




Chapter 14. Oral Contraceptives

Oral contraceptives: Mifepristone, Norgestril, Levonorgestrol

14.1. ORAL CONTRACEPTIVES PHARMACOLOGY


 Oral contraceptives are also called as '**Birth Control Pills**'. These are hormonal preparations used for reversible suppression of female fertility and prevent pregnancy. Most oral contraceptives contain a combination of 2 types of hormones: an **estrogen** and a **progestin**.

 The pills are either combination of hormones (**Combination Hormonal Contraceptives**) or contains only progestin, sometimes called the "**mini-pills**".


 Rock and Pincus (1955) announced the successful use of an oral progestin for contraception and further addition of oestrogen increase their efficacy and reduce the side effects of large dose of single hormone. So currently combined pills are more preferred method of contraception.

 **Combination Hormonal/Oral Contraceptives (CHCs or COCs) formulations:**

- Contraceptive patch
- Contraceptive ring
- Depot im or sc injections

 **Oestrogen** inhibits the secretion of follicle stimulating hormone (FSH) and prevent the development of the follicle and it also stabilize the endometrial lining to minimize breakthrough bleeding.

 **Oestrogen derivatives used:** ethinylestradiol,

 **Progestin** inhibits the secretion of luteinizing hormone (LH) and suppress the ovulation. Progestin only contraceptives also slow down the transport of sperm through the cervical canal by thickening the cervical muscles and causing alteration in the endometrial lining and also affect the oval transport.

 **Progestins derivatives used:** Desogestrel, Levonorgestrel, Norgestrel, Norgestimate, Northindrone

 **Advantages of CHCs/ Uses**

- ✓ Treatment of acne
- ✓ Hirsutism (unwanted male pattern hair growth in women)
- ✓ Premenstrual syndrome

- ✓ Endometrial cancer
- ✓ Menstrual cycle regulation
- ✓ Functional ovarian cyst

Types of Oral Contraceptives

1. Combined Pills: Combination of **estrogen** and **progestin**.

A. Monophasic: contains fixed dose of estrogen and progestin.

Phased Pills:

B. Biphasic: contains fixed dose of estrogen, while dose of progestin increases in 2nd half of the cycle.

C. Triphasic: contain fixed or variable dose of estrogen, while dose of progestin increases in 3 equal phases. Recommended for women over 35 years of age and for those with no withdrawal bleeding or breakthrough bleeding.

2. Mini Pills: Low dose of Progestin

3. Postcoital Pills: These are for use in a woman not taking any contraceptive who had a sexual intercourse risking unwanted pregnancy

Table: Preparations of Oral Contraceptives

SN	PROGESTIN	OESTROGEN
Combined Pills		
1	Norgestrel (0.3 mg)	Ethinylestradiol (30 ug)
2	Norgestrel (0.5 mg)	Ethinylestradiol (50 ug)
3	Levonorgestrel (0.25 mg)	Ethinylestradiol (50 ug)
4	Levonorgestrel (0.15 mg)	Ethinylestradiol (30 ug)
5	Levonorgestrel (0.1 mg)	Ethinylestradiol (20 ug)
6	Desogestrel (0.15 mg)	Ethinylestradiol (30 ug)
7	Desogestrel (0.15 mg)	Ethinylestradiol (20 ug)
Phased Pills (Triphasic Pills)		
8	Levonorgestrel (50-75-125 ug)	Ethinylestradiol (30-40-30 ug)
9	Norethindrone (0.5-0.75-1.0 mg)	Ethinylestradiol (35-35-35 ug)
Postcoital Pill		
10	Levonorgestrel (0.25 mg)	Ethinylestradiol (50 ug)
11	Levonorgestrel (0.75 mg or 1.5 mg)	Nil
Mini Pills		
12	Norethindrone (0.35 mg)	Nil
13	Norgestrel (75 ug)	Nil

Practical Considerations:

1. Discontinuation of all OCs results in full return of fertility within 1–2 months.
2. If a woman on combined pills misses to take a tablet, she should be advised to take two tablets the next day and continue as usual.
3. If pregnancy occurs during use of hormonal contraceptives—it should be terminated by suction-aspiration, because the risk of malformations, genital carcinoma in female offspring.
4. Most cases- 30 μg ethinylestradiol is sufficient, but in obese women may require a pill containing 50 μg . And cardiovascular patients or above 40 Y, 20 μg may be sufficient.
5. If breakthrough bleeding occurs—switch over to a pill containing higher estrogen dose.
6. In women with contraindications for estrogen progestin only contraceptive may be used.

Side Effects:

Non-Serious Side Effects: Nausea, Vomiting, headache, Migration, breakthrough bleeding, breast discomfort.

Serious Side Effects:

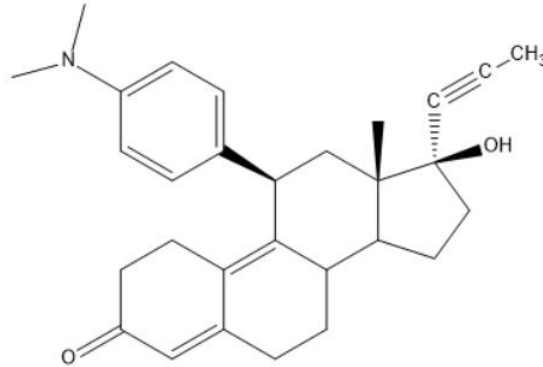
- ✓ Leg vein thrombosis, pulmonary embolism, Coronary and cerebral thrombosis due to OCs enhance the blood coagulation.
- ✓ Hypertension
- ✓ Genital Carcinoma
- ✓ Gallstone
- ✓ Prophyria

Contraindications:

- ✓ Diabetes: control may be vitiated.
- ✓ Obesity
- ✓ Undiagnosed vaginal bleeding
- ✓ Uterine leiomyoma
- ✓ Mentally ill
- ✓ Age above 35 years
- ✓ Mild hypertension
- ✓ Migraine
- ✓ Gallbladder disease

14.2. MEDICINAL CHEMISTRY OF SELECTED DRUGS

A) Mifepristone,



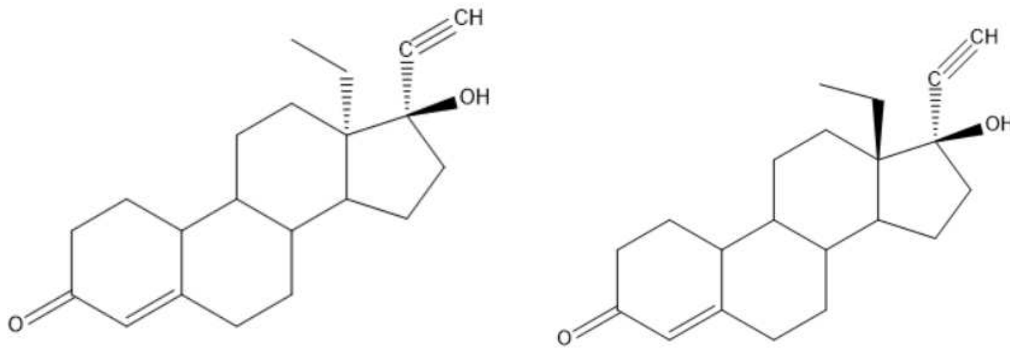
11 β -(4-(dimethylamino)phenyl)-17 α -(1-propynyl)estra-4,9-dien-17 β -ol-3-one

MOA:

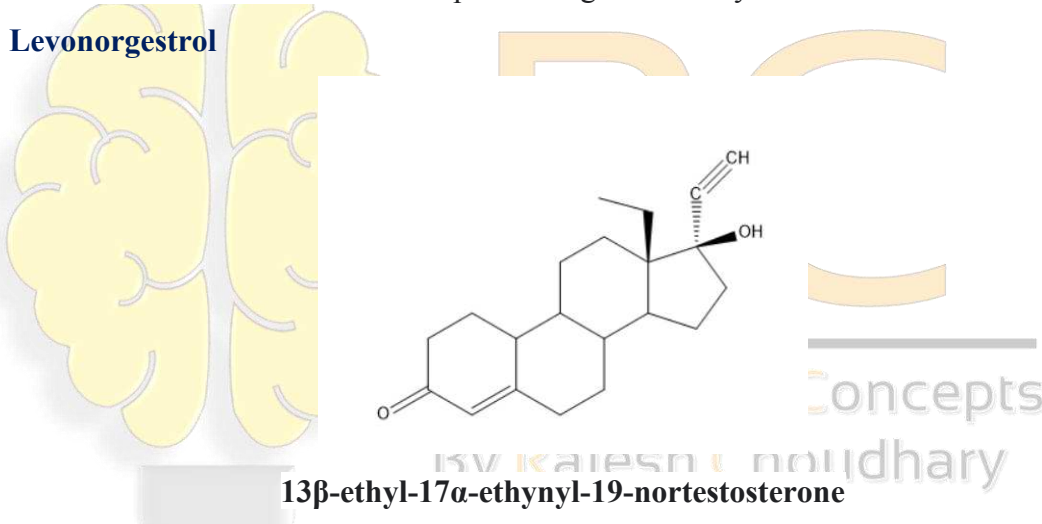
- ✓ Mifepristone is a 19-norsteroid (norethisterone) with potent antiprogesterogenic and significant antiglucocorticoid, and antiandrogenic activity
- ✓ It helps to terminate the pregnancy by inhibitory activity on endogenous and exogenous progesterone
- ✓ It decreases the rate of release of GnRH from the hypothalamus and rounded the preovulatory luteinizing hormone rush and resulted in suppress the ovulation.

Uses:

- ✓ Used to terminate the pregnancy for medical purpose.
- ✓ Used for labour induction after intrauterine foetal death.
- ✓ Used in postcoital contraception.
- ✓ Used in treatment of uterine fibroids.
- ✓ Used in management of Cushing Syndrome due to anti-glucocorticoid activity.
- ✓ Used to softening and dilation of cervix before surgical termination of pregnancy.

B) Norgestrel

Norgestrel, also known as **rac-13-ethyl-17 α -ethynyl-19-nortestosterone** or as **rac-13-ethyl-17 α -ethynyl estr-4-en-17 β -ol-3-one**, is a synthetic estrane steroid and a derivative of testosterone. It is used as oral contraceptive along with ethinylestradiol

C) Levonorgestrel

MOA: it is coupled with Estrogen and progesterone receptor located at female reproductive tract, mammary gland, hypothalamus, and pituitary. It suppress the release of GnRH from the hypothalamus and rounded the preovulatory luteinizing hormone rush and resulted in suppress the ovulation. Levonorgestrel is 2 times more potent than rac-norgestrol.

Uses:

- ✓ Used in birth control pill
- ✓ Used in the treatment of premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD; characterized by severe mood swings, depression, anxiety one to two weeks before the period starts),
- ✓ Used in endometrial cancer
- ✓ Management of menstrual cycle regulation