

# **FEMALE SEX** **HORMONES**

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# Female Gonadal Hormones

**1-Estrogen**



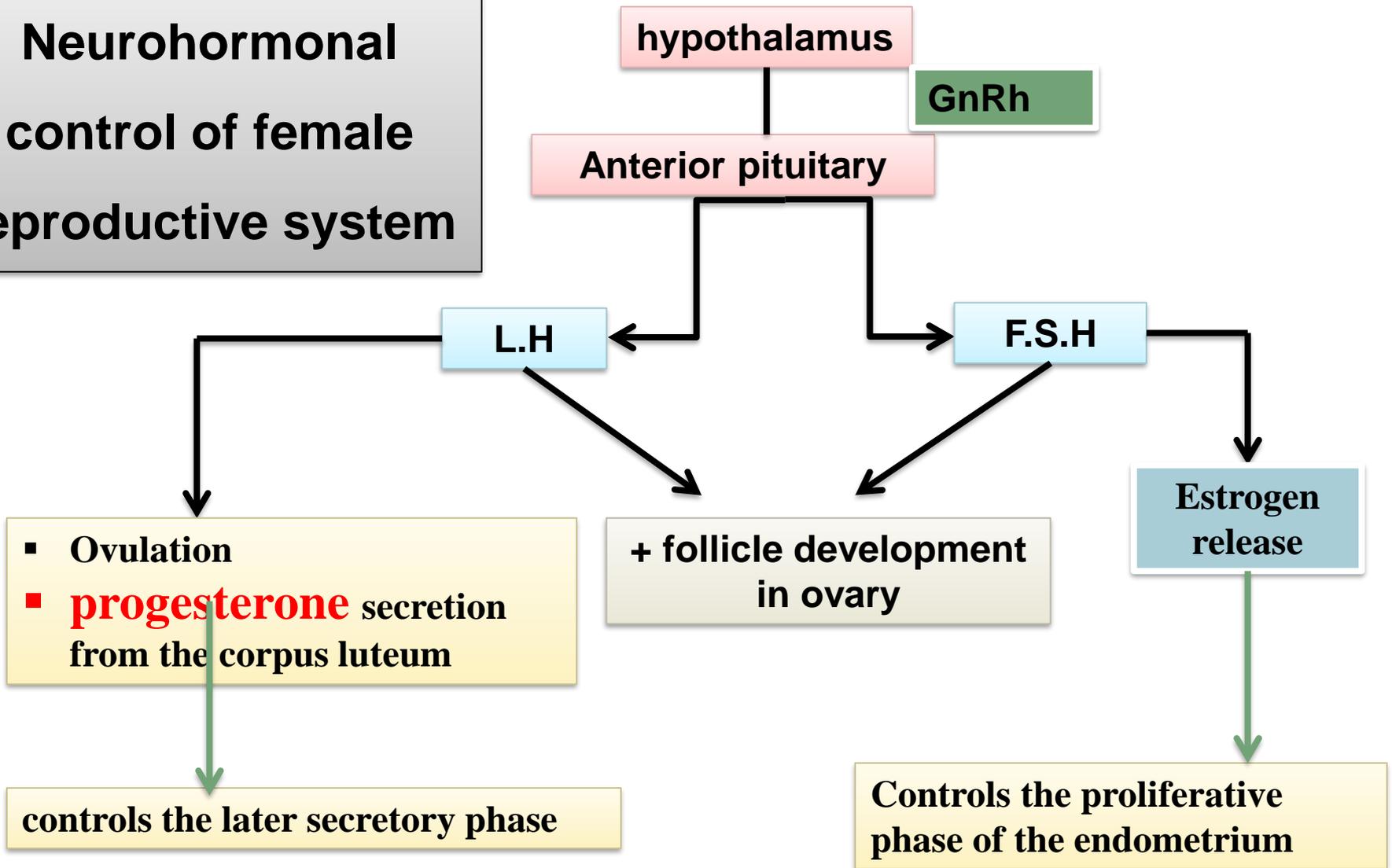
**2-Progestin**



# 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

# Neurohormonal control of female reproductive system



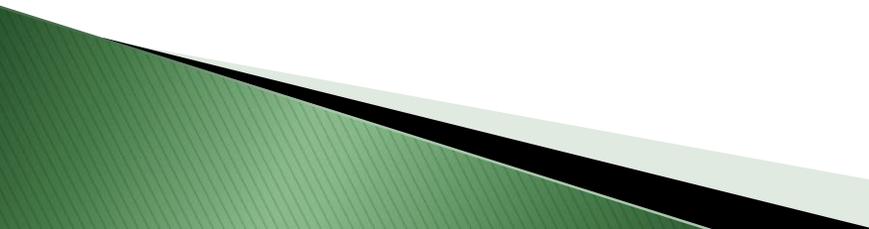
# Preparations

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)

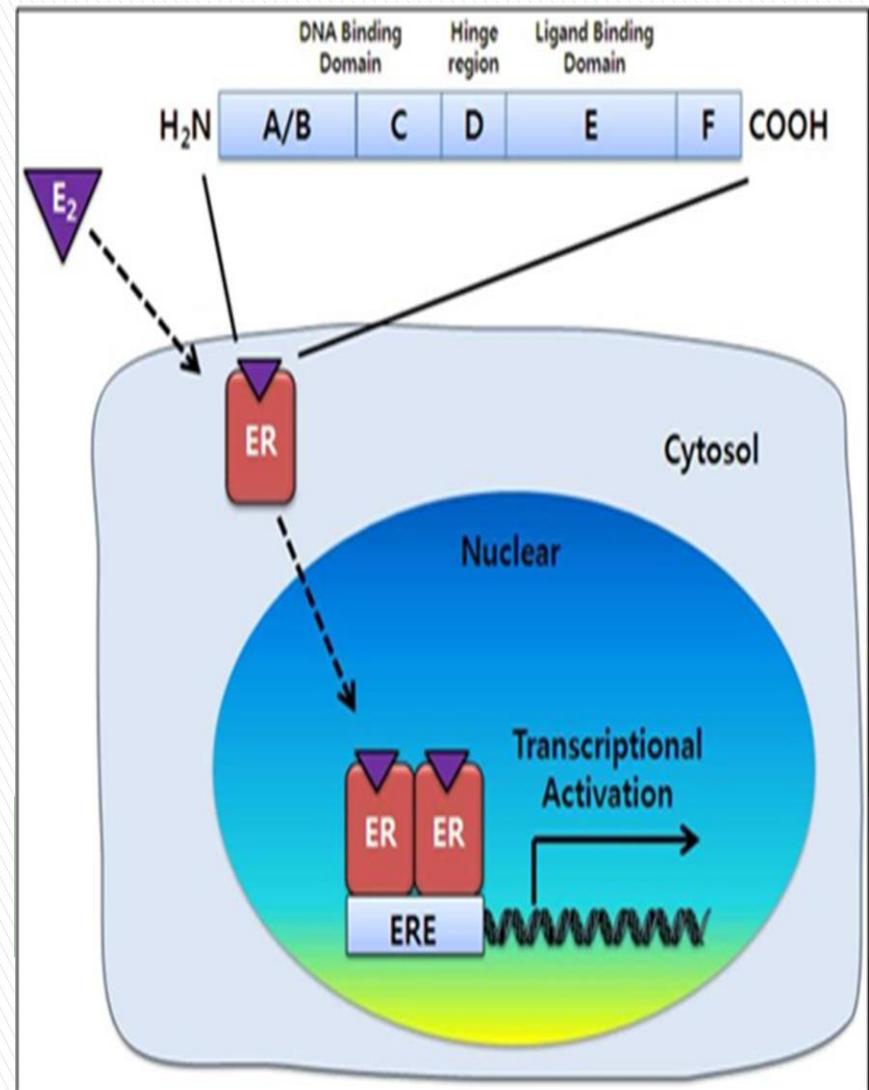


# Pharmacokinetic aspects:

- **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.

# Mechanism of action:

- binds to nuclear receptor.
- two types of estrogen receptor, termed ER $\alpha$  and ER $\beta$ .
- Binds to nuclear sites and subsequent genomic effect "either gene transcription or inhibition of transcription



# ACTIONS

## ▶ **ER $\beta$ (anti-estrogen)**

Hypothalamus and pituitary

+ ovulation due to inhibit –  
ve feedback on Gn RHM

L.H and FSH

Breast: cancer breast  
(estrogen dependent)

Used SERM

## ▶ **ER $\alpha$ (estrogenic effects)**

▶ Bone

( anti osteoporosis)

▶ Blood( thromboembolism)

▶ Lipid ( $\uparrow$ HDL and  $\downarrow$ LDL)

▶ endometrium (hyperplasia  
then turn to cancer)

# Effects of exogenous estrogen depend on the state of sexual maturity

- **In primary hypogonadism: (11-13 years)** estrogen with progestins to stimulates development of secondary sexual characteristics and accelerates 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-Cloimphene**

**2- Selective Estrogen Receptor Modulators (SERM)**

**3-Pure estrogen receptor antagonists (fulvestrant)**

**4- Synthesis inhibitors**

# Anti-estrogens

Anti-estrogens are **competitive antagonists or partial agonists**.

## 1-Cloimphene



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

**S/E:** multiple ovulation with multiple pregnancy

## 2- 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

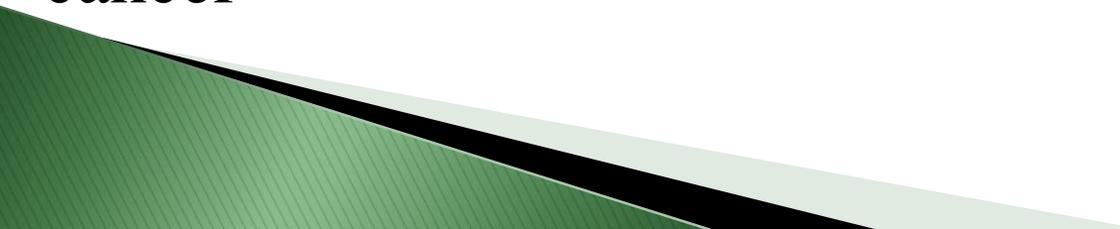
☐ Bone (↓↓ postmenopausal osteoporosis).

☐ ↑↑ Risk of thrombosis.

### 3-Pure estrogen receptor antagonists (fulvestrant)

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

cancer



## 4- 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 P<sub>450</sub> enzymes involved in gonadal steroid synthesis
- ✓ Anti GnRH relasing
- ✓ It is **used in** 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 testis and adrenal cortex

# Preparations:

## 1-Natural progestins:

❖ 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:

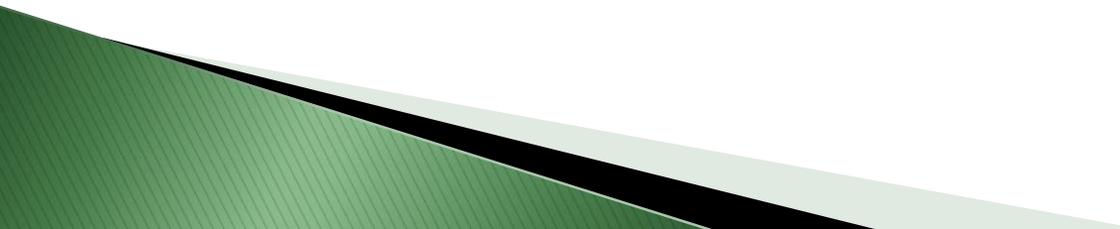
❖ Hydroxyprogesterone, medroxyprogesterone, megestrol are closely related to progesterone.

❖ 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

# 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
- 

# Clinical uses:

## (1) Contraception:

- ❖ With estrogen in combined oral contraceptive pills.
- ❖ As progesterone-only contraceptive pills.
- ❖ As injectable or implantable progesterone-only contraceptive.
- ❖ As part of 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.**

## 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<sub>1</sub> (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**



# Major classes of contraceptives

- A. oral contraceptives (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**

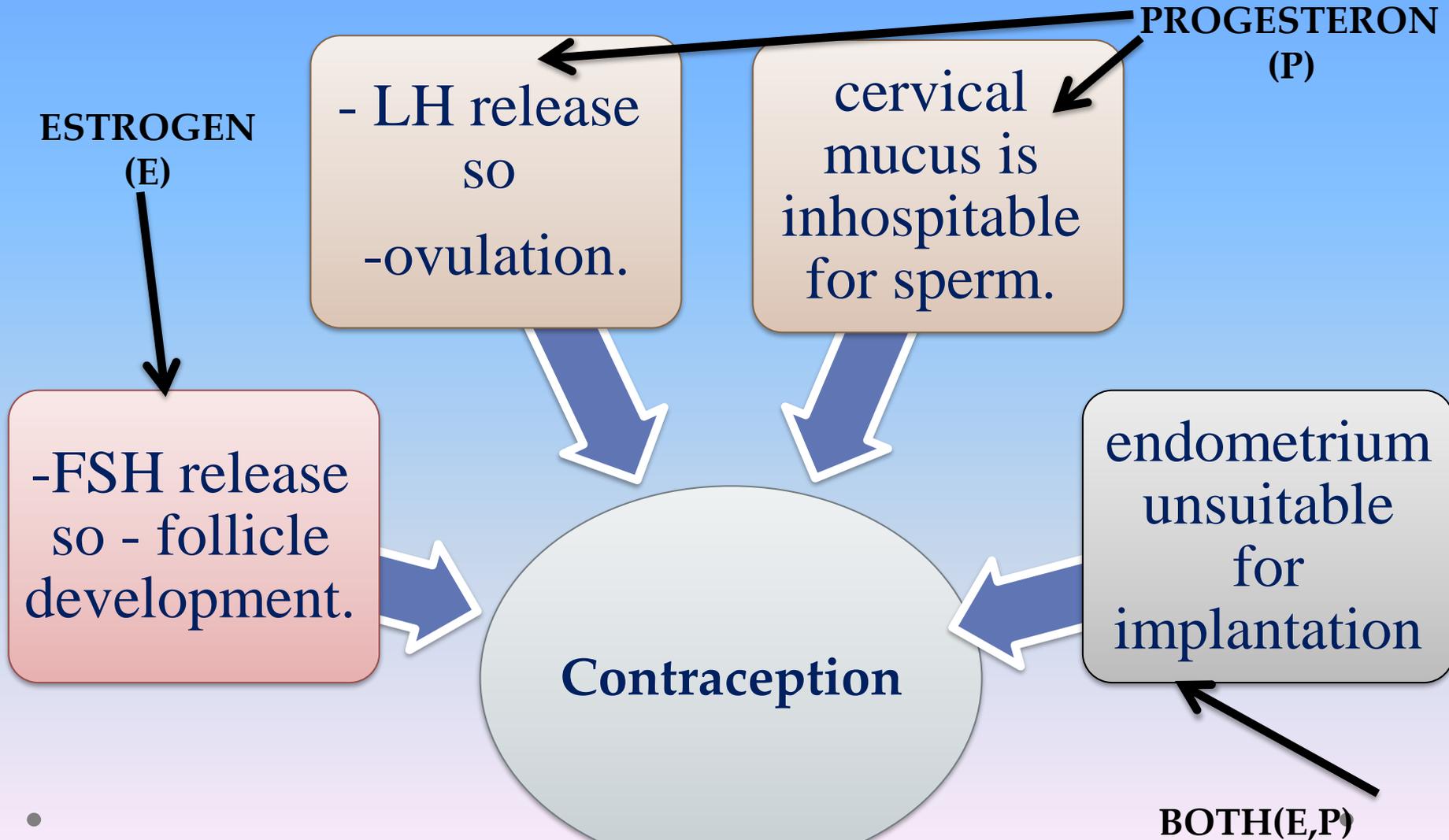
- The progestin-only pill may be **used for patients who are breast-feeding** (progestins do not have an effect on milk production)
- Patients who are **intolerant to estrogen**
- Patients have **other contraindications to estrogen-containing products**



## B. Combination 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**

# Mechanism of action of oral contraceptive pills



# Combination agents

## Monophasic forms

Fixed dose of estrogen and progestin for 21 days then 7 days placebo.

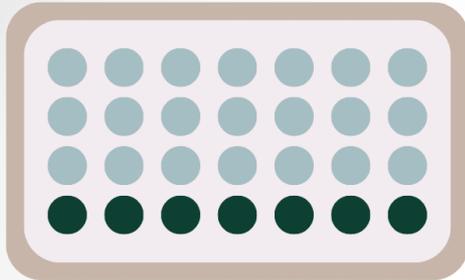
## Biphasic forms

Fixed dose of estrogen while progestin dose increase in 2<sup>nd</sup> 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.

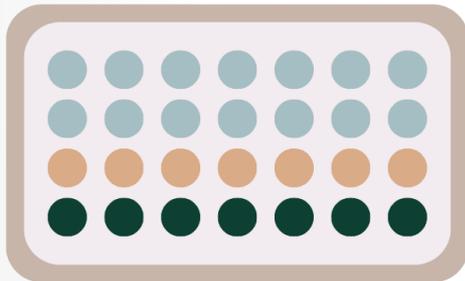
## Monophasic



Day 1-21: dose one

Day 22-26: placebo week

## Biphasic

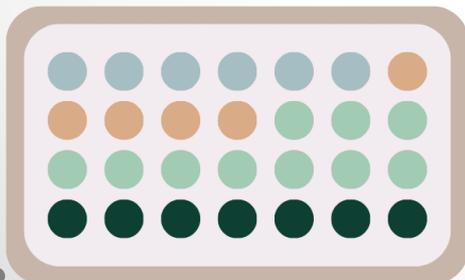


Day 1-14: dose one

Day 15-21: dose two

Day 22-26: placebo week

## Triphasic

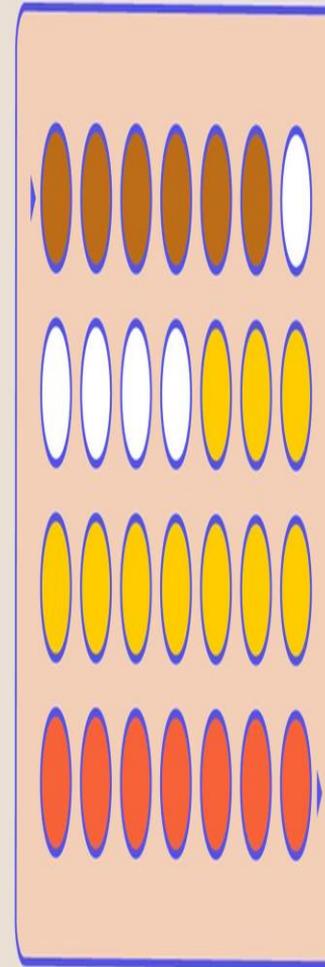


Day 1-6: dose one

Day 7-11: dose two

Day 12-21: dose three

Day 22-26: placebo week



Day 1-6: Ethinylestradiol = 30µg, Levonorgestrel 50 µg

Day 7-11: Ethinylestradiol = 40µg, Levonorgestrel 75 µg

Day 12-21: Ethinylestradiol = 30µg, Levonorgestrel 125 µg

Day 22-28: Ethinylestradiol = 0, Levonorgestrel = 0

- 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. Levonorgestrel:  
subcutaneous capsules.**

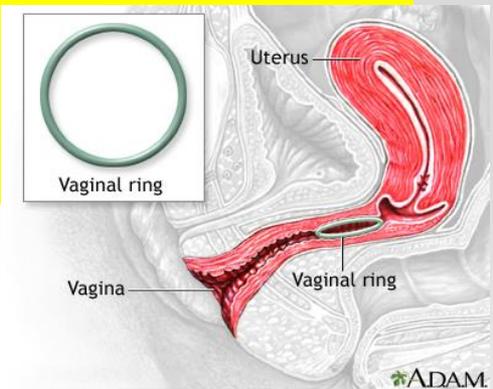




## C. Transdermal patch:

- 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**

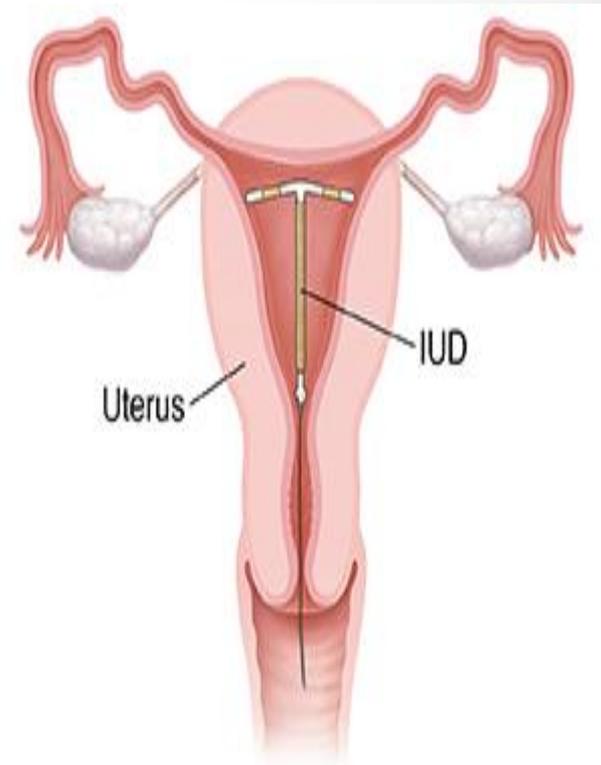
## D. Vaginal ring



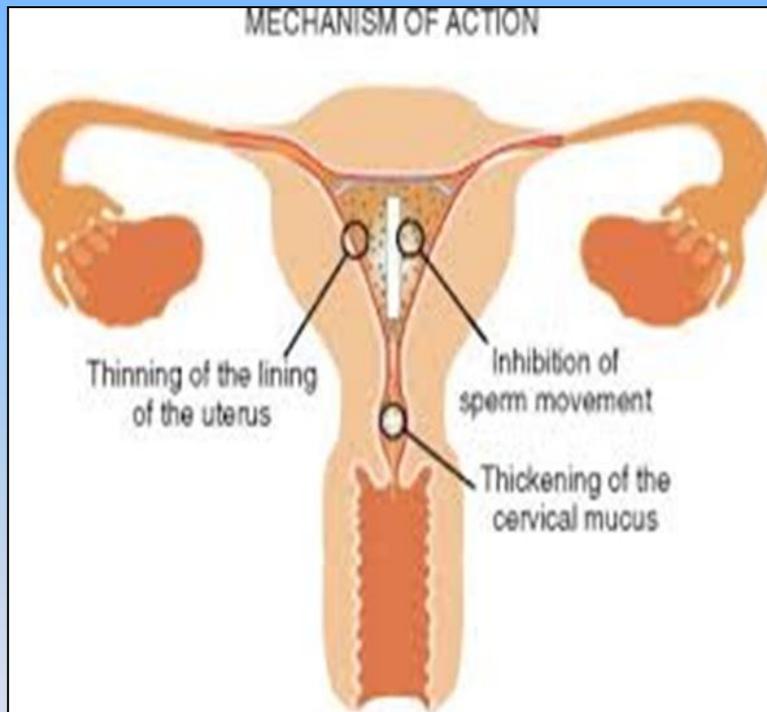
- **Ethinyl estradiol and etonogestrel**
- The ring is inserted into vagina and **is left in place for 3 weeks. Week 4 is ring-free, and withdrawal bleeding occurs**
- The contraceptive vaginal ring has **efficacy**, Vaginal ring may **occasionally slip or be expelled accidentally**

# 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**