



Pharmacology  
439



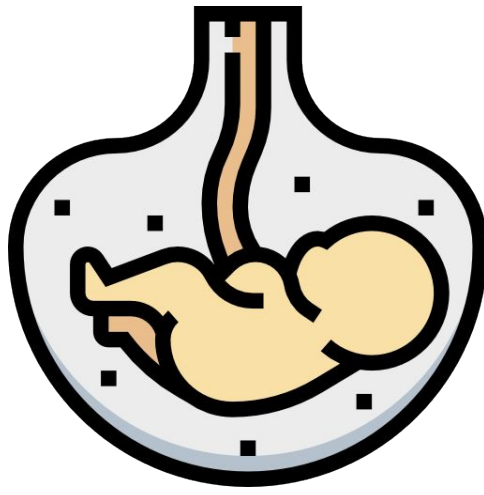
MED439  
KING SAUD UNIVERSITY



Revised & Approved



*Editing File*



## Reproduction Block

Pharmacology team 439

# Oral & Other Forms of Contraceptives

## Objectives:

By the end of the lecture , you should know:

- ◆ Perceive the different contraceptive utilities available.
- ◆ Classify them according to their site and mechanism of action.
- ◆ Justify the existing hormonal contraceptives present.
- ◆ Read the objectives for once.
- ◆ Compare between the types of oral contraceptives pills with respect to mechanism of action, formulations, indications, adverse effects, contraindications and possible interactions.
- ◆ Hint on characteristics & efficacies of other hormonal modalities.

### Color index:

Black : Main content

Red : Important

Blue: Males' slides only

Pink : Females' slides only

Grey: Extra info or explanation

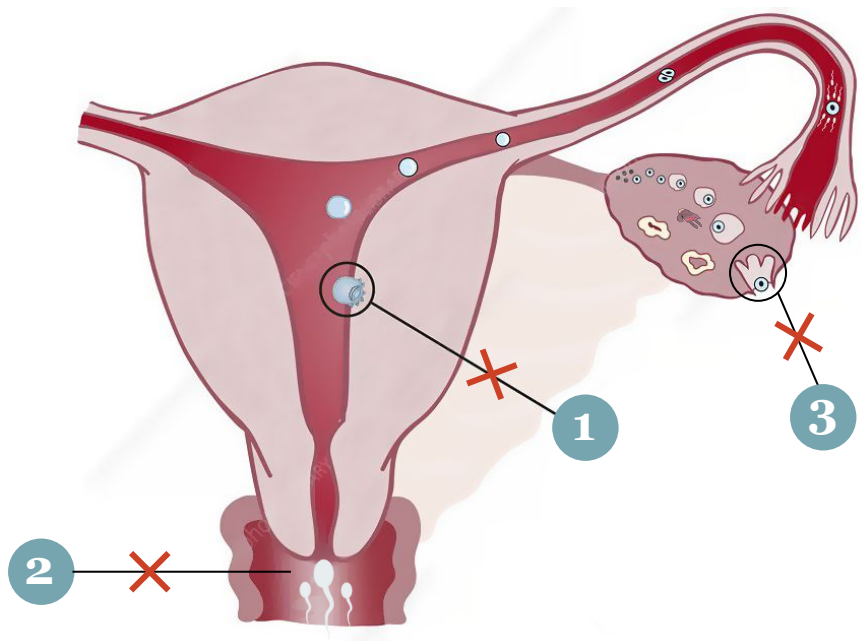
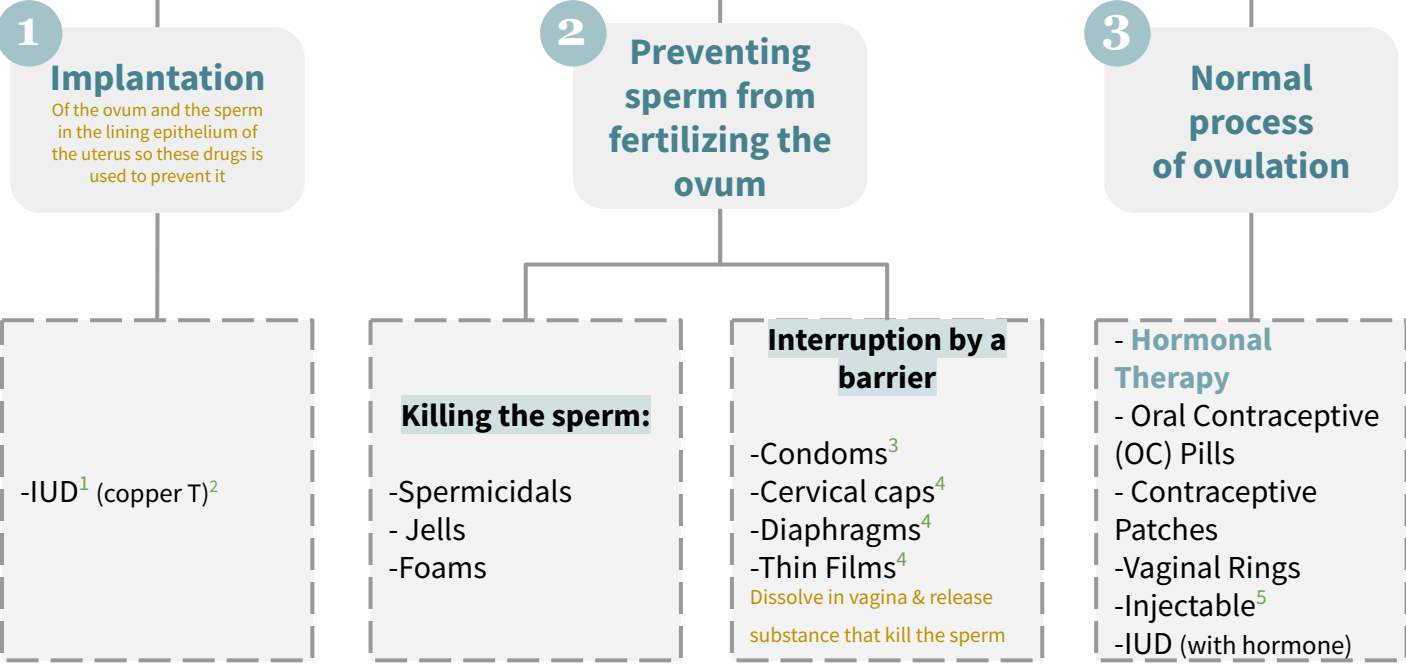
Yellow: Dr. notes (439)

Green: Dr. notes (438)

# Introduction

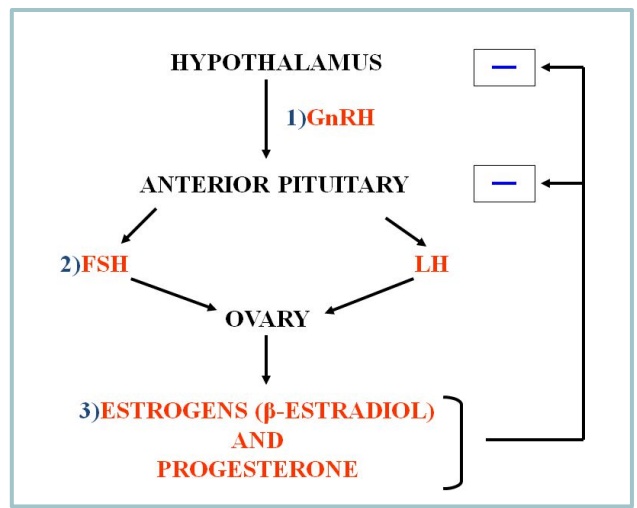
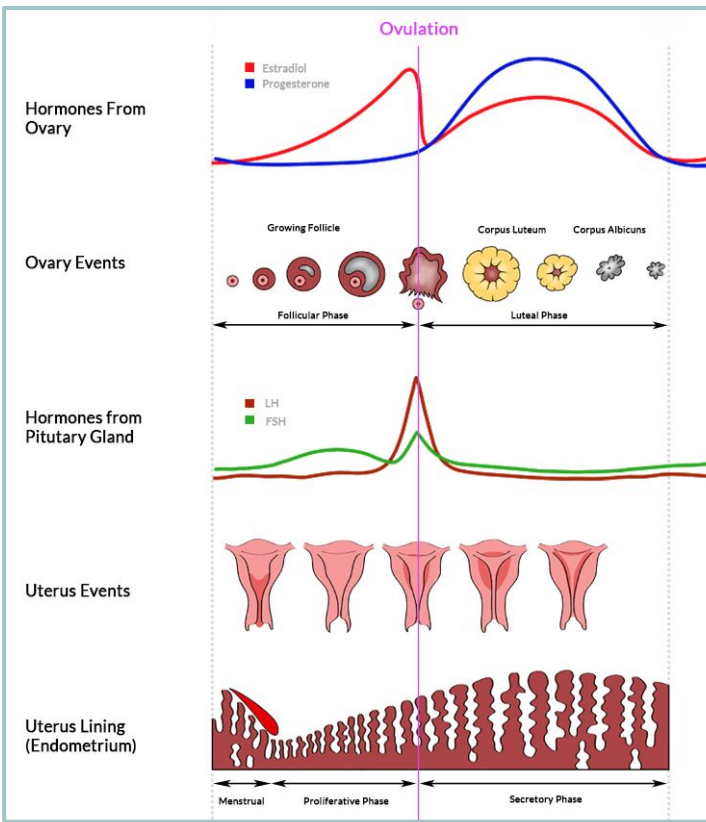
## Definitions

- **Conception:** There is **fusion** of the sperm & ovum to produce a new organism.
- **Contraception:** We are **preventing** this fusion to occur & This achieved by interfering with:



1: Intrauterine device  
 2: IUD with copper added to it, a form of non hormonal IUD that is wrapped in copper wires. Copper alters sperm mobility, preventing it from reaching the ovum.  
 3: male preventative barrier  
 4: female preventative barriers.  
 5: up to 3 months effect.

# Physiology Overview



Hypothalamo - pituitary - gonadal axis  
And the -ve feedback of estrogen and progesterone

-FSH (maturation of the follicles) and LH (induces ovulation)

Normally:

- **low dose** of estrogen has -ve feedback on LH (first 10 days); this is why in the case of contraception we give low and continues doses of estrogen to prevent the the ovulation
  - **High dose** of estrogen: has +ve feedback on LH (after 10 days)
- After ovulation, corpus luteum produces three important hormones: progesterone, estrogen, inhibin (inhibits FSH) under the action of LH, the degradation of corpus luteum causes the decline of these hormones -> new cycle

-estrogen and progesterone act on uterus (endometrial growth) to prepare it for pregnancy.

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

## Types of Oral Contraceptive Pills According to Composition & Intent of Use

### Combined (COC)

Contain Estrogen<sup>1</sup> & Progestins  
Is synthetic form of progesterone that give testosterone side effects but they developed it to reduce this SE (100% effective)

### MINI (POP)

Contain Only a Progestin  
(97% effective)

### Morning-After<sup>2</sup>

Contain both hormones or Each one alone (high dose)  
**OR** Mifepristone (Antiprogestin) ± Misoprostol (prostaglandin analogue)

Estrogen

Progestin  
(Synthetic progesterone)

- Norethindrone, Levonorgestrel (Norgestrel) & Medroxyprogesterone acetate (Has systemic androgenic effect: **acne, hirsutism, weight gain**).

- ★ Currently: Norgestimate, Desogestrel & Drospirenone (**Has no systemic androgenic effect**).

-progestins are synthetic form of progesterone.  
-progestins differ from progesterone in that it has less side effects, so it is used in drugs to avoid progesterone side effects.  
-progestins are testosterone derivatives so they have testosterone like effects.

- Ethinyl estradiol or mestranol [a "prodrug" converted to ethinyl estradiol].
- Currently<sup>3</sup> concentration used now is **very low to minimize estrogen hazards**. to reduce the risk of getting cancer by the effect of estrogen & reduces clotting

1: very effective in contraception.

2: = emergency contraceptives.

3: older preparations used to have higher conc.

Drug	Combined Oral Contraceptives (COC)	
MOA	<ul style="list-style-type: none"> <li>★ (1) <b>The main MOA is Inhibit ovulation</b> by suppressing the release of gonadotropins<sup>1</sup> (FSH &amp; LH) → no action on the ovary → ovulation is prevented. <b>estrogen inhibit LH release so no ovulation</b>, progestin have negative feedback effects on releasing LH/FSH</li> <li>• (2) <b>Inhibit implantation</b> by causing abnormal contraction of the fallopian tubes &amp; uterine musculature → ovum will be expelled rather than implanted.</li> <li>• (3) Increase viscosity of the cervical mucus making it so viscous → no sperm pass. <b>movement of sperm is difficult and slow so it will not reach to the ovum &gt; no fertilization</b></li> <li>• (4) Abnormal transport time through the fallopian tubes. <b>ovum move very slow from ovary to the Fallopian tube so sperm will wait for longer period &amp; degradation and death of the sperm</b></li> </ul>	
Admin.	<p style="text-align: center;"><b>Monthly Pills</b></p> <ul style="list-style-type: none"> <li>• Pills are better taken at the same time of day.</li> <li>• has 2 preparations: 21 day, 28 day</li> <li>• For <b>21 days</b>: starting on day 5<sup>2</sup> of the cycle / ending at day 26<sup>3</sup>. <b>taking every day at the same time</b></li> <li>• This is followed by a <b>7 day pill free period. not taking any pills</b></li> <li>• <b>To improve compliance we use a formulation of 28 pills:</b> <ul style="list-style-type: none"> <li>○ The <b>The first 21 pills are medicated</b> multiphasic formulation.</li> <li>○ Followed by the <b>last 7 pills (dummy pills)</b>. actually placebo.</li> </ul> </li> </ul>	<p style="text-align: center;"><b>Seasonal Pills</b></p> <ul style="list-style-type: none"> <li>• Are known as Continuous / Extended cycle to <b>cover 91 days schedule</b><sup>4</sup>.</li> <li>★ Taken continuously for 84 days, and then a break for 7 days.</li> <li>• Has very low doses of both estrogens and progestins.</li> <li>★ <b>Advantage:</b> It lessens menstrual periods to 4 times a year (1 period every 3 months), useful in those who have pain from endometriosis and can prevent migraines during period. useful in those who have <b>premenstrual or menstrual disorders</b>, and in perimenopausal<sup>5</sup> women with vasomotor symptoms.</li> <li>• <b>Disadvantages:</b> Higher incidence of breakthrough bleeding &amp; spotting during early use.</li> </ul>
Formulations of Monthly Pills	<ul style="list-style-type: none"> <li>• Currently, the formulation of monthly pills are improved to <b>mimic the natural ongoing changes in hormonal profile</b>.</li> <li>• Accordingly we have now the phase formulations: <ul style="list-style-type: none"> <li><b>1. Monophasic:</b> (a fixed amount of estrogen &amp; progestin <b>throughout the month</b>).</li> <li><b>2. Biphasic:</b> (2 doses) (a fixed amount of estrogen, while the amount of progestin increases stepwise in the second half of the cycle).</li> <li><b>3. Triphasic:</b> (3 doses) (a fixed or variable amount of estrogen &amp; while the amount of progestin increases stepwise in 3 phases).</li> </ul> </li> </ul>	
ADR	<p style="text-align: center;"><b>Estrogen Related</b></p> <ul style="list-style-type: none"> <li>• Nausea &amp; <b>Breast tenderness</b>.</li> <li>• Headache.</li> <li>★ <b>↑ Skin Pigmentation</b><sup>6</sup>. <b>estrogen stimulation of tyrosinase enzyme that produces the melanin</b>, سيب كلف الحمل</li> <li>★ <b>Impair glucose tolerance (hyperglycemia)</b>. C.I in DM (important)</li> <li>★ <b>↑ Incidence of breast, vaginal &amp; cervical cancer</b>. Bc it ↑ cell proliferation</li> <li>★ Cardiovascular - major concern: <ul style="list-style-type: none"> <li>○ <b>Thromboembolism</b><sup>8</sup></li> <li>○ <b>Hypertension</b>.<sup>9</sup></li> </ul> </li> <li>• ↑ Frequency of gallbladder disease.</li> </ul>	<p style="text-align: center;"><b>Progestin Related</b></p> <ul style="list-style-type: none"> <li>• Nausea &amp; Vomiting.</li> <li>• Headache.</li> <li>• Slightly higher failure rate.</li> <li>• Fatigue.</li> <li>★ <b>Depression of mood</b>. low serotonin level</li> <li>★ <b>Menstrual irregularities</b>.</li> <li>★ <b>Weight gain</b><sup>7</sup>. water retention and increase appetite</li> <li>★ <b>Hirsutism</b><sup>7</sup>.</li> <li>★ <b>Masculinization</b><sup>7</sup> (virilization) (<b>Norethindrone</b>).</li> <li>★ <b>Ectopic pregnancy</b>. in Fallopian tube</li> </ul>

**CONTRACEPTIVES:**  
Cancer (cervical, vaginal, breast)  
Oedema (water retention)  
Nausea, vomiting  
Tenderness of breast  
Raised BP  
Acne (masculinization)  
Cardiovascular: estrogen increases LDL  
Elevated blood sugar  
Pigmentation  
Thromboembolism  
Irregular menstrual cycle  
Virilization  
Ectopic pregnancy  
Serotonin deficiency (depression)

1: Normally released by negative feedback induced by low estrogen and progesterone.      2: after menstruation.  
3: to allow for menstruation.  
4: the women will only experience her period once every 3 months (4 times a year).  
5: during which the women experience very heavy periods accompanied by nervousness, mood swings, and other symptoms.  
6: which happens normally during pregnancy due to increased estrogen.  
7: androgenic effect.    8: it is contraindicated in women with varicose veins. 9. It increases hepatic renin-angiotensin

Drug	Combined Oral Contraceptives (COC)
C.I (Of estrogen containing pills)	<ul style="list-style-type: none"> <li>• Thrombophlebitis / thromboembolic disorders.(history of cardiovascular disease).</li> <li>• Chronic Heart Failure (CHF) or other causes of edema.</li> <li>• Vaginal bleeding of undiagnosed etiology<sup>1</sup>.</li> <li>• Known or suspected pregnancy.induce uterus contraction so that causes abortion</li> <li>• Known or suspected breast cancer, or estrogen-dependent neoplasms.</li> <li>• Impaired hepatic functions.(because estrogen may cause autoimmune hepatitis and damage the liver).</li> <li>• Dyslipidemia, diabetes, hypertension, migraine.</li> <li>★ Lactating mothers<sup>2</sup>: estrogen reduces the milk production <ul style="list-style-type: none"> <li>○ Instead, use <b>progestin</b> only pills (mini pills).</li> </ul> </li> <li>★ (Important) strogen CI in Obese female bcs it increases the lipid, smokers<sup>3</sup> risk of cancer, females who <b>are above 35 years</b> high risk of thrombus : <ul style="list-style-type: none"> <li>○ Instead, use <b>progestin</b> only pills.</li> </ul> </li> </ul>
Interactions	<ul style="list-style-type: none"> <li>• <b>Medications that cause contraceptive failure:</b> <ul style="list-style-type: none"> <li>○ Impairing absorption (Antibiotics that interfere with normal GI flora → ↓ absorption and ↓ enterohepatic recycling → ↓ its bioavailability).</li> <li>○ CYT P450 Inducers (Microsomal Enzyme Inducers → ↑ catabolism of OC). <ul style="list-style-type: none"> <li>■ e.g. Phenytoin, Phenobarbitone, Rifampin.</li> </ul> </li> </ul> </li> <li>• <b>Medications that ↑ COC toxicity:</b> <ul style="list-style-type: none"> <li>○ CYT P450 Inhibitors (Microsomal Enzyme Inhibitors → ↓ metabolism of OC → ↑ toxicity). <ul style="list-style-type: none"> <li>■ e.g. Acetaminophen, Erythromycin, SSRIs.</li> </ul> </li> </ul> </li> <li>• <b>Medications that is altered in clearance:</b> <ul style="list-style-type: none"> <li>○ COC decrease the clearance→ ↑ in their toxicity. <ul style="list-style-type: none"> <li>■ e.g. Warfarin, Cyclosporins, Theophylline.</li> </ul> </li> </ul> </li> </ul>

Drug	MINI Pills (POP) <sup>4</sup>
MOA	<ul style="list-style-type: none"> <li>• Contains only a progestin as <b>norethindrone</b> or <b>desogestrel</b>.</li> <li>• The main effect is → ↑ cervical mucus, so <u>no sperm penetration</u> &amp; therefore, <u>no fertilization</u>.effects movement of sperm and no penetration to the ovary and no fertilization</li> </ul>
Admin.	<ul style="list-style-type: none"> <li>• Should be taken <b>every day</b>, the <b>same time</b>, <b>all year round</b><sup>5</sup>.</li> <li>• <b>Oral</b> or I.M injection e.g. medroxyprogesterone acetate 150 mg every 3 months.</li> </ul>
Uses	<ul style="list-style-type: none"> <li>★ 97% effective</li> <li>★ Are <b>alternative when estrogen is contraindicated</b> <ul style="list-style-type: none"> <li>○ During breastfeeding, hypertension, cancer, smokers and/or over the age of 35.</li> </ul> </li> </ul>

Drug	Morning-After Pills
Uses	<ul style="list-style-type: none"> <li>★ <b>Emergency Contraceptives</b> <ul style="list-style-type: none"> <li>• Post Coital Contraceptives.</li> <li>• Contraception on instantaneous demand, secondary to unprotected sexual intercourse and when desirability for avoiding pregnancy is obvious: <ul style="list-style-type: none"> <li>○ Unsuccessful withdrawal before ejaculation.</li> <li>○ Torn, leaking condom.</li> <li>○ Missed pills.</li> <li>○ <b>Exposure to teratogen e.g. Live vaccine.</b></li> <li>○ Rape.</li> </ul> </li> </ul> </li> </ul>

1: due to suspected cancer, estrogen will only help the cancer grow.

2: estrogen decreases lactation.

3: they have increased risk of CVS side effects.

4: less effective than COC.

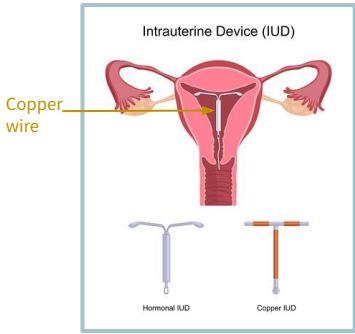

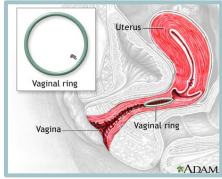
5: for oral preparation.

# Types of Emergency Contraceptives

Either contain both or each alone in high dose or mifepristone ± misoprostol

Composition	Method of Administration	Timing of 1 <sup>st</sup> Dose After Intercourse	Reported Efficacy
Ethinyl estradiol + Levonorgestrel	2 tablets twice with 12 hrs in between	0-72 hrs 0 hrs means immediately after intercourse	75%
Ethinyl estradiol (High-dose only)	Twice daily for 5 days		75-85%
Levonorgestrel (High-dose only)			70-75%
★ Mifepristone (Antiprogestin) ± Misoprostol <sup>1</sup> (Pg <sup>1</sup> synthetic prostaglandin E1 (PGE1) <sup>1</sup> )	A single dose	0-120 hrs	<b>85-100%</b>

## Other Forms of Contraceptives

Form of Contraceptive	Info.	Picture
<b>Intrauterine Device (IUD)</b>	<p>(Can be <u>hormonal</u> or <u>copper IUD</u>),</p> <ol style="list-style-type: none"> <li>Create a foreign body → inflammatory response → lysis of the blastocysts (mature fertilized egg) &amp; lysis of the sperm before reaching the ovum.</li> <li>Stimulate secretion of the prostaglandins → more contractility of the uterus → expelled of ovum rather the implant it.</li> <li>Works as a barrier prevent reaching the sperm to the ovum → prevent the fertilization. <ul style="list-style-type: none"> <li>Copper intrauterine system: <ul style="list-style-type: none"> <li>-T shaped plastic that insert into the uterus.</li> <li>-copper wire produce reaction that is toxic to sperm and ovum.</li> </ul> </li> </ul> </li> </ol>	
<b>Contraceptive Diaphragm</b>	<ol style="list-style-type: none"> <li>Works as a barrier prevent reaching the sperm to the ovum → prevent the fertilization.</li> <li>Can be covered with spermicidals (kill the sperm) → preventing the fertilization.</li> </ol>	
<b>Vaginal Ring</b>	<p>(Made of some hormones),</p> <p>Covered with hormones → prevent the ovulation and implantation at the same time.</p>	

1: Most effective one. They initiate powerful uterine contraction and bleeding.



# Quiz

## MCQ

- Q1: What is the main mechanism of action of progesterone only pills?  
A. Increase cervical mucus    B. Spermicidal    C. Inhibit ovulation    D. Makes sperm immotile
- Q2: Which of the following is a progesterone only pill?  
A. Ethinyl estradiol    B. Levonorgestrel    C. Misoprostol    D. Norethindrone
- Q3: Which of the following morning-after pills is given as a single dose?  
A. Ethinyl estradiol    B. Amitriptyline    C. Misoprostol    D. Norethindrone
- Q4: Which of the following is not an indication for a morning-after pill?  
A. Rape    B. Paracetamol intake    C. Recent Live vaccine    D. Torn condom
- Q5: Which of the following is a spermicidal?  
A. Condom    B. Cervical cap    C. Diaphragm    D. Certain jells
- Q6: Which of the following is a major concern as an adverse effect related to Estrogen?  
A. Menstrual irregularities    B. Cardiovascular problems    C. Headache    D. Hirsutism
- Q7: You use mini pills which contain only progestin with all of the following except?  
A. Obese female    B. Lactating female    C. Female > 35 years    D. Thrombophlebitis
- Q8: Which of the following increase combined pills toxicity by inhibiting microsomal enzymes?  
A. Erythromycin    B. Warfarin    C. Theophylline    D. Ampicillin

## SAQ

- Q1: A 34 years old lactating mother went to the gynecologist for check up, after that the doctor said to her she should use a contraceptive before the sexual intercourse, what's the most appropriate drug that should be given for her status?
- Q2: What's the most appropriate drug when she is Obese female or smokers or female > 35 years?
- Q3: A 32 years old women went to the gynecologist because of ↑ Skin Pigmentation in different areas of her body, the doctor immediately asked her about taken any contraceptives, what's the type of contraceptives that may cause this effect?
- Q4: Mention the Mechanism of action of this drug?
- Q5: Mention ONE indication for MINI pills contraceptives?

### MCQ

Q1	A
Q2	B&D
Q3	C
Q4	B
Q5	D
Q6	B
Q7	D
Q8	A

### SAQ

Q1	Progestin Pills Only (mini pills).
Q2	Progestin Pills Only
Q3	Combined Oral Contraceptive
Q4	<a href="#">Click for answer</a>
Q5	When estrogen is contraindicated

## Answers:

**Thank you for all the love and support you gave the team in those two years!**

**Hope we made the context much easier to study.**

**God bless you, Future doctors.**

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