

FEMALE SEX **HORMONES**

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Female Gonadal Hormones

1-Estrogen



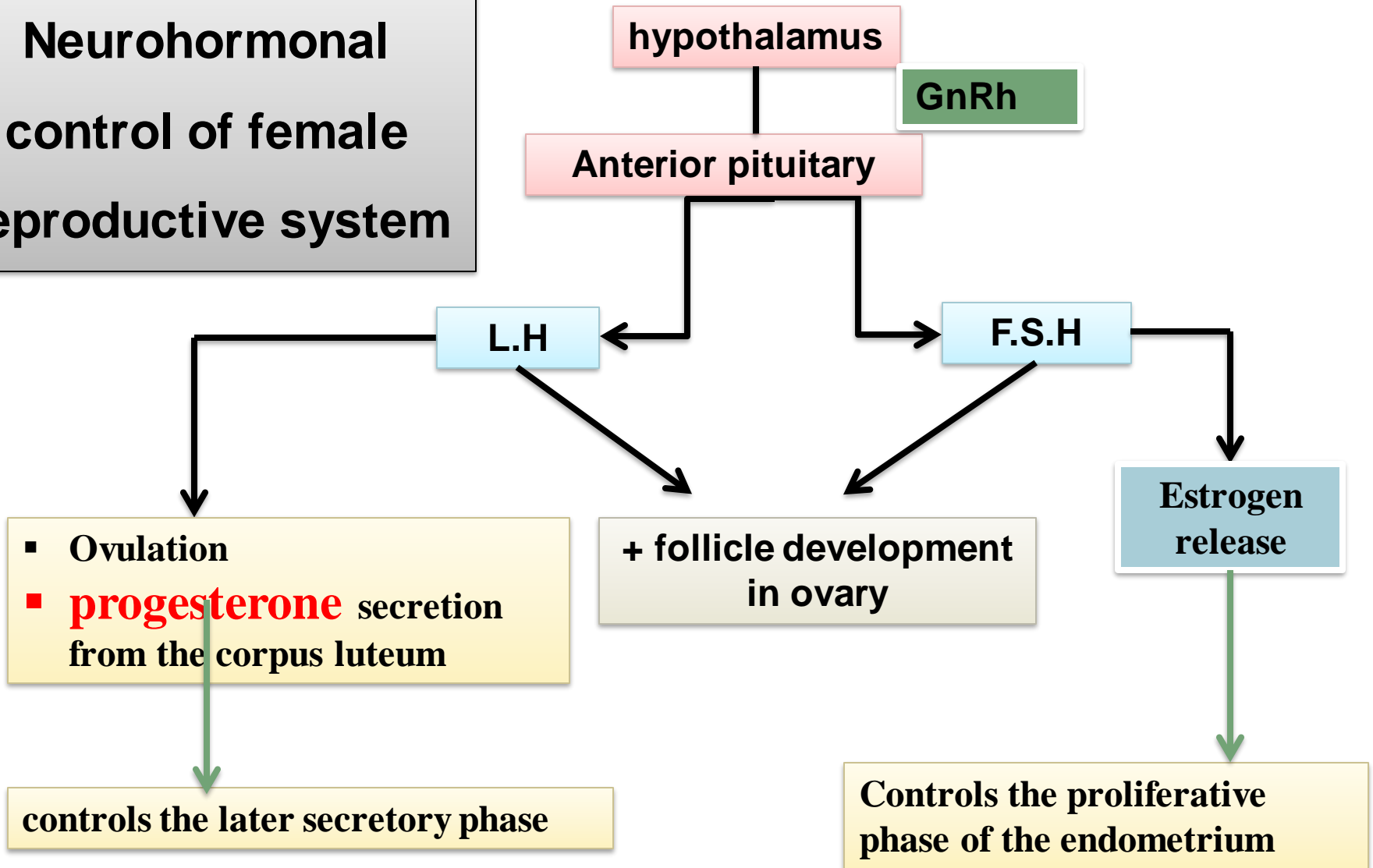
2-Progesterone



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)

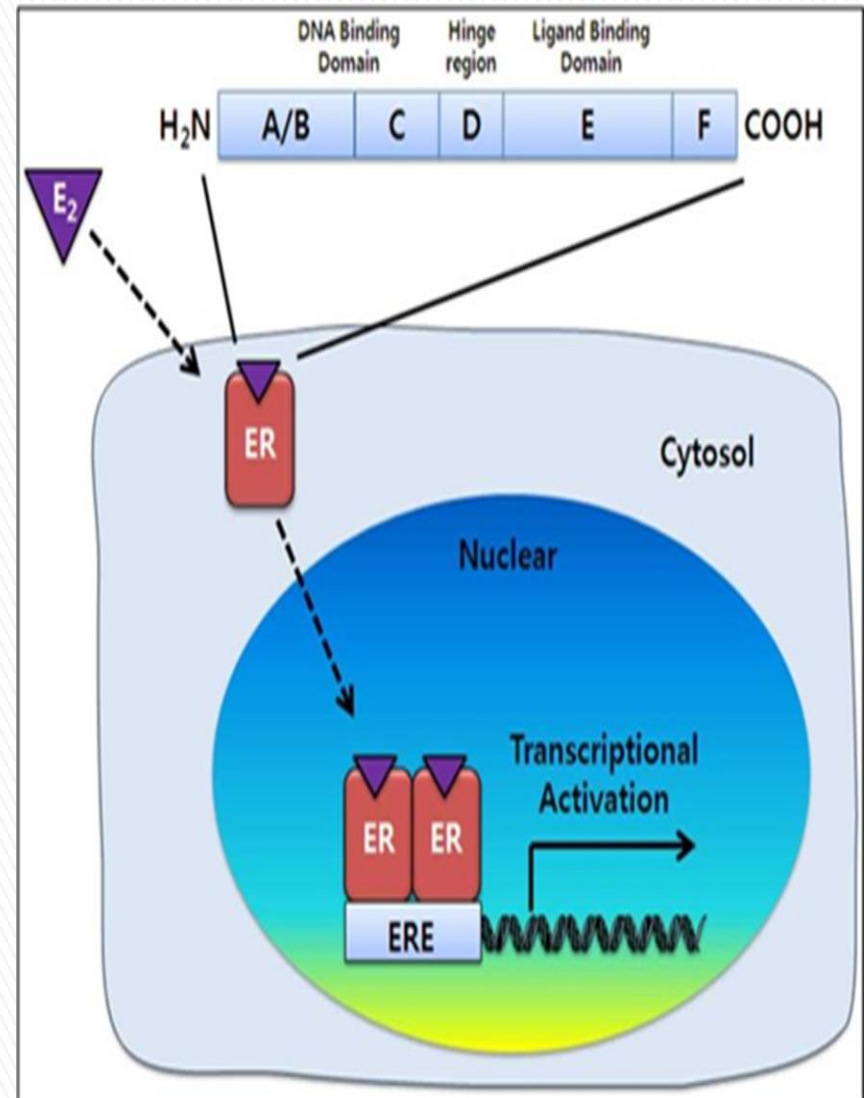


Pharmacokinetic aspects:

- **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 α and ER β .
- Binds to nuclear sites and subsequent genomic effect "either gene transcription or inhibition of transcription



ACTIONS

▶ **ER β (anti-estrogen)**

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

Breast: cancer breast
(estrogen dependent)

Used SERM

▶ **ER α (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- Selective Estrogen Receptor Modulators (SERM)

2- Pure estrogen receptor antagonists (Cloimphene and fulvestrant)

3- Synthesis inhibitors

Anti-estrogens

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



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 ($\downarrow\downarrow$ postmenopausal osteoporosis) and $\uparrow\uparrow$ Risk of thrombosis.

2-Pure estrogen receptor antagonists (fulvestrant)

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

Cloimphene

Selective block of estrogen receptors in the pituitary $\rightarrow \downarrow\downarrow$ negative feedback $\rightarrow \uparrow\uparrow$ FSH & LH \rightarrow stimulates ovulation.

S/E: multiple ovulation with multiple pregnancy

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 P₄₅₀ 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:

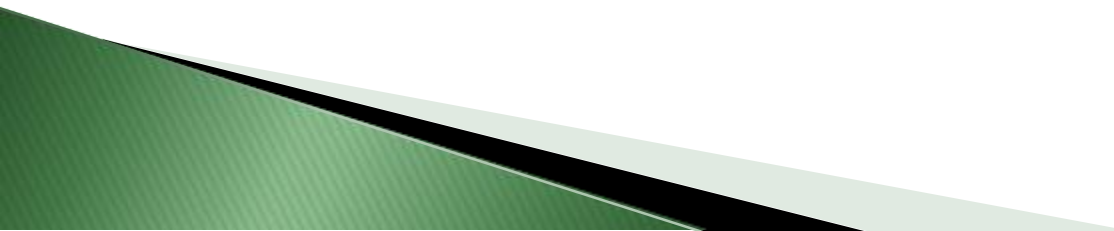
❖ Hydroxyprogesterone, medroxyprogesterone, megestrol are closely related to progesterone.

❖ 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 PGE₁ (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 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**

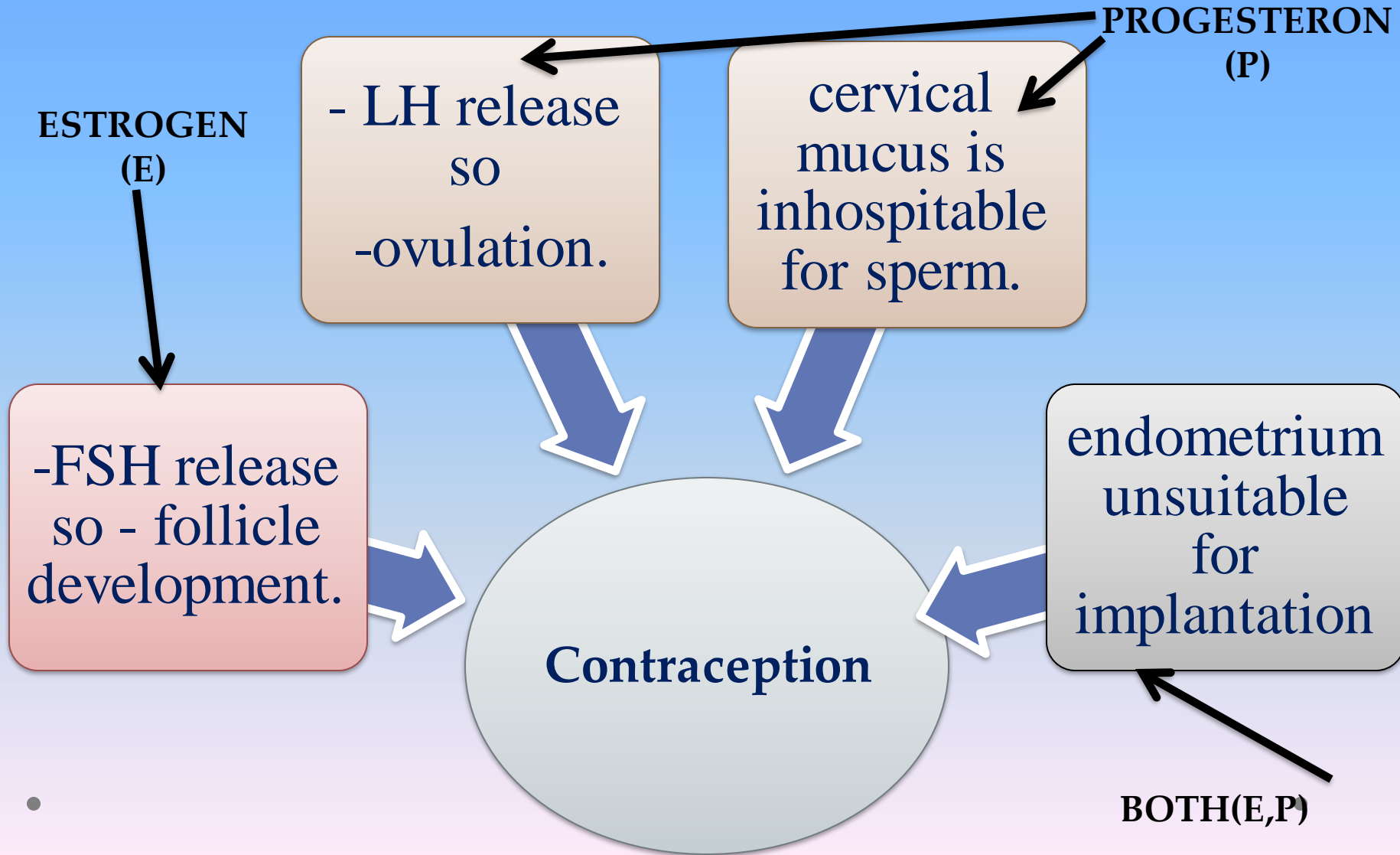
- The progestin-only pill may be **used for patients who are breast-feeding** (progestins do not have an effect on milk production)
- Patients who are **intolerant to estrogen**
- Patients have **other contraindications to estrogen-containing products**



B. 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.

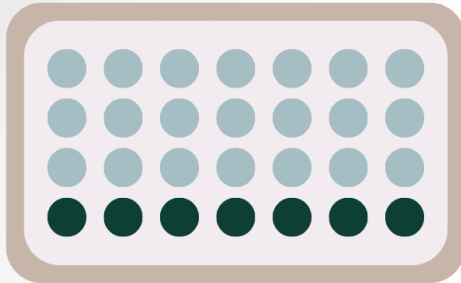
Biphasic forms

Fixed dose of estrogen while progestin dose increase in 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.

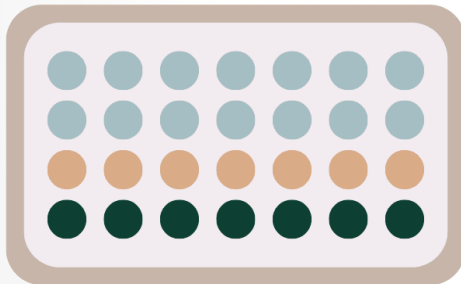
Monophasic



Day 1-21: dose one

Day 22-26: placebo week

Biphasic

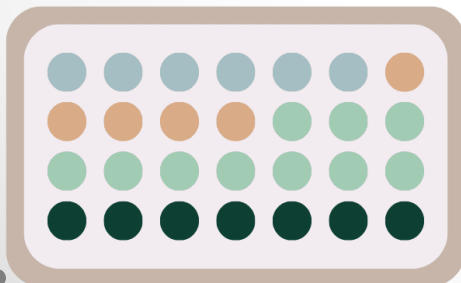


Day 1-14: dose one

Day 15-21: dose two

Day 22-26: placebo week

Triphasic

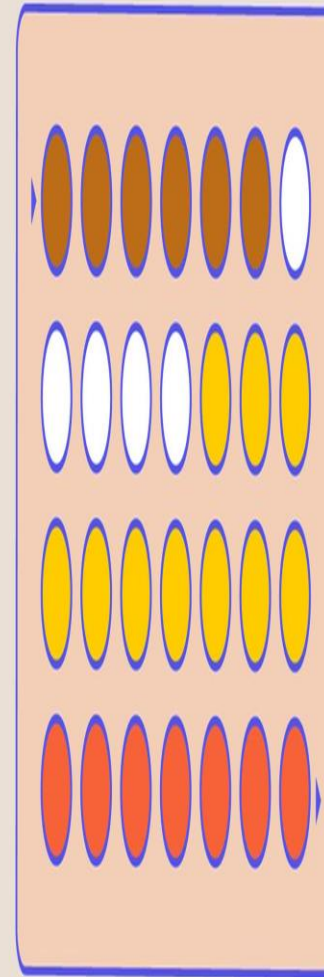


Day 1-6: dose one

Day 7-11: dose two

Day 12-21: dose three

Day 22-26: placebo week



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.

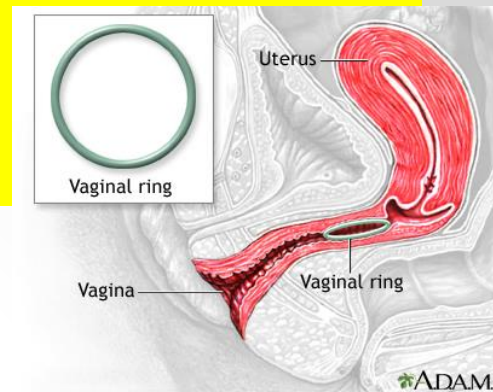




C. Transdermal patch:

- 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**

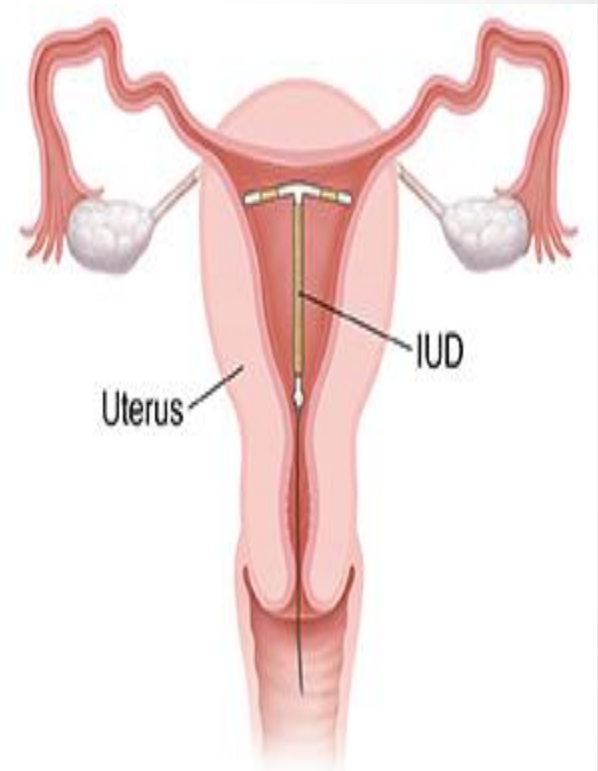
D. Vaginal ring



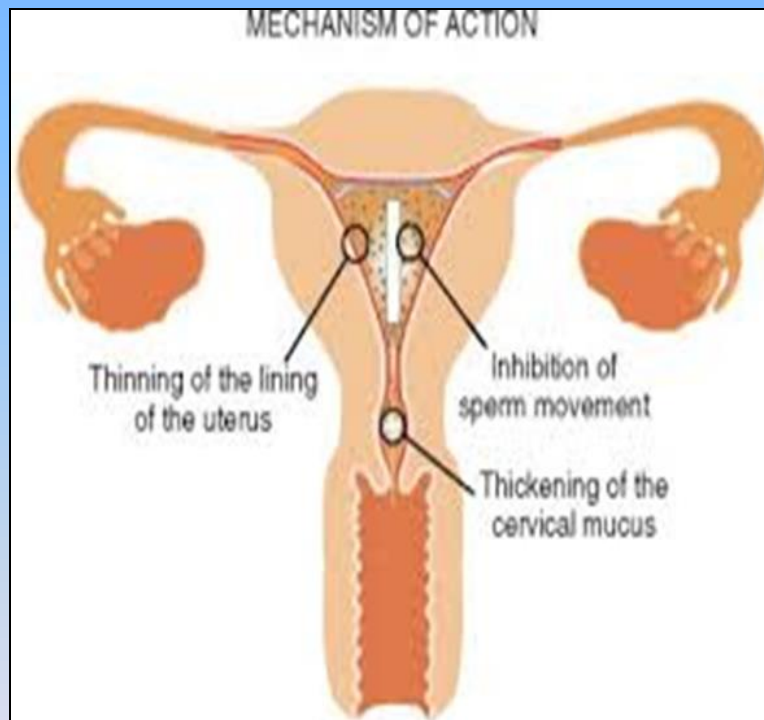
- **Ethinyl estradiol and etonogestrel**
- The ring is inserted into vagina and **is left in place for 3 weeks. Week 4 is ring-free, and withdrawal bleeding occurs**
- The contraceptive vaginal ring has **efficacy**, Vaginal ring may **occasionally slip or be expelled accidentally**

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**