



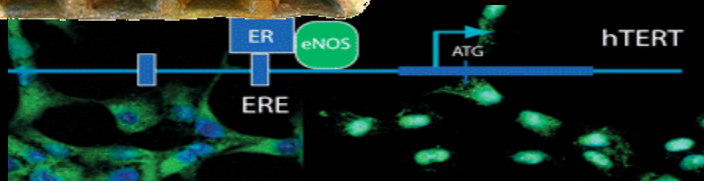
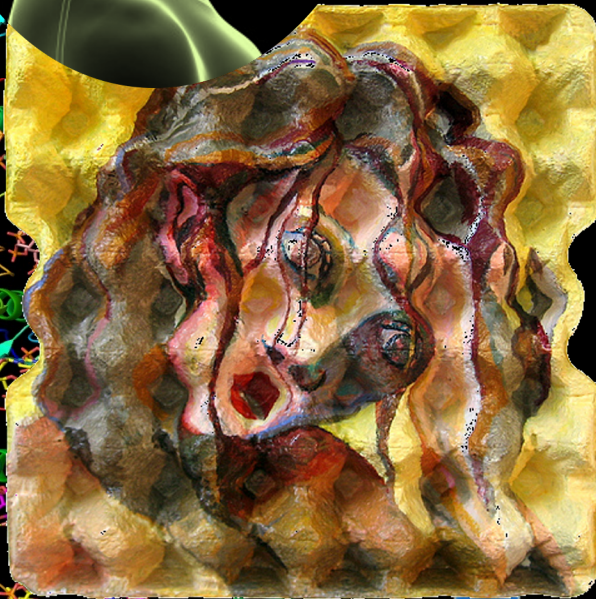
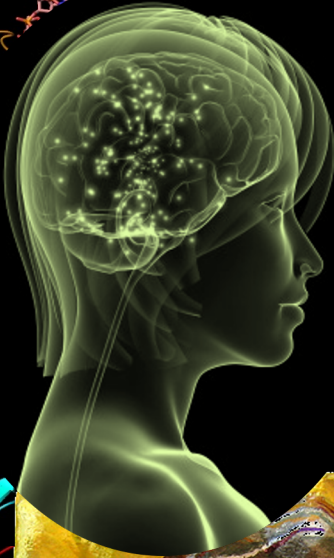
# HORMONE REPLACEMENT THERAPY

## Dr. Ishfaq Bukhari

# 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.





**MENOPAUSE**

**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

1/3<sup>rd</sup> of total female population

**PERI & POSTMENOPAUSE**

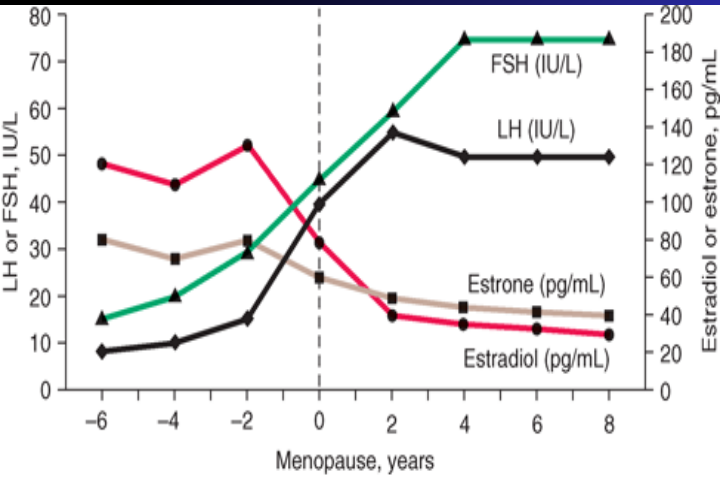
Natural, Pathological, Induced

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

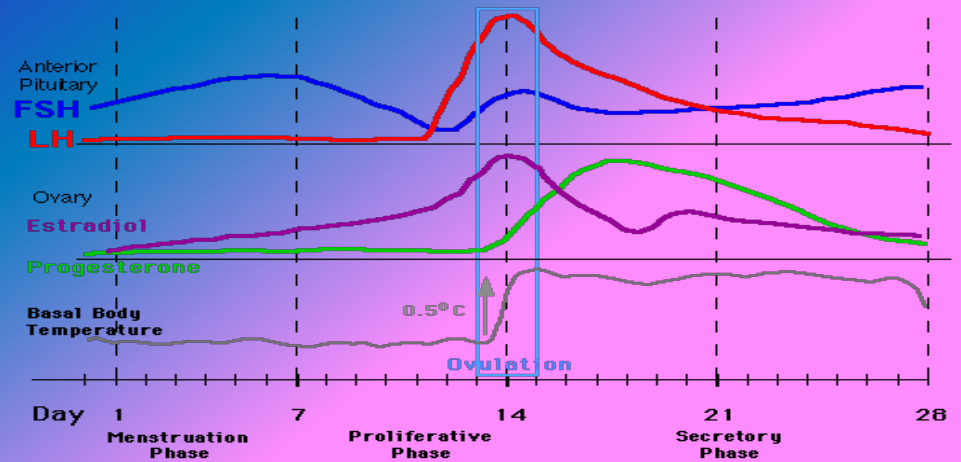
- ↓ Estrogen & Progesterone
- ↓ Androgens
- ↑ FSH & LH
- ↑ Insulin Resistance

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

**Normal menstruation**



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com  
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.



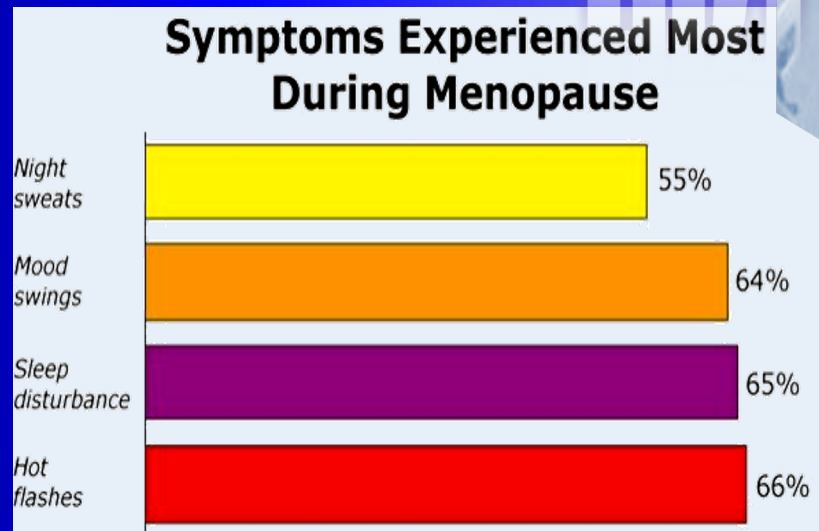


# SYMPTOMS & CONSEQUENCES of MENOPAUSE

# HRT



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



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

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

- 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 hysterectomy*

Selective ER-Modulators [SERMs]

Phytoestrogens

Androgens → *responsible for sexual arousal* → *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

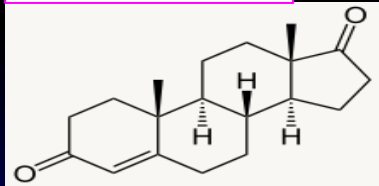
No more preferred

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

## HRT

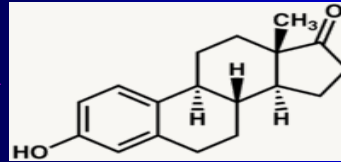
## 1. ESTROGEN

### In NATURE



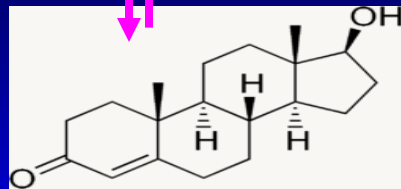
Androstenedione

Aromatase



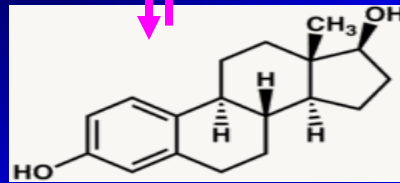
Estrone

Ovaries & adrenals pre-menopausal  
Adrenals in menopause



Testosterone

Aromatase



Estradiol

Dehydrogenase

Ovaries in pre-menopause

### 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** → mixture of Na salts of sulfate esters of estrone & equilin.

**Esterified estrogens**



What does estrogen do  
It binds to its receptors



## Types of Estrogen Receptors [ER]

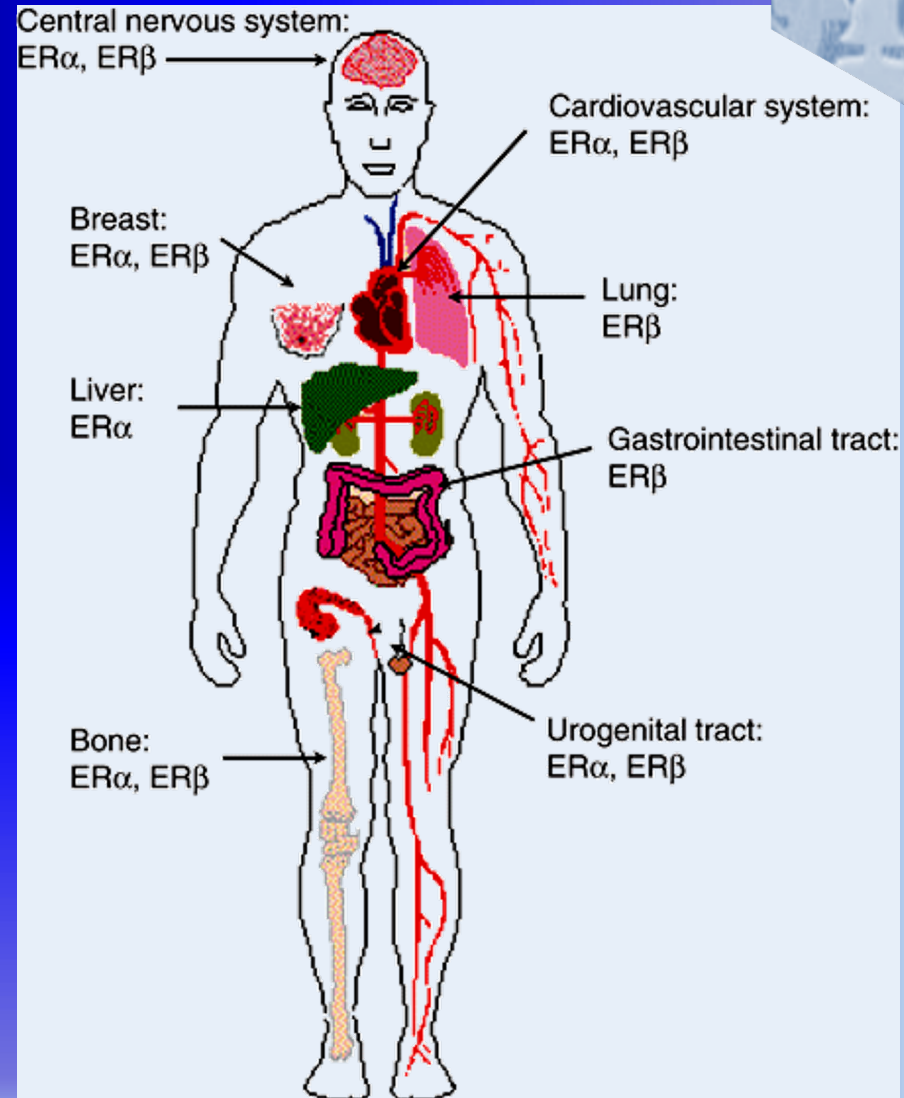
 ER  $\alpha$   $\rightarrow$

$>$  mediates female hormonal functions  
*Endometrium, breast, ovaries, hypothalamus,...*

 ER  $\beta$   $\rightarrow$

$>$  mediates other hormonal functions  
*brain, bone, heart, lungs, kidney, bladder, intestinal mucosa, endothelial cells,....*

## Distribution of ER

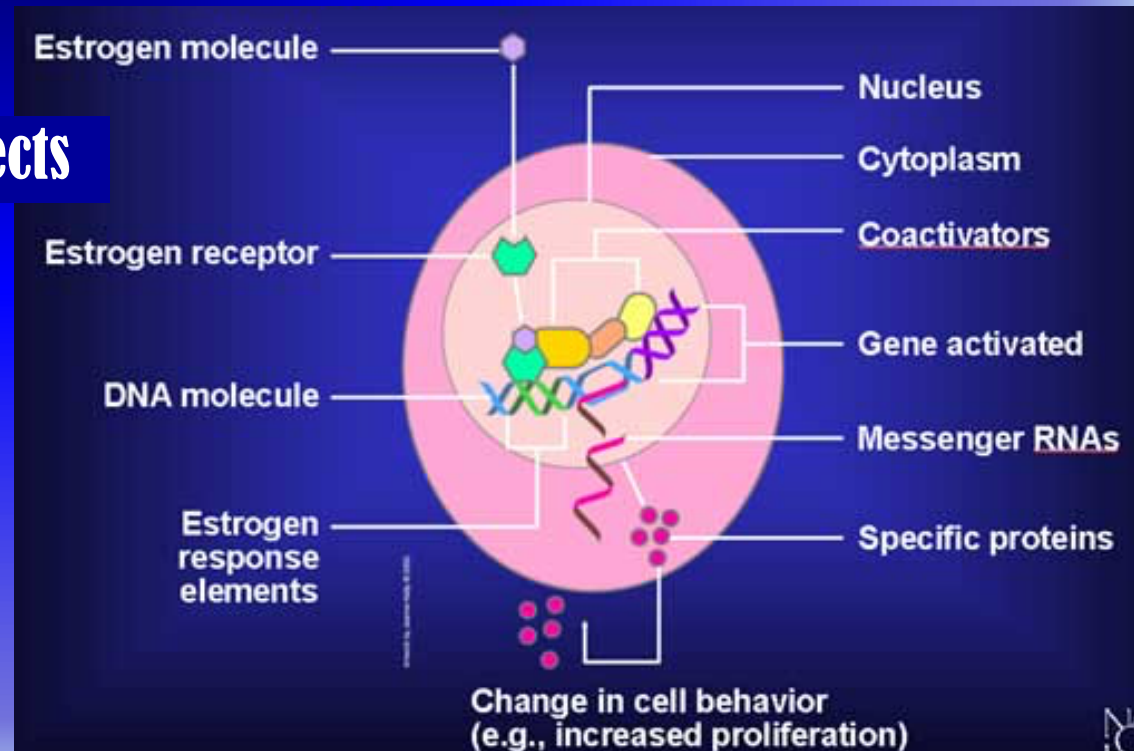


Estrogens bind to ER ( $\alpha$  or  $\beta$ ) that exist either;

🏠 **Cytoplasmic;** mediates its **genomic actions** → hrs– dys time scale  
 → development, neuro- endocrines, metabolism

🏠 **Membranous;** GPER → 2<sup>nd</sup> messenger → ↑ Ca or cAMP or ↑ MAP Kinase  
 > mediates its **non-genomic actions** → sec – min. time scale → on NO, neuro-  
 transmitters, endometrium, .....

## Genomic effects



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






# INDICATIONS

ESTROGEN★

- A. In Menopause** Not given unless presence of symptoms; alone only after hysterectomy or with progestin as HRT (never exceed 5 yrs administration)
- Improves hot flushes & night sweats
  - Controls sleep disturbance & mood swings by acting on NE, DA & 5HT at reticular formation
  - 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 (topical and systemic estrogens prep are effective)
  - Increases bone density by ↓ osteoclastic activity.
  - Progestins act synergistic by blocking cortico-steroid induced bone resorption. (Decrease incidence of hip fracture)

- 
- 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)**
  - 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



# Administration

ESTROGEN ★

Ⓢ Oral: -  
Conjugated equine

Estradiol valerate

Estrial succinate

Ⓢ Transdermal (estradiol);

Patches → 24 hour twice weekly.

Ⓢ Subcutaneous implant (estradiol) → 6 monthly.

Ⓢ Vaginal cream as such or as rings pessaries

Ⓢ These natural estrogen prep have less risk of adverse CVS effects associated with synthetic estrogen used in oral contraceptive e, ethinylestradiol

**ADRs** ➤ Irregular vaginal bleeding (**patients discontinue HRT**).

➤ Bleeding can be prevented if progesterone is given together with estrogen thorough out.

➤ Vaginal discharge.

➤ Fluid retention. Weight gain.

➤ Breast tenderness (**patients discontinue HRT**)..

➤ Spotting or darkening of skin (on face)





## Contraindications

### Absolute:

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

## Interactions

- ⚠ See contraception
- ⚠ NB. If given with
  - Ⓜ SERMs → additive side effects for both drugs
  - Ⓜ Aromatase inhibitors → ↓ efficacy
  - Ⓜ Corticosteroids ↑ side effects

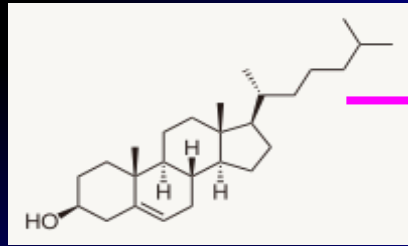


## 2. PROGESTINS

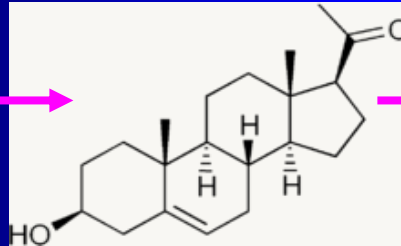
### In NATURE

Produced by; Adrenal glands, Gonads, Brain, Placenta

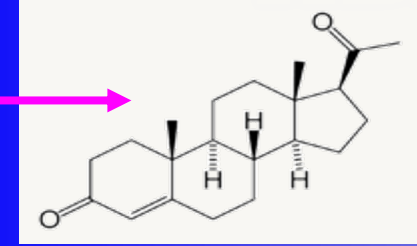
Synthesis;  
Induced by LH



Cholesterol



Pregnenolone



Progesterone

### 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.
- Progesterone (natural) protects against breast cancer development by anti-inflammatory & apoptotic mechanisms, but this effect is not as clear with synthetic progestins. Mamography recommended every 6ms.
- Counteract osteoporosis, directly +ve osteoblasts

## B. Other Uses

1. Contraception (Estradiol + Progestins)
2. Dysmenorrhea
2. Menopausal symptoms (Estradiol + Progestins given together)

## **Administration**

- ⊗ Oral; Micronized progesterone or progestins → see contraception
- ⊗ IU; as Levonorgestrel or Progestasert
- ⊗ Vaginal - natural progesterone gel / pessary.
- ⊗ Transdermal - sequential / continuous patch.

## **ADRs**

- Mood changes, as anxiety, irritability
- Headache, dizziness or drowsiness
- Nausea, vomiting, abdominal pain or bloating (distention).



# 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 (long term)
- Breast cancer (long term 5 yrs)
- **Uncertain benefits**
- Cognitive functions
- **Note: the risk of CVS problems and breast cancer with HRT is more than their benefits)**



**3. SERMs Tamoxifen, Raloxifene (oral and non-hormonal)**

- **Raloxifen** antagonist in breast and uterus and agonist in bone
- **Tamoxifen** Antagonist in breast and partial agonist in bone and endometrium.

An ideal SERM for use as 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
+ = agonist	Estradiol	++	++	++	++	++	++
- = antagonist	<u>Ideal SERM</u>	++	—	++	—	++	++
<b>Not Ideal</b>	Tamoxifen	—	+	—	—	+	+
	Raloxifene	—	—	—	—	++	+

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

Raloxifene → has no effect on hot flushes or (**very effective preventing vertebral bone fracture and CVs problems less compared to Estrogen**) for osteoporosis use of bisphosphonate is better than SERMs

## 5. PHYTOESTROGENS

supplements from plants; containing isoflavones (soya beans, flaxseeds) or lignans (whole grains). Avoid in estrogen dependent breast cancer

■ They mimic action of estrogen on ER- $\beta$  → alleviate symptoms related to hot flushes, mood swings, cognitive functions & possess CVS protective actions. (data limited on their efficacy)



## 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 → has some androgen agonistic properties. (androgens use is not approved by FDA in women)*

# The Women's Health Initiative (WHI) and HRT

- **Menopausal Hormone Therapy**
- For decades, hormone therapy 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

- Fluoxetine (SSRI)
- Clonidine (centrally acting antihypertensive)
- Gabapentin (anti-convulsant)
- Physical activity: exercise, smoking cessation and relaxation of mind will improve symptoms of menopause (e.g hot flashes) and fall preventing strategies prevents chances of fracture.

HRT



THANK YOU

