HORMONE REPLACEMENT THERAPY

(HRT)

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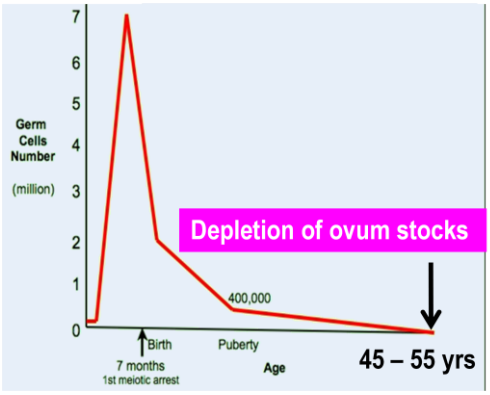
First page is introduction

Hormonal replacment therapy is used in patients who have symptoms due to a decrease in their hormone levels due to normal conditions (menopause) or pathological , induced conditions.

Menopause is defined as: A complex physiological change that occurs at the time when the last period ends generally as women age and loss fertility. And resulting from this physiological change a number of changes can be seen noticed in a female, like:

1. decrease estrogen levels
2. decrease progesterone levels
3. decrease in androgen levels
4. increase levels of FSH and LH
5. increase in insulin resistance



note: usually obese women are protected from insulin resistance (menopausal symptoms) due to their relatively large amounts of estrogen (which stored in adipocyte) and low sex hormone binding globulin (SHBG)

** what are the results of these decreased levels of circulating hormones ?

the symptoms range from the time of menopause :

1. immediate symptoms
    a. Hot Flushes / Night Sweats
    b. Insomnia, Anxiety, Irritability
    c. Mood Disturbances
    d. Reduction In Sexuality & Libido
    e. Poor Concentration / Memory Loss
2. Intermediate symptoms
    a. Rapid loss of collagen
    b. Dyspareunia & vaginal dryness
    c. Urethral syndrome *(dysuria, urgency & frequency)*
    d. Incontinence, difficulty in voiding
    e. Increased bruising
    f. Generalized aches and pains
3. Long term effects (most dangerous):
    a. Osteoporosis
    b. CVS Risks; ↑LDL/HDL ratio, CHD, stroke,..
    c. C N S deficits: Alzheimer's, dementia

HRT usually taken to treat immediate symptoms

So you see that they are a major concern for females

MAIN menopausal symptoms are due to >> decrease estrogen levels

So to get alleviate (improve) the symptoms of menopause >> the main therapy is >> replace estrogen

Drugs used:

خارطة الطريـــق مهمة لمعرفة الدواء المناسب لكل حالة !!

1. **Estrogen**

a. It has Some undesirable side effects (increased incidence of uterine hyperplasia & cancer & breast cancer)
b. Some time, it is given with combination **with progesterone** to reduce the symptoms of etrogen **BUT if a patient has undergone hysterectomy then no need for progestin** IMP!!

Note: * In case of hysterectomy use estrogen only

~progestin is a synthetic form similar to progesterone

2. **Selective ER-Modulators [SERMs]**
3. **Tibolone**
4. **Phytoestrogens**
5. **Androgens** given for sexual arousal only if there is loss of libido & orgasm IMP!!

- Hormone replacement therapy is **never given to a patient for more than 5 years**(given for short term) to control menopausal symptoms without allowing ample (sufficient) time for malignant transition that might be induced by estrogen.

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

1. estrogens :

How does estrogen works ?

Simply it binds to estrogen receptors in the body. And we have two types of estrogen receptors

A. Estrogen receptor α:
   a. Mediates female hormonal functions (Endometrium, breast, ovaries, hypothalamus)
   b. Estradiol binds equally to both receptors

B. Estrogen receptor β:
   a. Mediates other non hormonal functions (brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells)

**** Different estrogenic compounds have different binding affinities for ERa & ERb :**
   - Estrone binds preferentially to Er α
   - Estriol binds preferentially to ER β
   - Estradiol binds equally to both receptors

After binding to the receptors they affect the cell in 2 ways :

1. **Genomic action (cytoplasmic) :**

a. meaning that estrogen will bind to cytoplasmic Receptor then it migrate and affect the nucleus causing it to make a change in its DNA or RNA and transcription of new proteins and this usually takes <u>hours or days to develop an effect</u>

b. Estrogen binds to ERE (estrogen receptor element) activate, translocate, dimerize on ERE of DNA ➔ Transcription & Translation to regulatory proteins➔development, neuro- endocrines, metabolism

2. **Non genomic action (membranous):**

a. This means that after estrogen binds to a receptor on the cell membrane it will do its effect using a second messenger to do its effect and has nothing with altering DNA synthesis and it will have an effect <u>within seconds or minutes</u>

b. Estrogen binds to GPER(G protein estrogen receptor) ➔2nd messenger ➔ ↑ Ca or cAMP or ↑ MAP Kinase →NO(nitric oxide), neuro- transmitters, endometrium

MAP Kinase: mitogen activated protein kinase that activate transcription factors to promote mitogenesis

Mitogenesis : activate genomic effect meaning it starts as rapid action end up helping genomic effect (long term)

How does estrogen works ? imp. points

- **ER α :** female hormonal functions **&** **ER β :** other non hormonal functions
- **Genomic action (cytoplasmic) & Non genomic action (membranous)**

Indications : IMP!!

اللي بالأحمر مهم مع الـ Mechanism ... الباقي نقاط فقط ...

- In treating menopause symptoms:

○ **Rules :**
  - Treat only when presence of symptoms
  - Given alone only if patient has undergone hysterectomy
    <u>if not combine with progesterone</u>
  - never exceed 5 year administration

○ **improving hot flushes and night sweats, by:**
  - acting on opiate, NE & 5HT regulating heat dissipation at hypothalamus

○ **Controls sleep disturbance & mood swings by**
  - acting on NE, DA (Dopamine)& 5HT at reticular formation, perioptic areas & hypothalamus

○ **<u>Improves urethral & urinary symptoms by</u>**
  - ↑ epithelial thickness & vascularity, collagen content at urethra & NE transmission that contract sphincters & relax detrusal muscles

○ **Improves vaginal dryness by**
  - ↑ epithelial thickness & vascularity, collagen content

○ **<u>Increases bone density by</u>**
  - ↑ calcitonin release from thyroid to ↓ osteoclastic activity. Progestin act <u>synergestic</u> by blocking corticosteroid induced bone resorption

- **Protects CVS;**
  - enhance vasodilatation via ↑ NO (nitric oxide) 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(estrogen receptors) in brain & by ↓ amyloid deposition thus preventing Alzehimer 's.
- **Delays parkinsonism by acting on DA system in midbrain**
  - **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

Methods of administration :

1. Oral preparations
2. Transdermal (estradiol);
3. Subcutaneous implant (estradiol)
4. Vaginal cream as such or as rings pessaries

ADR's :IMP!!

- Nausea and breast tenderness
- Headache
- Skin Pigmentation; due to vitamin B6 deficiency
- Impair glucose tolerance (hyperglycemias) (can be very serious)
- Incidence of breast, vaginal & cervical cancer
- Cardiovascular — major concern a. Thromboembolism b. Hypertension : due to water/sodium retention and it is reversible
- frequency of gall bladder disease
- Irregular vaginal bleeding.
- Vaginal discharge.
- Weight gain.

Contraindications: IMP!!

- **Absolute contraindications** (never ever give hormonal replacement therapy)
  - Undiagnosed vaginal bleeding
  - Severe liver disease
  - Thromboembolic manifestations
  - Cancer; endometrial, breast (hormone sensitive), ovarian
- **Relative contraindication** (need to follow up)

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

Drug interaction:

N.B: If given with

- **SERMs** → additive side effects for both drugs (Hyperestrogenemia)
- **Aromatase inhibitors** → ↓ efficacy
- **Corticosteroids** → ↑ side effects

Same as contraception lecture :

1. Medication that cause the drug to fail

o Impaired absorption : like **taking antibiotics** that kill GI flora > this will lead to ↓absorption> ↓its bioavailability > failure of the drug

o **Drug inducers(CYT P450 inducers) : ↑ catabolism of drug;** like:

i. Phenytoin ii. Phenobarbitone iii. Rifampin

2. Medications that increase drug toxicity (CYT P450 inhibitors):

o ↓ **metabolism of drug→↑ toxicity** e.g.:

i. Acetominophen ii. Erythromycin.

3. Medications of altered clearance (↓) ;

o ↑ **toxicity** e.g.:

i. Cyclosporine ii. WARFARIN iii. Theophyline

2. progestins :

For therapeutic reasons they are manufactured into:

1. **Progesterone : it is destructed in GIT, so can <u>be given only parentally</u>**
2. **Progestins: are synthetic progestogens that have progestinic effects similar to progesterone but are <u>not degraded by GIT</u>.**
   Progestin preparations; as in contraceptive pills

From contraception lecture * Progestin Preparations *

✓ **so the less the selectivity for the receptors the more it might cause androgen effect in female like : acne, hirsutism, weight gain, and deleterious effects on lipid & carbohydrate metabolism;**

Drugs that have low selectivity (OLD) :

1. Norethindrone 2. Norethindrone acetate 3. Levonorgestrel 4. Medroxyprogesterone acetate

✓ **nowadays we give more specific receptor drugs to reduce progesterone side effects;**

preparations that are more specific (NEW) :

1. Norgestimate 2. Desogestrel 3. Drospirenone

How does progesterone work?

Same as estrogens

- binds to its receptors
- two types of **progesterone receptors : PR- A and PR-B**
- action could be cytoplasmic (genomic) long term effect s or membranous (non genomic) rapid effects

indications: IMP!!

اللي بالأحمر مهم مع الـ Mechanism ... الباقي نقاط فقط ...

- **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**
  - as you remember , progesterone is given in combination with estrogen to lower the effect of estrogen
  - estrogen causes: ↑ cell growth. If unopposed →endometrial cell lining can show (atypical hyperplasia)
  - But the progesterone cause :
    - matures endometrial cell lining (makes it differentiated more of resembling endometrium cells and less atypical)
    - **increase apoptosis of atypical cells by activation of p53 IMP!!**

Progesterone has Protection function from uterus cancer more than breast cancer

- **protects against breast cancer development**
  - it is a natural protector (Progesterone)
  - anti-inflammatory
  - apoptotic mechanism
  - this effect is not as clear with synthetic progestins.
  - Mamography recommended every 6ms.
- **confers neuro protection**
  - increase in cognition
  - decrease in Alzheimer incidence
- **controls the insomnia and depression**
  - Progesterone is a precursor of melatonin and 5HT
- **Contributes to CV protection →**
  - ↑ NO (nitric oxide) which promotes vasodilatation
  - has anti-atherogenic actions
- **Counteract osteoporosis**
  - directly +ve osteoblasts
  - indirectly blocking GC induced bone resorption

MCQ :

- **Pt with hot flushes (or any ADRs of estrogen)>> progestin is not effective they must given estrogen**
- **The same presentation in addition to hysterectomy >>> Estrogen only**
- **With no hysterectomy >> combination B/t estrogen & progestin**

Other uses:

- Contraception
- Dysmenorrhea
- 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's: IMP!!

- Nausea, vomiting, abdominal pain or bloating (distention).
- Headache, dizziness or drowsiness
- Fatigue, depression of mood, anxiety,irritability
- Weight gain
- Hirsutism
- Masculinization (Norethindrone)

} Not with new preparations

3. SERM (selective estrogen receptor modulators)

They are classified according to how they bind to the estrogen receptor :

1. **Antiestrogens that have agonist and antagonist actions**
    a. E.g. **Raloxifen** which is an agonist in the bone and antagonist in the breast

Raloxifene imp in breast cancer and osteoporosis

2. **Antiestrogens that stabilizes ER in a conformation allowing transcription to occur on only certain ER-responsive genes**
    a. **Tamoxifen**

An ideal SERM drug for use in hormonal replacement therapy should be , agonist in the brain , Bone , cardiovascular system , vagina and urinary system and antagonistic in the uterus and breast

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

- **tamoxifen**
    - not ideal
    - increases risk of venous thrombosis
    - precipitates vaginal atrophy and hot flushes
- **Raloxifene**
    - Not ideal
    - Has no effect on hot flushes

The difference between Tamoxifen & Raloxifene is the effect on uterus , Raloxifene hasn't estrogenic effect on uterus (it's protective against uterus cancer.)

So if u want to choose b/t them to treat breast cancer better to give Raloxifene .

4. Tibilone

It is a synthetic steroid that is metabolized in the body to products that **have estrogenic , progesterogenic and androgenic effects**

Effect on the body :

- It induces amenorrhoea
- Improves urogenital symptoms
- Enhances mood & libido.
- Protective on CVS system
- Prevents bone loss
- Protective on endometrium
- Least tendency of cancer breast

Because of its effect on body this drug is close to be

Ideal HRT on long term use. imp

Indications :

- **In menopause ,, imp**
  - history of endometriosis , fibroids or treated breast cancer
  - In diabetics and hypertriglyceridemics
  - In thromboembolic tendency
  - **In lack of sexual arousal**

5. phyoestrogens :

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

Action :

- **mimic the action of estrogen on receptor ER-beta , causing :**
  - 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 causing:**
  - Lowers 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 (in case of lack of sexual arousal.) ➔ has some androgen agonistic properties.***