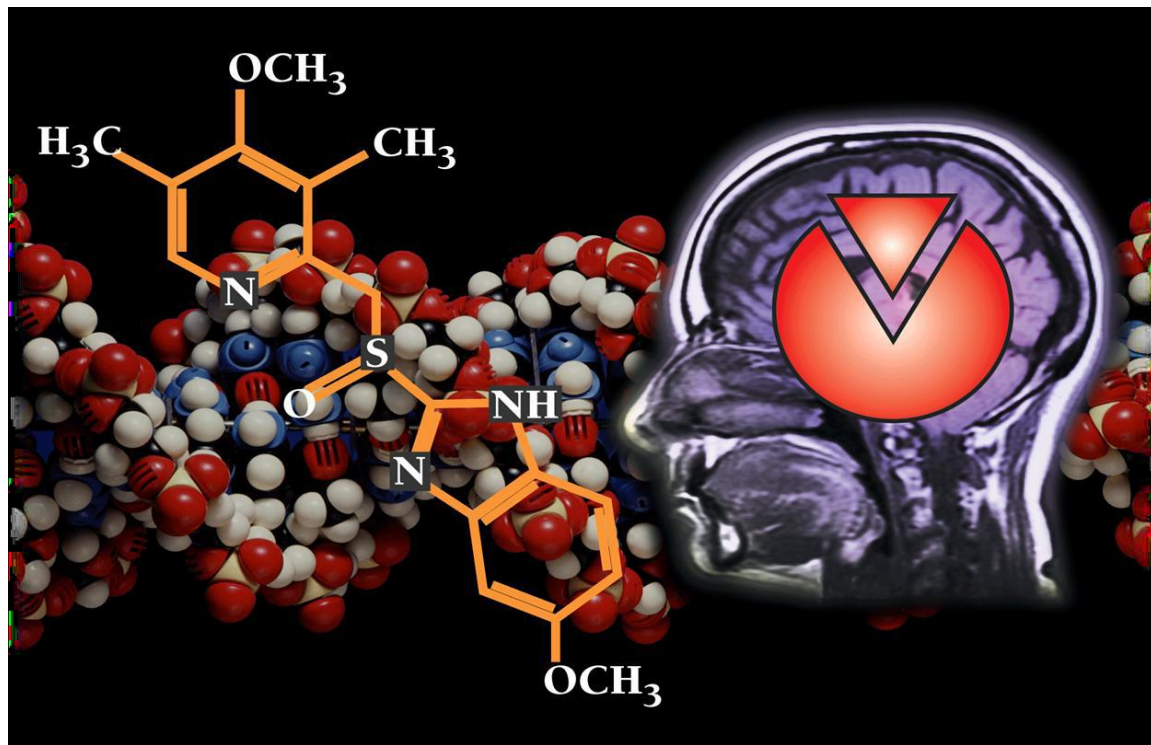


02-Pharmacology of Contraception



Note: First page is an introduction, text in blue and textboxes with thick light blue margins are additional info. **Text in red is important.**

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Introduction:

IN CONCEPTION → there is fusion of the **sperm & ovum** to produce a new organism.

IN CONTRACEPTION → we are preventing this fusion to occur

This achieved by interfering with

Normal process of ovulation

By using **HORMONAL THERAPY**: (the best method because it's inhibit the ovum (the beginning of ovulation))

- **Oral Contraceptives**
- **Contraceptive Patches**
- **Vaginal rings**
- **Injectable**
- **IUD (with hormone)**

Implantation

IUD (copper T)

(it inhibits the fertilization of the ovum)

Preventing sperm from fertilizing the ovum

Interruption by a barrier by using:

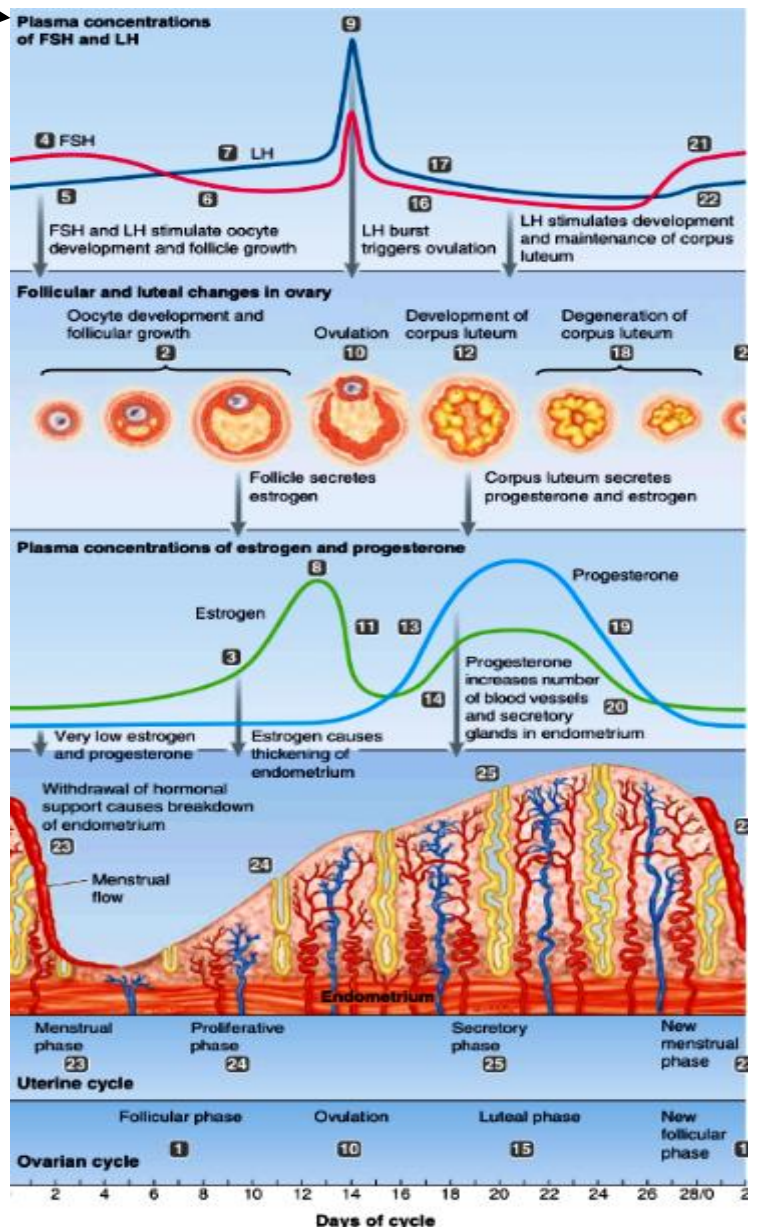
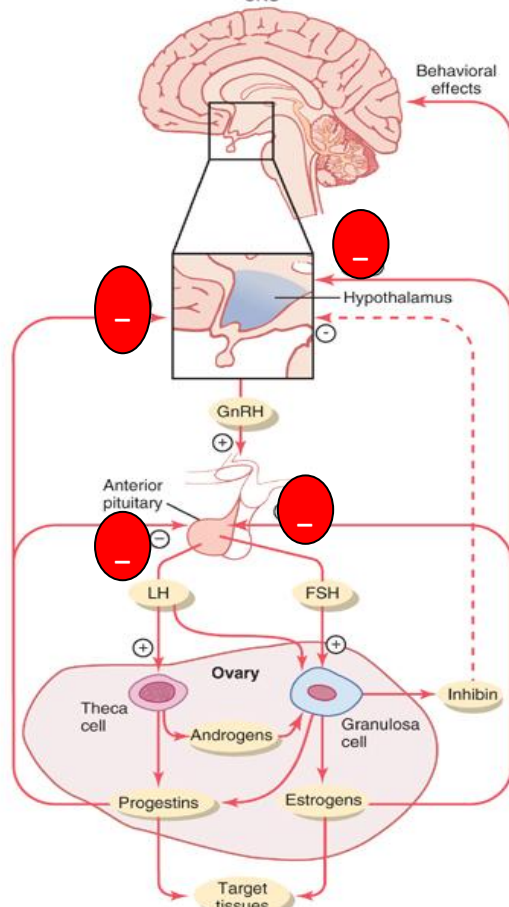
- **Condoms**
- **Cervical caps**
- **Diaphragms**
- **Thin films**

Killing the sperm by using:

- **Spermicidals**
- **Jells**
- **Foams**

Plasma concentrations of the gonadotropins & ovarian hormones during the normal female sexual cycle.

Rising levels of **Estrogens (β-ESTRADIOL)** AND **Progesterone** inhibit the secretion of **GnRH** in hypothalamus & the secretion of the **Gonadotrophs** from the A. pituitary



ORAL CONTRACEPTIVE

They are divided according to composition & intent of use into three types

1-COMBINED Oral contraceptives (COC) **most common**

- ✓ Contain **estrogen & progestin**(100% effective)

A-Estrogens

- ✓ **Ethinyl estradiol**
- ✓ **mestranol** [a “prodrug” converted to ethinyl estradiol]

Currently the concentration of estrogen in COC used now is very low to minimize estrogen hazards (uterus and breast cancer)

B-Progestins

- ✚ **Norethindrone**
- ✚ **Levonorgestrel (Norgestrel)**
- ✚ **Medroxyprogesterone acetate**

Have systemic androgenic effect; acne, hirsutism, weight gain. **(They are not currently used)**

The doctor said u don't have to memorize these drugs names, just have a look

- ✓ **Norgestimate**
- ✓ **Desogestrel**
- ✓ **Drospirenone**

Have no systemic androgenic effect, and they are the ones used currently

MOA

The main action is: It inhibits ovulation by suppressing the release of **Gonadotrophs (FSH & LH)** → no action on the ovary → **ovulation is prevented.**

Other actions:

- ✓ Inhibit **implantation** of the fertilized zygote **by causing abnormal contraction of the fallopian tubes & uterine musculature** → ovum will be expelled rather than implanted.
- ✓ **Increase viscosity** of the cervical mucus making it so viscous **(A progesterone effect)** → no sperm pass
- ✓ Abnormal transport time of sperm through the fallopian tubes.

Formulation

- ✓ Currently, their formulation is improved to **mimic the natural ongoing changes in hormonal profile.**

Accordingly we have now the phase formulations:

1. **Monophasic** → (a fixed amount of **estrogen & progestin**)
2. **Biphasic (2 doses)** → (a fixed amount of **estrogen**, while amount of **progestin** increases stepwise in the second half of the cycle)
3. **Triphasic (3 doses)** → (amount of **estrogen**; fixed or variable & amount of **progestin** increases stepwise in 3 phases).

Note: These tables are only for explanation.

	Estrogen (mg)		Progestin (mg)	
Monophasic combination tablets				
Loestrin 21 1/20	Ethinyl estradiol	0.02	Norethindrone acetate	1.0
Desogen, Apri, Ortho-Cept	Ethinyl estradiol	0.03	Desogestrel	0.15
Brevicon, Modicon, Necon 0.5/35	Ethinyl estradiol	0.035	Norethindrone	0.5
Demulen 1/35	Ethinyl estradiol	0.035	Ethynodiol diacetate	1.0
Nelova 1/35 E, Ortho-Novum 1/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ovcon 35	Ethinyl estradiol	0.035	Norethindrone	0.4
Demulen 1/50	Ethinyl estradiol	0.05	Ethynodiol diacetate	1.0
Ovcon 50	Ethinyl estradiol	0.05	Norethindrone	1.0
Ovral-28	Ethinyl estradiol	0.05	_{DL} -Norgestrel	0.5
Norinyl 1/50, Ortho-Novum 1/50	Mestranol	0.05	Norethindrone	1.0
Biphasic combination tablets				
Jenest-28, Ortho-Novum 10/11, Necon 10/11, Nelova 10/11				
Days 1—10	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 11—21	Ethinyl estradiol	0.035	Norethindrone	1.0

	Estrogen (mg)		Progestin (mg)	
Triphasic combination tablets				
Triphasil, Tri-Leven, Trivora				
Days 1—6	Ethinyl estradiol	0.03	_L -Norgestrel	0.05
Days 7—11	Ethinyl estradiol	0.04	_L -Norgestrel	0.075
Days 12—21	Ethinyl estradiol	0.03	_L -Norgestrel	0.125
Ortho-Novum 7/7/7, Necon 7/7/7				
Days 1—7	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 8—14	Ethinyl estradiol	0.035	Norethindrone	0.75
Days 15—21	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-TrI-Cyclen				
Days 1—7	Ethinyl estradiol	0.035	Norgestimate	0.18
Days 8—14	Ethinyl estradiol	0.035	Norgestimate	0.215
Days 15—21	Ethinyl estradiol	0.035	Norgestimate	0.25

Methods of administration (very imp)

- ✚ Pills are taken for 21 days, starting on 5th day of the cycle & ending at day 26. This is followed by a 7 day pill free period
- ✚ TO IMPROVE COMPLIANCE; a formulation of 28 pills available, but the last 7 pills of the 28 pills are actually placebo (non hormonal).
- ✚ Pills are better taken at same time of day
- ✚ If females are compliant the efficacy of COC can reach as high as (99.9%) in preventing pregnancy

ADRs (very imp) – u have to know the difference between the two:-

A. Estrogen Related (cause metabolic syndrome)

1. Nausea and breast tenderness
2. Headache
3. Increase Skin Pigmentation (effect the melanin)
4. Impair glucose tolerance (hyperglycemia)
5. Increase incidence of breast, vaginal & cervical cancer.

6. Cardiovascular - major concern

a. Thromboembolism (Estrogen increases some clotting factors)

b. Hypertension (increase in aldosterone secretion).

7. Increase frequency of gall bladder disease (because it's steroid _cholesterol driven _if it's accumulated it's cause stones)

Progestin Related

1. Nausea, vomiting, headache
2. Slightly higher failure rate of contraception.
3. Fatigue, depression of mood
4. Menstrual irregularities
5. Weight gain (It stimulates lipoprotein lipase activity and seems to favor fat deposition.)
6. Hirsutism
7. Masculinization (Norethindrone)
8. Ectopic pregnancy.

Note: Hirsutism & other androgenic effects are usually caused by the " **Norethindrone** " derivatives, and combinations containing nonandrogenic progestins like **Norgestimate** are preferred in these patients.

Contraindications

- ✓ Thrombophlebitis / thromboembolic disorders (metabolic syndrome manifestations)
- ✓ Congestive heart failure or other causes of edema
- ✓ Vaginal bleeding of undiagnosed etiology (Because it might be a uterine or cervical cancer)
- ✓ Known or suspected pregnancy
- ✓ Known or suspected breast cancer, or estrogen-dependent neoplasms
- ✓ Impaired hepatic functions
- ✓ Dyslipidemia, diabetes, hypertension, migraine
- ✓ Lactating mothers – use mini pill (Estrogen down regulates prolactin receptors)

N.B. Females that are obese, smokers (It cause interaction with the liver enzymes), Females > 35 years (because she more prone to cancer) are better given the mini pills

Interactions

A) Medications that cause contraceptive failure

- ✓ Antibiotics that interfere with normal GI flora → ↓ absorption
→ ↓ its bioavailability

- ✓ Microsomal **Enzyme Inducers** → ↑ catabolism of OC

e.g.: **Phenytoin** , **Phenobarbitone**, **Rifampin**

B) Medications that ↑ COC toxicity

Microsomal **Enzyme Inhibitors**; ↓ metabolism of OC → ↑ toxicity e.g.: **Acetaminophen**, **Erythromycin** , **SSRI** (antidepressant)

C) Medications that alter the clearance of COC → ↑ toxicity

e.g.: **Cyclosporine** , **Warfarin**, **Theophylline**

2-MINI Pills Progestin-Only Pills (POP)

Contains only a progestin (97% effective) → as **norethindrone** or **desogestrel** *and are used when estrogen containing pills are contraindicated*

Mechanism of action

- *The main effect is that it increases cervical mucus, so no sperm penetration & therefore, no fertilization. (the efficacy is lower than COC drugs)*

Indications

- ✚ Are alternative when **estrogen is contraindicated** (e.g.: during breast feeding, hypertension, cancer, smokers over the age of 35).

Method of administration

1. Oral tablets **should be taken every day**, all year round
2. I.M injection e.g. **medroxy-progesterone acetate** 150 mg every 3 months..

ADRs & Contraindications (very imp)

- ✓ That are related to progestins only

N.B. There is slightly higher contraception failure rates when mini pills are used

3- MORNING-AFTER Pills

Also known as:

- Post Coital Contraception
- Emergency Hormonal Contraception [EHC]

This is a form Contraception on instantaneous demand, 2ndry to unprotected sexual intercourse

Contain both **hormones** or **each one alone (high dose)** or **Mifepristone ± Misoprostol**
Contraception on instantaneous demand, 2ndry to unprotected sexual intercourse

Composition	Method of Administration	Timing of 1st dose After Intercourse	Reported Efficacy
Ethinyl estadiol + Levonorgestrel	2 tablets twice with 12 hrs in between	0- 72hrs	75%
High-dose only Ethinyl estadiol	Twice daily for 5 days	0- 72hrs	75 - 85%
High dose only levonorgestrel	Twice daily for 5 days	0- 72hrs	70 – 75%
Mifepristone ± Misoprostol	A single dose	0- 120 hrs	85 - 100%

Note: The hormones (First three) are often administered with antiemetics, since 40% of the patients have nausea or vomiting.

Note: Mifepristone a **progesterone antagonist** that binds strongly to the **progesterone receptor** and inhibits the activity of progesterone. A **single dose** of 600 mg is an effective emergency postcoital contraceptive, though it may result in delayed ovulation in the following cycle.

Note: Misoprostol augments **mifepristone postcoital contraception** by: increasing uterine contractions that will separating the implanted zygote from the endometrium. It also softens the cervix and to allow the uterine contents to pass.

To explain the method of administration of the drugs in the table (very imp):

- The first three drugs is can be given starting from 12 -72 hours after sexual intercourse after that it will not be effective
- The last one (mifepristone=misprostole) **can be given within 5 days**

Just to explain the way of administration of the first drug: → two tablets in morning ,two at night just for one day (the total 4 tablbs)

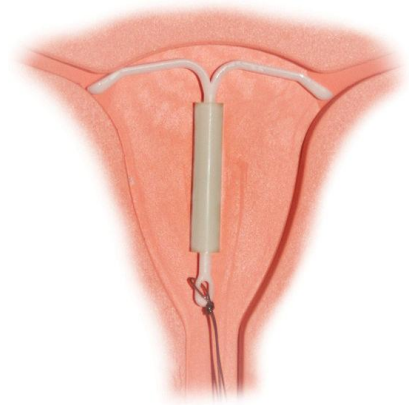
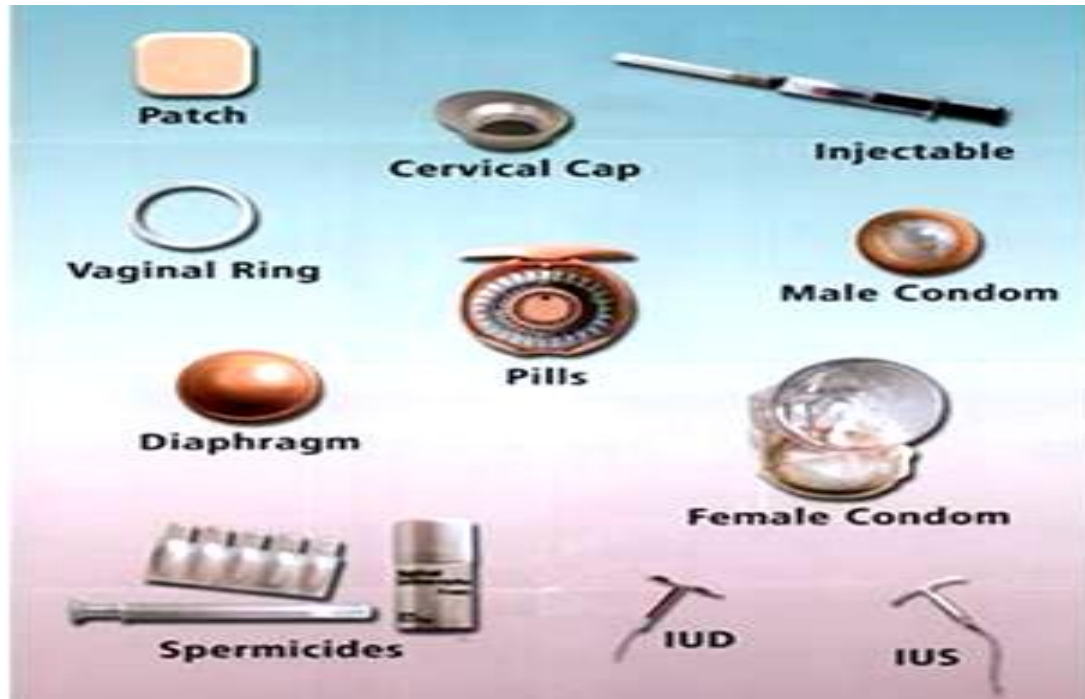
Indications

When desirability for avoiding pregnancy is obvious (for emergency_after sexual intercourse_):

- ✓ Unsuccessful withdrawal before ejaculation
- ✓ Torn, leaking condom
- ✓ Missed pills
- ✓ Exposure to teratogen e.g. Live vaccine
- ✓ Rape

Note: The Mirena levonorgestrel-releasing intrauterine system (IUS) contains the hormone levonorgestrel (LNg), which is similar to progesterone. The LNg IUS causes cervical mucus to thicken to prevent sperm from entering the cervix and reaching the egg.

Note: Copper intrauterine devices (IUDs) work by impairing the mobility of sperm and preventing them from fertilizing the ovum. Additionally, the foreign body irritates the lining and wall of the uterus making it hard for an embryo to implant



Focus on:

-the **ADRs** related to estrogen and progestin and the difference between them

-**The contraindication**

-**The method of administration of each one** (morning after pills in particular)

Remember that, we use morning after pills **for emergency after unprotected sexual** intercourse and COC for women seeking a method of conception

Summary

- ✓ Rising levels of **Estrogens (β -ESTRADIOL)** AND **Progesterone** inhibit the secretion of **GnRH** in hypothalamus & the secretion of the **Gonadotrophs** from the A. pituitary
- ✓ In contraception the goal is to prevent the sperm from fertilizing the ovum. This done by many different method e.g. (**Hormonal therapy** like Oral Contraceptives, **Intrauterine devices** that interferes with implantation, or **preventing sperm from fertilizing the ovum** through Condoms and spermaticocidals)
- ✓ The most controlled and effective way of contraception is **using oral contraceptives**.
- ✓ They are divided according to composition & intent of use into three types
- ✓ **1-COMBINED Oral contraceptives (COC)** that Contain estrogen & progestin(100% effective)
 - ✓ **A-Estrogens** like **Ethinyl estradiol or mestranol** [a “prodrug” converted to ethinyl estradiol]
 - ✓ **B-Progestins are divided into 2 subgroups:**
 - ✓ **1) Preparations that have systemic androgenic effect;** acne, hirsutism, weight gain. E.g(**Norethindrone ,Levonorgestrel (Norgestrel) ,and Medroxyprogesterone acetate**
 - ✓ **2)Preparations that do not have, and are the ones currently used** e.g (**Norgestimate,Desogestrel,Drospirenone**)
 - ✓ **COC's main action is:** that It inhibits ovulation by suppressing the release of Gonadotrophs (FSH & LH)→ **no action on the ovary → ovulation is prevented.**
 - ✓ Currently, their formulation is improved to mimic the natural ongoing changes in hormonal profile.
 - ✓ **Monophasic** →(a fixed amount of **estrogen & progestin**)
 - ✓ **Biphasic (2 doses)**→(a fixed amount of **estrogen**, while amount of **progestin** increases stepwise in the second half of the cycle)
 - ✓ **Triphasic (3 doses)**→(amount of **estrogen**; fixed or variable & amount of **progestin** increases stepwise in 3 phases).
 - ✓ **Pills are taken for 21 days, starting on 5th day of the cycle & ending at day 26.** This is followed by a **7 day pill free period**
 - ✓ **TO IMPROVE COMPLIANCE;** a formulation of **28 pills available**, but the **last 7 pills** of the 28 pills are **actually placebo.**
 - ✓ **Estrogen ADRs:** Impaired glucose tolerance (hyperglycemia),Increased incidence of breast, vaginal & cervical cancer, Thromboembolism,Hypertension.
 - ✓ **Progestin ADRs:**Menstrual irregularities,Weight gain,**Hirsutism,Masculinization** (The latter two are seen **Norethindrone derivatives**)
 - ✓ **Females that are obese, smokers, Females > 35 years** are better given the mini pills
 - ✓ **Interactions:**
 - 1)**Antibiotics** that interfere with normal GI flora → ↓ in its absorption
 - 2)**Microsomal Enzyme Inducers** →**e.g.: Phenytoin , Phenobarbitone, Rifampin**
 - 3)**Microsomal Enzyme Inhibitors** e.g.: **Acetaminophen, Erythromycin**
 - 4)**Medications that alter the clearance of COC** → ↑ toxicity e.g.: **Cyclosporine ,Warfarin,Theophylline**
- ✓ **2-MINI Pills Progestin-Only Pills (POP)** e.g(**norethindrone, desogestrel**)Contains only a progestin (97%effective). They are used as an alternative when **estrogens are contraindicated** (e.g.: during breast feeding, hypertension, cancer, smokers over the age of 35).
 - ✓ *The main effect is that they increase cervical mucus, so no sperm penetration & therefore, no fertilization.*
 - ✓ **There is slightly higher contraception failure rates when mini pills are used**
- ✓ **3- MORNING-AFTER Pills** **or** Post Coital Contraception(Emergency Hormonal Contraception [EHC])
 - ✓ **It either contains both synthetic hormones(Ethinyl estradiol and Levonorgestrel) or each one alone (in high doses) or Mifepristone** with or without **Misoprostol**
 - ✓ They are used when **When desirability for avoiding pregnancy is obvious:**Torn, leaking condom, Missed pills ,Exposure to teratogen e.g. Live vaccine,or Rape