



## Oral & other forms of contraception

### Objectives:

- **Perceive** the different contraceptive utilities available.
- **Classify** them according to their site and mechanism of action.
- **Justify** the existing hormonal contraceptives present.
- **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.

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**Drug's name** | **Doctors' notes** | **Important** | **Extra**

« قل سيروا في الأرض فانظروا كيف بدأ الخلق »

# Mind Map

## Oral Contraceptive Pills

### Combined pills (coc)

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

**Estrogens + Norgestimate, Desogestrel and Drospirenone**

### Mini pills (pop)

Contain **only** a **progestin** (97% effective)

**Systemic androgenic effect:**  
**Norethindrone, Levonorgestrel and Medroxyprogesterone**

**NO systemic androgenic effect**  
**Norgestimate, Drospirenone and Desogestrel**

### Morning-after pills

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

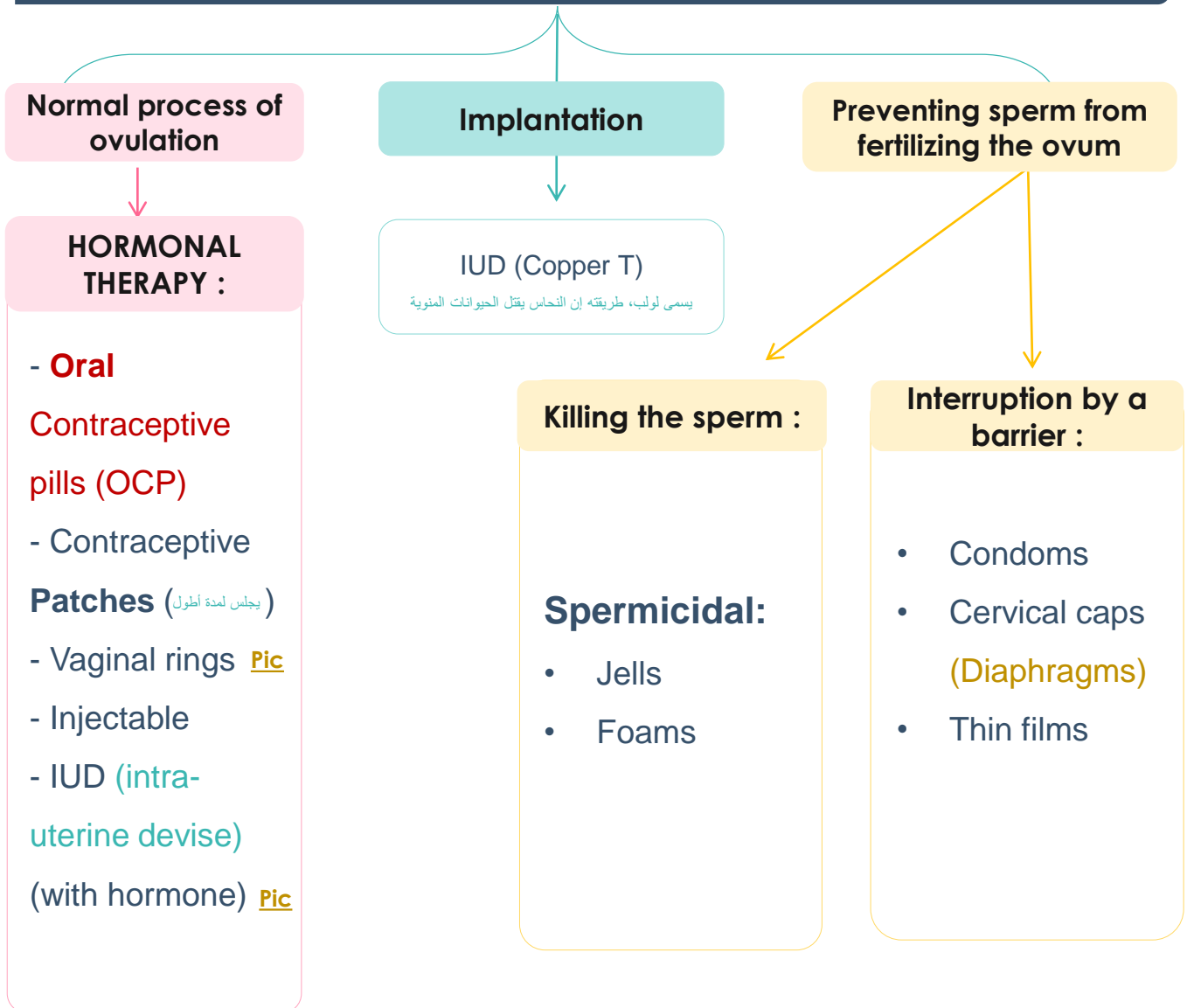


Nice introduction ^^  
4:20 min

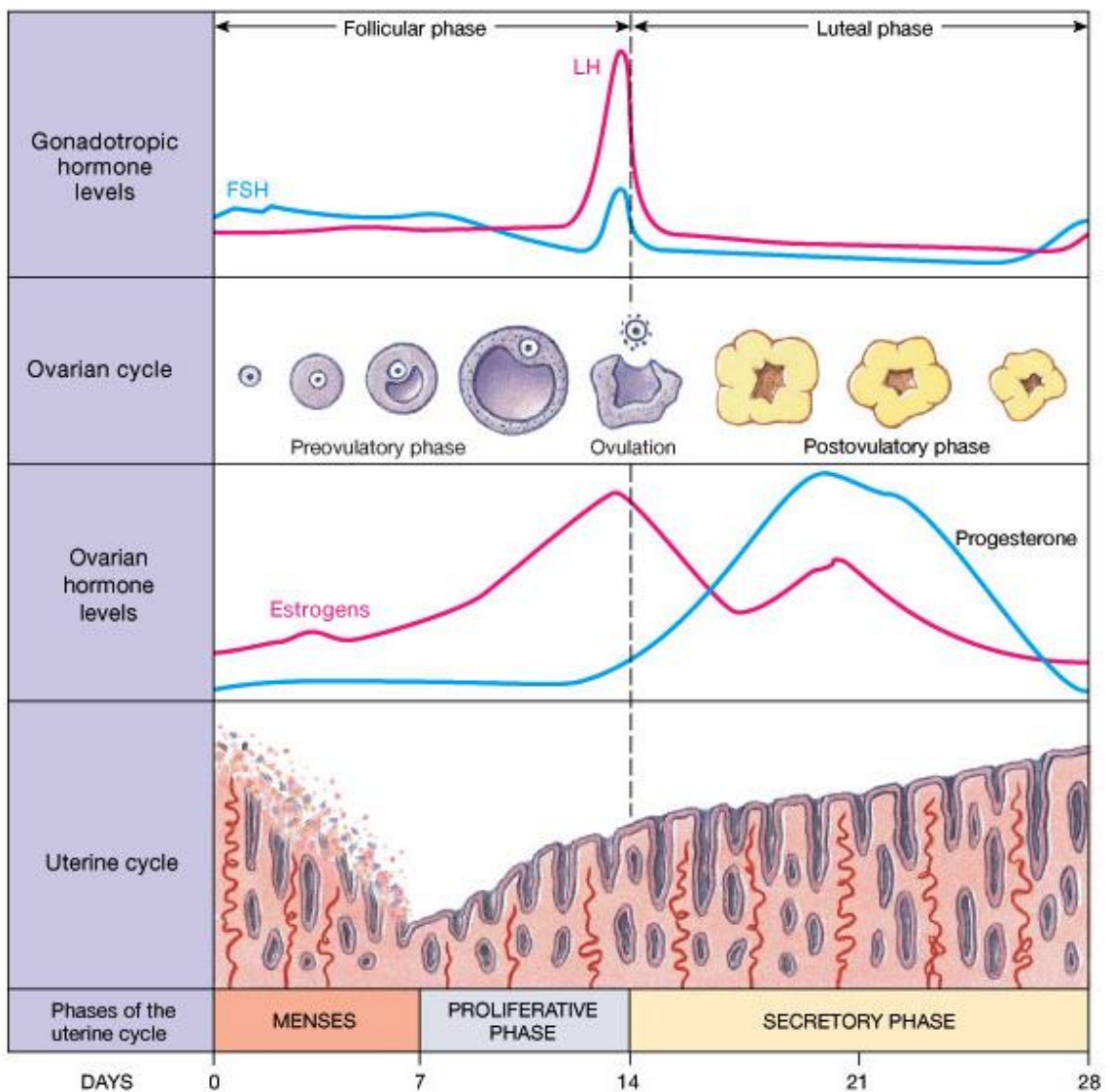
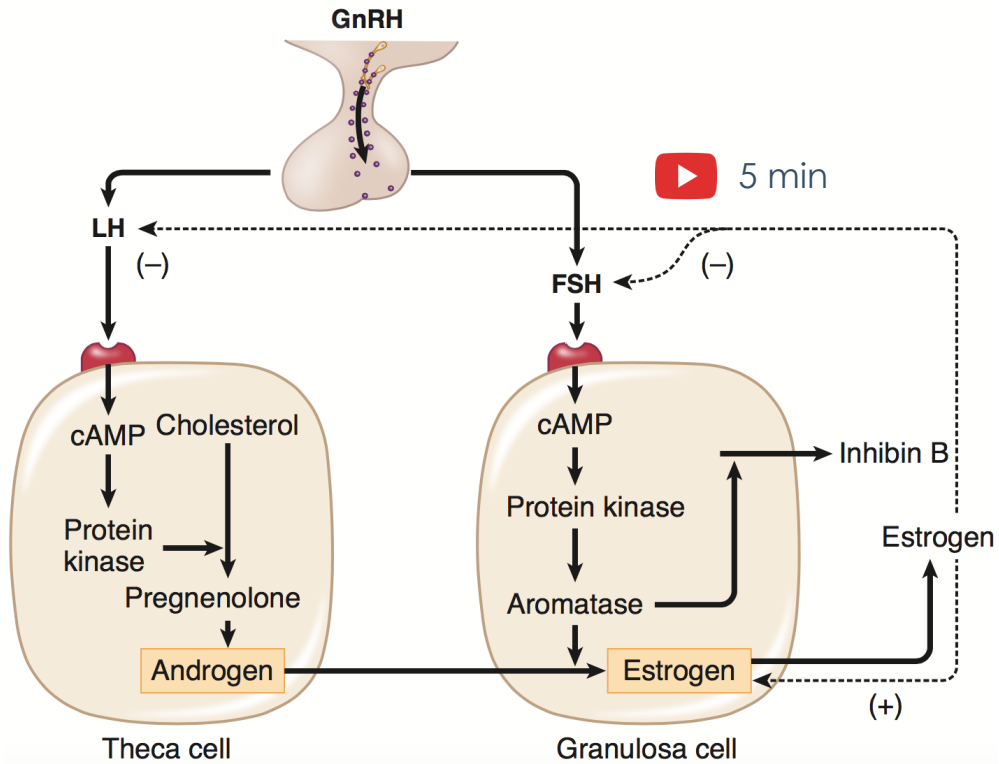
# Definition

Conception	Contraception
Fusion of the sperm & ovum to produce a new organism.	preventing the fusion between the sperm and ovum to occur.

## Contraception can be achieved by interfering with :



# Quick physiological revision



# Oral Contraceptive Pills

## Oral Contraceptive Pills

According to composition & intent of use; OC are divided into three types

### Combined pills (COC)

Contain  
estrogen & progestin  
(100% effective)

من اسمهم (كومبايند) يعني مكونة من  
إستروجين وبروجستين

### Mini pills (pop)

Contain **only** a  
progestin  
(97% effective)

فعاليتها أقل من الكومبايند بشوي

### Morning-after pills

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

Induce abortion

## Combined Pills (COC)

### Progestins

1. Norethindrone
2. Levonorgestrel (Norgestrel)
3. Medroxyprogesterone acetate

→ **Not used anymore** because it has **systemic androgenic effects**:  
**acne, hirsutism, weight gain** (weight gain in all types of oral contraceptives)

1. Norgestimate
2. Desogestrel
3. Drospirenone

#### MCQ:

Which of the following is devoid from systemic androgenic effect?

الإجابة هي واحد من الثلاثة

→ **Currently used** because it has **no systemic androgenic effects**


لأن أكيد مافيش سئة حنّبقى عايزة يطلع لها أكتي وشعر

### Estrogen

Ethinyl estradiol or mestranol [a "prodrug" converted to ethinyl estradiol]

→ **Currently concentration used is very low to minimize estrogen hazards**

# Combined Pills (COC)

<p style="writing-mode: vertical-rl; transform: rotate(180deg);">Mech. of action</p>	<ol style="list-style-type: none"> <li><b>Inhibit Ovulation</b> by Suppressing The Release Of Gonadotrophins (FSH &amp; LH) → no action on the ovary → ovulation is prevented. <b>(the main and most important mechanism)</b>  <small>في الحمل يزيد عندها الإستروجين والبروجستيرون بينما FSH &amp; LH يقلون عشان ما يصير فيه ovulation (بسبب I -ve feedback .. هنا نفس الحالة)</small></li> <li><b>Inhibit IMPLANTATION</b> by causing abnormal contraction of the fallopian tubes &amp; uterine musculature → ovum will be expelled rather than implanted.</li> <li><b>Increase viscosity of the cervical mucus</b> making it so viscous → <b>no sperm pass.</b>  <small>تذكروا في ال luteal phase ال viscosity of cervical mucus (تحت تأثير البروجستيرون غالبًا) لأن وقت الليوتال فيس مو مناسب للسبيرم يدخل ويسوي فرتليزيشن! هنا نفس الميكانيزم صارت.</small></li> <li><b>Abnormal transport time</b> through the fallopian tubes .</li> </ol>	
	<p style="text-align: center;">❖ <b>Monthly Pills:</b></p> <ul style="list-style-type: none"> <li>Pills are better taken at the <b>same time of day.</b> <small>الهدف هو المحافظة على تركيز ثابت في الدم</small></li> <li>For <b>21 days:</b> starting on <b>day 5</b> / ending at day 26. (26-5=21dys)</li> <li>This is followed by a 7 day pill free period (<b>7 days without pills</b>)  <small>يعني تبدأ المرأة تأخذها أثناء الدورة الشهرية حقتها (اليوم الخامس)، ضروري تبدأ قبل ما تخلص دورتها لأن مفعول الدواء ما راح يطلع إلا بعد ٧ أيام، تستمر تأخذها لمدة ٢١ يوم، بعدين توقف لمدة ٧ أيام.. في هذي ال ٧ أيام، راح تنزل عليها الدورة ثانية.. وبعدها تأخذ الدواء وهكذا كل شهر</small></li> <li>❖ <b>To improve compliance: we use a formulation of 28 pills.</b></li> <li>The <b>first 21 pills</b> are of <b>multiphasic formulation (medicated)</b></li> <li>Followed by the last <b>7 placebo pills (dummy pills)</b> (so in this case there is no break , but the last 7 pills have <b>no effect</b>)  <small>في هذا النوع بيصير أخذ الحبوب شهريًا بدون أي أيام بريك زي اللي قبل، واحد من الأهداف إنه يصير أخذ الحبة بموعد ثابت ومنظم طوال الشهر، وتصير الوحدة ما تضيق متى أخذتها وتلخبط موعد أخذ الأدوية.</small></li> </ul> <p> <b>Helpful video</b></p>	<p style="text-align: center;">❖ <b>Seasonal Pills:</b></p> <ul style="list-style-type: none"> <li>Are known as <b>Continuous / Extended cycle</b> → Cover <b>91 days</b> schedule. → cover 3 months, each 3 months she will have 1 period → she will have 4periods\year instead of 12 p\year.</li> <li>Taken continuously for 84 days , and then a <b>break for 7 days.</b></li> <li><b>Has very low doses of both estrogens and progestins</b></li> <li>❖ <b>Benefit:</b> It lessens menstrual periods to <b>4 times a year</b> → <b>useful in those who have pre - menstrual or menstrual disorders</b>, and in <b>perimenopausal women</b> with vasomotor symptoms on pill free days  <small>يعني هي تنظم الدورة، لأن المرأة ال pre &amp; peri-menopausal تصير الدورة متخصصة عندها وكل شوي تجي وتضايقها Useful in those who have pain from endometriosis and can prevent migrains during period.</small></li> <li>❖ <b>Disadvantages:</b> Higher incidence of <b>breakthrough bleeding &amp; spotting</b> during early use.</li> </ul>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">Phase Formulation</p>	<p>Currently, the formulation of <b>monthly pills</b> are improved to mimic the <u>natural</u> on going changes in hormonal profile.</p> <p>❖ Accordingly we have now the phase formulations:</p> <ol style="list-style-type: none"> <li><b>Monophasic</b> → (a <b>fixed amount</b> of <b>estrogen &amp; progestin</b>) <small>كلهم ثابتين</small></li> <li><b>Biphasic</b> (2 doses) →(a <b>fixed amount</b> of <b>estrogen</b>, while the amount of <b>progestin increases stepwise in the second half</b> of the cycle) <small>الإستروجين ثابت، البروجستيرون متغير</small></li> <li><b>Triphasic</b> (3 doses) →(amount of <b>estrogen; fixed or variable</b> &amp; amount of <b>progestin increases stepwise in 3 phases</b>). <small>الإستروجين ثابت أو متغير ، البروجستيرون متغير</small></li> </ol> <p><small>هنا لما نستخدم الإستروجين، نستخدمه على شكل Ethinyl estradiol ولما نستخدم البروجستيرون، نستخدم وحدة من ال formulas المذكورة في السلايد السابق</small></p> <p><b>(2<sup>nd</sup> and 3<sup>rd</sup> mimics the real cycle)</b></p>	

الدكتورة قالت ما راح أسألكم عن هذي التفاصيل

# Combined Pills (COC) (cont.)

- ❖ All you have to know from the tables:
- ✓ the Biphasic and Triphasic tablets have a **stepwise increase in the concentration of Progestin** (twice in Biphasic , and 3 times in Triphasic)

الجدول بس لتوضيح المفهوم حق المونو والباي والترايفيزك، لا تضيعون وقتكم عليه + نلاحظ ان الأستروجين غالبًا قليل عشان نقتلل أعراضه الجانبية

1				2			
Monophasic combination tablets		Estrogen (mg)	Progestin (mg)	Triphasic combination tablets		Estrogen (mg)	Progestin (mg)
Loestrin 21 1/20	Ethinyl estradiol	0.02	Norethindrone acetate	1.0	Triphasil, Tri-Levlen, Trivora		
Desogen, Apri, Ortho-Cept	Ethinyl estradiol	0.03	Desogestrel	0.15	Days 1—6	Ethinyl estradiol	0.03
Brevicon, Modicon, Necon 0.5/35	Ethinyl estradiol	0.035	Norethindrone	0.5	Days 7—11	Ethinyl estradiol	0.04
Demulen 1/35	Ethinyl estradiol	0.035	Ethinodiol diacetate	1.0	Days 12—21	Ethinyl estradiol	0.03
Nelova 1/35 E, Ortho-Novum 1/35	Ethinyl estradiol	0.035	Norethindrone	1.0	Ortho-Novum 7/7/7, Necon 7/7/7		
Ovcon 35	Ethinyl estradiol	0.035	Norethindrone	0.4	Days 1—7	Ethinyl estradiol	0.035
Demulen 1/50	Ethinyl estradiol	0.05	Ethinodiol diacetate	1.0	Days 8—14	Ethinyl estradiol	0.035
Ovcon 50	Ethinyl estradiol	0.05	Norethindrone	1.0	Days 15—21	Ethinyl estradiol	0.035
Ovral-28	Ethinyl estradiol	0.05	D,L-Norgestrel	0.5	Ortho-Tri-Cyclen		
Norinyl 1/50, Ortho-Novum 1/50	Mestranol	0.05	Norethindrone	1.0	Days 1—7	Ethinyl estradiol	0.035
<b>Biphasic combination tablets</b>				2			
Jenest-28, Ortho-Novum 10/11, Necon 10/11, Nelova 10/11					Days 1—7	Ethinyl estradiol	0.035
Days 1—10	Ethinyl estradiol	0.035	Norethindrone	0.5	Days 8—14	Ethinyl estradiol	0.035
Days 11—21	Ethinyl estradiol	0.035	Norethindrone	1.0	Days 15—21	Ethinyl estradiol	0.035

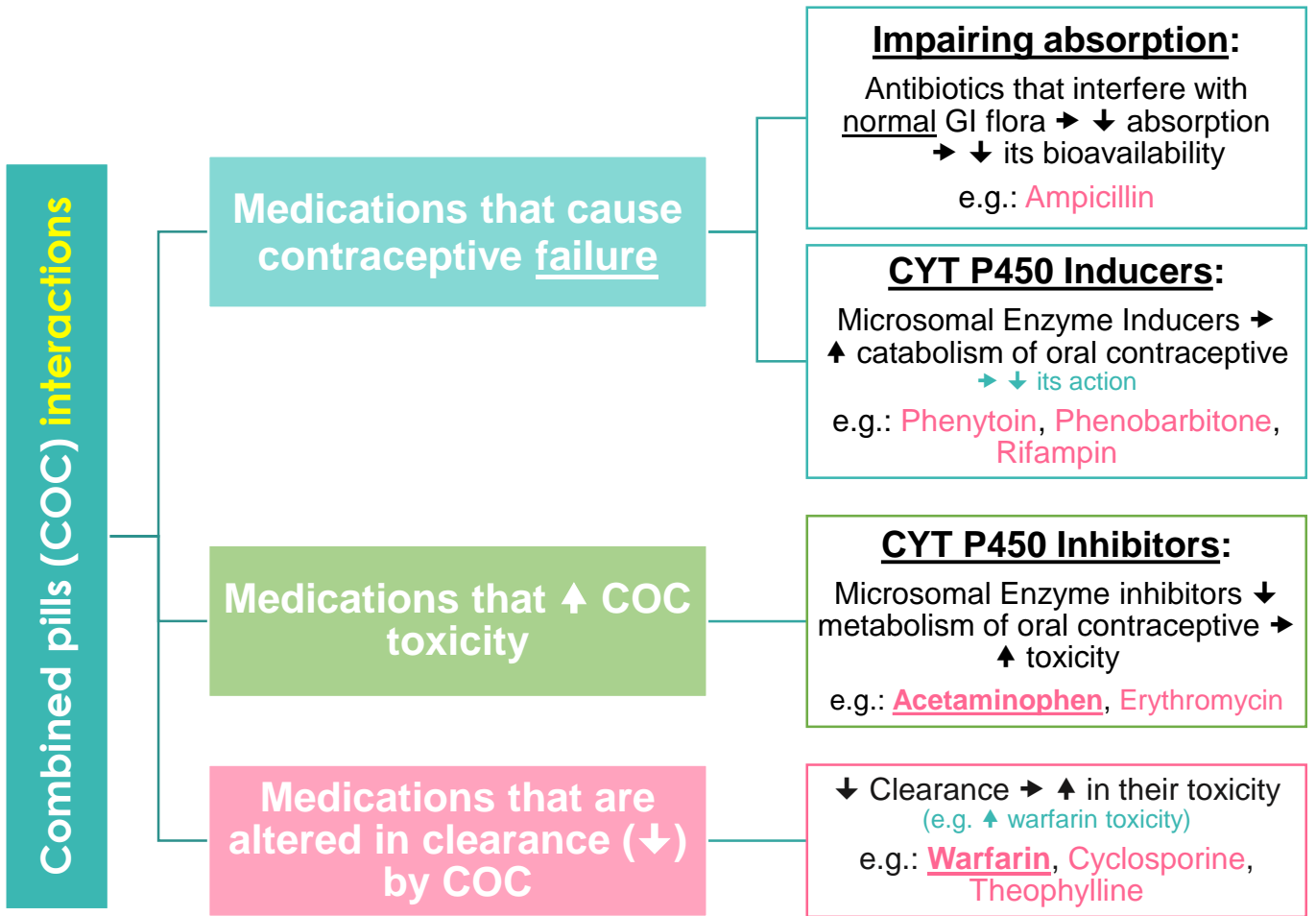
ADRS	Estrogen Related	Progestin Related:
	<ol style="list-style-type: none"> <li>1. Nausea and breast tenderness.</li> <li>2. Headache .</li> <li>3. ↑ Skin Pigmentation <small>”الكلف” ويطلع أثناء الحمل ويسمى “كلف الحمل” (البقع السوداء)</small></li> <li>4. <b>Impaired glucose tolerance (hyperglycemia)</b></li> <li>5. ↑ incidence of breast, vaginal &amp; cervical cancer. <small>عشان كذا يفضل إنه يؤخذ مع البروجستين عشان يقلل الكانسر إفكت</small></li> <li>6. Cardiovascular: (major concern) <ol style="list-style-type: none"> <li>a. <b>Thromboembolism</b></li> <li>b. <b>Hypertension</b></li> </ol> </li> <li>7. ↑ frequency of <b>gall bladder</b> disease</li> </ol>	<ol style="list-style-type: none"> <li>1. Nausea, vomiting &amp; headache</li> <li>2. Slightly higher failure rate.</li> <li>3. Fatigue, <b>depression of mood</b></li> <li>4. Menstrual irregularities</li> <li>5. <b>Weight gain</b> <small>Progestin causes weight gain, why use it with obese women? Estrogen causes increased risk of developing cancer in obese women up to 2-4 times</small></li> <li>6. <b>Hirsutism</b> .</li> <li>7. <b>Masculinization (Norethindrone)</b></li> <li>8. <b>Ectopic pregnancy.</b></li> </ol>

CI	Contraindications of <b>Estrogen</b> containing pills:
	<ul style="list-style-type: none"> <li>❖ <b>Contraindications of Estrogen containing pills:</b></li> <li>1. <b>Thrombophlebitis / thromboembolic disorders</b> (Estrogens enhance the coagulability of blood)</li> <li>2. CHF or other causes of edema</li> <li>3. <b>Vaginal bleeding of undiagnosed etiology</b> (fear of neoplasm)</li> <li>4. Known or suspected <b>pregnancy</b> (it may cause <b>miscarriage</b>)</li> <li>5. Known or suspected <b>breast cancer</b>, or estrogen-dependent neoplasms</li> <li>6. Impaired hepatic functions</li> <li>7. <b>Dyslipidemia*</b>, <b>diabetes</b>, <b>hypertension</b>, <b>migraine</b>. (* bc of increase triglyceride by estrogen, Estrogens decrease hepatic oxidation of adipose tissue lipid to ketones and increase synthesis of triglycerides.)</li> </ul>

You use **Mini pills** (which contain **only progestin**) with 4 types of females:

- ✓ **Lactating mothers** (nursing women)
- ✓ **Obese**
- ✓ **Smokers.**
- ✓ **Females > 35 years.**

# Combined Pills (COC) (cont.)



## Mini pills (POP)

Contain only a progestin (97% effective)

Drug	Norethindrone, Levonorgestrel & Medroxyprogesterone	Norgestimate, Drospirenone & Desogestrel
MOA	○ The main effect is <b>increasing cervical mucus</b> , so no sperm penetration and therefore, <b>no fertilization</b> .	
P.K	○ Contraceptives containing only a progestin should be taken <b>every day, the same time, all year round</b> . ○ I.M injections e.g. <b>medroxyprogesterone acetate 150 mg every 3 months</b> . <i>هذي للناس اللي ممكن ينسون أو ما يلتزمون بالجرعة يوميًا بنفس الوقت، ياخذون ال IM inection كل ٣ شهور أريح لهم</i>	
Uses	○ Alternative <b>when estrogen is contraindicated</b> (during <b>breast feeding</b> , hypertension, cancer, smokers over the age of 35) <i>نفس اللي قلناهم في السلايد السابق</i>	
ADRs	○ It has <b>systemic androgenic effect: acne, hirsutism, and weight gain</b> .	○ Has <b>No systemic androgenic effect</b>



# Morning-after pills

## Indications

- ❖ Contraception on instantaneous demand, 2ndry to unprotected sexual intercourse.
- ❖ When desirability for avoiding pregnancy is **obvious**: (emergency contraception and post-coital (after the sexual intercourse) contraception)
  - Unsuccessful withdrawal before ejaculation.
  - Torn, leaking condom.
  - Missed pills.
  - **Exposure to teratogen e.g live vaccine.** جاء سؤال السنة الماضية عن هذي النقطة
  - Rape اغتصاب
- They may cause nausea & vomiting → we may add anti-emetic with it.

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- 72hrs	75%
High-dose only Ethinyl estradiol	Twice daily For 5 days	0- 72hrs	75 - 85%
High dose <u>only</u> levonorgestrel	Twice daily For 5 days	0- 72hrs	70 – 75%
<b>Mifepristone<sup>1</sup> ± Misoprostol<sup>2</sup></b> (Used to induce abortion)	<b>A <u>single</u> dose</b>	<b>0- 120 hrs</b>	<b>85 - 100%</b>

<sup>1</sup> Mifepristone is a synthetic steroid with **antiprogestational** effects indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

<sup>2</sup> Misoprostol is a prostaglandin E1 (PGE1) analogue.

# Summary-1

estrogens		Progestin's				
Ethinyl estradiol or mestranol (a prodrug converted to ethinyl estradiol)		Has systemic androgenic effect; acne, hirsutism, weight gain.		Has no systemic androgenic effect		
		<ul style="list-style-type: none"> <li>Norrthindrone</li> <li>Levonorgestrel (norgestrel)</li> <li>Medroxyprogesterone acetate</li> </ul>		Currently: <ul style="list-style-type: none"> <li>Norgestimate.</li> <li>Desogestrel</li> <li>Drospirenone.</li> </ul>		
Drug	<b>Combined pills (COC)</b> Contains <b>estrogen &amp; progestin</b> (100% effective)		<b>Mini pills (POP),</b> contains only a <b>progestin</b> (97% effective)	<b>Morning-after pills</b> Contain both hormones or each one alone ( <b>high dose</b> ) or <b>Mifepristone ± misoprostol</b> )		
Mech. of action	<ol style="list-style-type: none"> <li>Inhibits ovulation by suppressing the release of gonadotrophins (FSH &amp; LH) &gt; no action on the ovary &gt; ovulation is prevented.</li> <li>Inhibits implantation by causing abnormal contraction of the fallopian tubes and uterine musculature &gt; ovum will be expelled rather than implanted.</li> <li>Increase viscosity of the cervical mucus making it so viscous &gt; no sperm pass.</li> <li>Abnormal transport time through the fallopian tubes.</li> </ol>		Contains only progestin > as <b>norethindrone</b> or <b>desogestrel</b> ....  The main effect is increase cervical mucus, so no sperm penetration and therefore, no fertilization.	Emergency contraception, post coital contraception. Contraception of instantaneous demand, 2ry to unprotected sexual intercourse.		
				composition		
Ethinyl estradiol + levonorgestrel	High dose only ethinyl estradiol	<b>Mifepristone</b> + <b>misoprostol</b>				
P.K	Pills are better taken same time of day. For 21 days starting on day 5 ending at day 26. this is followed by 7 day pill free period.  <b>TO IMPROVE COMPLIANCE:</b> The first 21 pills are of multiphasic formulation followed by the last 7 pills are actually placebo.		Should be taken every day, the same time, all year round. I.M injection e.g. <b>medroxy progesterone</b> acetate 150 mg every 3 months.	-		
Indications	<b>Seasonal pills</b>	<b>monthly pills</b>	Are alternative when estrogen is contraindicated (e.g.; during breast feeding, hypertension, cancer, smokers over the age of 35)	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>		

## Combined pills (COC)

Drug	Seasonal pills		Monthly pills				
Mech. of action	- Knows as continuous/extended cycle > cover 91 days schedule taken continuously for 84 days, break for 7 days. - Has very low doses of both estrogens and progestin's.		Currently, their formulation is improved to mimic the natural on going changes in hormonal profile.				
	benefit		disadvantages		Accordingly we have now the phase formulations:		
	It lessens menstrual period to 4 times a year > useful in those who have pre-menstrual disorders, and in peri-menopausal women with vasomotor symptoms		Higher incidence of breakthrough bleeding and spotting during early use.		1-monophasic	2-biphasic	3-triphasic
				A fixed amount of estrogen and progestin.	2 doses> a fixed amount of estrogen while amount of progestin increases stepwise in the second half of the cycle.	3 doses>amount of estrogen; fixed or variable and amount of progestin increases stepwise in 3 phases.	

# Summary-2

## Combined pills (COC) (cont.)

<b>ADRs</b>	<b>Estrogen related</b>	<ol style="list-style-type: none"> <li>1. Nausea and breast tenderness.</li> <li>2. Headache.</li> <li>3. Increase skin pigmentation.</li> <li>4. <b>Impair glucose tolerance (hyperglycemia)</b></li> <li>5. Increase incidence of breast, vaginal and cervical cancer.</li> <li>6. CVS- major concern. (thromboembolism and hypertension)</li> <li>7. Increase frequency of gall bladder disease.</li> </ol>
	<b>Progestin related</b>	<ol style="list-style-type: none"> <li>1. Nausea, vomiting and headache.</li> <li>2. Slightly higher failure rate.</li> <li>3. Fatigue, depression of mood.</li> <li>4. Menstrual irregularities.</li> <li>5. Weight gain.</li> <li>6. Hirsutism.</li> <li>7. Masculinization (<b>Norethindrone</b>)</li> <li>8. Ectopic pregnancy.</li> </ol>
<b>contraindication</b>	<b>Of <u>estrogen</u> containing pills</b>	<ol style="list-style-type: none"> <li>1. Thrombophlebitis / thromboembolic disorders.</li> <li>2. CHF or other causes of edema.</li> <li>3. Vaginal bleeding of undiagnosed etiology.</li> <li>4. Known or suspected breast cancer, or estrogen-dependent neoplasms.</li> <li>5. Impaired hepatic functions.</li> <li>6. Dyslipidemia, diabetes, hypertension, migraine.....</li> <li>7. Lactating mothers – use <b>progestin</b> – only pills (mini pills)</li> </ol> <p>N.B. <b>obese females, smokers, females &gt; 35 years.</b> Better given <b>progestin</b> only pills.</p>

## Combined pills (COC) - interactions

<b>Medications that cause contraceptive failure</b>		<b>Medications that increase COC toxicity</b>	<b>Medications that is altered in clearance by COC</b>
<b>1-Impairing absorption</b>	<b>2-CYT P450 inducers</b>	<b>CYT P450 inhibitors</b>	
<ul style="list-style-type: none"> <li>• Antibiotics that interfere with normal GI flora &gt; decrease absorption &gt; decrease its bioavailability.</li> <li>• Microsomal enzyme inducers &gt; increase catabolism of OC e.g.: <b>phenytoin, phenobarbitone, rifampin.</b></li> </ul>		<p>Microsomal enzyme inhibitors; decrease of OC &gt; increase toxicity e.g.:</p> <p><b>acetaminophen, erythromycin.</b></p>	<p>Increase in their toxicity.</p> <p><b>Warfarin, cyclosporine, theophylline.</b></p>

# MCQs

**1- The toxicity of combined pills can be increased by:**

- A. Sildenafil
- B. CYT P450 inducers
- C. CYT P450 inhibitors
- D. Carbamazepine

**2- In combined pills, which of the following is a major side effect related to estrogen?**

- A. Nausea
- B. Cardiovascular disease
- C. Breast tenderness
- D. Headache

**3- A woman had an unprotected sexual intercourse, she remembered after 4 days that she didn't take any oral contraceptive, what's the best drug for her situation?**

- A. Ethinyl estadiol + Levonorgestrel.
- B. High-dose Ethinyl estadiol.
- C. Misoprostol
- D. High dose levonorgestrel

**4- A breast feeding woman was taking oral contraceptives, after few months she noticed some hair growing on her face and acne, which one of the following drugs would cause her symptoms?**

- A. Norethindrone
- B. Drospirenone
- C. Norgestimate
- D. Desogestrel

**5- Select the drug which administered orally causes cervical ripening in pregnant women to facilitate surgical abortion or induction of labour:**

- A. Mifepristone
- B. Raloxifene
- C. Levonorgestrel
- D. Natural progesterone

**6- Mifepristone possesses the following activities:**

- A. Potent anti-progestin + weak androgenic
- B. Potent anti-progestin + weak antigluocorticoid
- C. Potent anti-estrogenic + weak antiprogestin
- D. Potent anti-estrogenic + weak glucocorticoid

**7- Which of the following can act as a single dose postcoital contraceptive:**

- A. Clomiphene citrate
- B. Ethynyl estradiol
- C. Norgestimate
- D. Mifepristone

**8- In which of the following forms of oral contraception, pills are taken continuously without interruption:**

- A. Combined pill
- B. Phased pill
- C. Minipill
- D. Both B & C

**9- Which side effect of the oral contraceptive subsides after 3-4 cycles of continued use:**

- A. Glucose intolerance
- B. Rise in blood pressure
- C. Headache
- D. Fluid retention

**10- Concurrent use of the following drug is likely to cause failure of oral contraception:**

- A. Isoniazid
- B. Rifampicin
- C. Cimetidine
- D. Propranolol

**11- Actions of progesterone include the following except:**

- A. Rise in body temperature
- B. Endometrial proliferation
- C. Proliferation of acini in mammary gland
- D. Suppression of cell mediated immunity

**12- Which of the following is devoid from systemic androgenic effect?**

- A. Norethindrone
- B. Norgestrel
- C. Medroxyprogesterone acetate
- D. Norgestimate

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**Thank you for checking our team!**

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Pharmacology 435

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### **Sources:**

1. 435's slides.
2. Basic & Clinical Pharmacology by Katzung, chapter 40, 12<sup>th</sup> edition.