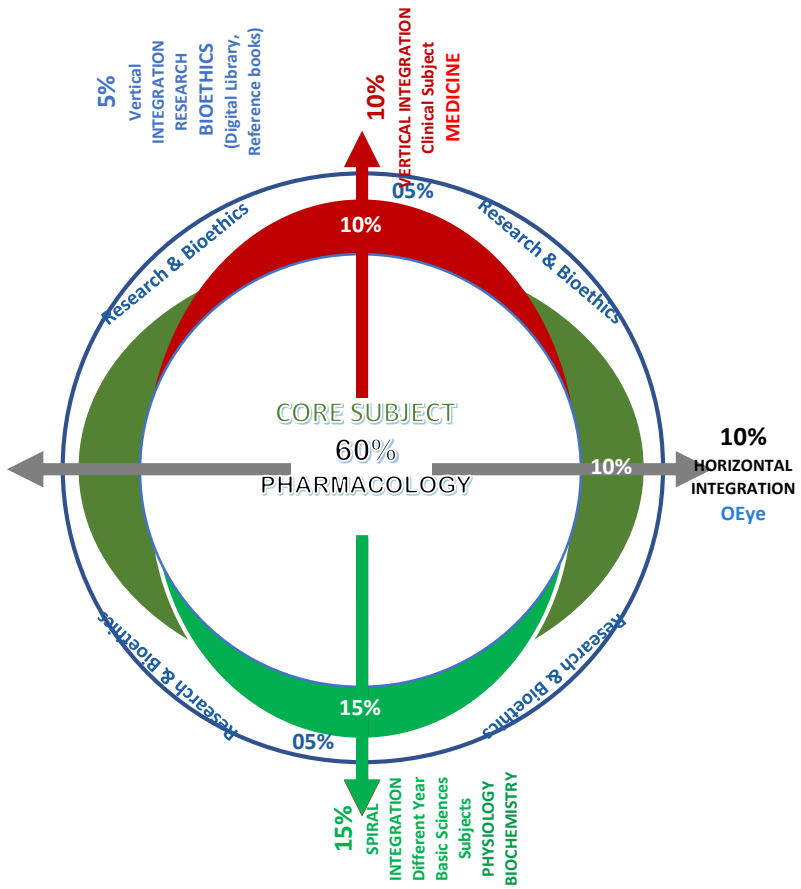
FEMALE GONADAL HORMONES

UMAR'S MODEL OF INTEGRATION



4rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Eye • Pathology
Vertical Integration – 10%	
Clinical Subjects	• Medicine • Surgery
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Research & Bioethics, Digital library – 05%	

Learning Objectives

At the end of this lecture, students of 4th Year MBBS will be able to

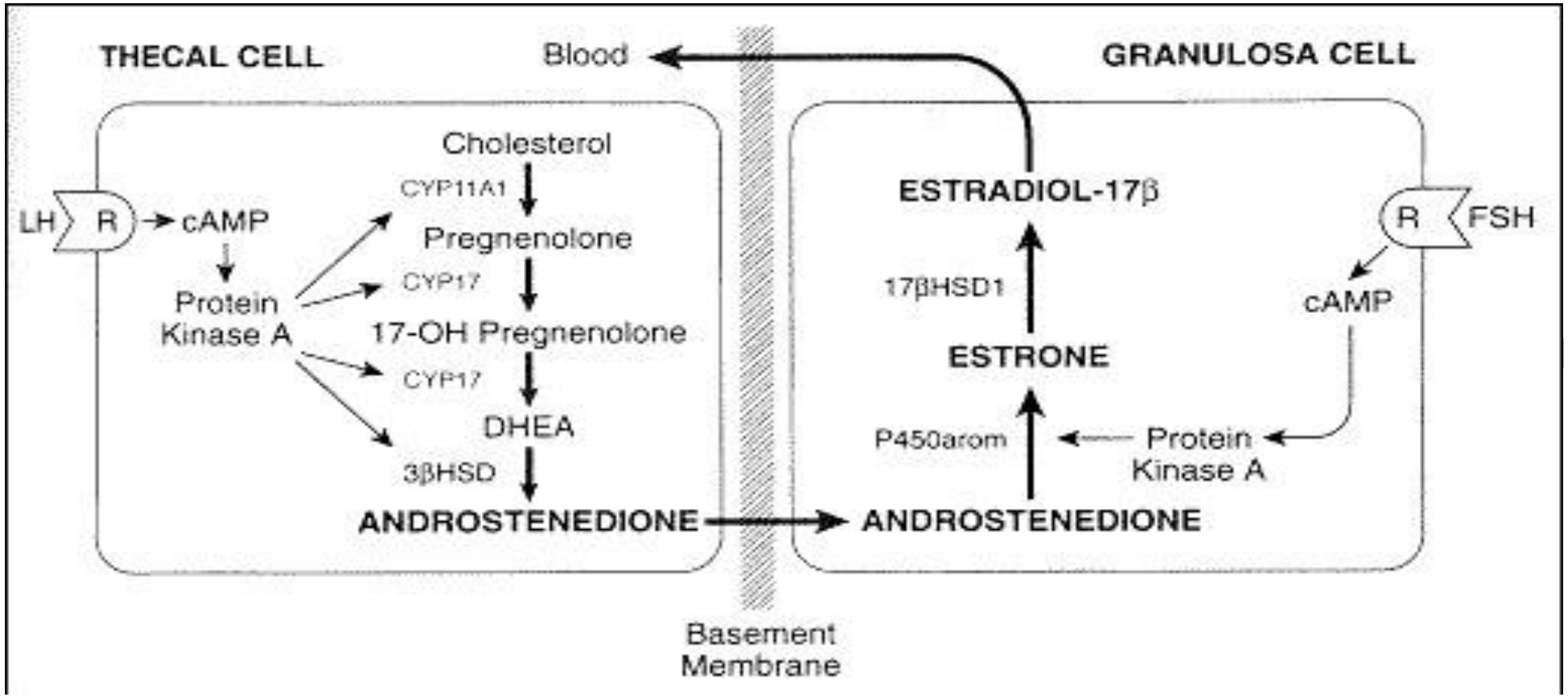
- Recall the synthesis and physiological role of female gonadal hormones
- Enumerate the synthetic preparations of female gonadal hormones
- Discuss the clinical pharmacology of female gonadal hormones
- Describe the therapeutic indications of synthetically available hormones
- Correlate the adverse effects of hormonal preparations with their physiological role

Female Gonadal Hormones

- Estrogen
- Progesterone
- Androgens (testosterone, androstenedione and dehydroepiandrosterone)
- Relaxin
- Inhibin and activin

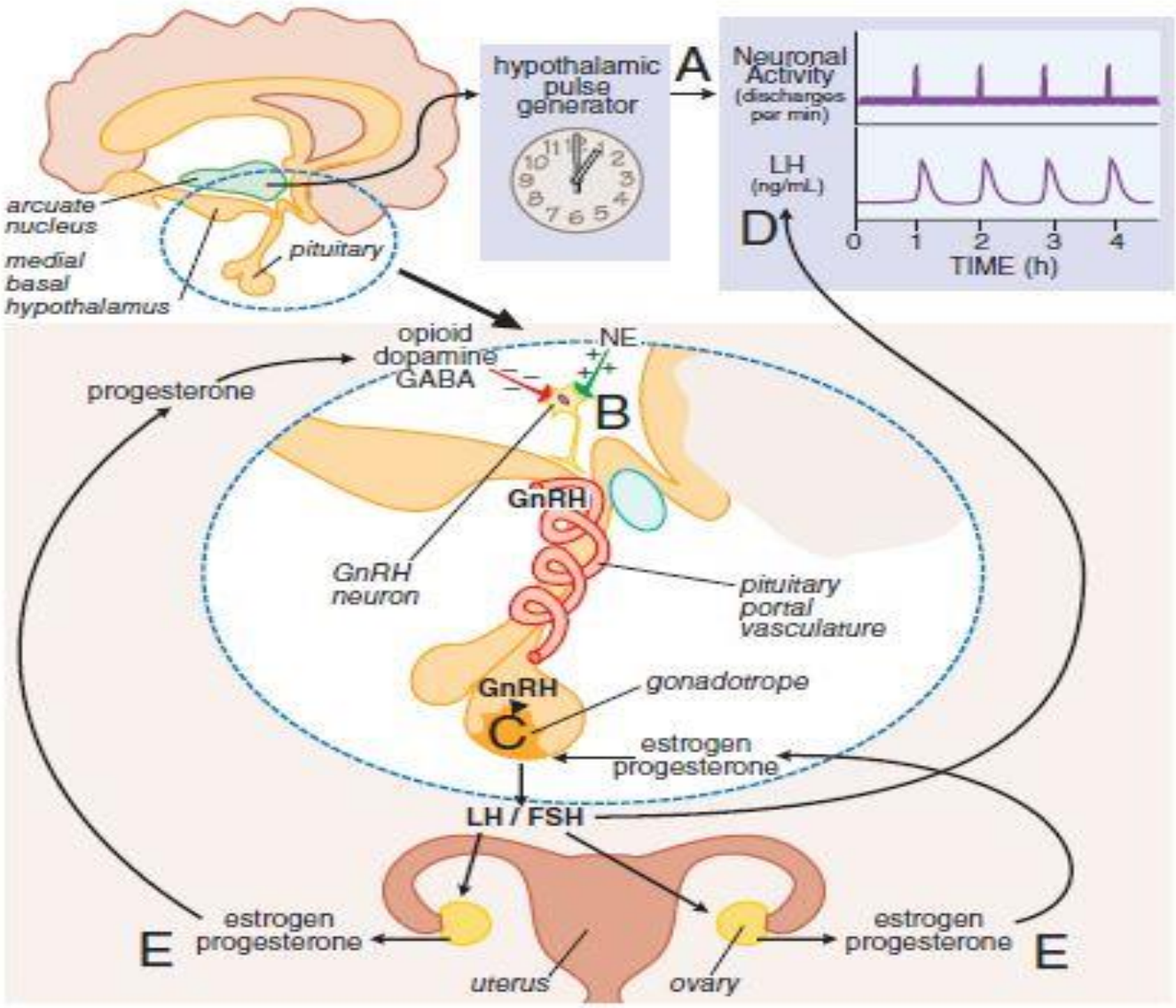
ESTROGEN
&
ITS
ANALOGUES

SOURCES & SYNTHESIS OF ESTROGEN



SPIRAL INTEGRATION WITH PHYSIOLOGY

REGULATION OF ESTROGEN



SPIRAL INTEGRATION WITH PHYSIOLOGY

ESTROGEN

❖ Natural

Estradiol, Estrone, Estriol

Equine estrogens : Black stallion (equilenin & equilin)

❖ Synthetic

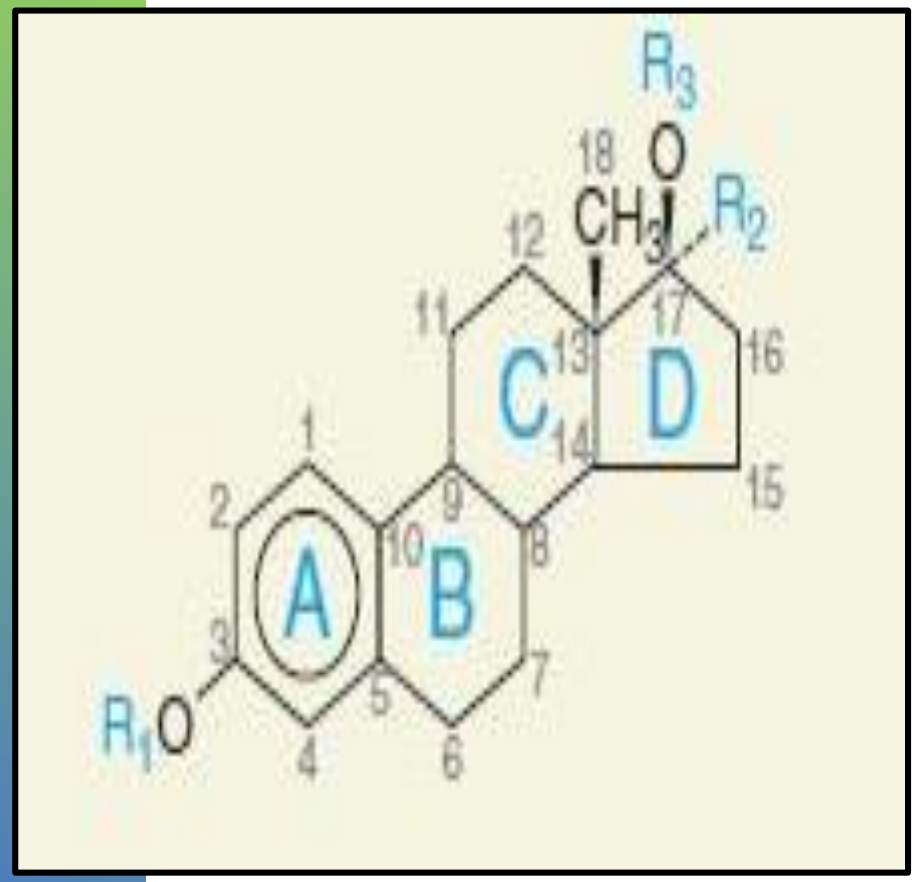
- Steriodal

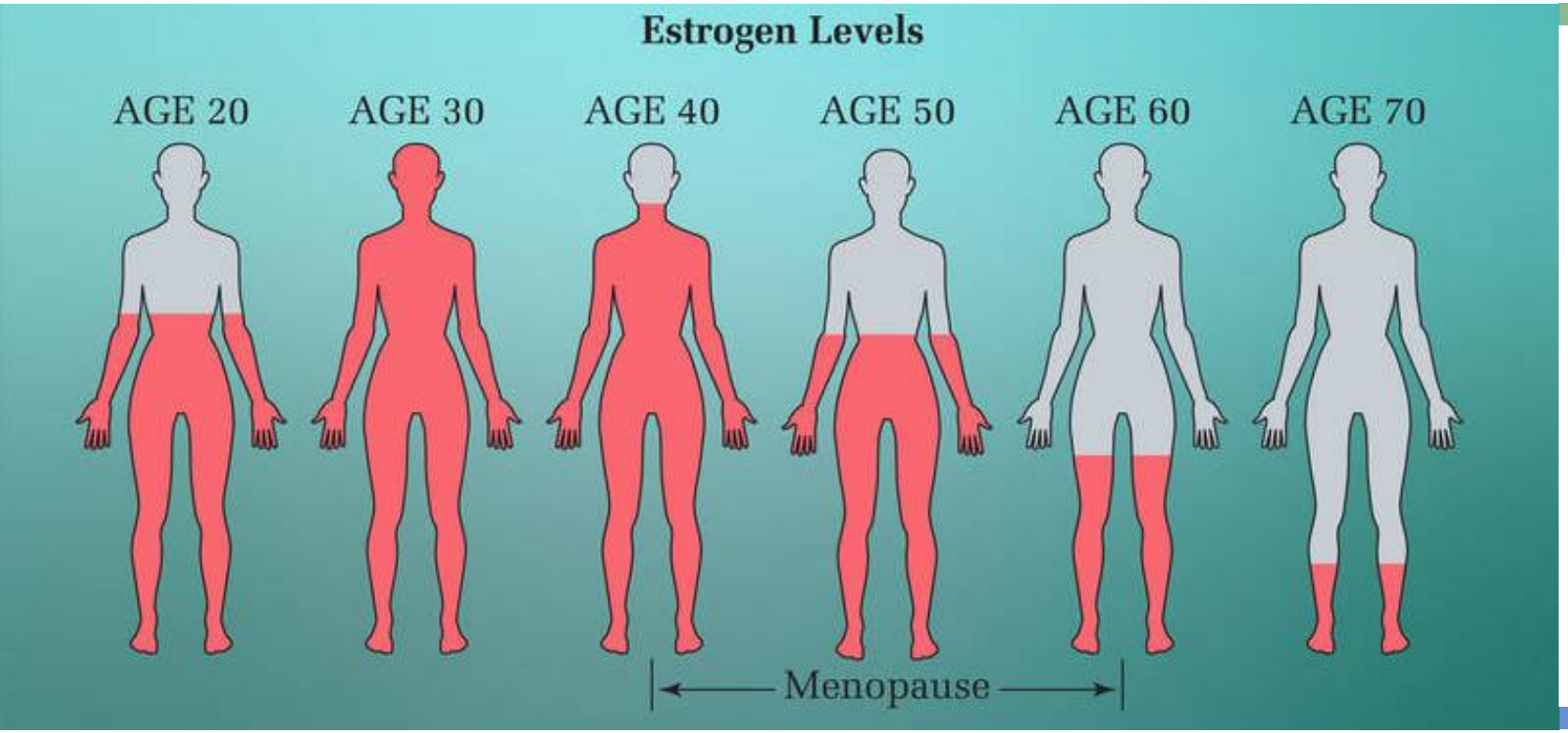
  Ethinyl estradiol, Mestranol & Quinestrol

- Non-steroidal

  Diethylstilbestrol ,Chlorotrianisene Methallenestril,Hexestrol,Benzestrol, Methestrol & Dienestrol

❖ Estrogen-mimetic compounds





Production Rates of Estrogen

- During menstrual cycles, estradiol production varies cyclically, with the highest rates and serum concentrations in the preovulatory phase followed by luteal and follicular phase

- Lowest concentration in premenstrual and postmenopausal stage of life

PHARMACOKINETICS

- Good oral absorption due to lipophilic nature with appropriate preparation (micronized preparations)
- Bound to α_2 globulin (SHBG) > albumin (ethinyl estradiol more for albumin >SHBG)
- Metabolized in liver, 2-hydroxylation & then conjugation (sulfate and glucuronide)
- Extrahepatic metabolism occurs in GIT, skin, brain by CYP3A4, 1A and 1B1

  Ethinyl estradiol & **mestranol** are **semisynthetic** derivatives
  of estradiol modified by the addition of an ethinyl group, which reduces first-pass metabolism

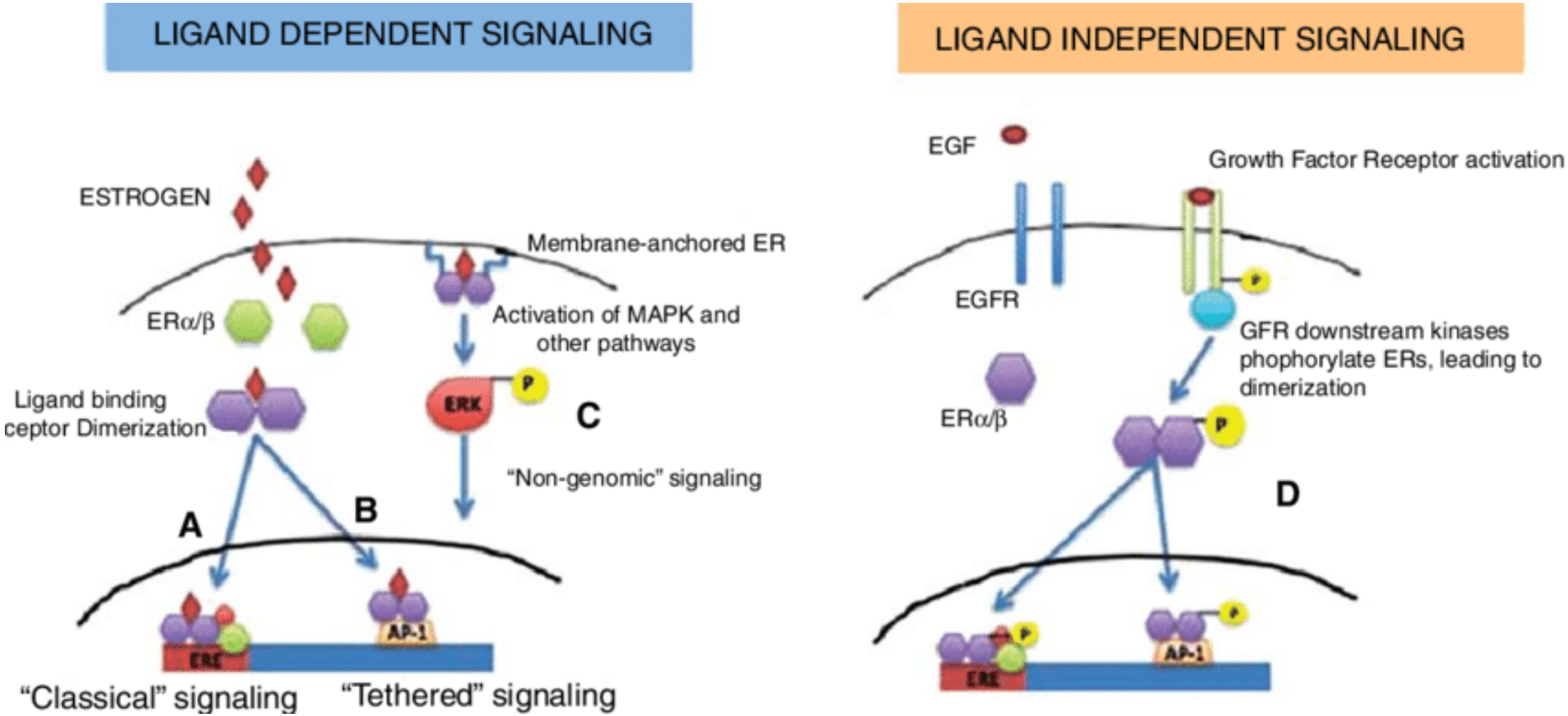
- Undergoes enterohepatic circulation causing some undesirable hepatic effects (transdermal, vaginal & injections)
- **t ½ =** 12-24 hrs
- Excreted in urine, bile (20%) & breast milk (small amount)

PREPARATIONS & DOSAGES

- Transdermal patches
- Gel and emulsion
- Implants
- Intramuscular injections
- Oral tablets
- Vaginal tablets and ring

Preparation	Average Replacement Dosage
Ethinyl estradiol	0.005–0.02 mg/d
Micronized estradiol	1–2 mg/d
Estradiol cypionate	2–5 mg every 3–4 weeks
Estradiol valerate	2–20 mg every other week
Estropipate	1.25–2.5 mg/d
Conjugated, esterified, or mixed estrogenic substances:	
Oral	0.3–1.25 mg/d
Injectable	0.2–2 mg/d
Transdermal	Patch
Quinestrol	0.1–0.2 mg/week
Chlorotrianisene	12–25 mg/d
Methallenestril	3–9 mg/d

Mechanism of Action



PHYSIOLOGIC EFFECTS

Little effect on mood and behavior

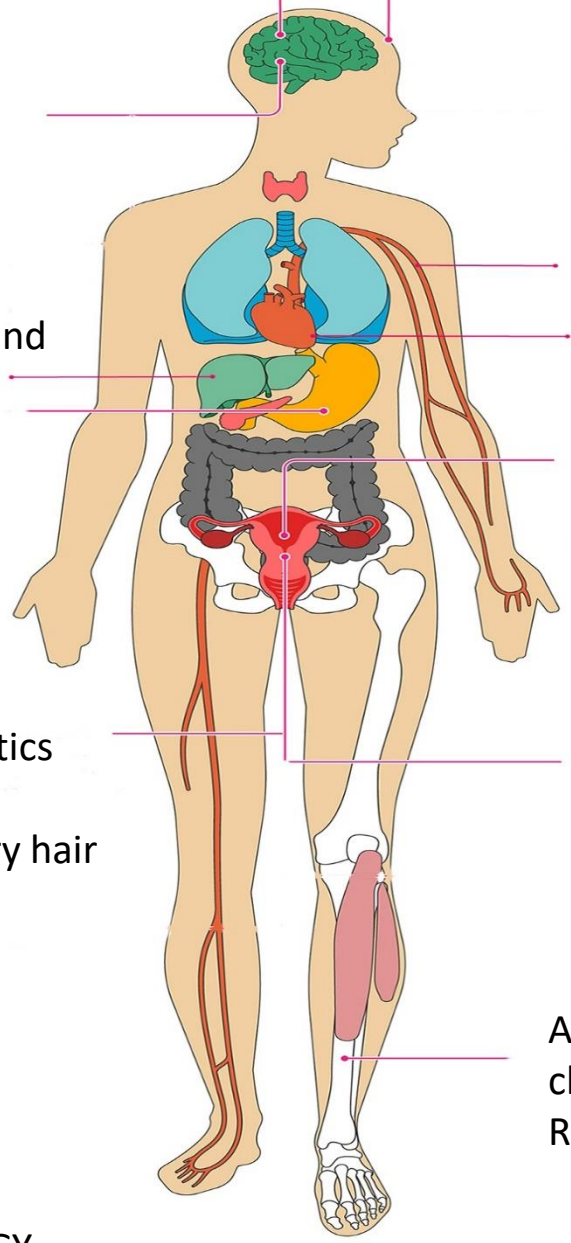
Promotion of sense of well being

Increase levels of CBG,TBG,SHBG,
plasma renin substrate, transferrin and
fibrinogen

Increase in HDL & TGs
while reduction in LDL and TC

Increase cholesterol content of bile

Secondary sexual characteristics
Growth of breasts
appearance of pubic & axillary hair
feminine body contour &
pigmentation of skin



Stimulation of central components of stress system
Production of CRH
Activation of sympathetic system

Increase blood coagulability due to
increase in clotting factors(II,VII,IX AND X)
decrease in antithrombin III

Increase in CO, SBP,DBP and HR
Edema due to loss of intravascular fluid

Growth of uterus, fallopian tubes
& vagina
proliferation of endometrium

Influence libido

Accelerated growth phase
closure of epiphyses of long bones at puberty
Reduce rate of bone resorption

SPIRAL INTEGRATION WITH PHYSIOLOGY

THERAPEUTIC USES

- **Hormone Replacement Therapy**
  - Postmenopausal hormonal replacement therapy
    Women without uterus: continuous estrogen therapy
    Women with uterus : Estrogen combined with progesterone (continuous & sequential)
  - Primary hypogonadism (Induction of sexual maturation)
    conjugated estrogens, micronized 17β-estradiol, ethinyl estradiol and transdermal 17β-estradiol
  - Secondary hypogonadism (hypopituitarism)
- Hormonal contraception
- Intractable dysmenorrhea
- Androgen induced hirsutism and amenorrhea

ADVERSE EFFECTS

Females

- Abnormal uterine bleeding
- Cancer (breast, endometrial and vaginal adenocarcinoma)
- Hypertension and thromboembolic states
- Nausea
- Migraine
- Mastalgia and breast tenderness
- Gall stones and cholestasis
- Hyperpigmentation

Male

- Decreased libido, gynecomastia & feminization

Children

- Fusion of epiphyses & reduction of adult stature

CONTRAINDICATIONS

- CA endometrium
- CA breast
- Undiagnosed vaginal bleeding
- Liver disease
- H/O of thrombo-embolic disorders.
- Heavy smokers
- Pregnancy

SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERMs)

Tamoxifen

Raloxifene

Toremifene

Ospemifene

Bazedoxifene

MECHANISM OF ACTION

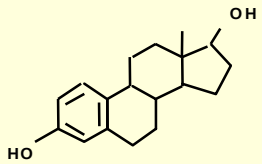
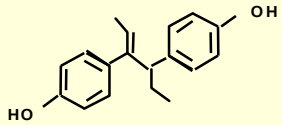
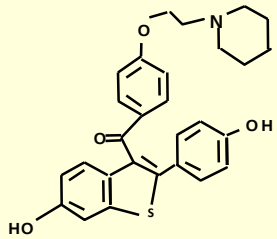
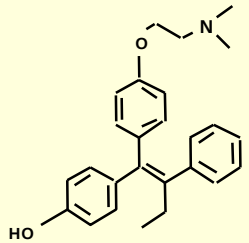
- Act at ERs to exhibit either agonist or antagonist action, depending on the tissue that expresses the ERs

- After ligands bind to the ERs, the signaling pathway is regulated by protein cofactors, either coactivators to give an estrogenic response (agonist) or corepressors to yield an antiestrogenic (antagonist) response

- The ratio of coactivators and corepressors differs in estrogen receptor tissues, and the predominant cofactor determines the agonist or antagonist response

Allow the effects of estrogen to be specifically inhibited in target tissues without the adverse effects associated with loss of estrogen signaling in other tissues

Estrogen receptor ligands elicit different tissue-specific responses

Estrogen target tissues	estradiol 	Z-pseudo diethylstilbestrol 	raloxifene 	4-hydroxytamoxifen (Z-OHT) 
Breast	agonist	agonist	antagonist	antagonist
Uterus	agonist	partial agonist	antagonist	partial agonist
Bone	agonist	agonist	agonist	partial agonist
Liver	agonist	agonist	????	partial agonist
CNS	agonist	agonist	antagonist	antagonist

Tamoxifen

- Non steroidal partial agonist/antagonist at ER

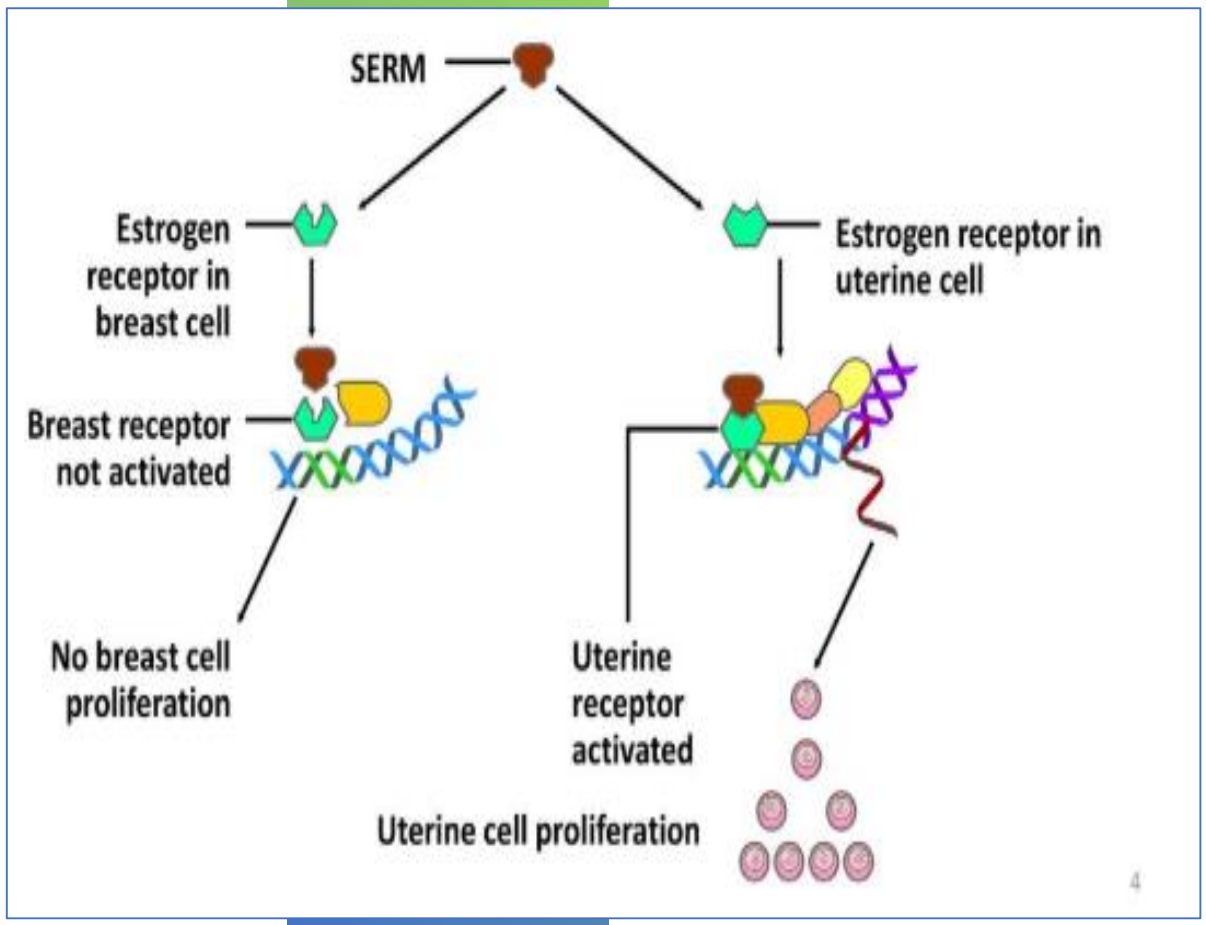
  Act as potent estrogen antagonist in breast

  Act as partial agonist in uterus, bone, liver & endometrium and coagulation system

  Causes ↓ in total & LDL cholesterol without any change in HDL & TGs

- Used in the palliative treatment of breast cancer in postmenopausal women & chemoprevention of breast cancer in high risk women

- A/E: Increase risk of endometrial cancer



SELECTIVE ESTROGEN RECEPTOR DOWNREGULATOR (SERD)

FULVESTRANT

- SERDs are **pure antiestrogens** that function by binding to and inducing the degradation of ER, thereby inhibiting dimerization and abolishing the ER signaling pathway
- Pure receptor antagonist available either alone or in combination with a CDK4/6 inhibitor (palbociclib)
- Administered intramuscularly
- Used in metastatic breast cancer (tamoxifen resistant)
- Adverse effects: pain, asthenia, nausea, hot flashes, arthralgia and headache

ESTROGEN SYNTHESIS INHIBITOR (Aromatase inhibitors)

AROMATASE INHIBITORS

Chemistry

- Steroidal (Type I irreversible aromatase inhibitors)

  Formestane and exemestane
- Nonsteroidal (Type II reversible aromatase inhibitors)

  Anastrozole, letrozole, and vorozole

Generations:

- First Generaton

  Aminoglutethimide
- Second Generation

  Formestane
- Third Generation

  Exemestane, anastrozole, letrozole

PROGESTERONE
&
ITS DERIVATIVES

PROGESTERONE

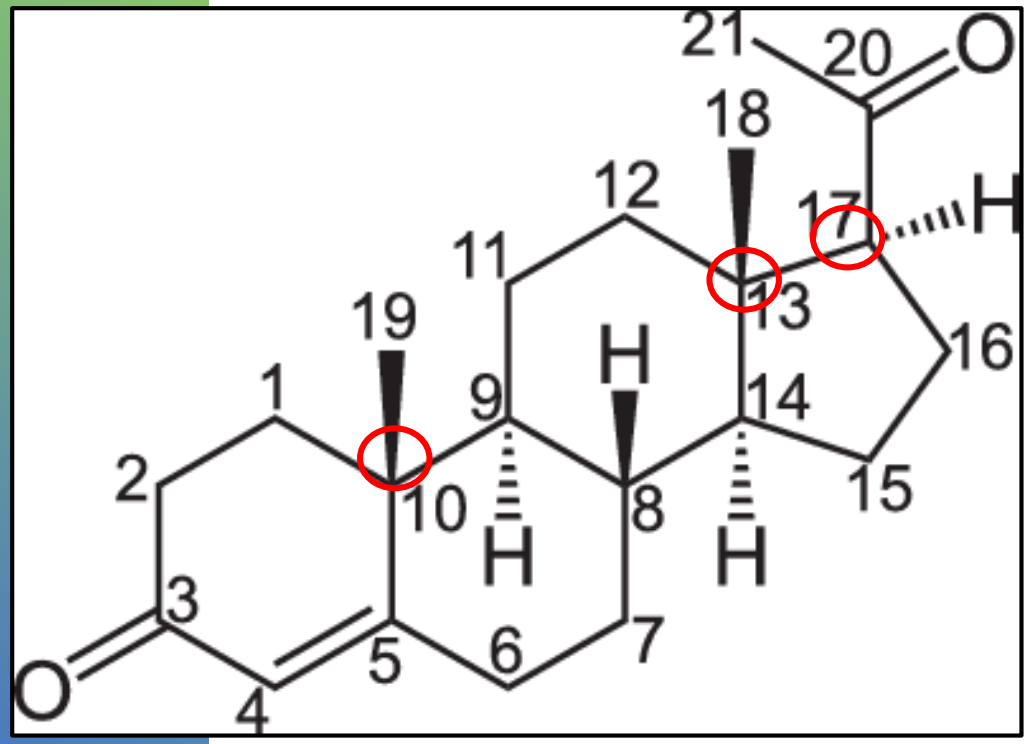
Progestins, progestational agents, progestagens, progestogens, gestagens, or gestogens

❖ Natural

Progesterone

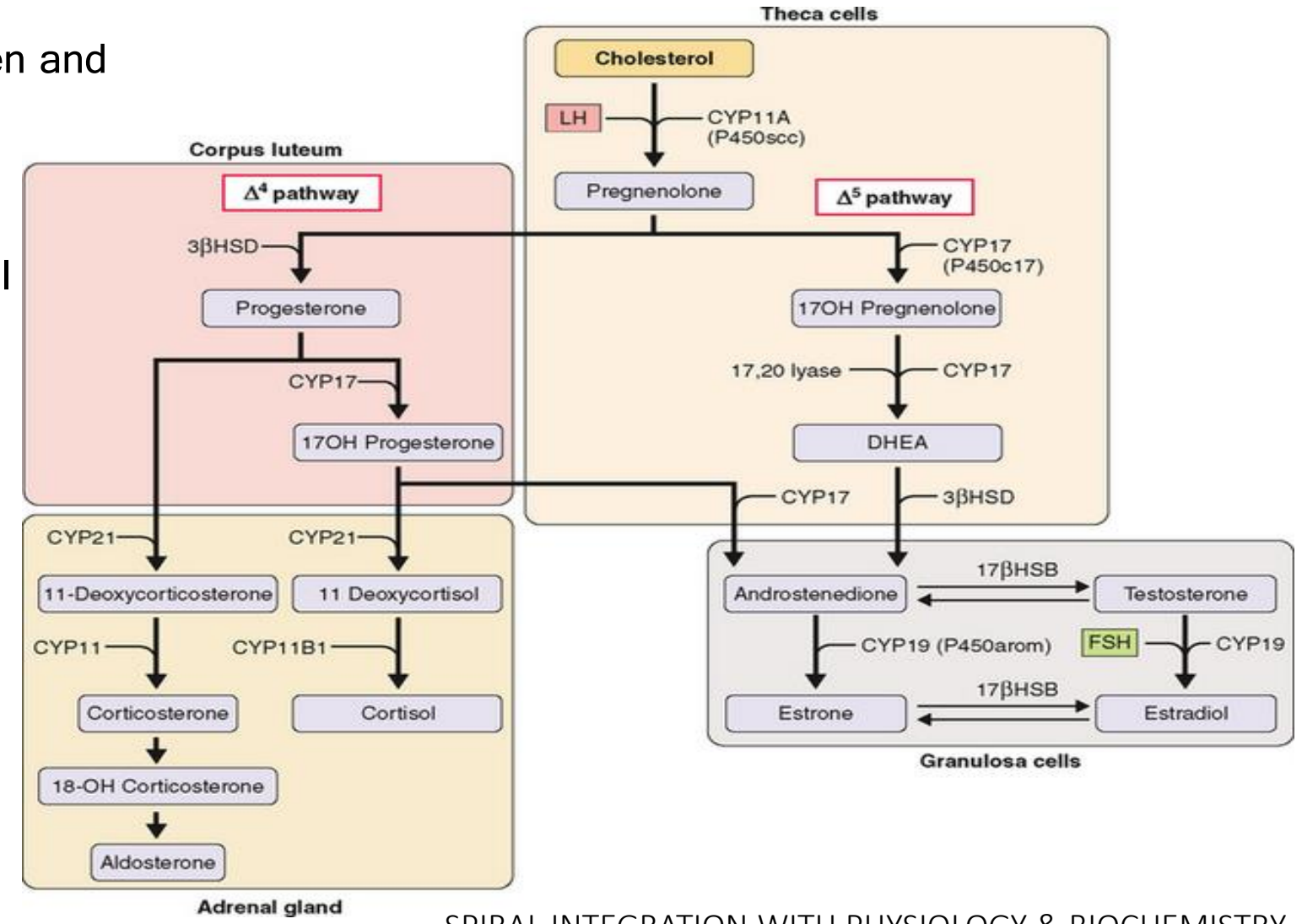
❖ Synthetic

- C-21 Progestin derivatives (Pregnanes)
  Hydroxyprogestrone caproate, Medroxyprogesterone acetate, Megestrol acetate
- 17-Ethinly testosterone derivatives
  Dimethisterone
- 19 Nortestosterone derivatives (Impeded androgens)
  Estranes Norethindrone,Norethindrone acetate,norethynodrel,ethynodiol diacetate
  Gonanes Norgestrel, Norgestimate, Desogestrel, Gestodene
- Spironolactone Drosiperone



SOURCES & SYNTHESIS OF PROGESTERONE

- Precursor of estrogen, androgen and adrenocortical steroids
- Produced from corpus luteum in the luteal phase of menstrual cycle and by the placenta if pregnancy occurs



GENERATIONS OF PROGESTERONE

Activity of Progestin Agents

Generation	Progestin	Estrogenic	Progestational	Androgenic
First	Norethindrone	++	++	++
	Ethynodiol diacetate	++	+++	+
	Norgestrel	–	+++	+++
	Norethindrone acetate	++	++	++
Second	Levonorgestrel	–	++++	++++
Third	Norgestimate	–	++	++
	Desogestrel	+/–	++++	++
Fourth	Drospirenone	–	+/–	–

+/– indicates low to no activity.
– indicates no activity.
Source: References 3, 8, 18.

ACTIVITY OF PROGESTERONE

Progestogen Classification	Progesterone		Androgen			Estrogen			Glucocorticoid		Mineralocorticoid	
	Receptor Binding Affinity	Activity	Receptor Binding Affinity	Androg. Activity	Anti-Androg. Activity	Receptor Binding Affinity	Estrogen Activity	Anti-Estrogen Activity	Receptor Binding Affinity	Activity	Receptor Binding Affinity	Anti-Mineraloc. Activity
Progesterone derivatives												
Natural progesterone	50	+	0	−	+/−	0	−	+	10	+	100	+
Dydrogesterone	75	+	NA	−	+/−	NA	−	+	NA	NA	NA	+/−
Medrogestone	NA	+	NA	−	+/−	NA	−	+	NA	NA	NA	−
17 α-hydroxyprogesterone derivatives—Pregnanes												
Medroxyprogesterone acetate	115	+	5	+/−	−	0	−	+	29	+	0	−
Megestrol acetate	65	+	5	+/−	+	0	−	+	30	+	0	−
Cyproterone acetate	90	+	6	−	++	0	−	+	6	+	8	−
Chlormadione acetate	67	+	5	−	+	0	−	+	8	+	0	−
19-norprogesterone derivatives—Non-pregnanes												
Nomegestrol acetate	125	+	42	−	+/−	0	−	+	0	−	0	−
Promegestone	100	+	0	−	−	0	−	+	5	+	0	−
Trimegestone	330	+	1	−	+/−	0	−	+	9	+/−	120	+/−
Nestorone	136	+	0	−	−	0	−	+	38 *	−	NA	NA
Spironolactone derivative												
Drospirenone	25	+	2	−	+	0	−	+	0	−	230	+
19-nortestosterone derivatives—Estranes												
Noretisterone	75	+	15	+	−	0	+	+	0	−	0	−
Lynesterol	NA	+	NA	+	−	NA	+	+	NA	−	NA	−
Noretinodrel	6	+	0	+/−	−	2	+	+	NA	−	NA	−
19-nortestosterone derivatives—Gonanes												
Levonorgesterel	150	+	45	+	−	0	−	+	1	−	17	+/−
Desogestrel	1	+	0	−	−	0	−	+	0	−	0	−
Norgestimate	15	+	0	+	−	0	−	+	1	−	0	−
Gestodene	90	+	85	+	−	0	−	+	27	+	290	+
Etonogestrel	150	+	20	+	−	0	−	+	14	+/−	0	−
Dienogest	5	+	10	−	+	0	−	+	1	−	0	−

(+) effective; (+/−) weakly effective; (−) not effective. NA—data not available. * Nestorone showed significant binding to glucocorticoid receptors; however, it showed no glucocorticoid activity in vivo [153].

PHARMACOKINETICS

TABLE 40–2 Properties of some progestational agents.

	Route	Duration of Action	Activities[1]				
			Estrogenic	*Androgenic*	*Antiestrogenic*	*Antiandrogenic*	*Anabolic*
Progesterone and derivatives							
Progesterone	IM	1 day	–	–	+	–	–
Hydroxyprogesterone caproate	IM	8–14 days	sl	sl	–	–	–
Medroxyprogesterone acetate	IM, PO	Tabs: 1–3 days; injection: 4–12 weeks	–	+	+	–	–
Megestrol acetate	PO	1–3 days	–	+	–	+	–
17-Ethinyl testosterone derivatives							
Dimethisterone	PO	1–3 days	–	–	sl	–	–
19-Nortestosterone derivatives							
Desogestrel	PO	1–3 days	–	–	–	–	–
Norethynodrel	PO	1–3 days	+	–	–	–	–
Lynestrenol[2]	PO	1–3 days	+	+	–	–	+
Norethindrone	PO	1–3 days	sl	+	+	–	+
Norethindrone acetate	PO	1–3 days	sl	+	+	–	+
Ethynodiol diacetate	PO	1–3 days	sl	+	+	–	–
L-Norgestrel[2]	PO	1–3 days	–	+	+	–	+

[1] *Interpretation:* + = active; – = inactive; sl = slightly active. Activities have been reported in various species using various end points and may not apply to humans.

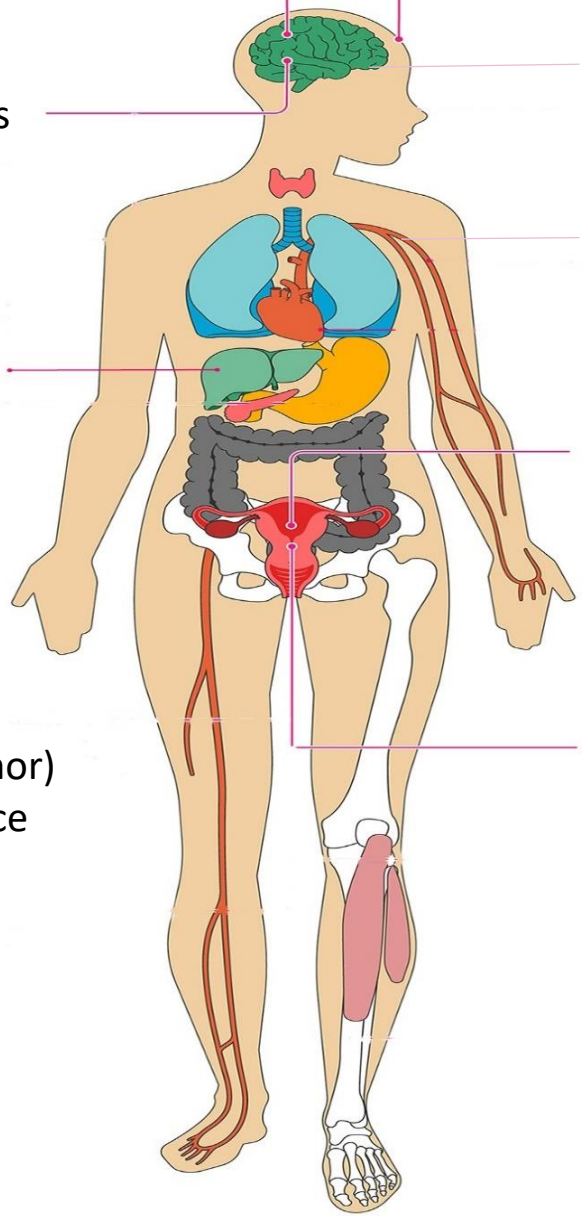
[2] Not available in USA.

Physiologic Effects

Depressant and hypnotic action
(bedtime,help patient sleep)

Suppression of GnRH pulses
(contraception use)

Stimulate lipoprotein lipase activity
leading to fat deposition
↑ basal insulin level & response to Glucose
Promote ketogenesis
↑ nitrogen excretion
Little effect on protein metabolism
↓ plasma level of many AA
Increase LDL and decrease HLD (19 nor)
Competition with aldosterone, reduce Na reabsorption



Increase in ventilatory response to PCO2
Increase in basal body temperature

Increase sebum production

Growth and development of mammary gland with estrogen (pregnancy & luteal phase)

Makes cervical mucosa more viscus
Reduces uterine contractility

Decrease estrogen dependent endometrial proliferation
Enhancement of estrogen induced maturation of vaginal epithelium (cytological smear)

Therapeutic uses

- Hormonal contraception
- HRT
- Endometriosis
- Premenstrual syndrome
- Endometrial carcinoma/ endometrial hyperplasia due to unopposed estrogens
- IVF (assisted pregnancy)
- Diagnostic use (as test of estrogen secretion) & response of endometrium in amenorrhic pts
- Threatened/Habitual abortion, in pts who have established progesterone deficiency
- Preventing premature labor in high risk pregnancy

ADVERSE EFFECTS & CONTRAINDICATIONS

- Headache
- Acne
- Mood disturbances
- Menstrual irregularities
  (Spotting, bleeding & amenorrhea)
- Delay in the return of fertility
  (18 months)
- Weight gain
- Reduced bone marrow density
- Changes in lipoproteins
- Masculinization of female fetus & other congenital abnormalities if given in early pregnancy
- Increase risk of breast CA

SELECTIVE PROGESTERONE RECEPTOR MODULATOR/ANTI-PROGESTIN

- Mifespristone
- Ulipristal
- Danazol

RESEARCH

- Sfogliarini C, Pepe G, Dolce A, Della Torre S, Cesta MC, Allegretti M, Locati M, Vegeto E. Tamoxifen twists again: On and off-targets in macrophages and infections. Frontiers in Pharmacology. 2022 Mar 30;13:879020.

ARTIFICIAL INTELLIGENCE

Rajitha, G., Rani, M.V., Vankadoth, U.N. and Umamaheswari, A., 2021. Design of Novel Selective Estrogen Receptor Inhibitors using Molecular Docking and Protein-Ligand Interaction Fingerprint Studies.

BIOETHICS

Key HRT Counseling Points

Treatment	Counseling Points	Side Effects
All estrogen-containing products	Be aware of signs of PE, DVT, stroke, and MI Report vaginal bleeding Smoking abstinence is important	Common: headache/migraine, nausea and vomiting, stomach cramps, breast pain and tenderness, mood disturbance Severe: CVA, DVT, breast, endometrial, or ovarian cancer, retinal vascular disorder
Conjugated estrogen	Take at the same time every day	
Micronized 17β estradiol Transdermal 17β estradiol IM estrogen	May cause chloasma or melasma, so sunscreen use is important	Common: edema, hirsutism, bloating, withdrawal bleeding
Conjugated estrogen with bazedoxifene	May cause fetal harm Not recommended if breastfeeding Tablet must be swallowed whole	Common: diarrhea, indigestion, dizziness, pain in throat
Depot progestin	Reduces BMD and causes irreversible bone loss Should not be used for >2 y Report any unexplained partial or complete loss of vision	Common: injection-site reaction, weight change, abdominal pain, cholestatic jaundice, dizziness, headache, nervousness, amenorrhea, reduced libido, fatigue Severe: decreased BMD, bone fracture
Combination estrogen-progestin	Application-site reactions Do not place transdermal products on the breast or waistline, rotate application site, and allow ≥1 wk between applications to a particular site Do not expose patches to the sun for prolonged periods of time	Common: application-site reaction, depression, vaginal bleeding, upper respiratory infection Severe: MI, disorders of gallbladder

END OF LECTURE ASSESSMENT

1. **A postmenopausal 72-year-old woman with breast cancer was taking anastrozole to suppress the conversion of androgens to estrogens. Which enzyme does anastrozole inhibit?**

A. **Aromatase.**
B. Desmolase.
C. 17α-hydroxylase.
D. 17β-hydroxysteroid dehydrogenase.
E. 5α-reductase.

2. **Which of the following best explains why raloxifene is an estrogen agonist in bone but an estrogen antagonist in the breast? Raloxifene:**

A. Has different affinities for ER subtypes in bone and breast tissues.
B**. Produces distinct conformational changes in ERs in different tissues.**
C. Causes increased turnover of ERs in the breast.
D. Is more readily transported into bone cells.
E. Is more rapidly inactivated in the breast.

3. **As menstruation ends estrogen levels in the blood rise rapidly. What is the source of the estrogen?**

A) Corpus luteum
B) **Developing follicles**
C) Endometrium
D) Stromal cells of the ovaries
E) Anterior pituitary gland