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.

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ادرسوا محاضرة oral contraceptives أول + المحاضرة هذي أغلبها فسيولوجي، فادرسوا فسيولوجي زين، بعدين ادرسوا هذي وركزوا على جانب الأدوية: ROA, ADRs, CI ؛ ما راح تأخذ منكم وقت كثير.

Drug's name | Doctors' notes | Important | Extra

« قل سيروا في الأرض فانظروا كيف بدأ الخلق »

سورة العنكبوت

To Understand Better

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

Menopause

1/3rd of total female population

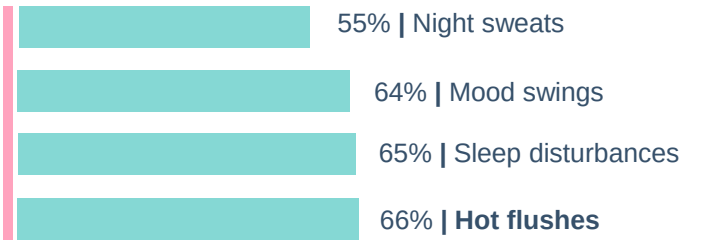
- A complex physiological change that occurs at the time when the last period ends generally as women age and loss fertility (age late 40s)

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

Menopause

- ↓ Estrogen & Progesterone
- ↓ Androgens → ↓ libido
- ↑ FSH & LH
- ↑ Insulin Resistance*

Symptoms experienced most during menopause



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

* Bc estrogen acts directly on beta-cells to make them resistant to apoptosis.

Symptoms & Consequences of Menopause

Immediate

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

Intermediate

- Dyspareunia (difficult of painful sexual intercourse) & vaginal dryness
- Urethral syndrome (dysuria, urgency & frequency)
- Incontinence, difficulty in voiding (problems with empting the bladder)
- ↑ bruising
- Generalized aches and pains

Long Term

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

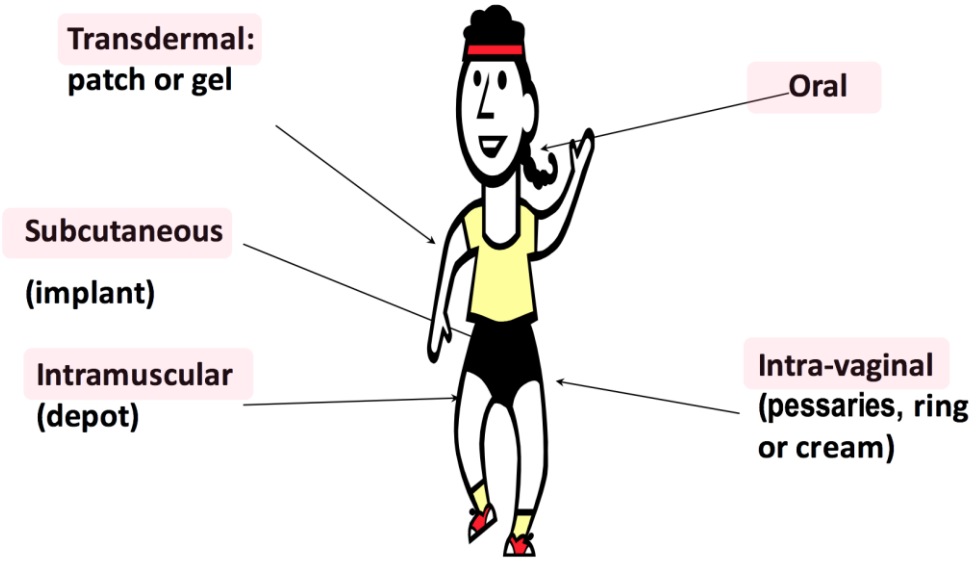
- Menopausal Symptoms are due to ↓ estrogen level
- Replace the Estrogen to alleviate the symptoms
- Estrogen → Some undesirable side effects → add: **Progestins**; but not if there is hystrectomy. SERMs, phytoestrogens or androgen (androgen is responsible for sexual arousal → given only if there is loss of libido & orgasm)

Hormone replacement therapy

- Estrogen
- Progestins
- SERMs
  - Tamoxifen
  - Raloxifene
- Phytoestrogens
- Androgen

- They are 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 administration is no more preferred, it was only indicated in osteoporosis & CVS protection, but now better drugs are available.

Prescription of HRT: ROUTES



1- Estrogen

Estrogen Receptors

مش حنركز على الفسيولوجـي ☺

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,….

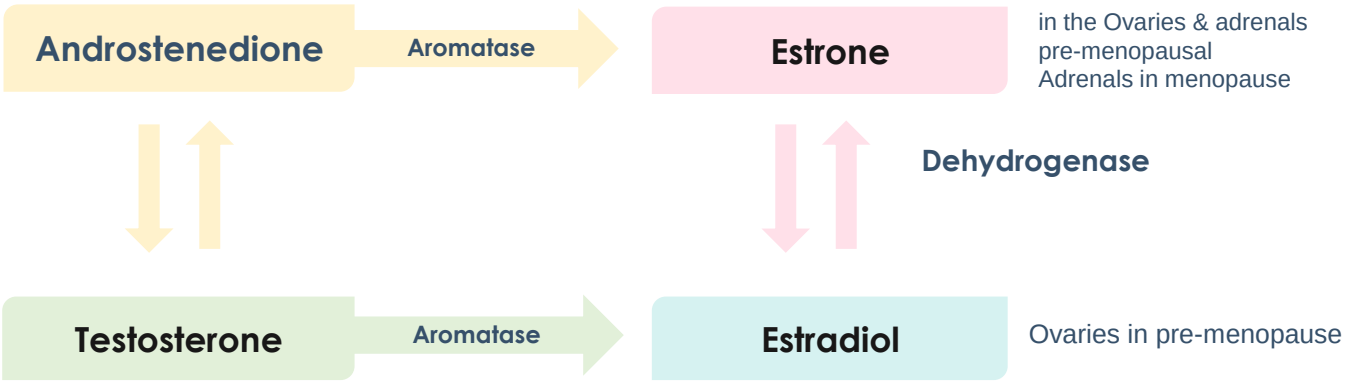
1- Estrogen (cont.)

❖ **P. K**

- **Estrogens bind to ER (α or β) that exist either:**
  - **Cytoplasmic**; mediates its genomic actions → hrs– dys time scale → development, neuro- endocrines, metabolism
  - **Membranous**; GPER → 2nd messenger → ↑ Ca^{2+} or cAMP or ↑ MAP Kinase → mediates its non-genomic actions → sec –min. time scale on NO, neuro- transmitters, endometrium, ….

GPER; G protein ER
MAP Kinase; mitogen activated protein kinase that activate transcription factors to promote mitogenesis

How does it produced?



Estrogen Forms

Drug	Estradiol	Conjugated estrogens	Esterified estrogens
P.K	○ **Oral bioavailability** is low due to its rapid oxidation in the liver → so used only in **transdermal patch**, **intradermal implant**, …	○ Mixture of Na^+ salts of sulfate esters of estrogen & equilin (estrogen from horses)	–

1- Estrogen (cont.)

Indications (أغلبها فسيولوجي)

A. In Menopause: (Not given unless presence of symptoms. Estrogen alone only after hysterectomy or with progestin as HRT (never exceed 5 yrs administration)

- **Improves hot flushes & night sweats** → Estrogen treatment reestablishes feed-back on hypothalamic control of norepinephrine secretion, leading to decreased frequency of "hot flashes.. In this case, the use of the lowest dose of estrogen required for symptomatic relief is recommended
- **Controls sleep disturbance & mood swings** by acting on NE, DA & 5HT at reticular formation.
- **Improves urethral & urinary symptoms** by increasing epithelial thickness & vascularity, collagen content at urethra & NE transmission that contract sphincters & relax detrusal muscles
- **Improves vaginal dryness** by increasing epithelial thickness & vascularity, collagen content (topical and systemic estrogens prep are effective)
- ↑ **bone density** by increasing calcitonin release from thyroid to ↓ osteoclastic activity.
- **Progestins act synergestic** by blocking corticosteroid induced bone resorption. (↓ incidence of hip fracture)
- **Protects CVS**; enhance vasodilatation via increasing NO production, & ↑ HDL & ↓ LDL thus ↓ atherosclerosis & ischemic insults (HRT started at the beginning of menopause will prevent CVS problems). However, HRT ↑ CVs problems (long term)
- **Improves insulin resistance** & glycaemic control in diabetics
- **Improves cognitive function** via increasing expression of ER in brain & by ↓ amyloid deposition thus preventing Alzehimer's.
- Delays parkinsonism by acting on DA system in midbrain.

B. Other Uses:

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

*It stimulates the development of the vagina, uterus, and uterine tubes as well as the secondary sex characteristics.

Administration

- **Oral**:
  - Conjugated equine
  - Estradiol valerate
  - Estriol 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 → useful in the treatment of urinary tract symptoms in these patients

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)

C.I

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

interaction

- If given with
- **SERMs** → additive side effects for both drugs
- Aromatase inhibitors → ↓ efficacy
- **Corticosteroids** → ↑ **the side effects**

2- Progesterone

Drug

Progesterone & Progestin's (synthetic form of progesterone)

The nature

- Produced by: adrenal gland, brain, placenta, gonads
- Synthesis by: LH → cholesterol → pregnenolone → progesterone
- They are precursor to estrogens, androgens, and adrenocortical steroids.
- Progesterone forms:
  1. **Progesterone** (natural) is destructed in the GIT → so give it parentally only.
  2. **Progestin's** are synthetic form of progesterone and have the similar effect but are not destructed by GIT → can be taken orally → e.g. mini pills

MOA

- Binds to its Progesterone receptors (PR-**A** & PR-**B**)
- Two ways they could exit
  1. **cytoplasmic**: mediate genomic **long term effect**
  2. **membranous**: mediate non-genomic **rapid effect**

Indications

- ❖ **In menopause**: Given combination with estrogen or alone to **avoid cancer** (endometrial carcinoma) but doesn't eliminate all menopausal symptom.
- **Protect against estrogen induced endometrial cancer.**

  Estrogen ↑ **cell growth** if unopposed this will lead to **atypical hyperplasia**

  But when we combine progesterone with estrogen, **progesterone** will beneficially ↑ differentiation **&** ↑ apoptosis of atypical cells **by activation of p53)**
- **Progesterone protects against breast cancer** by **anti-inflammatory** & **apoptotic mechanism, but this effect is not clear with progestin's** (synthetic). Mammography is recommended every 6 month.
- Confers (يعطي) **neuroprotection**, mild effect.
- **Controls insomnia & depression**, little effect.
- **Counteract osteoporosis**, direct ↑ of osteoblast.
- ❖ **Other uses**:
- Contraception, menopausal symptoms (Estradiol + Progestins given together), dysmenorrhea.

ROA

- **Oral**: progestin's or micronized progesterone (Natural Progesterone)
- **Intra-uterine (IU):** Levonorgestrel or progestasert.
- **Vaginal:** progesterone gel/pessary
- **Transdermal**: sequential or continues patch

ADRs

- Mood change (anxiety & irritability), Headache & dizziness
- Nausea, vomiting, abdominal pain or bloating.
- **Hirsutism, masculinization (Not with new preparations)**

Benefit & risk of HRT (estrogen + progesteron)

Definite benefit	Definite risk
○ Alleviates symptoms of menopausal (vasomotor, genitourinary) (mainly estrogen) ○ Osteoporosis (estrogen & progesterone) ○ Uncertain → cognitive functions	○ Endometrial cancer (estrogen) ○ Venous thromboembolism (long term) ○ **Breast cancer** (5yrs long term)

NOTE: The risk of CVS Problems and breast cancer with HRT is more than their benefits.

3- SERMs (Oral & non-hormonal therapy)

Drug

Raloxifene & Tamoxifen

- **Raloxifene:** is **antagonist** in **both** breast **&** uterus, And **agonist** in bone.
- **Tamoxifen:** is **antagonist** in **only** breast, And partial **agonist** in bone **&** endometrial (**uterus**).
- ❖ **An ideal SERM** for use as HRT should be **agnostic** in brain, bone & CVS **but antagonistic** in uterus & breast.
  - ✓ **Raloxifene & Tamoxifen** are **NOT ideal SERM.**

Why? Bc Raloxifen is not an agonist of brain & tamoxifen is not an antaonist for uterus

❖ **Raloxifene**:
- Has **no** effect on **hot flushes** or ↟ hot flushes.
- Very effective preventing **vertebral bone fracture** and CVs problems less compared to Estrogen, (for osteoporosis use of bisphosphonate is better)
- (Raloxifene is better than Tamoxifen)

❖ **Tamoxifen**:
- ↟ **risk of venous thrombosis**
- **Tends to precipitate vaginal atrophy**
- **Hot flushes**

+: agonist, -:antagonist	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERM	++	-	++	-	++	++
Tamoxifen	-	+	-	- used w\ breast cancer	+	+
Raloxifene	-	-	-	-	++	+

4- Phytoestrogen

Drug

Phytoestrogen

- Supplements from plants; containing isoflavones (soya beans, flaxseeds) or ligans (whole grain). We should Avoid them in **estrogen dependent breast cancer**

- They **mimic** action of estrogen on ER-**b** → **alleviate symptoms** related to hot flushes, mood swings, cognitive functions & possess CVS protective actions. **(data limited on their efficacy).** لما الست تيقي بالمينوبوزال سمبتمز، ما نستخدم هذا العلاج لحاله لأن تأثيره بسيط خالص
- They **block** actions mediated by ER-**a** in some target tissues → lower risks of developing endometrial & breast cancer.

5- Androgens

Drug

Testosterone (androgens use is not approved by FDA)

لا ينصح به بشكل عام للإناث،

- 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. (synthetic steroid drug with estrogenic, progestogenic & week androgenic action)

Non-hormonal agents used in management of menopausal symptoms

- **Fluoxetine** (SSRI) reduce vasomotor symptom
- **Clonidine** (centrally acting antihypertensive) alpha 2 agonist reduce vasomotor symptom. In patients in whom estrogen replacement therapy is contrain- dicated, such as those with estrogen-sensitive tumors, relief of vasomotor symptoms may be obtained by the use of clonidine.
- **Gabapentin** (anti-convulsant) reduce severity and frequency of hot flushes.
- **Physical activity:** exercise, smoking cessation and relaxation of mind will improve symptoms of menopuase (e.g hot flushes) and fall preventing strategies prevents chances of fracture.

The Women's Health Initiative (WHI) and HRT

الدكتورة ما قرأت هذي الجزئية

- 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 ↑ risk of stroke and blood clots. In addition, the estrogen plus progestin medication resulted in an ↑ 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.

Summary-1

Drug

Estrogen

Important roles while taking estrogen :
1-taken Alone only after hysterectomy
2-With progestin as HRT (to avoid uterine cancer)
3-When given never exceed 5 years administration

Indications

In **menopause** :
Improves : **hot flushes** & night sweats ,mood , **urinary** symptoms , **vaginal** dryness , **insulin resistance**
↑**bone density**,↓ osteoclast activity (used with **progestins** in **osteoporosis**)
Protects CVS; ↓stroke (but **long term use ↑ cvs problems)**
Delays parkinsonism & prevent Alzheimer
Other Uses :
1- As **contraceptive**
2- primary **ovarian failure** (in young girls)
3- **amenorrhea & hirsutism** caused by excess Androgen

Adminstration

Oral **1-Conjugated equine** 2- **Estradiol valerate** 3- **Estrial succinate**
Transdermal (**estradiol**) Patches or Gel
Subcutaneous implant (**estradiol**) >> 6 monthly.
Vaginal cream or rings pessaries

ADRs

breast tenderness
↑ Skin Pigmentation.
Irregular vaginal bleeding + vaginal discharge
Fluid retention

C.I

Absolute;
*__Undiagnosed vaginal bleeding__ .
*Severe **liver disease.**
*__Thromboembolic manifestations__ .
*__Cancer__; endometrial, breast (hormone sensitive), ovarian

Interactions

If given with :
SERMs >> additive side effects for both drugs
Aromatase inhibitors → ↓ efficacy
Corticosteroids → ↑ side effects

Drug

Phytoestrogens

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

Indication

1-They mimic action of estrogen by ER-b (improve menopausal symptoms) **Avoid in estrogen dependent breast cancer**
2-They block actions mediated by ER-a in some target tissues = lower risks of developing endometrial & breast cancer.

Drug

SERMs used for breast cancer

Raloxifene
agonist in **bone** & an antagonist in breast and uterus(has lower chance of getting uterine cancer so its better than Tam)
Used mainly for osteoporosis (prevent vertebral fracture)
has no effect on hot flushes or vaginal atrophy

Tamoxifen agonist in **uterus** & bone
Antagonist in breast
increase risk of venous thrombosis & cause vaginal atrophy & hot flushes
(high risk of uterine cancer)

Summary-2

Drug	**Progestins**
In Nature	1-Produced by; Adrenal glands, Gonads, Brain, Placenta 2-Are precursor to estrogens, androgens, and adrenocortical steroids.
As therapy	Natural **Progesterone** is destructed in GIT (given parentally) , synthetic **Progestin's** **not** degraded by GIT (orally)
What does progesterone do?	Bind to its receptors and mediate its effect in the body . types of progesterone receptors: 1-PR-A 2-PR-B They could exist 1- cytoplasmic : long term effects 2- membranous : rapid effects
Indications & MOA	In menopause : **1-Used as HRT with estrogen to Protects against possibility of estrogen induced endometrial cancer . (How ?)** Estrogen → ↑ cell growth. If unopposed → atypical hyperplasia Progesterone >> differentiation of endometrial cell lining & apoptosis of atypical cells **2-Natural progesterone protects against breast cancer**, but with **synthetic progestins** protection not confirmed so mamography every 6ms. 3- Confers neuroprotection 4- Controls insomnia & depression **5- osteoporosis,** directly +ve osteoblasts Other Uses : **Contraception** & **menopausal symptoms** (used with estrogen) ,and for **dysmenorrhea**
Administration	Oral; Micronized progesterone or progestin's Intra uterine Levonorgestrel or progestasert Vaginal progesterone (gel / pessary). Transdermal - sequential / continuous patch.
ADRs	Headache. mood change Hirsutism , masculinization.
Drug	**Androgen**

Testosterone is responsible for promotion of Sexual desire in females.
Tibolone synthetic steroid drug with estrogenic, progestogenic & week androgenic action→ improve sexual desire

Non-hormonal agents for management of menopausal symptoms

Physical Activity & life style
Gabapentin > reduce hot flushes
Fluoxetine & **Clonidine** > help in vasomotor symptoms

MCQs

1- Most of menopausal Symptoms occurs due to :

A. Decrease the estrogen level
B. Increase the estrogen level
C. Increase progesterone level
D. Decrease progesterone level

2- Long term menopause will cause :

A. Osteoporosis
B. Hot Flushes
C. Insomnia
D. Dyspareunia

3- Estrogen supplements are contraindicated in case of :

A. Undiagnosed vaginal bleeding
B. Severe liver disease
C. Thromboembolic manifestations
D. All above

4- Progesterone have a protective effect on estrogen induced cancer, by which mechanism?

A. Deactivating of P53
B. Increase cell growth
C. Decrease apoptosis
D. Increase cell death

5- Tamoxifen has an agonist effect on?

A. Brain
B. Vagina
C. Uterus
D. Breast

6- Progestin's have a protective role against breast cancer?

A. True
B. False

7- which receptor will bind with phytoestrogen and mimic the action of estrogen?

A. PR-a
B. PR-b
C. ER-a
D. ER-b

8- We should avoid the use of phytoestrogen in estrogen dependent breast cancer?

A. True
B. False

Answers: 1-A 2-A 3-D 4-D 5-C 6-A 7-D 8-A

Thank you for checking our team!

Pharmacology 435

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Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 25, 5th edition.
3. Basic & Clinical Pharmacology by Katzung, chapter 40,12th edition.
4. http://www.livestrong.com/article/412793-insulin-resistance-estrogen/