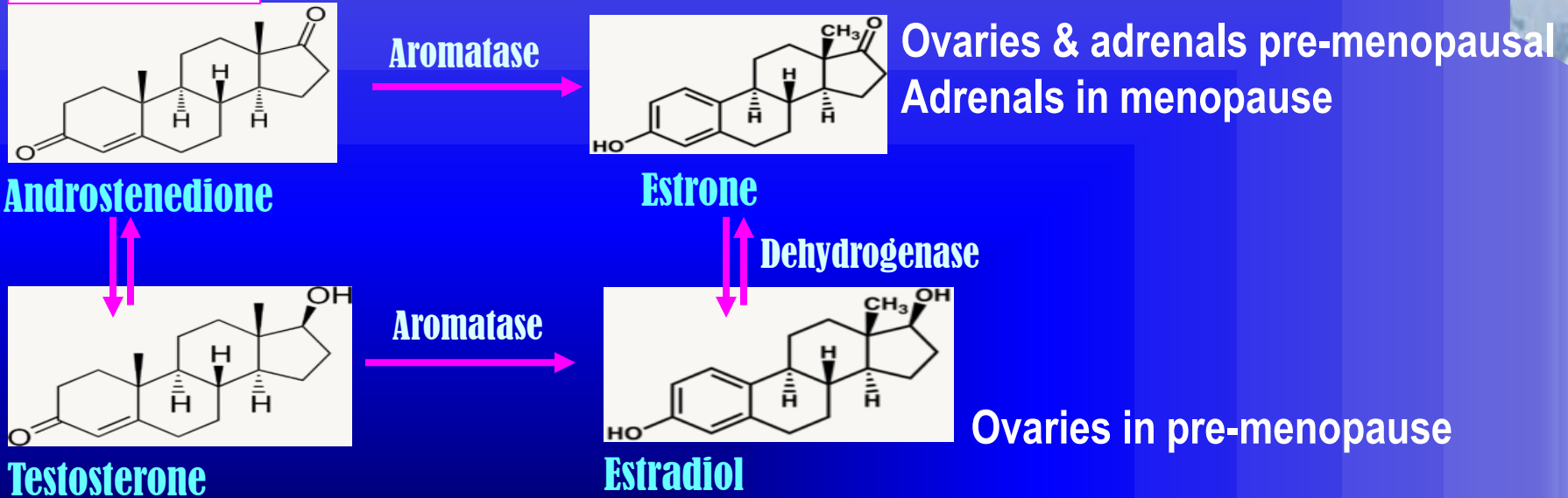
~~Long-term~~ administration was only indicated in osteoporosis & CVS protection but now better drugs are available

HRT ★



1. ESTROGEN

In NATURE



As Therapy

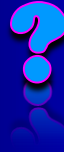
Estradiol; Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, intradermal implant, ...

Conjugated estrogens

Esterified estrogens

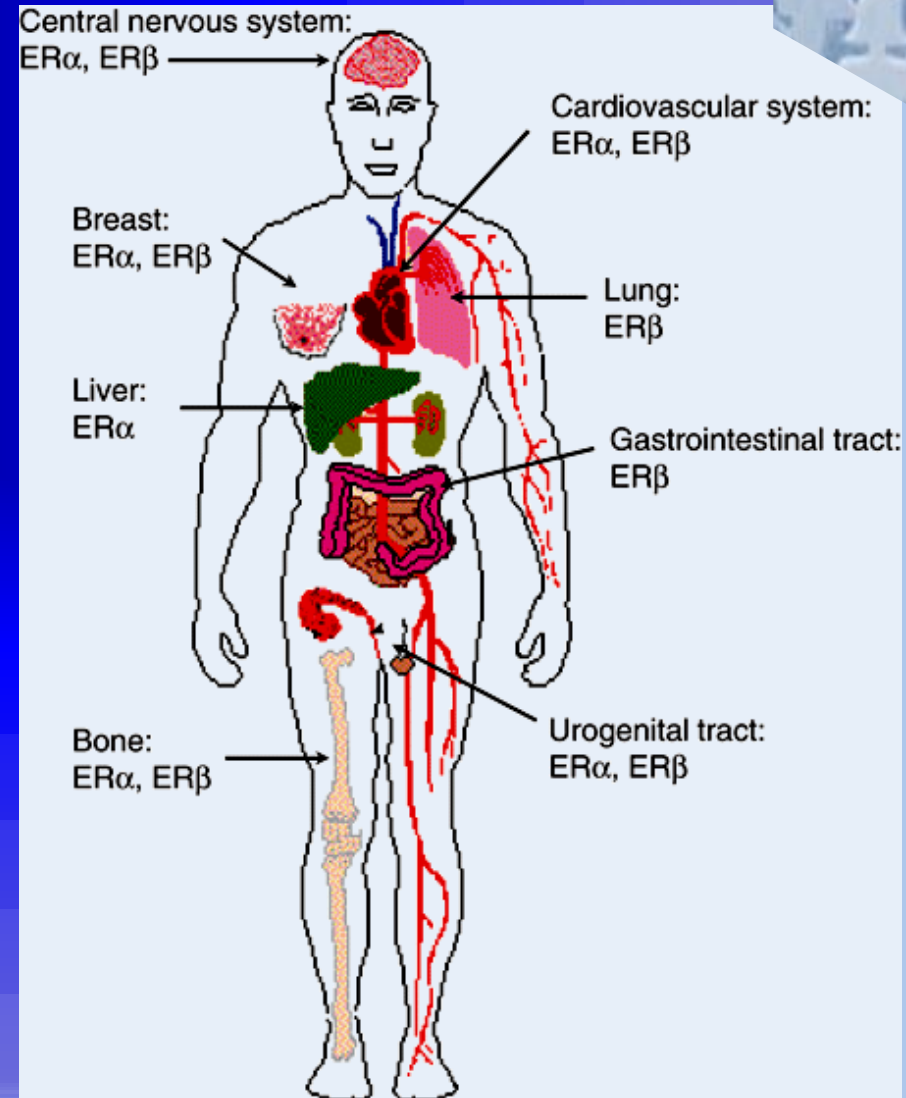


What does estrogen do
It binds to its receptors



ESTROGEN ★

Distribution of ER



Types of Estrogen Receptors [ER]

ER α →

> mediates female hormonal functions

Endometrium, breast, ovaries, hypothalamus,...

ER β →

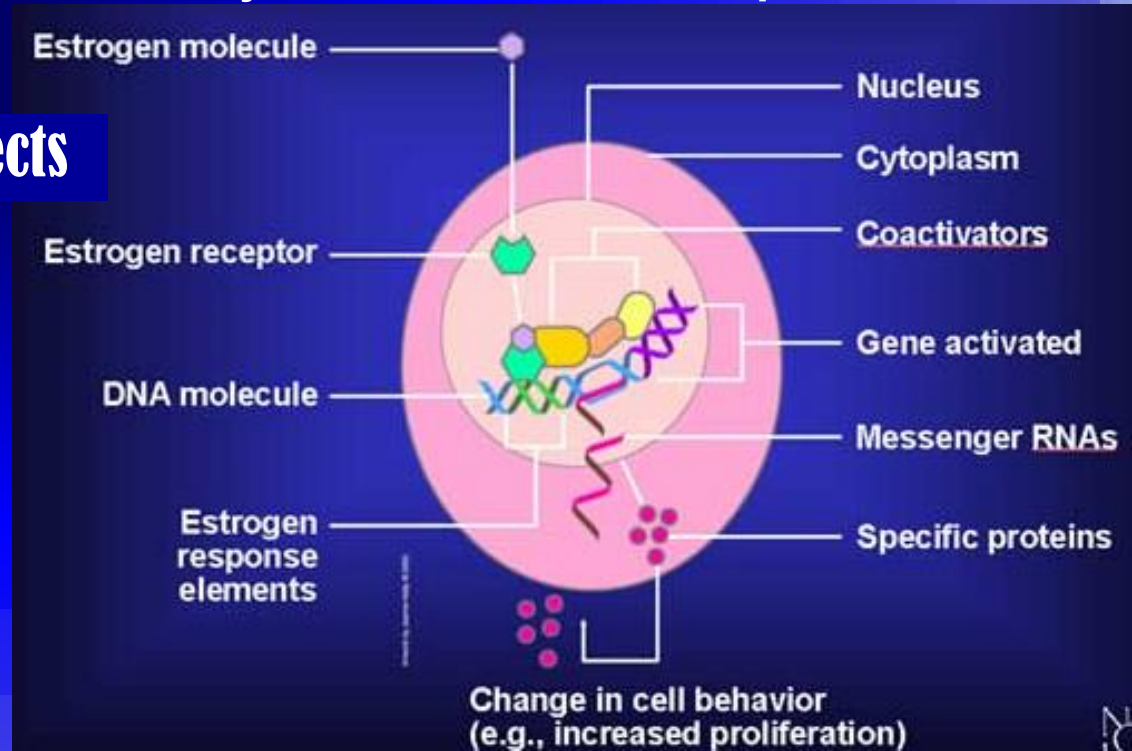
> mediates other hormonal functions

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

Estrogens bind to ER (α or β) that exist either;

- **Cytoplasmic:** activate, translocate, dimerize on ERE of DNA → Transcription & Translation to regulatory proteins
- > mediates its **genomic actions** → hrs– dys time scale → development, neuro-endocrines, metabolism

Genomic effects



Membranous: G protein ER → 2nd messenger → ↑ Ca or cAMP ...etc → mediates its **non-genomic actions** → sec – min. time scale → as on NO, neurotransmitters,



INDICATIONS

ESTROGEN★

A. In Menopause 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

➤ 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 ↑ calcitonin release from thyroid

■ ↑ osteoclast apoptosis & growth factors from osteoblasts

■ ↓ No. & depth of resorption cavities & release of cytokines



- Protects CVS: enhance vasodilatation via ↑ NO production, & cholesterol clearance via ↑ HDL & ↓ LDL hepatic expression thus ↓ atherosclerosis & ischemic insults
- 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

B. Other Uses

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





ADMINISTRATION

Ⓢ Oral: -

Conjugated equine estrogen (CEE); (*Estrone Sulphate + equilin sulphate + 17 d dihydro equilin*) from female horse

Estradiol valerate

Estrial 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 & INTERACTIONS

See contraception

NB. If given with

Ⓢ SERMs → additive side effects for both drugs

Ⓢ Aromatase inhibitors → ↓ efficacy

Ⓢ Corticosteroids ↑ side effects





Contraindications

Absolute:

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

Relative:

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

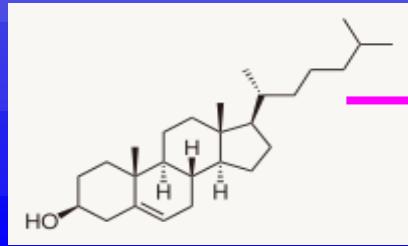


2. PROGESTINS

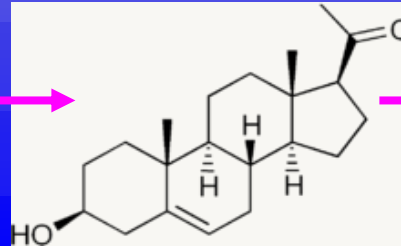
In NATURE

Produced by; Adrenal glands, Gonads, Brain, Placenta

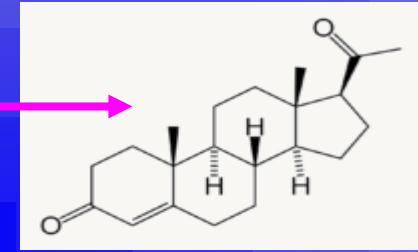
Synthesis;
Induced by LH



Cholesterol



Pregnenolone



Progesterone

Are precursor to estrogens, androgens, and adrenocortical steroids.

As Therapy

- Progesterone is destroyed 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

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 by activation of p53.
- Natural progesterone protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, BUT WITH SYNTHETIC PROGESTINS protection not confirmed → so mammography every 6ms.
- Confers neuroprotection. ↑ cognition & ↓ incidence of Alzheimer's
- Controls insomnia & depression → precursor of melatonin & release 5HT
- Contributes to CV protection → ↑ NO & has anti-atherogenic actions
- Counteract osteoporosis, directly +ve osteoblasts & indirectly blocking GC induced bone resorption

B. Other Uses

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 - natural progesterone gel / pessary.
- Ⓢ Transdermal - sequential / continuous patch.

ADRs

See contraception



3. SERMs Tamoxifen, Raloxifene

Classified according to how they bind to ER

- Antiestrogens that exhibits partial agonistic action ; acting as an agonist in bone & an antagonist in breast → **Raloxifene**
- Antiestrogens that stabilizes ER in a conformation allowing transcription to occur on only certain ER-responsive genes **Tamoxifen**

An ideal SERM for use as HRT should be agonistic in brain, bone, CV system, vagina & urinary system but antagonistic in breast & uterus

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
<u>Ideal SERM</u>	++	—	++	—	++	++
Not Ideal {	Tamoxifen	—	+	—	+	+
	Raloxifene	—	—	—	+	+

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

Raloxifene → has no effect on hot flushes.

4. PHYTOESTROGENS

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

- They mimic action of estrogen on ER- β → alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions.
- They block actions mediated by ER- α in some target tissues → lower risks of developing endometrial & breast cancer.

5. ANDROGENS

- **Testosterone** is responsible for promotion of sexual desire in females. It is given as the sole therapy to menopausal women in whom their menopausal symptoms are focused on lack of sexual desire. It is given as adjuvant to combined estrogen & progestin if all other menopausal symptom exist.

HRT

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