FEMALE SEX HORMONES

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Estrogen

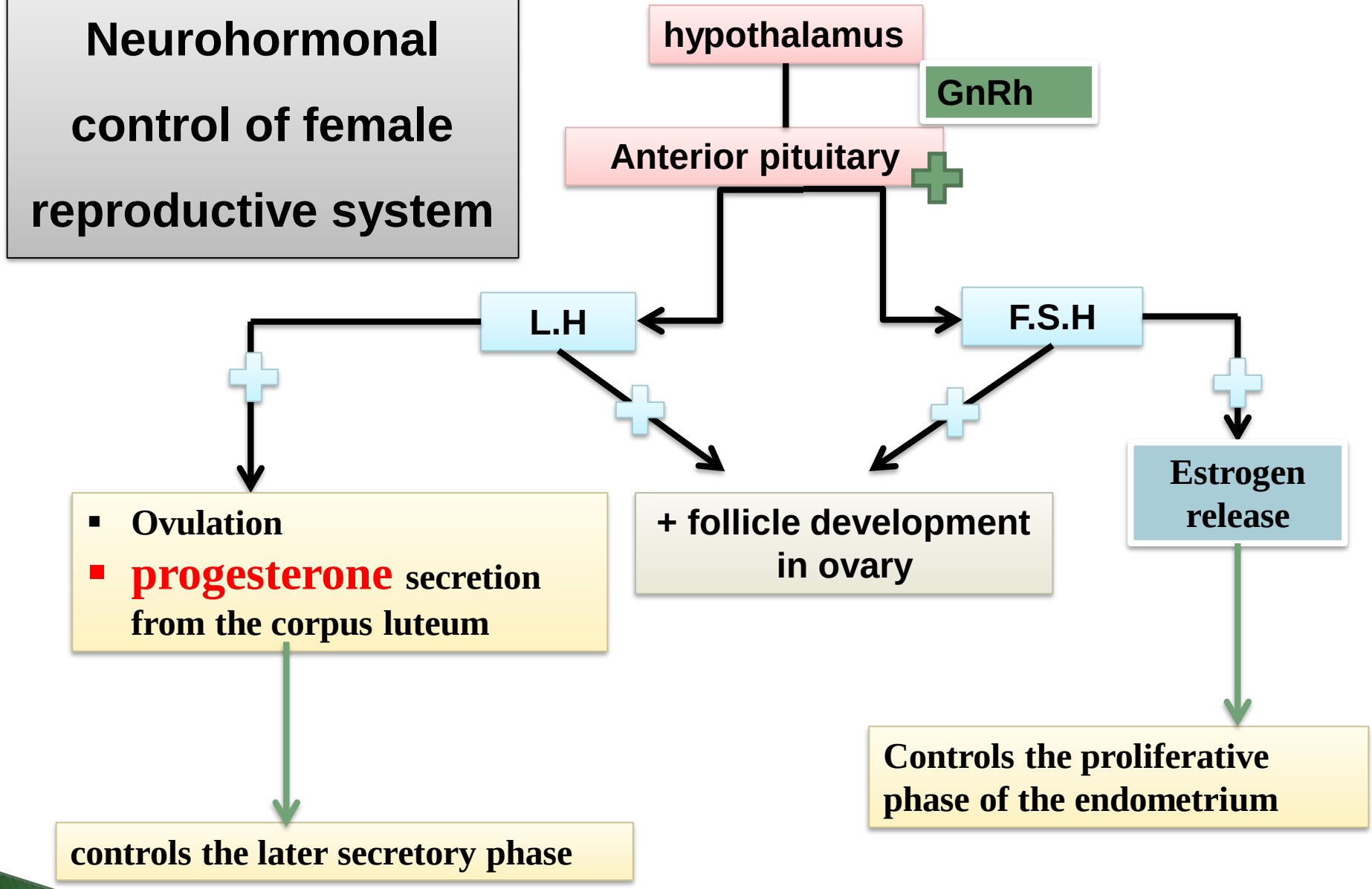
- **Synthesized by** the ovary, placenta and in small amounts by the testis and adrenal cortex.
- There are three main endogenous estrogens in humans: **estradiol, estrone and estriol**.
- **Estradiol** is the most potent and is the principal estrogen secreted by the ovary

Preparations

1. Many preparations (oral, transdermal, intramuscular, implantation and topical)
2. Natural (e.g. estradiol, estriol) and synthetic (e.g. Mestranol, Ethinyl estradiol, Stilbestrol).

- Estrogens (single agent or combined with progesterone)

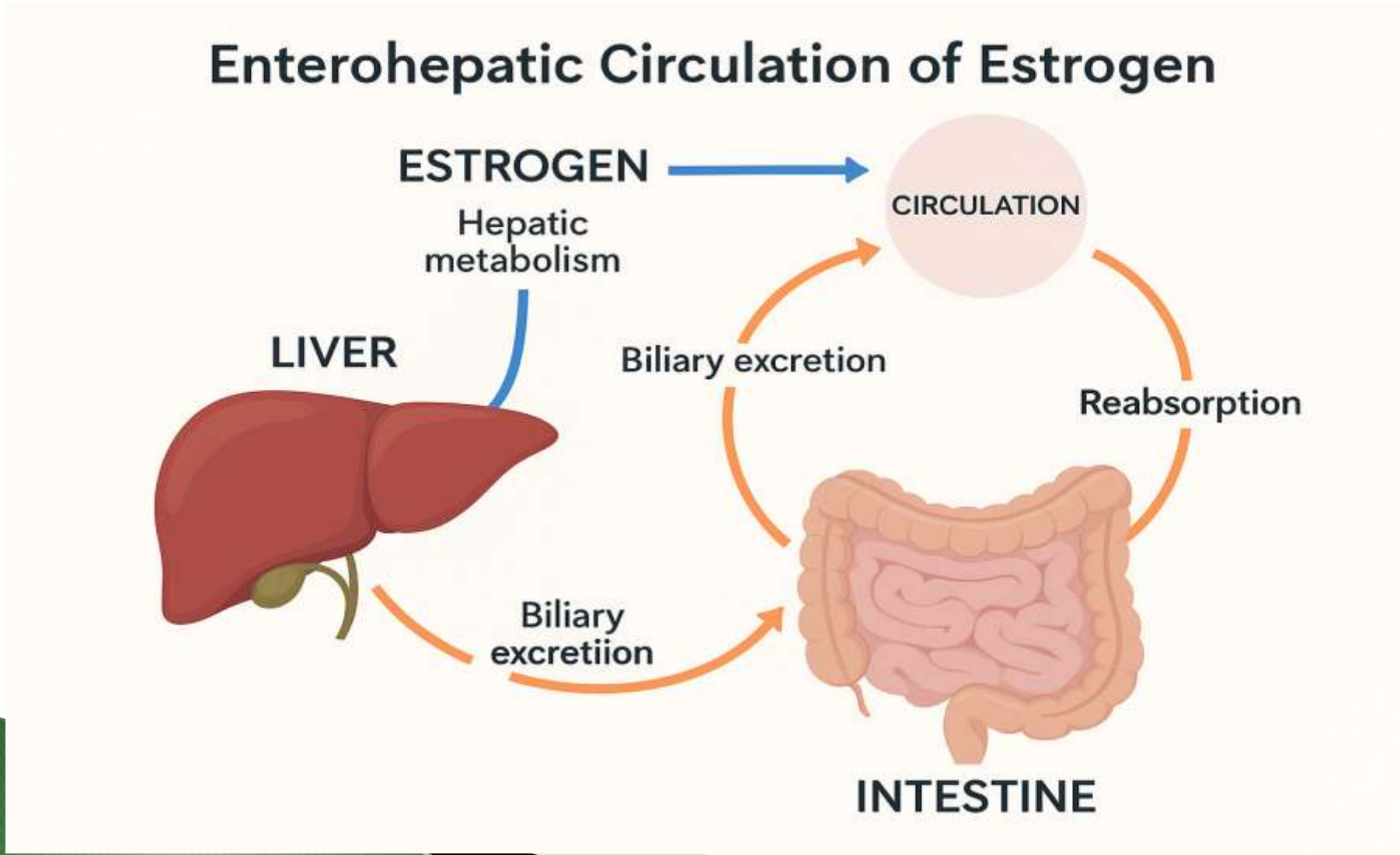
Neurohormonal control of female reproductive system



Pharmacokinetic aspects:

- **Absorption** : well absorbed in the gastrointestinal tract, readily absorbed from skin and mucous membranes.
- **Distribution**: bound to globulin (SHBG). Pass BBB, placenta. High lipid soluble
- **Metabolism:** natural estrogens are rapidly metabolized in the liver, whereas synthetic estrogens are degraded less rapidly. variable amount of enterohepatic cycling
- **Excretion:** in the urine as glucuronides.

Enterohepatic circulation of estrogen



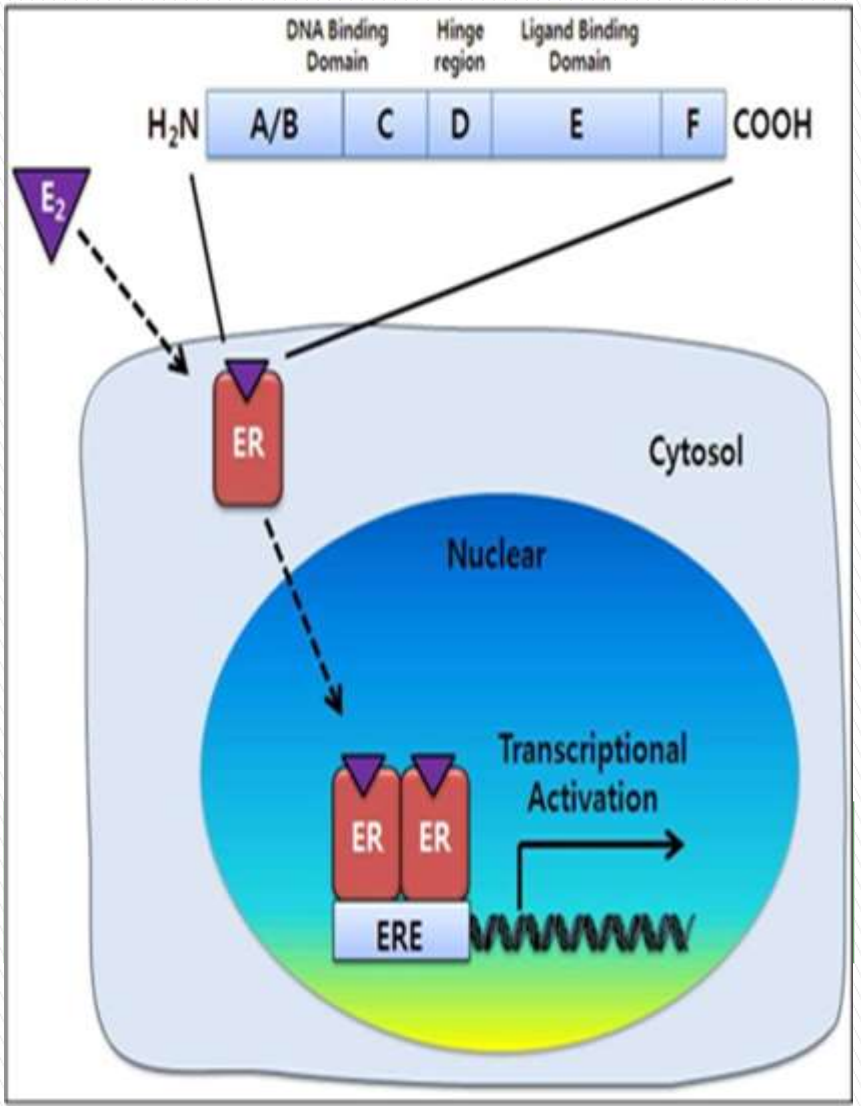
Mechanism of action:

1- binds to the nuclear receptor.

two types of estrogen receptor, termed ERα and ERβ.

Binds to nuclear sites and subsequent genomic effect,

"either gene transcription or inhibition of transcription



Pharmacological actions

System	Action
Reproductive	**Uterus**: Stimulates growth of endometrium; increases uterine muscle mass and blood flow. **Vagina**: Promotes thickening of vaginal epithelium and increases vaginal secretions. **Breasts**: Promotes ductal development during puberty and pregnancy. **Ovaries**: Regulates follicle development and ovulation via feedback on gonadotropins.
Bone	Inhibits **osteoclast activity**, thus **reducing bone resorption**. Stimulates **osteoblast survival** → maintains **bone density**. Deficiency (e.g., in menopause) → **osteoporosis**.
Cardiovascular	**Lipid profile**: Increases **HDL**, decreases **LDL**; may slightly increase triglycerides. **Vasodilation**: Promotes **nitric oxide (NO)** production; protects vascular endothelium. May **reduce atherosclerosis risk** pre-menopause.
Coagulation	↑ **Clotting factors**: II, VII, IX, X.• ↓ **Antithrombin III**.• Net effect: **Pro-thrombotic** – ↑ risk of **venous thromboembolism** • **(VTE)**, especially with **oral estrogen**
Skin	↑ **Collagen production** → firmer, more elastic skin. Maintains **skin thickness** and **hydration**. Delays signs of **skin aging** (wrinkles, dryness).
On Endocrine and Feedback Systems	Suppresses **FSH and LH** via **negative feedback** at the **hypothalamic-•** **pituitary axis**. Mid-cycle **positive feedback** triggers **LH surge** → ovulation.• Increases **sex hormone-binding globulin (SHBG)** synthesis in the liver, • modulating free estrogen levels.

- **ERβ (anti-estrogen)**

Hypothalamus and pituitary: + ovulation due to inhibit –ve feedback on Gn RH, L.H, and FSH

Breast: protective in cancer breast (estrogen dependent) Used SERM

ERα (estrogenic effects)

Hypothalamus and pituitary: –ve feedback on Gn RH, L.H, and FSH

Bone (anti-osteoporosis)

Blood (thromboembolism)

Lipid (↑HDL and ↓LDL)

endometrium (hyperplasia then turn to cancer)

Breast: hyperplasia and cancer breast

Effects of exogenous estrogen depend on the state of sexual maturity

- **In primary hypogonadism: (11-13 years)** estrogen with progestins stimulate the development of secondary sexual characteristics and accelerate growth.
  - **In adults with primary amenorrhea:** estrogen, given cyclically with a progestogen, induces an artificial cycle.
  - **In sexually mature women:** estrogen (with progesterone) is contraceptive.
- **At or after the menopause:** estrogen replacement prevents menopausal symptoms and bone loss

Clinical uses of estrogens:

1. **Hormonal replacement therapy:**
   a. **Primary ovarian failure** (e.g. Turner's syndrome).
   b. **Secondary ovarian failure** (menopause for flushing, vaginal dryness and to preserve bone mass)

2-Contraception.

3- Cancer prostate

Adverse effects

1. Tenderness in the breasts.
2. Nausea, vomiting, anorexia.
3. Salt and water retention with edema.
4. Increased risk of thromboembolism.
5. Intermittent use for post-menopausal replacement therapy → menstruation-like bleeding.
6. Endometrial hyperplasia unless given with a progestogen.
7. It causes genital abnormalities of the fetus if a pregnant woman was given estrogen

Anti-estrogens

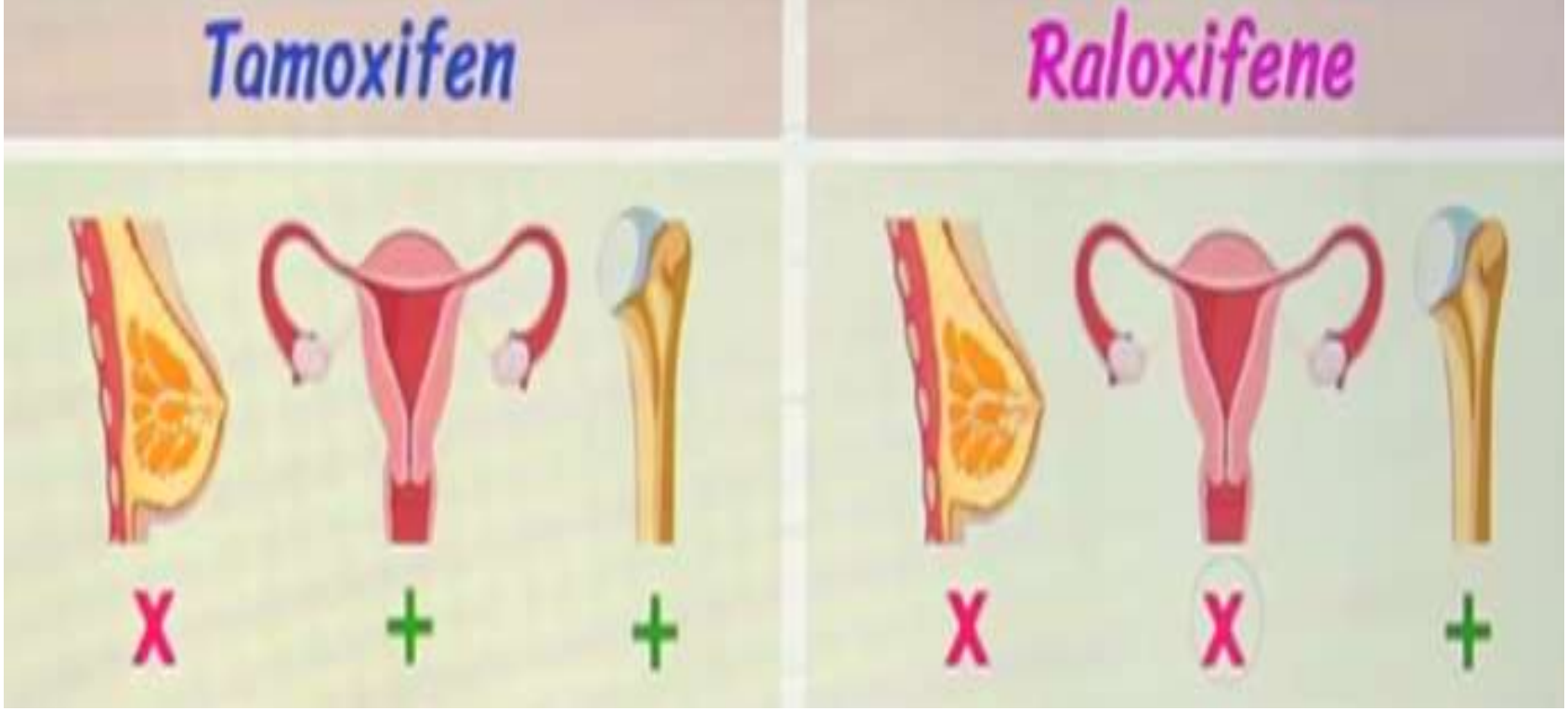
1- Selective Estrogen Receptor Modulators (SERM)

2-Pure estrogen receptor antagonists (Cloimphene and fulvestrant)

3- Synthesis inhibitors

1- Selective Estrogen Receptor Modulators (SERM)

- Selective drugs that are estrogen agonists in some tissues but antagonists in others.
- **Tamoxifen** is used in estrogen-dependent breast cancer. Increases risk of endometrial carcinoma.
- **Raloxifene** is used to treat & prevent osteoporosis. No increased risk of endometrial carcinoma.



Both drugs

- Bone (↓↓ postmenopausal osteoporosis).
- ↑↑ Risk of thrombosis.

3-Pure estrogen receptor antagonists

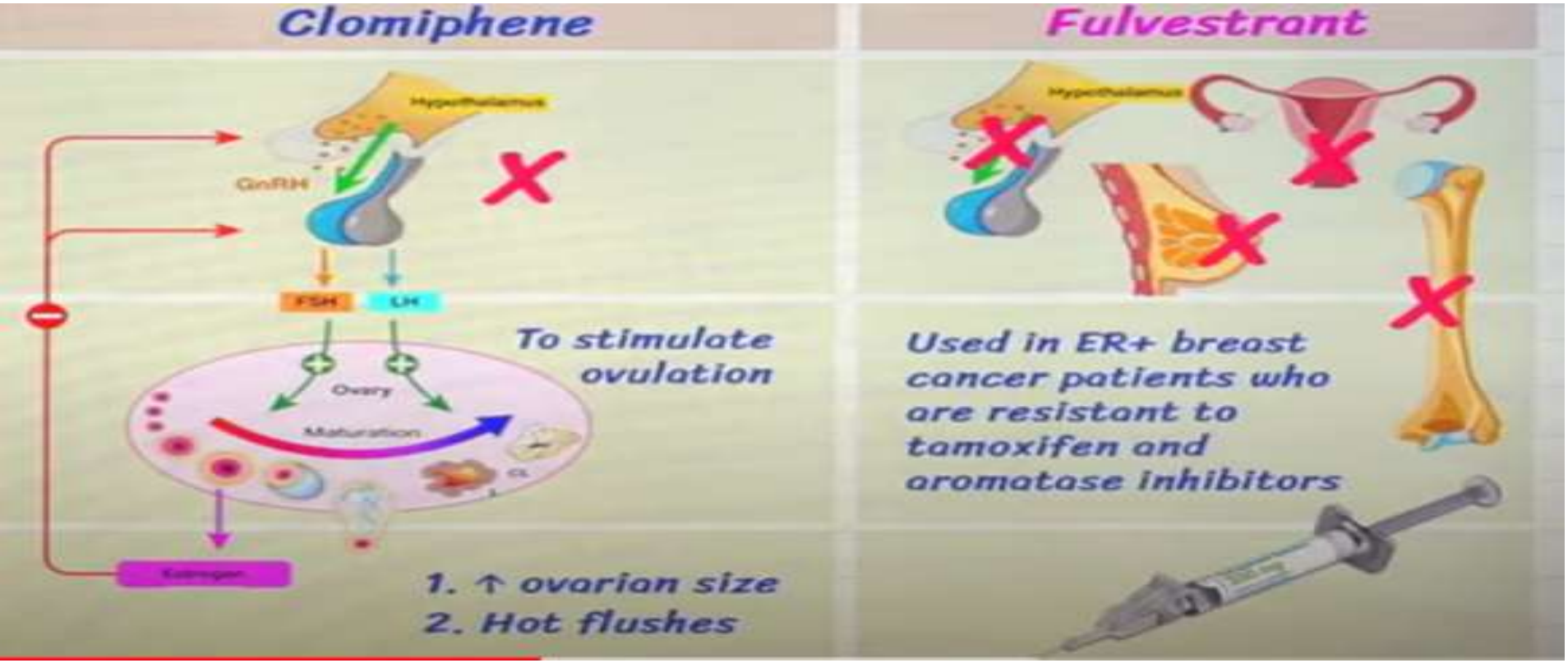
fulvestrant

- It is **used for** the treatment tamoxifen-resistant breast cancer

Cloimphene

Selective block of estrogen receptors in the pituitary → ↓↓ negative feedback → ↑↑ FSH & LH → stimulates ovulation.

S/E: multiple ovulation with multiple pregnancy.



SERM	Breast	Bone	Uterus	Main Use	A/E
Tamoxifen	-	+	+	Breast cancer	Increases risk of endometrial carcinoma, ↑↑ Risk of thrombosis
Raloxifene	-	+	-	Osteoporosis, cancer	No increased risk of endometrial carcinoma. ↑↑ Risk of thrombosis
Clomiphene	-	-	-	Infertility	multiple ovulation with multiple pregnancy

3- Synthesis inhibitors

1. Aromatase inhibitors (anastrozole):

✓ It inhibits aromatase (responsible for the last step in estrogen synthesis).

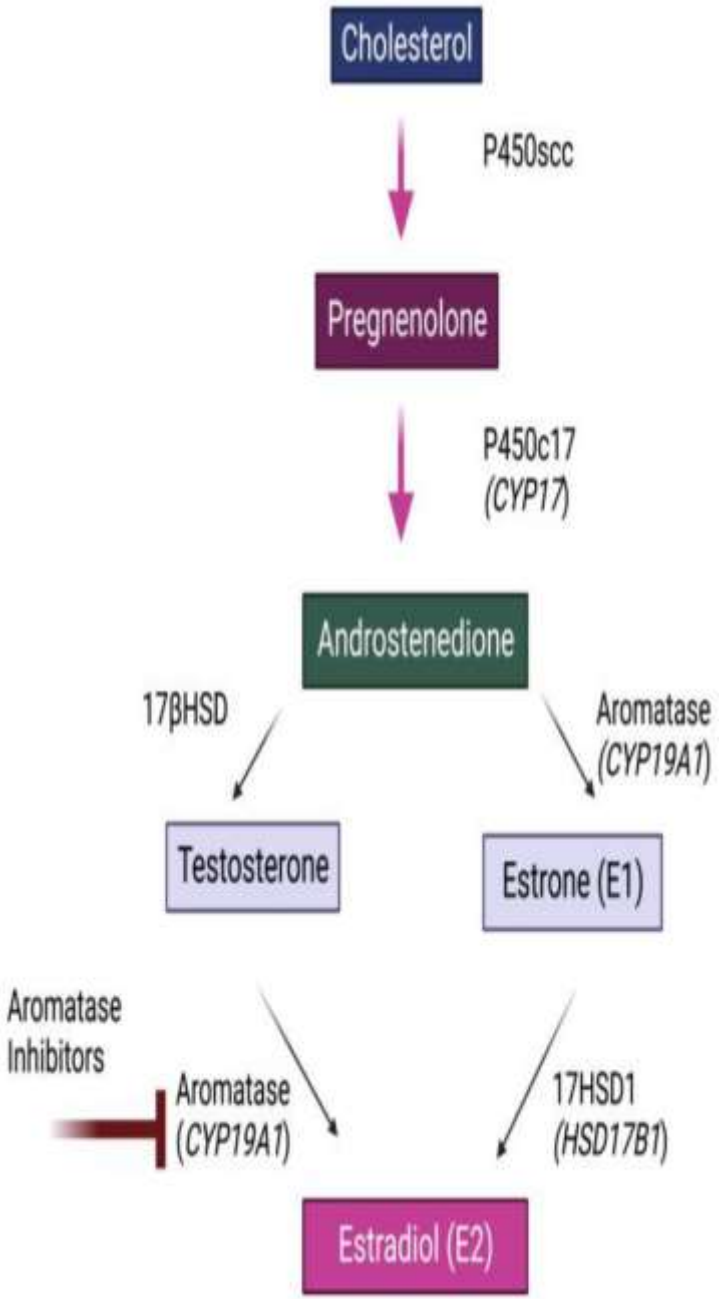
✓ They are **used in** the treatment of breast cancer.

2. Danazol:

✓ It inhibits the cytochrome P450 enzymes involved in gonadal steroid synthesis

✓ Anti GnRH-releasing

✓ It is **used in the** treatment of endometriosis and fibrocystic disease of the breast.



The Progestins

- Progesterone is secreted by the corpus luteum in the second part of the menstrual cycle, and by the placenta during pregnancy.
- Small amounts are also secreted by the testis and adrenal cortex
- **Pharmacokinetics:**
  - **Distribution**: bound to albumin, stored in adipose tissue.
  - **Metabolism**: in the liver, and the products are conjugated with glucuronic acid
  - **Excreted**: in the urine

Preparations:

1-Natural progesterone:

- **It is synthesized in the ovary, testis, and adrenal from circulating cholesterol.**
- **Large amounts are also synthesized and released by the placenta during pregnancy.**

2-Synthetic progestins:

- **Hydroxyprogesterone, medroxyprogesterone, megestrol are closely related to progesterone.**
- **third-generation : desogestrel, gestodene, and norgestimate (lower androgenic activity than older synthetic progestins**

Mechanism of action:

- Bind intracellular receptor.
- Estrogen stimulates synthesis of progesterone receptors, whereas progesterone inhibits synthesis of estrogen receptors
- Relax uterus by decrease sensitivity to oxytocin

Clinical uses:

(1) **Contraception:**
- ❖ With estrogen in combined oral contraceptive pills.
- ❖ As progesterone-only contraceptive pills.
- ❖ As an injectable or implantable progesterone-only contraceptive.
- ❖ As part of an intrauterine device.

(2) Combined **with estrogen** for estrogen **replacement therapy** in women with an intact uterus, to prevent endometrial hyperplasia and carcinoma.

(3) **Endometriosis.**

(4) **Endometrial carcinoma.**

(5) **Delay menstruation for medical purposes**

clinical Use	Mechanism of Progesterone/Progestin Action
Contraception (all forms)	Suppresses ovulation, thickens cervical mucus, alters endometrium
Combined with estrogen (HRT)	Prevents endometrial hyperplasia/cancer by opposing estrogen’s action
Endometriosis	Suppresses ectopic tissue growth, induces atrophy of endometrial tissue
Endometrial carcinoma	Anti-proliferative, induces differentiation and apoptosis
Delay menstruation	Maintains endometrial lining, postpones withdrawal bleeding

Adverse effects:

1. Weak androgenic actions.
2. Other unwanted effects include acne, fluid retention, weight change, depression, change in libido, breast discomfort, irregular menstrual cycles, and breakthrough bleeding.
3. Increased incidence of thromboembolism.

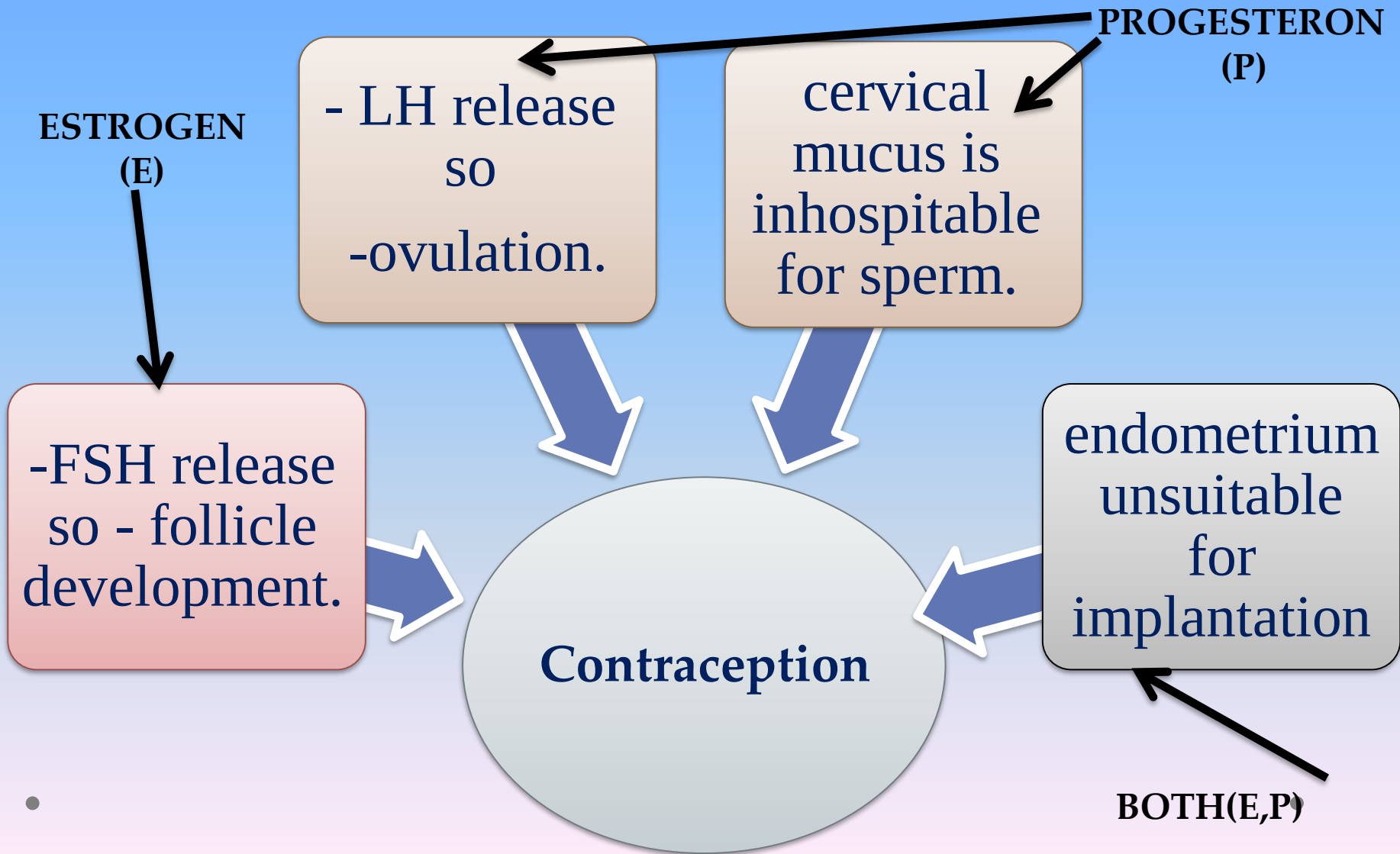
Antiprogestins

- **Mifepristone** is a partial agonist at progesterone receptors.
- It sensitizes the uterus to the action of prostaglandins.
- It is given orally and has a plasma half-life of 21 hours.
- Mifepristone is used, **in combination with a PGE_1 (e.g. misoprostol)** for **termination of pregnancy**.

Contraceptives

- **Drugs can decrease fertility by a number of different mechanisms:**
- **Preventing ovulation**
- Currently, **interference with ovulation** is the **most common pharmacologic intervention for preventing pregnancy**

Mechanism of action of oral contraceptive pills



Major classes of contraceptives

A. **Oral contraceptives pills (progesterone only and combined)**
B. **Long-acting progestogen-only contraception**
C. **Transdermal patch**
D. **Vaginal ring**
E. **Progestin intrauterine device (IUD)**
F. **Postcoital contraception**

A. Progestin-only pills

- **Primolut**
- **norethindrone or norgestrel (called mini-pill), are taken daily on a continuous schedule**
- **Deliver low, continuous dosage of drug**
- they **produce irregular menstrual cycles** more frequently than combination products
- **Has limited patient acceptance** due to **increased possibility of pregnancy & frequent occurrence of menstrual irregularities**

- **The progestin-only pill** may be **used for patients who are breast-feeding** (progestins do not have an effect on milk production)
- **Patients who are intolerant to estrogen**
- **Patients have other contraindications to estrogen-containing products**

B. Combined oral contraceptives

- **Yasmine**
- Products containing **a combination of estrogen & progestin** are the most common type of oral contraceptives
- **They are highly effective in achieving contraception**
- **Monophasic combination pills** contain **constant dose of estrogen and progestin** given **over 21 days**
- **Triphasic oral contraceptive products** mimic natural female cycle and **contain constant dose of estrogen with increasing doses of progestin**

Combination agents

Monophasic forms

Fixed dose of estrogen and progestin for 21 days then7 days placebo.

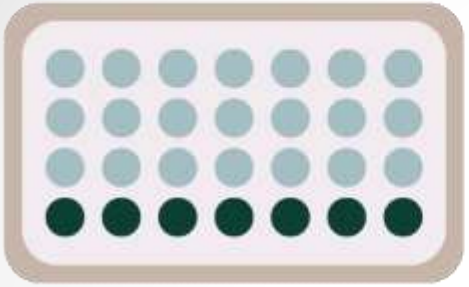
Biphasic forms

Fixed dose of estrogen while progestin dose increase in 2nd half of the cycle(21 days) then 7 days placebo

triphasic forms

Dose of estrogen fixed or variable and progestin dose change in 3 equal phases during the cycle (21 days) then 7 days placebo.

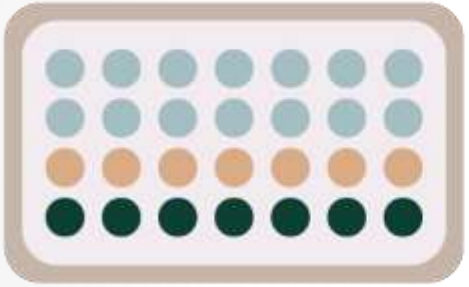
Monophasic



Day 1-21: dose one

Day 22-26: placebo week

Biphasic

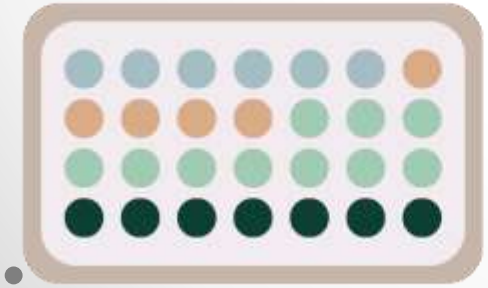


Day 1-14: dose one

Day 15-21: dose two

Day 22-26: placebo week

Triphasic

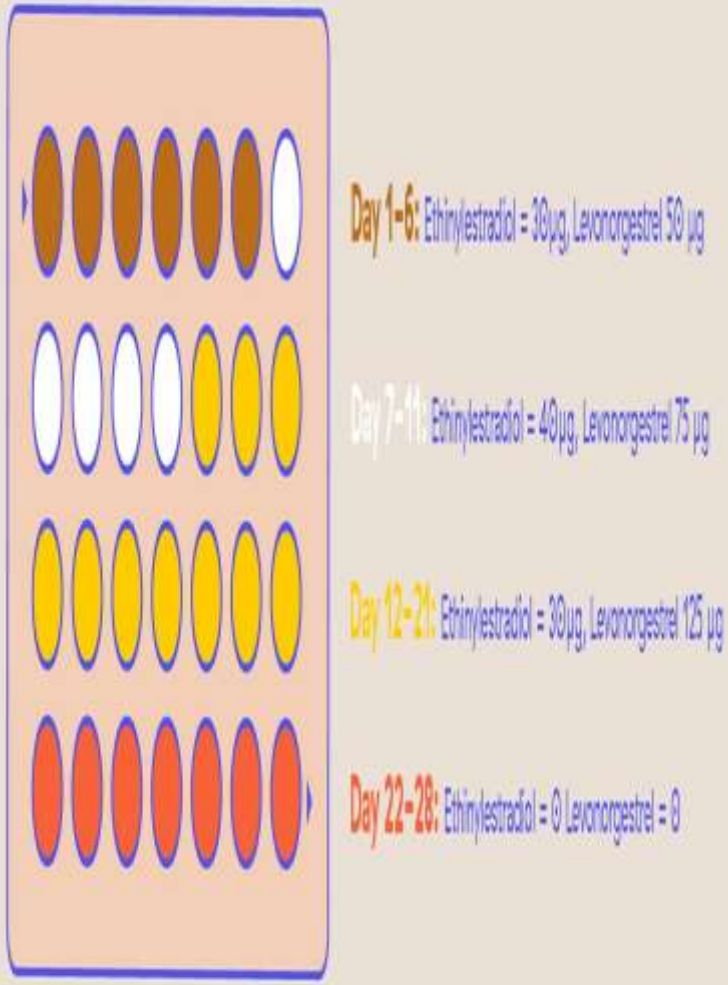


Day 1-6: dose one

Day 7-11: dose two

Day 12-21: dose three

Day 22-26: placebo week



- combination oral contraceptive, active pills are taken **for 21 days followed by 7 days of placebo**
- **Withdrawal bleeding occurs** during **hormone-free interval**
- **Estrogens that are commonly present in combination pills are ethinyl estradiol & mestranol**
- **The most common progestins** are **norethindrone, norethindrone acetate, norgestrel, levonorgestrel, desogestrel, norgestimate, and drospirenone**

B. Long-acting progestogen-only contraception

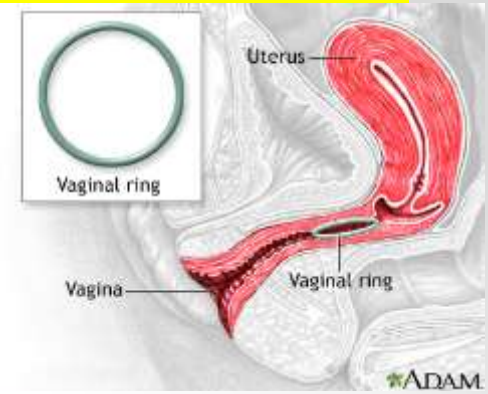
a. Medroxyprogesterone: intramuscular

b. Levoprogestrol: subcutaneous capsules.

C. Transdermal patch:

- An alternative to combination oral contraceptive pills is transdermal contraceptive patch
- Containing **ethinyl estradiol and progestin norelgestromin**
- One contraceptive patch is applied **each week for 3 weeks to abdomen, upper torso, or buttock**
- **Week 4 is patch-free**, and **withdrawal bleeding occurs**
- The transdermal patch has **efficacy comparable to that of oral contraceptives**
- however, it has been shown to be **less effective in women weighing greater than 90 kilograms**

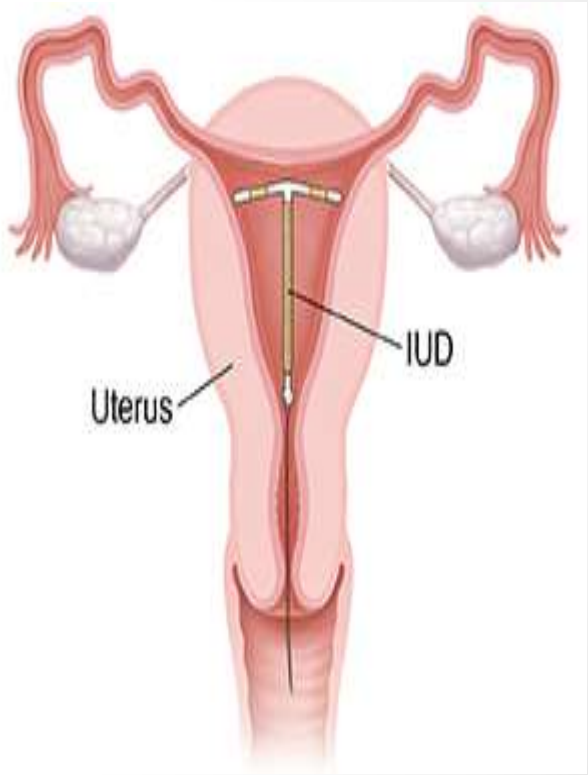
D. Vaginal ring



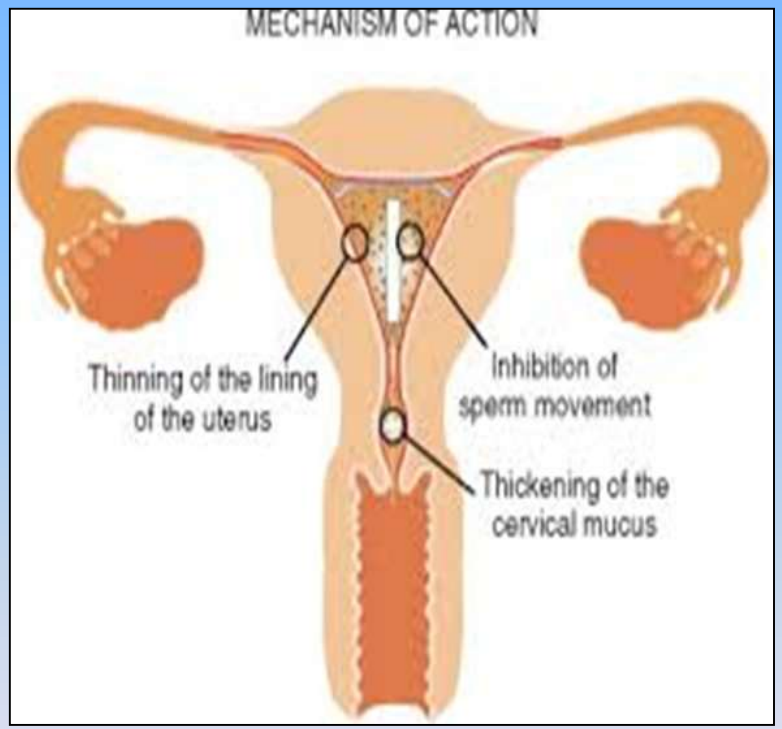
- **Ethinyl estradiol and etonogestrel**
- **The ring is inserted into vagina** and **is left in place for 3 weeks**. **Week 4 is ring-free**, and **withdrawal bleeding occurs**
- The contraceptive vaginal ring has **efficacy, Vaginal ring** may **occasionally slip or be expelled accidentally**

5. Progestin intrauterine device (IUD)

- **Mirena**
- **levonorgestrel-releasing intra-uterine system** offers **a highly effective method of long-term contraception**
- **This intrauterine device provides contraception for up to 5 years**



Levonorgestrol-impregnated intrauterine device



6. Postcoital contraception

- **Postcoital or emergency contraception** reduces probability of pregnancy to between **0.2 & 3 percent**
- **Emergency contraception** uses **high doses of progestin (0.75 mg of levonorgestrel)** or **high doses of estrogen (100 µg of ethinyl estradiol) plus progestin (0.5 mg of levonorgestrel)**
- The **progestin-only emergency contraceptive** regimens **are better tolerated than estrogen-progestin combination regimens**

- **For maximum effectiveness**, **emergency contraception** should be taken **as soon as possible after unprotected intercourse**
- **Should be administered within 72 hours of unprotected intercourse (the morning-after pill)**
- **A second dose of emergency contraception should be taken 12 hours after the first dose**

Adverse effect

- **Major adverse effects:** are breast tenderness, depression, fluid retention, headache, nausea & vomiting
- **Cardiovascular: rare, most serious** including **venous thromboembolism, thrombophlebitis, hypertension, increased incidence of MI & cerebral & coronary thrombosis**. These adverse effects are **most common among women who smoke & who are older than 35 years**

- **Metabolic: Abnormal glucose tolerance .**
- **Weight gain** is common in women who are taking **nortestosterone derivatives**
- **Serum lipids:** The combination pill causes change in serum lipoprotein profile
- **Estrogen causes increase in HDL and decrease in LDL (a desirable occurrence)**
- Whereas **progestins may negate some of beneficial effects of estrogen**
- Therefore, **estrogen-dominant preparations are best for individuals with elevated serum cholesterol**

Contraindications

- **Cerebrovascular & thromboembolic disease**
- **breast Cancer**
- **Liver disease**
- **Pregnancy**
- **Combination oral contraceptives should not be used in patients over age of 35 who are heavy smokers**