Risks and Benefits Associated with Hormone Replacement Therapy for the Treatment of Menopause Symptoms.

NMPhA Mid-Winter Meeting
January 20th, 2024
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Learning Objectives

- **Pharmacists**

  Upon completion of this activity, participants will be able to:

  1. Discuss how estrogen and progesterone concentrations are regulated in the female body and main physiological functions of each hormone.
  2. Discuss the pharmacological mechanisms of action of hormone replacement therapy to relieve menopausal symptoms.
  3. Discuss the underlying mechanisms of action driving risks associated with hormone replacement therapy.

- **Pharmacy Technicians**

  Upon completion of this activity, participants will be able to:

  1. Understand how estrogen and progesterone are regulated and main physiological functions.
  2. Know how hormone replacement therapy is used to relieve menopausal symptoms.
  3. Know the risks associated with hormone replacement therapy.

Female Reproductive Hormones – synthesized in ovaries

Estrogens

1. **17β Estradiol = E2 = estrogen**
   - Major secretory product from the ovaries
   - **Synthesized from androstenedione or testosterone**
2. **Estriol – metabolite of estradiol**, principle **placental** estrogen, pregnancy
3. **Estrone – metabolite of estradiol**, in ovaries

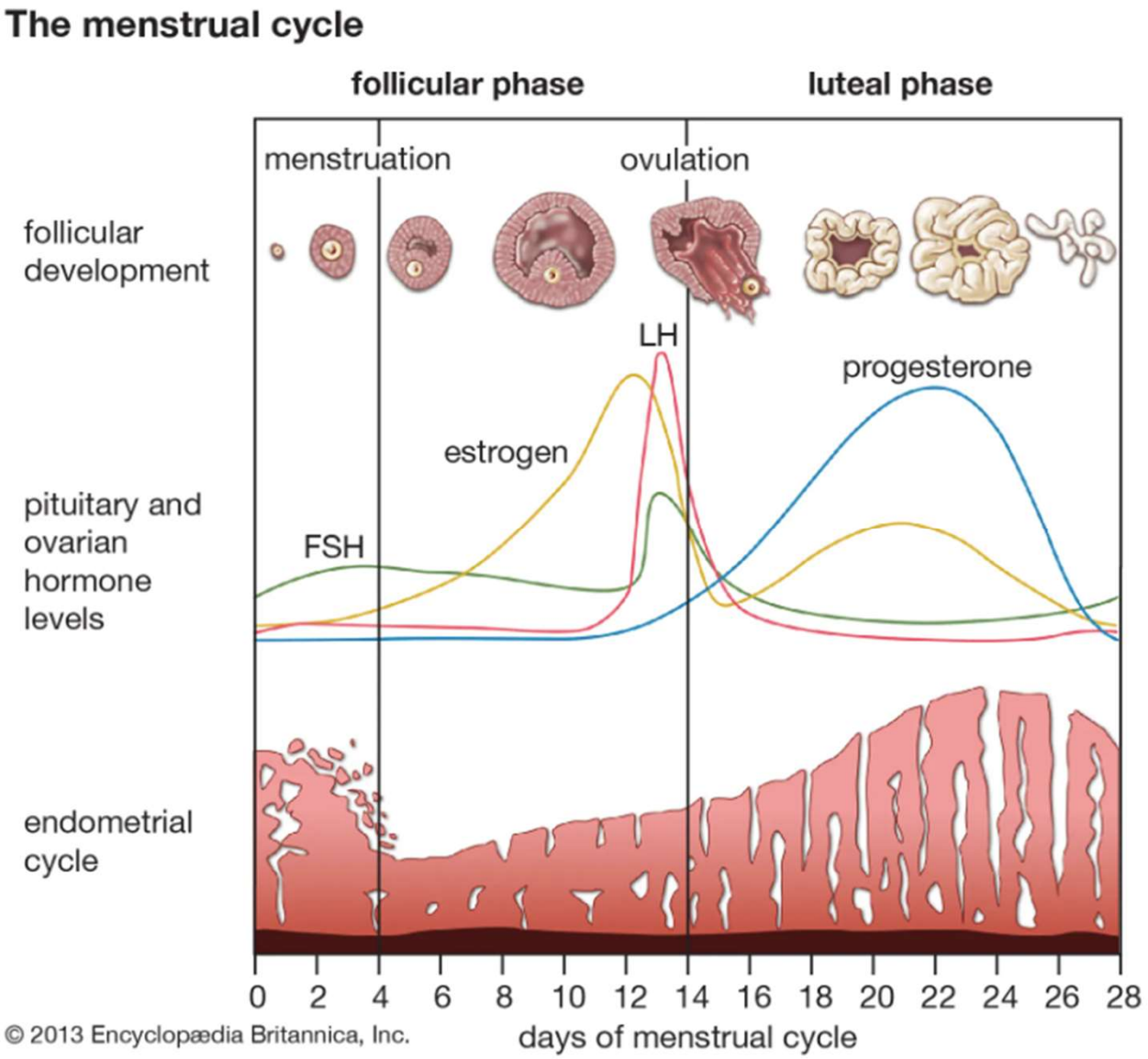
Progesterone **Precursor to androgens and estrogens**

Primarily secreted by **corpus luteum** (ovulated follicle)

Weak Androgens

Dehydroepiandrosterone (DHEA) & androstenedione

Small amounts of testosterone



Ovaries

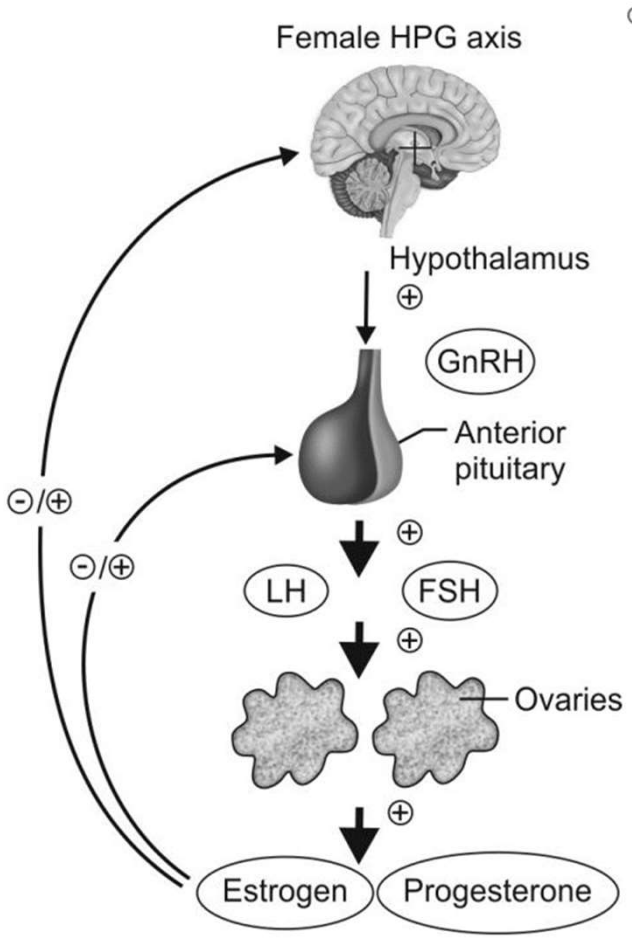
Blood

Uterus

Female reproductive hormone production is under hypothalamic - pituitary - gonadal axis control.

FEEDBACK

IMPORTANT CONCEPT!



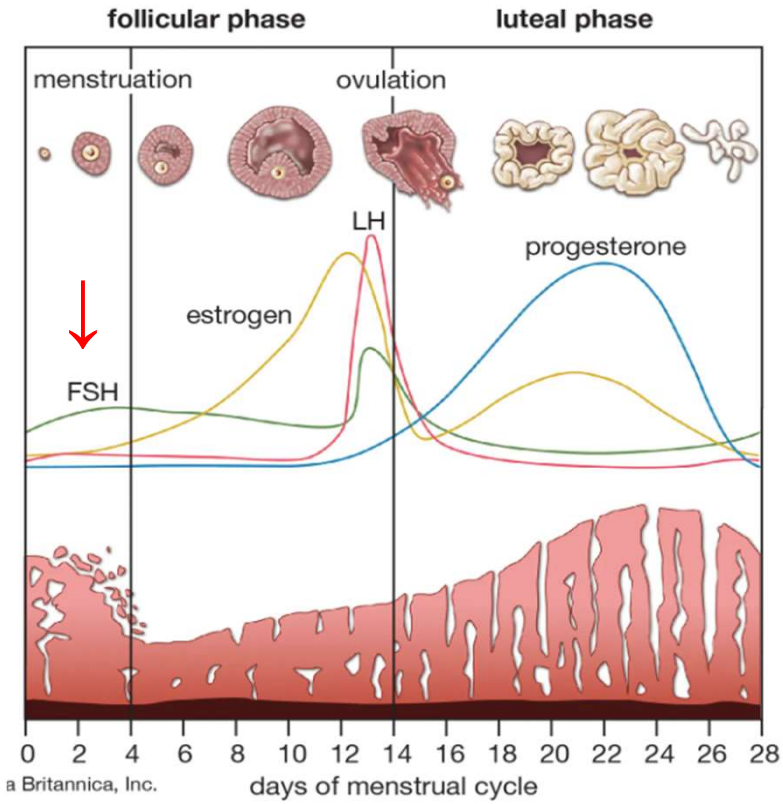
Endocrinology in Obstetrics & Gynecology. Jaypee. 2015

Follicular Phase – Menstrual Cycle

1. **Menses** – endometrium is being shed.
2. **FSH** ↑ early & **stimulates estrogen production** (+LH)

   follicular recruitment and growth. (Start with 6-12 primary follicles)

3. **6th day one follicle dominates** and **secretes estrogen** and **inhibits both FSH** and further follicle development.



Estrogen - Follicular Phase

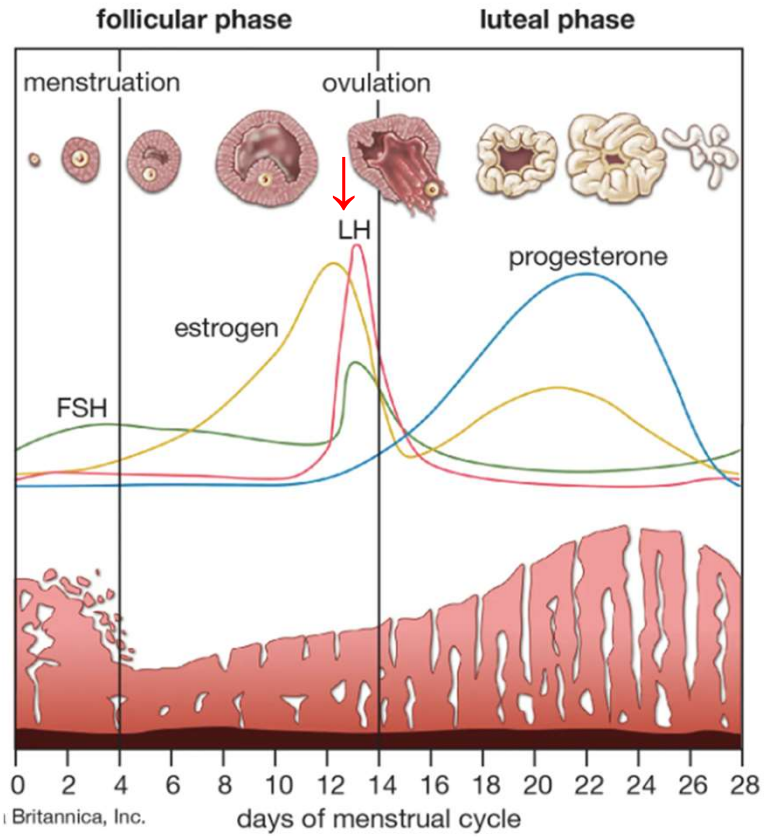
- **Stimulates <u>proliferation of uterine lining</u>** (endometrium) – "Thickening"
- **<u>Increases progesterone receptors</u>** in endometrium

4. This **increases LH receptors** late in follicular phase and **the granular cells start producing progesterone.**

5. **Ovulation: <u>24-36 hrs after</u> estrogen peak** & onset of **<u>LH surge</u> (10 hr after peak).**

6. Oocyte has ~**<u>24 hrs</u>** to be fertilized or it dies.

7. **<u>At-home ovulation</u> -** test for **LH surge**, present before ovulation.



Luteal Phase – Menstrual Cycle

1. **Corpus luteum** (remnants of follicle)
   estrogen and progestin secretion increases.

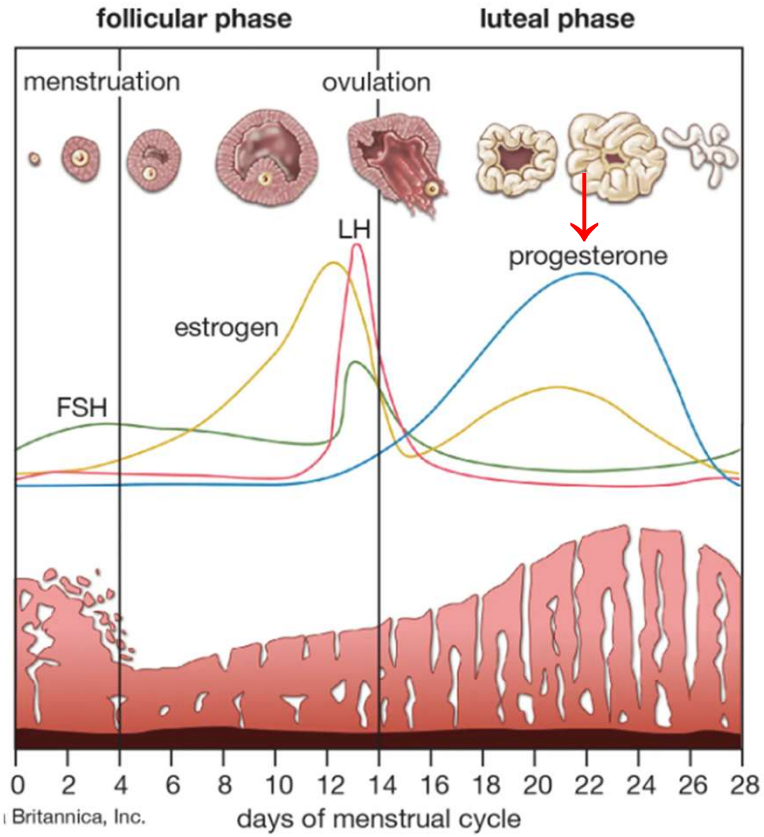
2. **FSH and LH are inhibited** due to feedback inhibition.

   Consistently last 14 days, progesterone **stimulates endometrium differentiation.**

   - **Stimulates mucus secretion**
   - **Increases vascular supply**

   Viscous acidic mucus is hostile to sperm.

   Body temperature increases about 0.5 to 1°F at ovulation & persist. (Predict Ovulation)



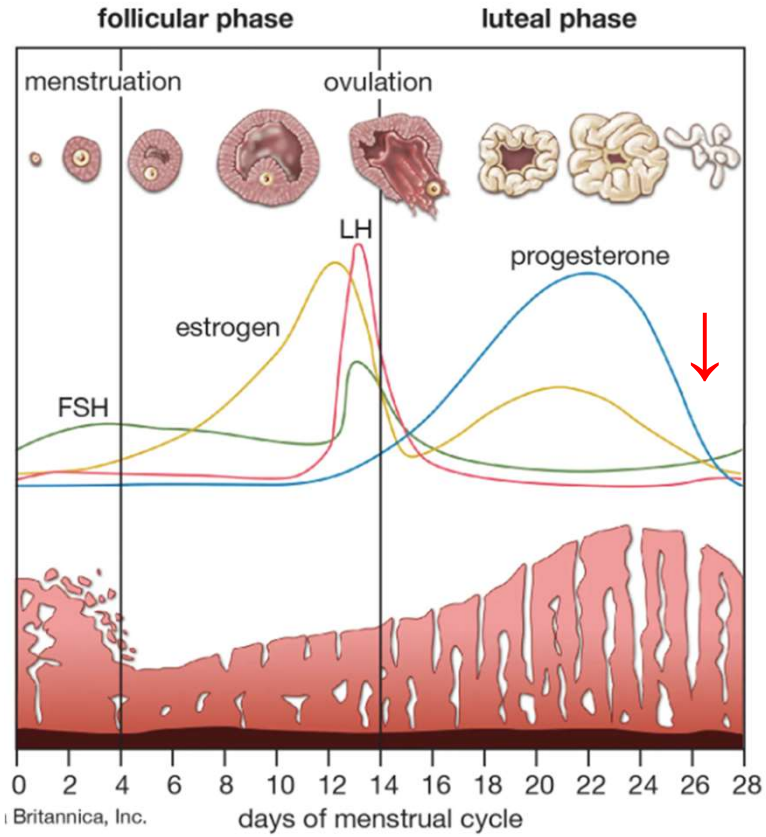
4. If **not pregnant, corpus luteum** reaches **peak** steroid **production in 7 days & degenerates & hormone levels decrease = menses.**

5. If **pregnant** implanted embryo:

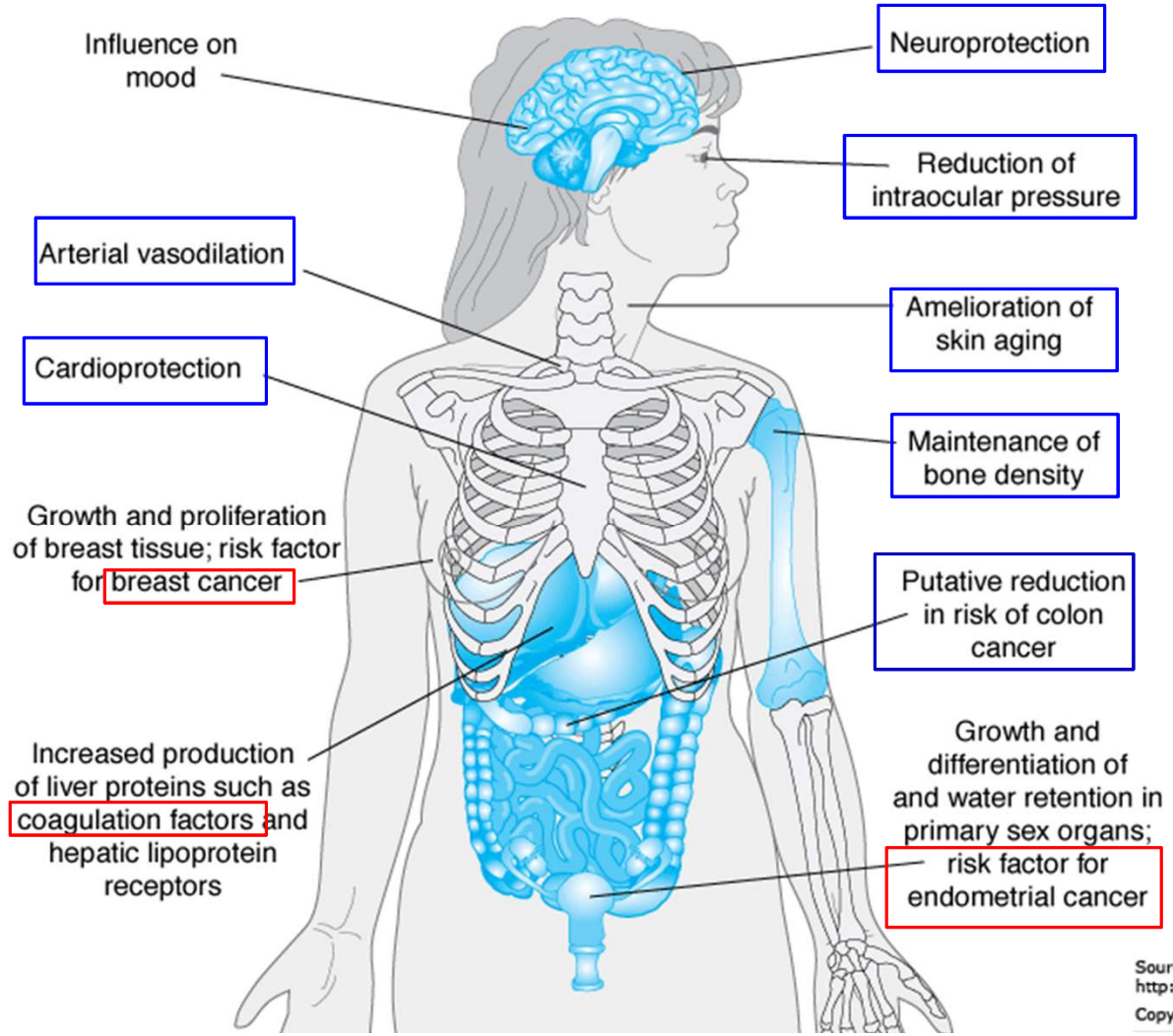
   - Produces **HCG (human chorionic gonadotropin).**
   - **This sustains pregnancy** by **<u>stimulating the corpus luteum</u>** to continue secreting **progesterone and estrogen**.
   - Placenta takes over (**~3 mo**).
   - **Pregnancy Tests Measure HCG.**
   - **During Pregnancy – Progesterone:**

Suppress menstruation and uterine contraction (antagonizes prostaglandins).

Stabilize uterine membrane:↓RMP, ↓ Ca^{++} uptake, ↓ PG synthesis – Suppresses uterine contraction.



Overview of the Physiological Effects of Estrogen

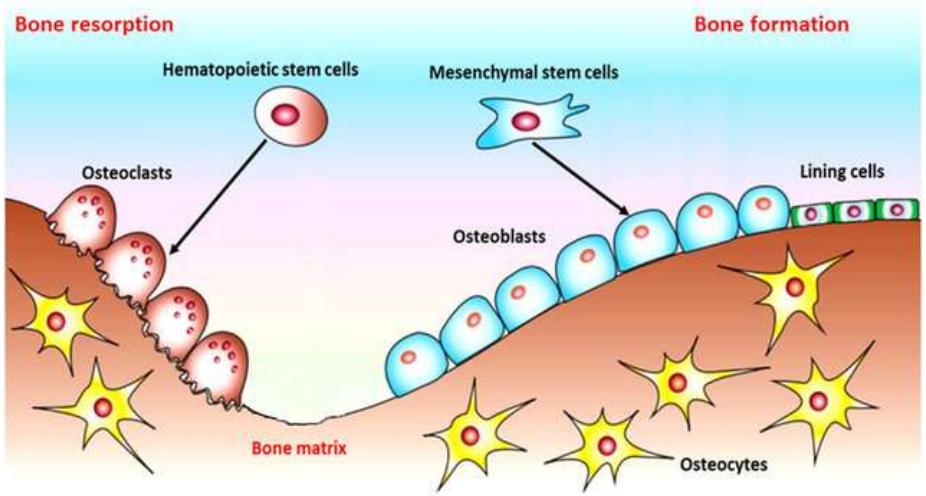


Other Physiological Functions of Estrogen

1. Bone:

Estrogen receptors:

- **On the osteoclast: blocks <u>resorption of bones</u>, by inhibiting osteoclast differentiation**
- **Balance may lean toward osteoblast increasing bone formation but not a direct effect.**



Sebastian and Loots. Metabolism. 2017.

2. Lipid metabolism (Liver): overall effect is thought to be **beneficial**

- **Increases serum triglycerides and HDL.**
- **Reduces LDL and Total Cholesterol.**

3. Blood vessels: Cardio Protective

- **Promotes vasodilation – increases nitric oxide synthase**.
- Stimulates renal **sodium and water retention.**
- **Promotes healing of vascular injury**:
  - **↑endothelial cells, ↓smooth muscle cell proliferation**
  - **This inhibits the development of atherosclerosis.**

4. Liver

- **Stimulates** production of:
  - **Hormone binding proteins**.
  - **<u>Clotting factors (may produce thromboembolic disorders)</u>**.

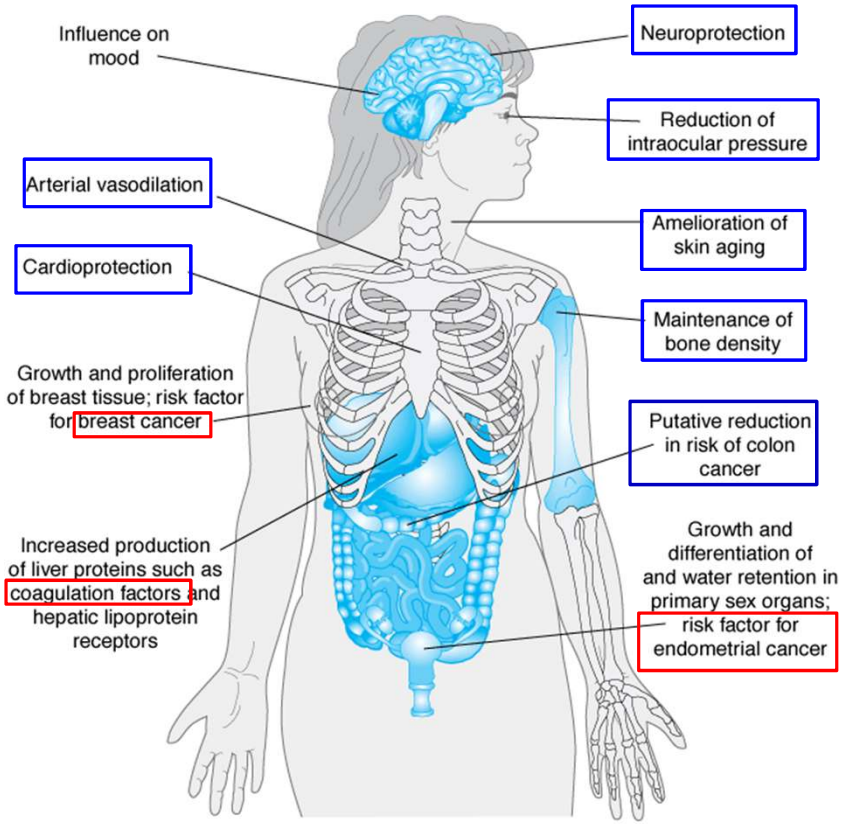
5. Central Nervous System:

- Experimentally estrogen has **neuroprotective actions.**
  - **Microvascular –Increase vasodilation, decrease vascular inflammation – mediated through Nitric Oxide Synthase.**
  - **Protection against stroke.**
  - **Improves Mood (neurotransmitters), Cognition.**

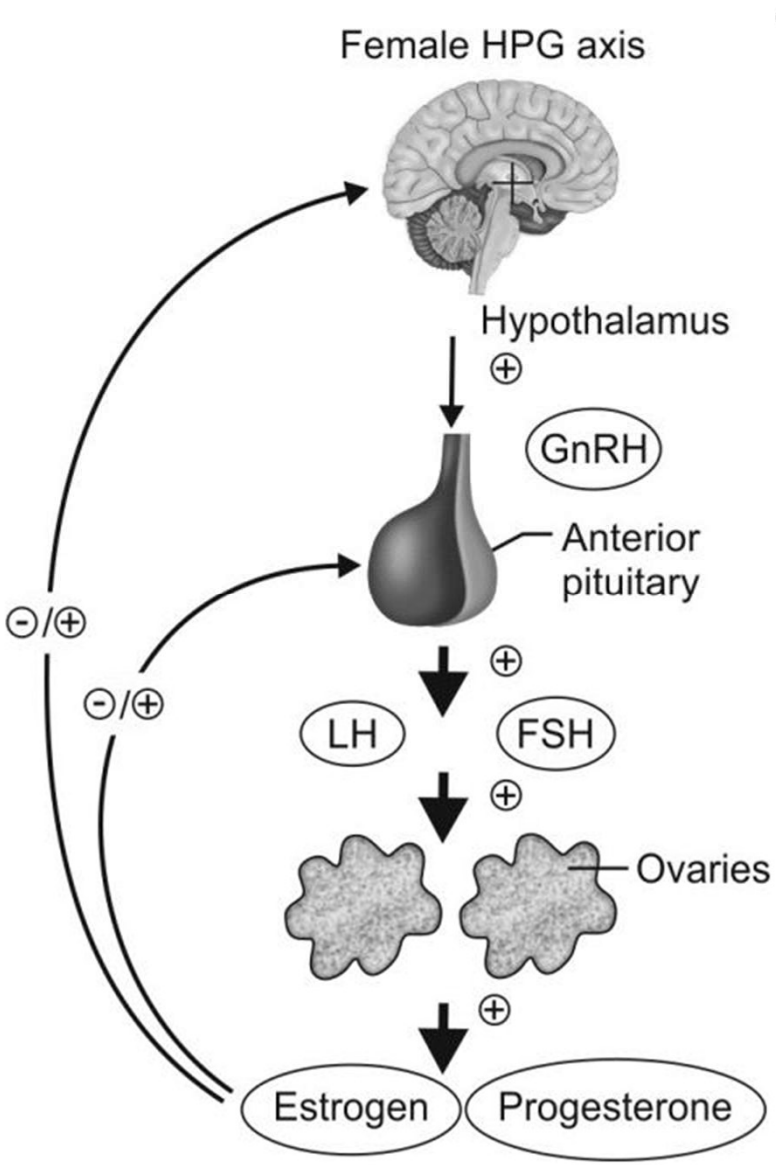
ESTROGEN + PROGESTIN
THERAPEUTIC USES

1. Hormone replacement therapy in postmenopausal women

- **At menopause** (12 months of amenorrhea), no functional follicles = no **estrogen/progesterone produced.**
- **Menstrual cycles end**, levels of **FSH and LH increase**, and **physiologic benefits of estrogens are lost**.



Source: Molina PE: *Endocrine Physiology, 3rd Edition:* http://www.accessmedicine.com

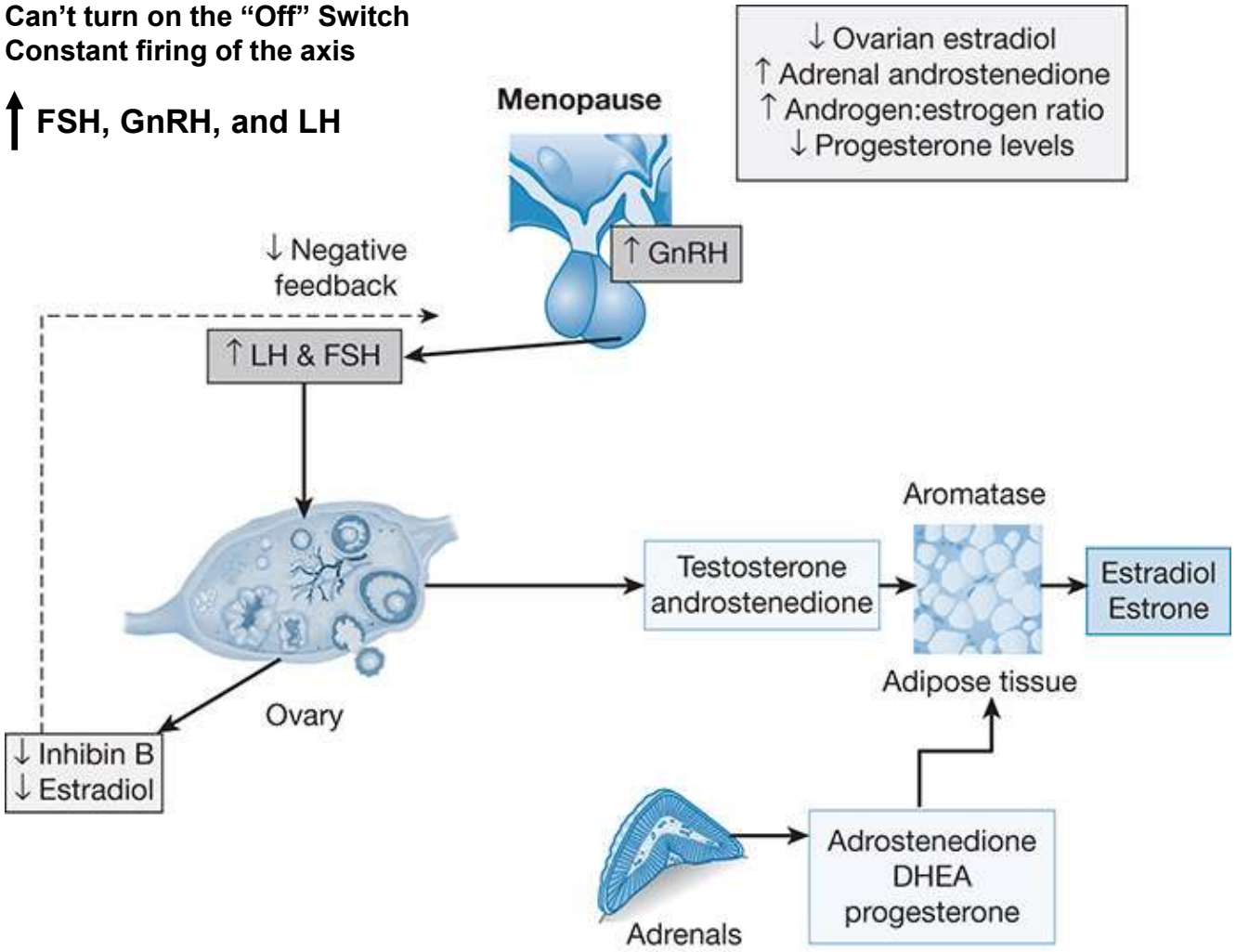


Endocrinology in Obstetrics & Gynecology. Jaypee. 2015

MENOPAUSE

Can't turn on the "Off" Switch
Constant firing of the axis

↑ FSH, GnRH, and LH



Source: Patricia E. Molina: *Endocrine Physiology*, 5e

Hormone Levels During Menopause
Estradiol = 5 – 20 pg/ml
Progesterone <0.4 ng/ml

Menopause: Potential Problems & Symptoms

1. **Vasomotor Symptoms:** Hot flashes, Night Sweats
2. **Osteoporosis – major long term problem**
3. **Genitourinary Syndrome:** Vaginal dryness, burning, irritation, vaginal mucosa atrophy, impaired sexual function, urinary urgency
4. Mood changes, sleep disturbance, dermal aging
5. **Increase in incidence of cardiovascular disease – Rise plasma cholesterol and Increased LDL levels**
6. **Increase in incidence of colorectal cancer**
7. **More malignant forms of breast cancer**
8. Loss of neurons in brain leading to a **decrease in cognitive function, Alzheimer's disease?**
9. Macular degeneration, **cataract** formation possible

Mechanism of Action- Hormone Replacement Therapy

Goal: **provide PHYSIOLOGICAL levels of estrogen** to maintain the benefits seen premenopause. **"Reestablish" relatively physiologic levels of circulating estrogens.**

FDA advises women who choose to use hormones to use the lowest dose that helps, for the shortest time needed.

- Estrogens alone cause **uterine hyperplasia and increase the risk of endometrial cancer**; thus, the **addition of a progestin** helps to **prevent uterine hyperplasia and reduce the risk of endometrial cancer.**
- Progestins **counteract effects** of estrogen on the uterus.
- **Doses for replacement therapy are generally lower than those used in oral contraceptives** but this is changing with some recent medications.

Sites of Action of replacement therapy: Bone, Liver, CNS, Cardiovascular, and Genitourinary Systems.

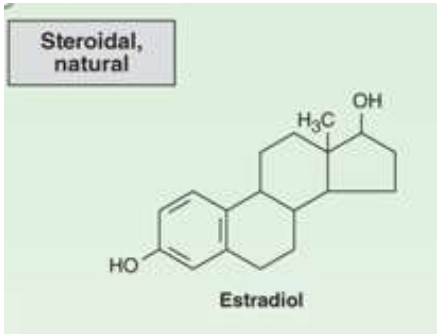
Therapeutic Benefits of Hormone Replacement Therapy

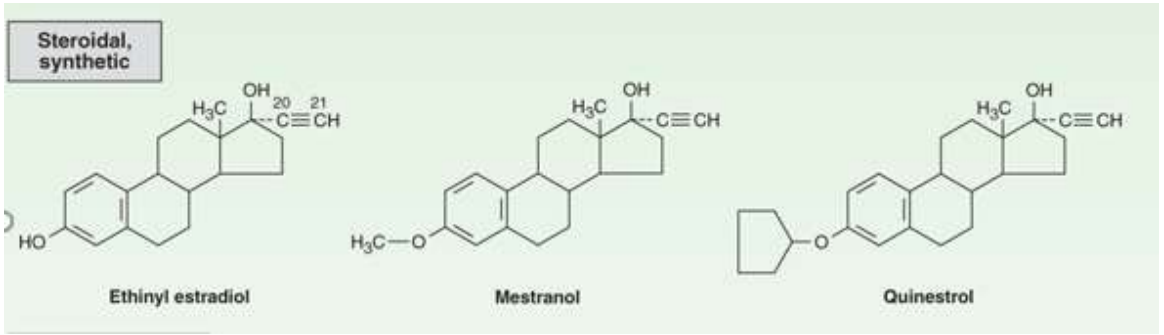
1. **Prevent vasomotor symptoms - hot flashes, chills**
2. **Prevent osteoporosis - prevent bone loss.**
3. **Prevent genitourinary symptoms - dryness, burning, genital itching, frequent urination (incontinence)**

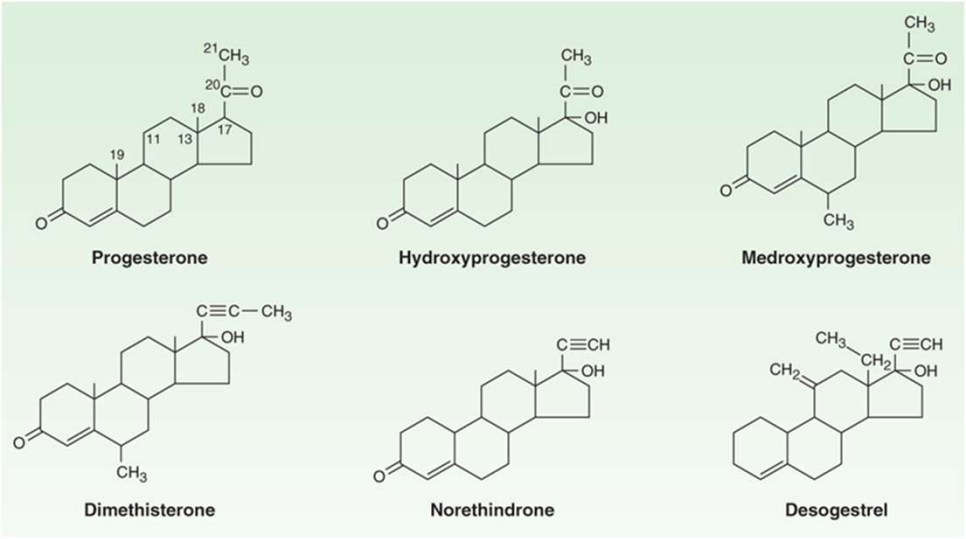
Systemic HRT (Oral, Transdermal, Topical) – Vasomotor and Osteoporosis
To Avoid undesirable hepatic/liver physiological effects of synthetic estrogens (Increased triglycerides, clotting factors) – Transdermal or Topical administration should be chosen.

Intravaginal HRT - Vaginal atrophy, dryness, irritation

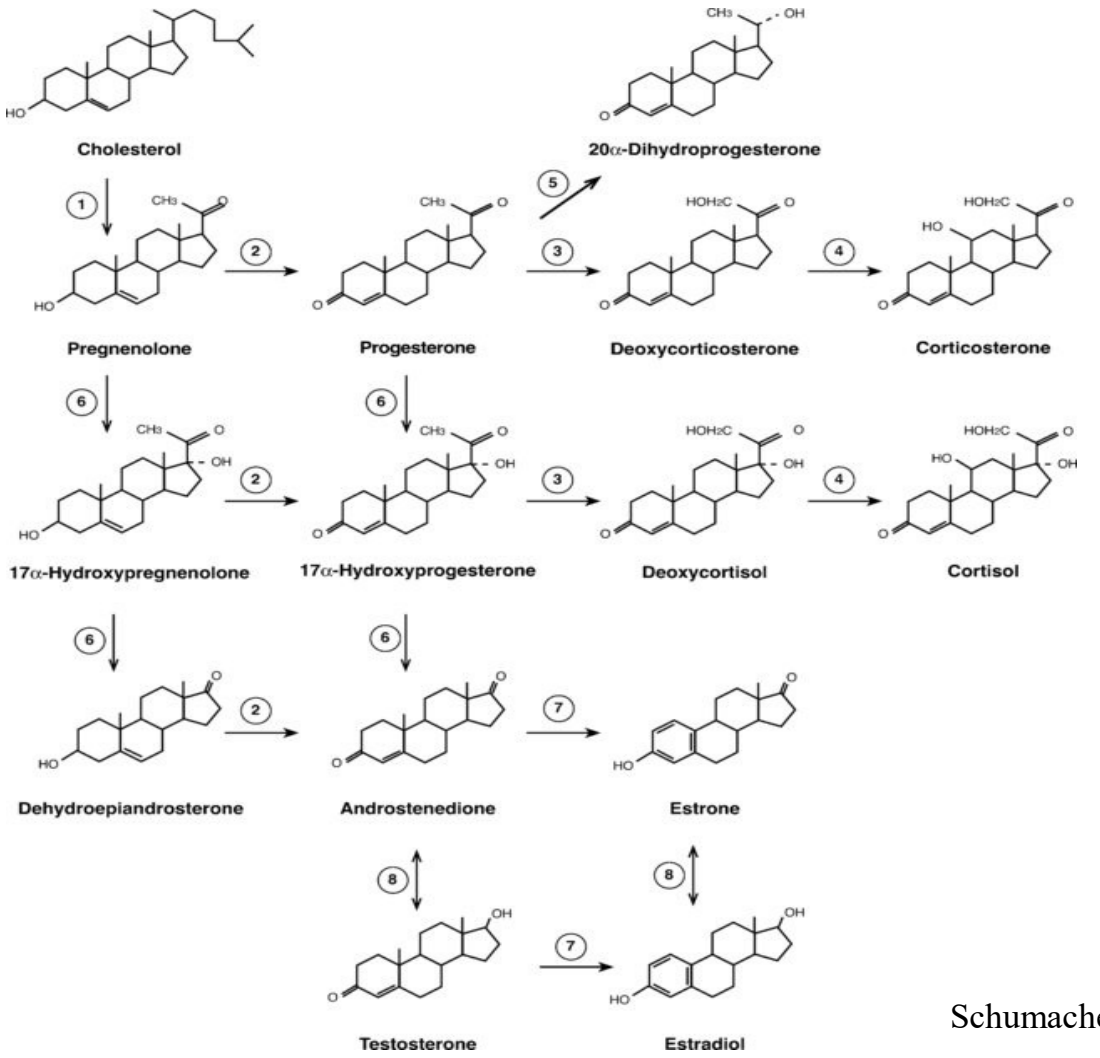
Synthetic Hormones Used Therapeutically







Steroid hormones synthesized from cholesterol



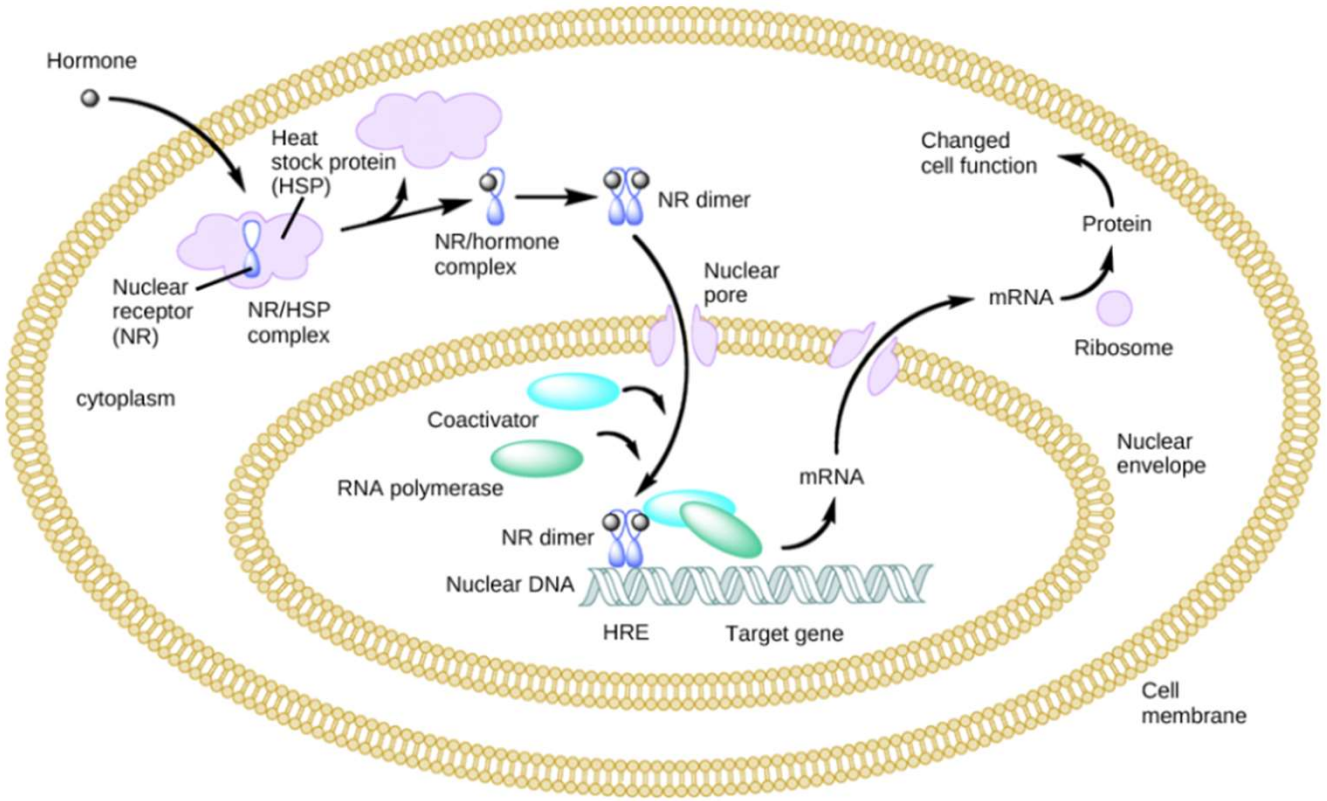
Steroid hormones are lipids

Pass through cell membranes
Bind steroid hormone receptors

Carried in blood, bound to carrier proteins (increases solubility in water)

Schumacher et. al. Progress in Neurobiology. 2003.

General scheme for steroid hormone signaling



1. **Steroid hormone crosses cell membrane into cytoplasm.**
2. **Steroid hormone binds cytosolic receptor which is kept inactive by heat – shock proteins (HSPs).**
3. **Binding alters receptor confirmation, releasing HSPs.**
4. **Active receptors bind directly to DNA and initiate transcription.**
5. **mRNA enters cytoplasm and a new protein is synthesized.**

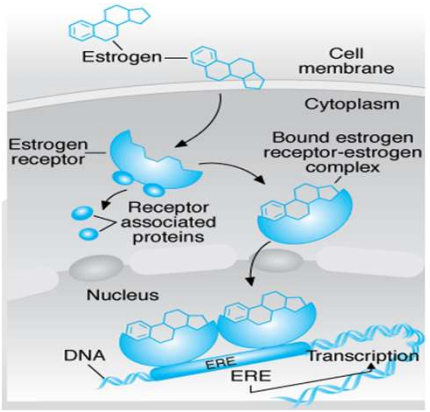
Estrogen
- **Binds to ERα / ERβ receptors**

Progesterone
- **Binds to PR B and PR A receptors**

Lumen Learning. https://courses.lumenlearning.com/wm-biology2/chapter/intracellular-hormone-receptors/

Mechanism of Action:

1. **Estradiol binds to two different estrogen receptors**:
   - **Estrogen receptor** α (**ER** α) expressed in **uterus**, **mammary gland**, **ovary**, **bone**, **liver**, **CNS**, and **adipose tissue**.
   - **Estrogen receptor** β (**ER** β) expressed in ovary (granulosa cells), colon, adipose tissue, **CNS**, and immune system.
   - **Two-thirds of breast cancers express ER** α
     - Initiation and Progression, Stimulate Tumor Growth
     - Drug Target



Source: Molina PE: *Endocrine Physiology, 3rd Edition:* http://www.accessmedicine.com
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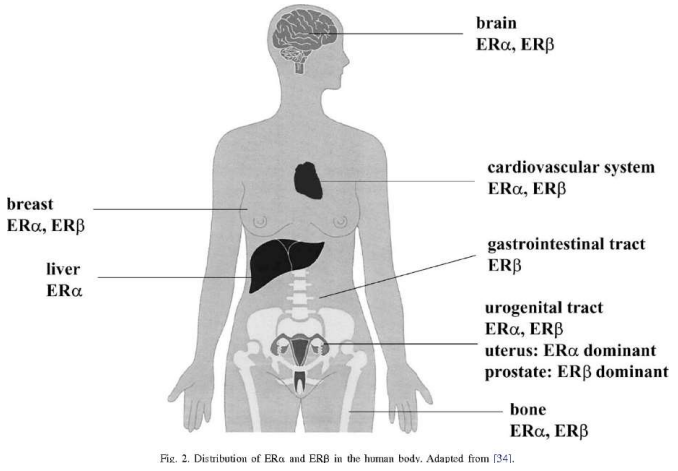


Fig. 2. Distribution of ERα and ERβ in the human body. Adapted from [34].

Pearce and Jordan. Critical Reviews in Oncology and Hematology. 2003.

Synthetic Estrogens and Progestins Pharmacokinetics

- **Oral** - Extensive Gut and 1st pass liver metabolism - Micronized Formulations (enhance absorption)

- **Transdermal/Topical/Implants/Injections** – Directly into systemic circulation -Bypass gut and 1st pass liver metabolism – more consistent blood hormone levels

- **Intrauterine Implants (IUDs)** – Localized in Uterus - Bypass gut and 1st pass liver metabolism
- **Intravaginal** - Bypass gut and 1st pass liver metabolism
  - Low concentrations – Localized to vaginal effects

HRT for treatment of Vasomotor Symptoms

- **Vasomotor Symptoms:**
  - Site of Action: Central Nervous System
  - Mechanism of Action – Synthetic Estrogens bind to ERα and ERβ receptors in CNS
  - Therapeutic Benefit – Relieve or prevent vasomotor symptoms

Common Medications Prescribed:

Oral: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens

Transdermal: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens

SERMs: Bazedoxifene + Conjugated Estrogen

When does progesterone need to be added?

- Intact Uterus!
- Prevent Uterine Hyperplasia and Endometrial Cancer
  - Site of Action – Uterus
  - Mechanism of Action – Synthetic Progestins bind to PR B and PR A receptors in the uterus.
  - Therapeutic Benefit: prevents uterine hyperplasia – counteracts estrogen in the uterus.

Common Medications Prescribed:

Oral: Synthetic estrogen (ethinyl estradiol) or Conjugated Estrogens + Progestin (Medroxyprogesterone, Levonorgestrel); Also prescribe Progesterone Alone: Progesterone, Medroxyprogesterone

Transdermal: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens + Progestin

HRT for treatment of Genitourinary Symptoms

- **Genitourinary Symptoms:**
  - Site of Action: Kidneys, Bladder, Urethra, Uterus, Ovaries, Fallopian Tubes, and Vagina
  - Mechanism of Action – Synthetic Estrogens bind to ERα and ERβ receptors in genitourinary organs
  - Therapeutic Benefit – Prevent genitorurinary symptoms

Common Medications Prescribed:

Vaginal Estrogens: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens (ring or cream)

Transdermal Estrogens: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens

Oral Estrogens: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens

SERMS: Ospemifene

HRT for treatment of Osteoporosis

- **Osteoporosis:**
  - Site of Action: Bone
  - Mechanism of Action – Synthetic Estrogens bind to ERα and ERβ receptors in bone – Inhibits osteoclasts, inhibits RANKL, increases osteoprotogerin (OPG)
  - Therapeutic Benefit – Prevent bone loss

Medications Prescribed:

Oral Estrogen: Synthetic estrogen (ethinyl estradiol), Conjugated Estrogens

SERMs: Raloxifene, Bazedoxifene + Conjugated Estrogen

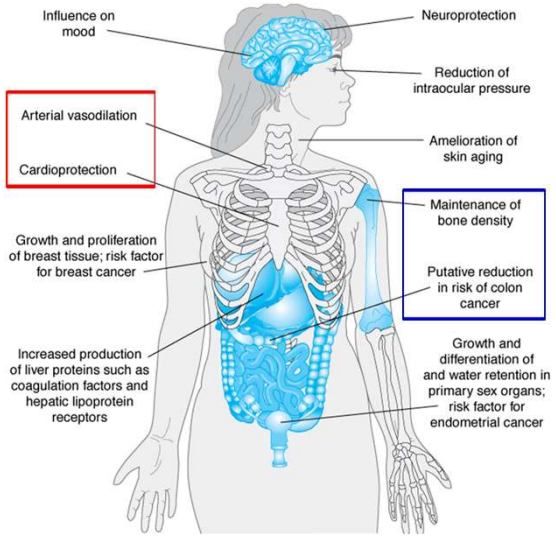
- **Not the first line treatment option for postmenopausal women**

Women's Health Initiative Study – Citation - JAMA. 2002; 288(3):321-333.

27,347 postmenopausal women, **50-79 yrs. old** (63). Intact uterus at baseline (16,608 women). (**5.6 yrs. E2+P/ 7.2 yrs. E2 only) – 13 yrs. Total**

For: Conjugated estrogen & medroxyprogesterone (Prempro™) combination (E2+P) Cohort.

1. **Increased risk:**
   - **cardiovascular disease and stroke**
   - **breast cancer**
   - **venous thromboembolic disease**
   - **pulmonary embolism**
2. **Decreased risk:**
   - **osteoporosis & fractures**
   - **colorectal cancer**



This has **increased interest in therapy with SERMs**.

Main Findings

RELATIVE AND ABSOLUTE RISK OR BENEFIT SEEN IN OESTROGEN PLUS PROGESTOGEN ARM OF WHI
(n =16,608, placebo and study drug)

Health Event	Relative Risk vs. Placebo Group at 5.2 Years (Nominal 95% CI)	Increased Absolute Risk per 10,000 Women/Year	Increased Absolute Benefit per 10,000 Women/Year
Heart Attacks	1.29 (1.02-1.63)	7	
Strokes	1.41 (1.07-1.85)	8	
Breast Cancer	1.26 (1.00-1.59)	8	
Thromboembolic Events	2.11 (1.58-2.82)	18	
Colorectal Cancer	0.63 (0.43-0.92)		6
Hip Fractures	0.66 (0.45-0.98)		5

Adapted from *JAMA* 2002; **288**: 321-

General Toxicity/Side Effects of Estrogen (HRT)

1. **Uterine/vaginal bleeding**, nausea, breast tenderness

2. **Cancer - increased risk of breast cancer -** concern in women who have multiple risk factors for breast cancer

3. **Estrogen alone increases risk of endometrial cancer** (preventable by addition of a progestin)

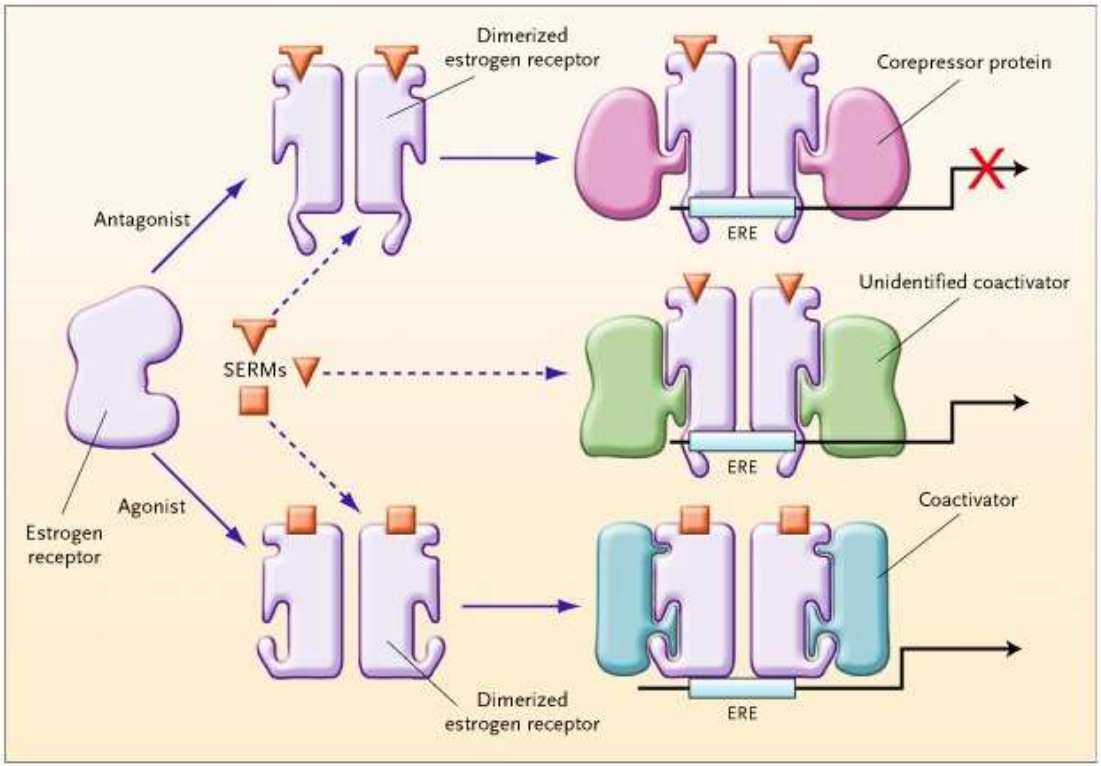
4. **Gallbladder Disease**

5. **Increased risk of Cardiovascular Disease (Heart Attack) and Stroke**

6. **Hypertension** and Elevation in **Triglycerides**

7. **Thromboembolic disorders – greater in smokers**

SERMs – Selective Estrogen-Receptor Modulators: Exert selective agonist or antagonist effects on various estrogen target tissues.



Pickar, MacNeil, & Othleth. Maturitas. 2010.

Conjugated estrogens +bazedoxifene

3rd Generation Selective Estrogen Receptor Modulator (SERM)

Therapy: 1) Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause

Agonist Effects: Agonist in CNS. Treat vasomotor symptoms.

2) Prevention of Postmenopausal Osteoporosis

Agonist Effects: Agonist in bone. <u>Prevents bone loss.</u> Use to **treat osteoporosis** through an **antiresorptive** effect predominantly. Approved therapeutic use.

Antagonist Effects: **Antagonist in endometrium**. Decrease endometrial hyperplasia.

Side Effects: Muscle spasms, nausea, vomiting, diarrhea, indigestion, dizziness

Warning: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, AND PROBABLE DEMENTIA

Ospemifene: 3rd Generation SERM

Estrogen agonist/antagonist approved for the **vulvovaginal atrophy symptoms of dyspareunia** (pain with intercourse), **may not be effective for vaginal dryness.**

May help retain bone and may be antiestrogenic in the breast.

Agonist Effects: Vaginal epithelium and Bone

Antagonistic Effects: Breast

Side Effect: Hot Flashes, vaginal discharge, muscle spasms, sweating

FDA Warning for Ospemifene:

- **Can stimulate the lining of the uterus (endometrium – slight agonist) and cause it to thicken (unopposed estrogens).**
- **Incidence rates of thrombotic & hemorrhagic strokes (0.72 and 1.45 per 1000 women) & incidence rate of deep vein thrombosis (1.45 per 1000 women)**

Raloxifene: SERM

Estrogen agonist/antagonist approved for the **treatment and prevention of postmenopausal osteoporosis**.

May help retain bone and may be antiestrogenic in the breast.

Agonist Effects: Bone

Antagonistic Effects: Breast and uterine tissue

Side Effect: Hot Flashes, leg cramps, sweating, headache, upset stomach

FDA Warning for Raloxifene:

- **Incidence rates of thromboembolic evens – Deep vein thrombosis, Pulmonary embolism**
- **Hypertriglyceridemia – monitor triglycerides, females with history of increased triglycerides in response to oral estrogens.**
- **Increased risk of Cardiovascular disease.**

Alternatives? - useful in patients who cannot or will not take hormonal therapies

SNRIs: Venlafaxine, Desvenlafaxine

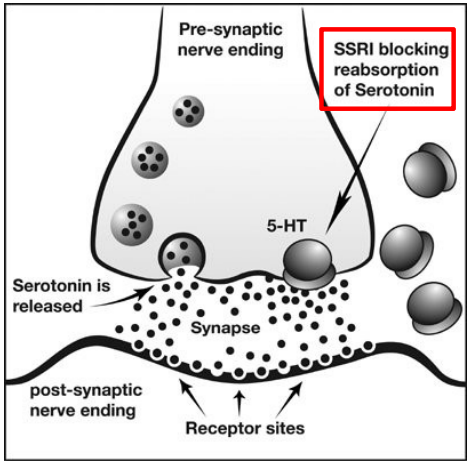
GABA mimic: Gabapentin (anticonvulsant)

α2-Agonist: Clonidine

Moderately effective for controlling hot flashes.

Paroxetine - SSRI (Hot Flashes – Imbalance of serotonin)

- **7.5 mg – moderate to severe hot flashes; 20 mg - antidepressant**
- **No benefit for vaginal atrophy and bone density**
- **Labeling contains a Black Box Warning regarding increased risk of suicide. (Dispensed with a Medication Guide)**



Lattimore et.al. J of Perinatology. 2005.

Fezolinetant – Approved in 2023

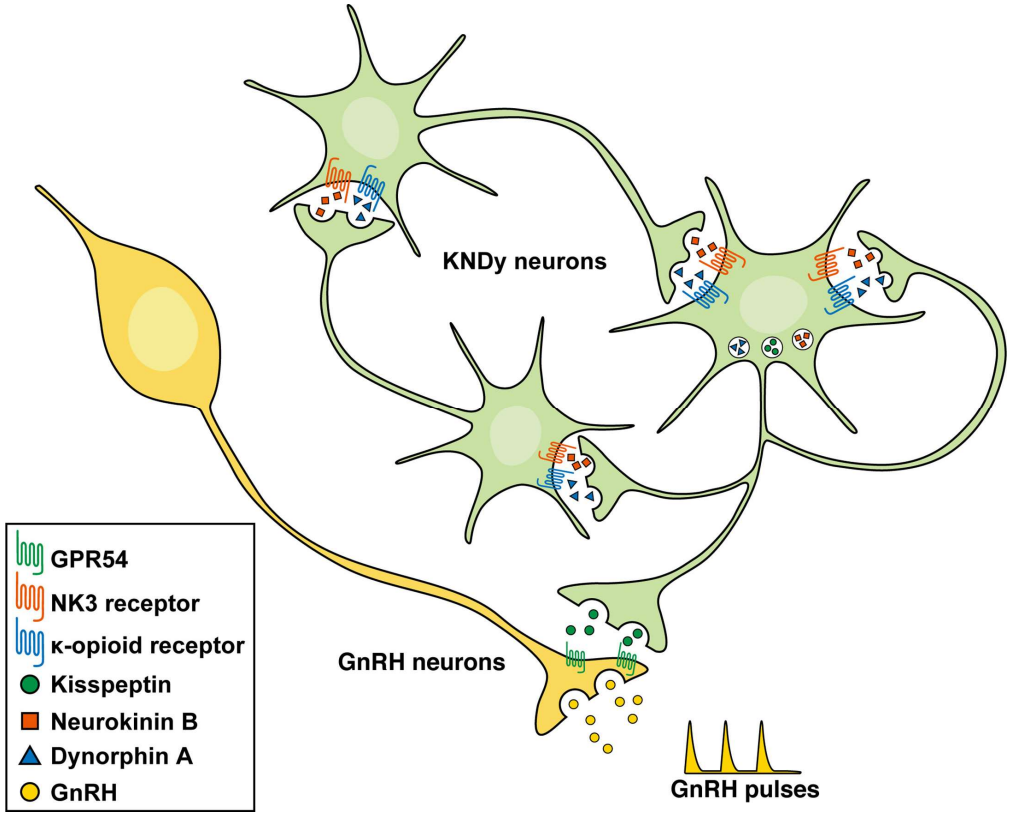
Site of action: Brain, Hypothalamus

Mechanism of action: Neurokinin 3 Receptor Antagonist

Metabolism: CYP1A2

Side effects: Stomach Pain, Diarrhea, Trouble Sleeping, Back Pain

Warnings/Cautions: LIVER TOXICITY



Uenoyama et. al. Front Endocrinology. 2021

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