



Reproductive
System



PHARMACOLOGY
432 TEAM



LECTURE'S TITLE

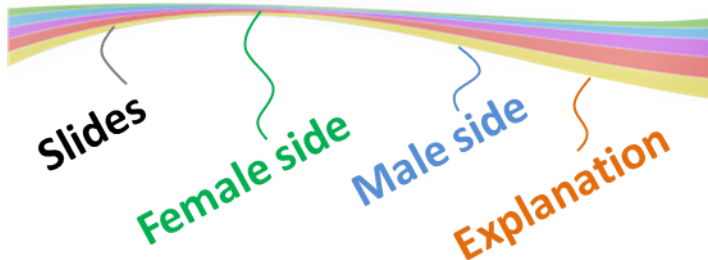
Learning Objectives:

1. Recognize menopausal symptoms and consequences.
2. Classify drugs used to alleviate such symptoms that are used as Hormonal Replacement Therapy (HRT).
3. Expand on the mechanism of action, indications, preparations, side effects, and contraindications of such agents.

This lecture was done by:

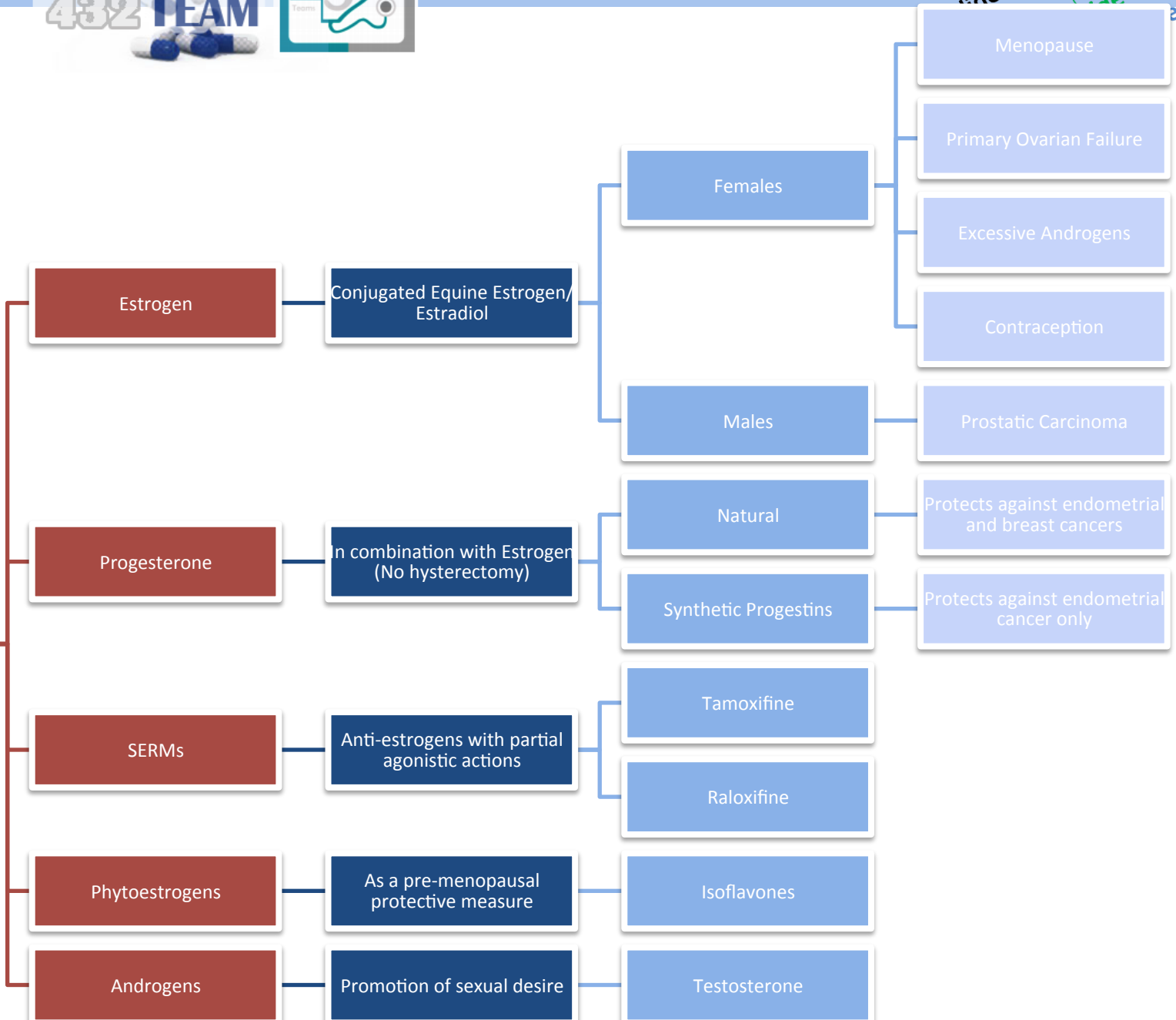
Shatha Al-Shanqeeti,
Rana AlOhaly, and Heba
AlSharif

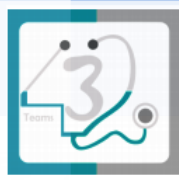
And reviewed by:
Member's Name





HRT



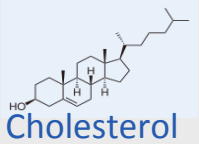


(2) PROGESTINS

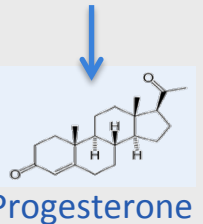
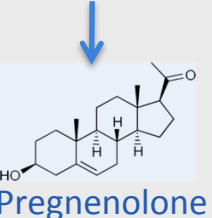
Grey= Not important

In Nature

- **Produced by:** Adrenal glands, Gonads, Brain, Placenta
- **Synthesis:** Induced by LH
- Progestins are precursor to estrogens, androgens, and adrenocortical steroids.



Cholesterol is the parent compound of all these



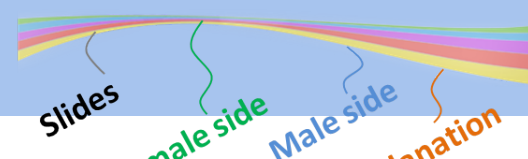
As Therapy

Progesterone

- It is *destroyed in GIT*, so can be *given only parentally*

Progestins

- They are synthetic progestogens that have progestinic effects similar to progesterone but *are not degraded by GIT*.
- **Progestin preparations:** as in contraceptive pills
- **Mechanism of action:**
 - Two types of Progesterone Receptors (PR):
 - ◇ PR-A Remember: Estrogen= α, β
 - ◇ PR-B Progesterone= A, B
 - Binding site:
 - ◇ Cytoplasmic: Mediating *genomic long term effects*
 - ◇ Membranous: Mediating *non-genomic rapid effects*



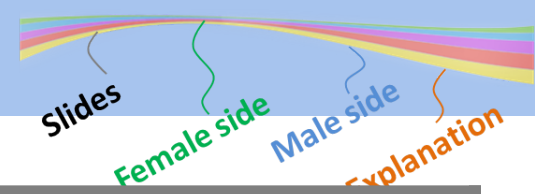
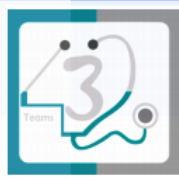
(A) In Menopause

- As HRT
- Usually given in combination with estrogen (**If she has a uterus to reduce the risk of cancer**)
- Some use it alone in risk of cancer
- Does not ↓ all menopausal symptoms

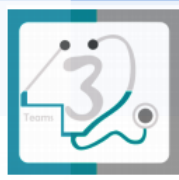
- **Protects against possibility of estrogen induced endometrial cancer**
 - Estrogen → ↑ cell growth. If unopposed → endometrial cell lining can show (**atypical hyperplasia**) **become undifferentiated and may progress to cancer**
 - Progesterone beneficially → matures endometrial cell lining (become 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 mamography every 6ms. **Especially if taking HRT**
- **Confers neuroprotection:**
 - **↑ cognition & ↓ incidence of Alzheimer's (+ controls mood swings)**
- **Controls insomnia & depression :**
 - precursor of melatonin & release 5HT
- **Contributes to CV protection (not confirmed):**
 - **↑ 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 (**the corpus luteum is not producing appropriate amounts of progesterone so we supply it exogenously until the placenta starts to form it**)



Administration	<ul style="list-style-type: none"> ○ Oral: Micronized <ul style="list-style-type: none"> ▪ Micronized Progesterone or ▪ Progestins such as: <table border="1" style="width: 100%; margin-left: 20px;"> <tr> <td style="width: 50%;">Old (have androgenic effect)</td> <td style="width: 50%;">New (no androgenic effect)</td> </tr> <tr> <td> <ul style="list-style-type: none"> • Norethindrone • Levonorgestrel (Norgestrel) • Medroxyprogesterone acetate </td> <td> <ul style="list-style-type: none"> • Norgestimate • Desogestrel • Drospirenone (anti-minerato-corticoid action) </td> </tr> </table> 	Old (have androgenic effect)	New (no androgenic effect)	<ul style="list-style-type: none"> • Norethindrone • Levonorgestrel (Norgestrel) • Medroxyprogesterone acetate 	<ul style="list-style-type: none"> • Norgestimate • Desogestrel • Drospirenone (anti-minerato-corticoid action)
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	<ul style="list-style-type: none"> ○ IUS: <ul style="list-style-type: none"> ▪ Levonorgestrel ▪ Progestasert 				
<ul style="list-style-type: none"> ○ Vaginal: <ul style="list-style-type: none"> ▪ Natural progesterone gel ▪ Pessary (a small soluble block that is inserted into the vagina) 					
<ul style="list-style-type: none"> ○ Transdermal: <ul style="list-style-type: none"> ▪ Sequential ▪ Continuous patch 					
Adverse Drug Reactions	<ol style="list-style-type: none"> 1. Nausea, vomiting 2. Headache 3. Fatigue, depression of mood 4. Menstrual irregularities 5. Weight gain 6. Hirsutism , masculinization 7. Ectopic pregnancy. <p style="margin-left: 300px;">} Androgenic effect</p>				



(3) SERMs (Selective Estrogen Receptor Modulators)

The mechanism of action isn't very important

Raloxifene

- **Mechanism of binding to Estrogen receptor:** Antiestrogen that exhibits **partial** agonistic action
- **Acting as an** agonist in bone antagonist in breast
- **ADR:** has no effect on hot flushes.

Tamoxifen (used in treatment of breast cancer)

- **Mechanism of binding to Estrogen receptor:** Antiestrogen that stabilizes ER in a conformation allowing transcription to occur on only certain ER-responsive genes
- **ADR:**
 - ↑ risk of venous thrombosis
 - tends to precipitate vaginal atrophy & hot flushes

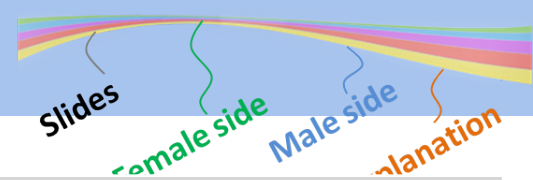
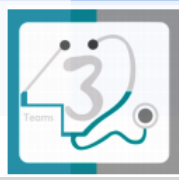
An ideal SERM for use as HRT should be:

- **Agonistic in:** 1)brain (to prevent hot flushes which are caused by **central** estrogen deficiency) 2)bone 3)CV system 4)vagina(to prevent dryness) 5)urinary system **but**
- **Antagonistic in:** breast & uterus (to prevent development of cancer)

You don't need to know the action of each drug. Just know that it can be variable

Not Ideal

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERM	++	—	++	—	++	++
Tamoxifen	—	+	—	—	+	+
Raloxifene	—	—	—	—	+	+



(4) Phytoestrogens

- Are supplements from **plants** (**phyto= plant source**) which contain:
 - isoflavones (soya beans)
 - lignans (whole grains)
- They're good as a preventive therapy that a woman takes before menopause but if she starts it once she becomes menopausal it won't have as much effect.
- Some doctors give it at first to see if it is effective instead of giving HRT
- 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 \rightarrow 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*.
 - **adjuvant to combined estrogen & progestin:** if all other menopausal symptoms exist.



What does estrogen do?

It binds to its receptors (the role of estrogen is gene expresser that will aid the synthesis of proteins involved in development of female sexual characteristics)

Types of Estrogen Receptors [ER]

ER α →

mediates female hormonal functions

Endometrium, breast, ovaries, hypothalamus,...

(responsible for the feminizing characteristics and mainly induced by genomic effect)

ER β →

mediates other hormonal functions

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

(affect other tissues in the body either be genomic or rapid effect)



Estrogens bind
to ER (α or β)

Cytoplasmic :

- Activate, translocate, dimerize on ERE of DNA →
Transcription & Translation of regulatory proteins
- mediates its genomic actions → hours– days time scale
 - 1)development
 - 2) neuro- endocrines
 - 3)metabolism

Membranous:

- G protein ER → 2nd messenger → ↑ Ca or cAMP ...etc
- mediates its non-genomic actions → second to minutes time scale
 - as on NO, neuro- transmitters .

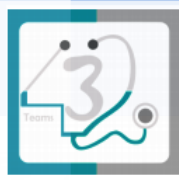


Indications

A. In Menopause: Not given unless presence of symptoms: (hot flushes, mood swings)

- 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 (useful in incontinence)
- **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

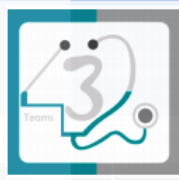


Indications

- **Protects CVS** enhance vasodilatation via \uparrow NO production, & cholesterol clearance via \uparrow HDL & \downarrow LDL hepatic expression thus \downarrow atherosclerosis & ischemic insults.
- **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 (**in first marital stage infertility**)
- Amenorrhea & Hirsutism caused by excess androgens (**Ex.PCOS**)
- Prostatic carcinoma in males ; but cause feminizing characters so other drugs better given.



Administration

ADRS & interactions

Contraindication

- **Oral:**
 - Conjugated equine estrogen (CEE);(Estrone Sulphate + equilin sulphate+17 d dihydro equilin) from female horse.
 - Estradiol valerate
 - Estrial succinate (most common way of administration)
- **Transdermal (estradiol);**
 - Patches ➔ 24 hour twice weekly.
 - Gel ➔ 24 hours daily.
- **Subcutaneous implant (estradiol) ➔ 6 monthly.**
- **Vaginal cream** as such or as rings pessaries

See contraception

NB. If given wit

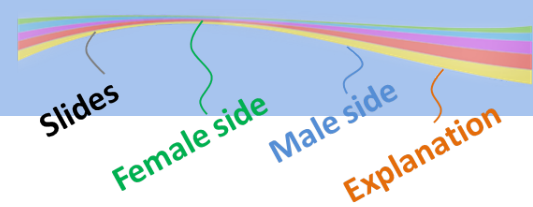
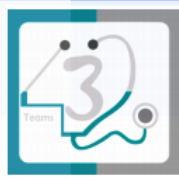
- SERMs ➔ additive side effects for both drug.
- Aromatase inhibitors ➔ ↓ efficacy of estrogens.
- Corticosteroids ↑ side effects (when estrogens and corticosteroids are combined with each other this will increase the side effect .Such as both of them cause salt and water retention)

• **Absolute;**

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

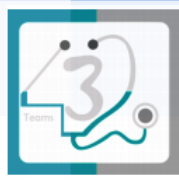
• **Relative;**

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



Summery

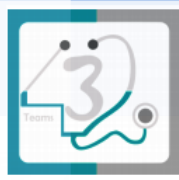
- HRT is designed to boost low circulating female hormones.
- HRT is not used as a long-term therapy.
- The drugs used are: Estrogen, Progesterone, SERMs, Phytoestrogens, and Androgens.
- Estrogen predisposes to endometrial, breast, cervical, and vaginal cancers.
- When given in combination with Estrogen, Progesterone decreases the incidence of endometrial cancer.



- 1. A 70-year-old woman is being treated with Tamoxifen for osteoporosis. There is an increased risk of developing:**
 - A. Breast Cancer
 - B. Uterine Cancer
 - C. Vein thrombosis
 - D. Atrophic Vaginitis

- 2. A 54-year-old woman walks into the primary care clinic complaining of hot flushes and night sweats in addition to difficulty in urinating. She also mentions that she has been experiencing some mood swings and a decreased libido. She says that she has generalized aches and feels tired most of the time. Which one of the following should be prescribed to relieve her symptoms?**
 - A. Tamoxifen
 - B. Estrogen
 - C. Estrogen + Progesterone
 - D. Estrogen + Progesterone + Testosterone

Answers: 1- C, 2- D



- 3. In which one of the following conditions is estrogen absolutely contraindicated?**
- A. Undiagnosed vaginal bleeding
 - B. Amenorrhea
 - C. Polycystic ovaries
 - D. Osteoporosis
- 4. Which one of the following is used for dysmenorrhea?**
- A. Tamoxifen
 - B. Estrogen
 - C. Progesterone
 - D. Testosterone



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