PT431 Team Pharmacology

Reproductive Block

Lecture 6
Hormonal replacement therapy

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Blue>>boys lecture pink>>female lecture green>> information from dr.omniah red>>important

Objectives:

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.

Introduction:

When do we use hormonal replacement therapy?

1-hormonal deficiency :

e.g: young patient had ovarian tumor then she removed the ovaries with the uterus, that cause decreasing in progesterone and estrogen

e.g: young female exposure to radiation and its affect her ovaries (will not produce follicles and hormones), that will decrease progesterone and estrogen

2-menopausal woman

a. women use it to protect her beauty and to be young (unacceptable ☹)

b. women use it to remove the severe symptoms of menopause :for short time because it has many side effects e.g: carcinogenesis

Hormonal Replacement Therapy (HRT):

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

MENOPAUSE: "*' menos'(month) , 'pausis'(cessation)*"

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

also there is a pathological menopause e.g: young female has ovarian failure because she exposed to radiation and her hormonal profile like a menopausal woman

-hormonal profile of menopause:

1-Decrease estrogen and progesterone >>because there is no follicles and ovulation

2-Decrease androgen

3-Increase FSH and LH >>before many years they take urine from menopausal women to extract the FSH and LH and use it in drugs of infertility.

4-Increase insulin resistance >>because she lose the estrogen and progesterone, so she will have the apple shape body instead of pear shape that leads to insulin resistance.

-in obese women their fat cells will produce estrogen(by aromatase enzyme), so the menopausal symptoms

SYMPTOMS & CONSEQUENCES of MENOPAUSE:

A- Immediate: these symptoms which cause the woman go to the doctor

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

Estrogen receptors concentrate in the brain

B- Intermediate:

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

C- **Long Term:** in the past they use estrogen to treat these symptoms but nowadays they have drugs better than estrogen

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

Dr.Omniah said The first page it is only introduction and no question about it. for understanding ☺

Menopausal Symptoms are due to ↓Estrogen, to Alleviate the symptoms Replace the Estrogen !

Types of HRT:

1- **Estrogen**→Some undesirable side effects
add **Progestins**; *but not if there is hystrectomy*
2- **Selective ER-Modulators [SERMs]**
3- **Phytoestrogens**
4- **Androgens**→*responsible for sexual arousal* → *given only if there is loss of libido & orgasm*

1-estrogen:

General rule in estrogen :
If there is uterus>> don't take estrogen alone (in menopause or young in any woman). should be estrogen with progesterone
If there is no uterus (hysterectomy)>> she can take estrogen alone
If there side effects for estrogen we add progestin

-progestrone: 1-not given orally 2-protect against uterus and breast cancer
-progestin : 1-given orally 2- protect only against uterus cancer

2-SERMs:estrogenic effect in HRT

SERM In infertility (antiestrogenic effect): SERMS in infertility will decrease estrogen level >> potentiate hypothalamus and pituitary >> increase secretion of gonadotrophes

3-phytoesterons: found in soy milk, soy sauce, soy bread
They found women who are eating soy products when they were young they have less menopausal symptoms
They use it as drug but it is weak

4-androgen :it is responsible for sexual arousal

-HRT: Given for short term(1-2 years); **never exceed 5 years**→to control meno-pausal symptoms without allowing ample time for malignant transition that might be induced by estrogen

-nowadays we don't use HRT for long term symptoms (osteoporosis, CVS)because there are better drugs for these symptoms

Q:Menopausal woman doesn't have the desire for sexual intercourse with her husband only . What is the drug of choice ??androgen alone

Q:Menopausal woman has hot flushes, insomnia, mood disturbances without sexual problems. What is the drug of choice??Estrogen alone and we can use SERMs

Q:Menopausal woman has hot flushes, insomnia, mood disturbancesAND doesn't like to do sex. What is the drug of choice?Both androgen with estrogen or SERMs

Very important box

1- Estrogen:

-Estrogen forms: 1-estrone:in menopausal woman 2-estradiol: in fertile age

a- **Estradiol**: ***Oral bioavailability is low due to its rapid oxidation in the liver so used only in transdermal patch, intradermal implant,....***
(it is very short action in the body, so they use conjugated and esterified estrogen)
b- **Conjugated estrogens** ➔ **mixture of Na salts of sulfate esters of estrone&equilin.**
c- **Esterified estrogens.**

-Types of Estrogen Receptors [ER]:

1- **ER α➔ mediates female hormonal functions**
Found in Endometrium, breast, ovaries, hypothalamus,... (sexual organs)
2- **ER β➔ mediates other hormonal functions**
Found inbrain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells,....
(1-for the cognitive function as studying,thinking,memorizing
2-related to integrity of NO level
3-has function in increase HDL)

-Estrogens bind to ER (a or b) that exist either;

1-Cytoplasmic: activate, translocate, dimerize on ERE of DNA ➔ Transcription & Translation to regulatory proteins**>>mediates its genomic actions➔hrs– dys time scale➔development, neuroendocrines, metabolism.**
(produce proteins for sexual function)

2-Membranous; G protein ER➔2nd messenger ➔⬆Ca or cAMP or ⬆ MAP Kinase
>> mediates its non-genomic actions➔ sec – min. time scale ➔on NO, neuro- transmitters,.....
(for cognitive function)

-INDICATIONS of Estrogens:

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

A- In Menopause:

1- **Improves hot flushes & night sweats**by acting on opiate, NE & 5HT regulating heat dissipation at hypothalamus.
2- **Controls sleep disturbance & mood swings** by acting on NE, DA & 5HT at reticular formation, perioptic areas & hypothalamus.
3- **Improves urethral & urinary symptoms** by ⬆ epithelial thickness & vascularity, collagen content at urethra &NE transmission that contract sphincters & relax detrusal muscles
4- **Improves vaginal dryness** by ⬆ epithelial thickness & vascularity, collagen content (topical and systemic estrogens prep are effective)
5- **Increases bone density by**⬆ calcitonin release from thyroid to ⬇osteoclastic activity
⬆ osteoclast apoptosis & growth factors from osteoblasts
⬇No. & depth of resorption cavities & release of cytokines
6- Progestins act synergestic by blocking cortico- steroid induced bone resorption. (Decrease incidence of hip fracture)
7- **Protects CVS;** enhance vasodilatation via ⬆ NO production,&⬆ HDL &⬇ LDL thus ⬇ atherosclerosis & ischemic insults (HRT started at the beginning of menopause will prevent CVS problems) HRT increases CVs problems (long term)(can cause thrombosis)
8- **Improves insulin resistance&glycaemic controlin** diabetics
9- **Improves cognitive function** via ⬆ expression of ER in brain & by ⬇ amyloid deposition thus preventing Alzehimer 's.
10- **Delays parkinsonism** by acting on DA system in midbrain

Dr.omniah said study only the **bold words**

B- Other uses:

1- Contraception
2- Primary ovarian failure
3- Amenorrhea &Hirsutism caused by excess androgens

-Administration:

- **Oral:**
  - Conjugated equine estrogen (CEE);**(EstroneSulphate + equilinsulphate** +17 d dihydroequilin) 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.**

(the most common use are oral and transdermal)

-ADRs:

1- Irregular vaginal bleeding.
2- . Vaginal discharge.
3- Fluid retention. Weight gain.
4- Nausea and breast tenderness
5- Headaches
6- Spotting or darkening of skin (on face) (increase skin pigmentation)
7- **Impair glucose tolerance**
8- **Cardiovascular - major problem**
   a. Thromboembolism
   b. Hypertension
9- **↑ incidence of breast, vaginal & cervical cancer**
10- **↑ frequency of gall bladder disease**

-Contraindications:

Absolute: don't take it ever

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

Relative:

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

-Interactions: **See contraception**

- NB. If given with
1- SERMs➔ additive side effects for both drugs
2- Aromatase inhibitors ➔↓ efficacy for both drugs
3-Corticosteroids ↑ side effects (hypertension, water salt retension)

2- PROGESTINs:

-In NATURE:(not imp)

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

-As Therapy:

- **Progesterone** is 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

-Binds to its receptors:

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:

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.

1- **Protects against possibility of estrogen induced endometrial cancer**
   a. **Estrogen**➔↑ cell growth. 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.

Q:why progesterone has protective effect against utrine cancer?
It has the ability to activate P53 that will make any cell altered by estrogen go on apoptosis
Q:does protect breast also?
Only progesterone can protect againstbreast cancer , but progestin protect only against uterine cancer

2- **Progesterone (natural) protects against breast cancer development**by anti-inflammatory & apoptotic mechanisms, but this effect is not as clear with synthetic progestins. Mamographyrecommended every 6ms.
3- **Confers neuroprotection**, mild effect
4- **Controls insomnia & depression**➔ little ffect
5- **Counteract osteoporosis**, directly +ve osteoblasts
6- **Contributes to CV protection**by ↑ NO & has anti-atherogenic actions

B- Other uses:

1- Contraception (Estradiol + Progestins)
2- Infertility due to inadequate luteal phase
(in infertility they do hormonal investigation if progesterone decrease that means may there fertilization but there is not implantation because)
3- Dysmenorrhea

-Administration:

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

-ADRs:

1- Mood changes, as anxiety, irritability
2- Headache, dizziness or drowsiness
3- Nausea, vomiting, abdominal pain or bloating (distention).
4- Hirsutism , masculinization (Not with new preparations)
5- Weight gain
6- Ectopic pregnancy

Benefits and Risks of HRT:

- **Definite benefits:**
  - Symptoms of menopause (vasomotor, genitourinary).
  - Osteoporosis (Definite increase in bone mineral density; probable decrease in risk of fractures).
- **Definite risks:**
  - Endometrial cancer (estrogen only)
  - Venous thromboembolism
  - Breast cancer (long term 5 yrs)
- **Uncertain benefits:**
  - Cognitive functions

3- SERMs:

Tamoxifen, Raloxifene (oral and non-hormonal)

Classified according to how they bind to ER

A. **Raloxifen:** **Antiestrogens that exhibits partial agonistic action ; acting as an agonist in bone & an antagonist in breast**

antagonist in breast and uterus and agonist in bone

(for osteoporosis)

B. **Tamoxifen:** **Antiestrogens that stabilizes ER in a conformation allowing trans- cription to occur on only certain ER-responsive genes**

Antagonist in breast and partial agonist in bone and endometrium.

(for mood , insomnia , memory loss)

An ideal SERM for useas HRT should be agonistic in brain, bone, CV system (not necessarily the liver), vagina & urinary system but antagonistic in breast & uterus

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Ideal SERM	++	—	++	—	++	++
Not ideal — Tamoxifen	—	+	—	—	+	+
Not ideal — Raloxifene	—	—	—	—	++	+

+ = agonist
- = antagonist

-Tamoxifen → ↑ risk of venous thrombosis & tends to precipitate vaginal atrophy & **hot flushes**
-Raloxifene → has no effect on hot flushes, increases hot flushes *(very effective preventing vertebral bone fracture and CVs problems less comp to Estrogen)* for osteoprosis use of bisphosphonate is bettere than SERMs
(if women come to the doctor for hot flushes, we don't treat her with Tamoxifen it will increase hot flushes or Raloxifen)

4- PHYTOESTROGENS:

supplements from plants; containing isoflavones (soya beans, flaxseeds) or lignans (whole grains). Avoid in esterigen 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)
- **They block actions mediated by ER-ain some target tissues➔**lower risks of developing endometrial & breast cancer.

(it's good as a prophylactic. if you eat soy products, you will get less menopausal symptoms)

5- 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. (androgens use is not approved by FDA in women)

6- TIBOLONE

Dr.ominiah did not explain it
It will not include in the exam

- **The Women's Health Initiative (WHI) and HRT:**
- Menopausal Hormone Therapy:
  For decades, hormone therapy was a widely used in menopausal symptoms.
- **Estrogen** has been used alone in menopausal women who have had their uterus removed.
- **Progestin**, the synthetic form of an estrogen-related hormone called progesterone, is combined with estrogen in menopausal women who still have their uterus.
- 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 increased risk of stroke and blood clots. In addition, the estrogen plus progestin medication resulted in an increased 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.

- **Non-hormonal agents used in management of menopausal symptoms:**
- **Fuoxetins (SSRI)**
- **Clonidine (centrally acting antihypertensive)**
- **Gabapentin (anti-convulsant)**
- **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.

Summary

estrogen	**-Estradiol(short)** **-Conjugated estrogens** **(** Conjugated equine estrogen) **-Esterified estrogens** **(**Estradiol valerate Estrial succinate)	**Use in :** hot flushes sleep disturbance mood swings Protects CVS cognitive function **side effects:** -Cardiovascular - major problem a. Thromboembolism b. Hypertension -↑ incidence of breast,vaginal &cervical cancer -↑ frequency of gall bladder Disease **Contraindication**: -Undiagnosed vaginal bleeding -Thromboembolic manifestations -Cancer; endometrial, breast (hormone sensitive), ovarian **-Interactions:** - SERMs→ additive side effects for both drugs - Aromatase inhibitors →↓ efficacy for both drugs -Corticosteroids ↑ side effects (hypertension, water salt retension)	**-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**
progestrone	**-progestrone** 1-not given orally 2-protect against breast and uterus cancer **-progestin** 1given orally 2-protect only against uterus cancer	-usually given in combination with estrogen in menopause.	-It has the ability to activate P53 that will make any cell altered by estrogen go on apoptosis
SERMs	**Raloxifen: (for osteoporosis),** no effect on hot flushes **Tamoxifen:(for mood , insomnia , memory loss),**increase risk of venous thrombosis and **hot flushes**		
PHYTOESTROGENS	**They mimic action of estrogen on ER-b:** hot flushes, mood swings, cognitive functions **They block actions mediated by ER-ain some target tissues:**		
ANDROGENS	Give it alone if woman >>lack of sexual arousal combined estrogen & progestin if all other menopausal symptom exist (sexual with other symptoms		

Questions:

1- A woman had hysterectomy and she developed vaginal dryness, hot flushs. What's the best HRT that we can use ?

a. Etstradiol
b. Progestin
c. Tamoxifin

2- A woman was having early menopausal symptoms and she complained from loss of libido. what's the best drug that can be added to the HRT?

a. Androgen
b. Estradiol
c. Progestin

3- Tamoxifen is :

a. Antiprogestin
b. Antiestrogen
c. Androgen
d. Antiandrogen

1- A
2- A
3- B