



Reproductive  
System



**PHARMACOLOGY**  
**432 TEAM**



# PHARMACOLOGY OF CONTRACEPTION

Learning 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

This lecture was done by:

Lama Al-Taweel ,Najoud Al-  
otaibi,Alanoud Al-hokail

And reviewed by:

Alhanouf Aljaser  
Abdullah AlFaifi

Slides

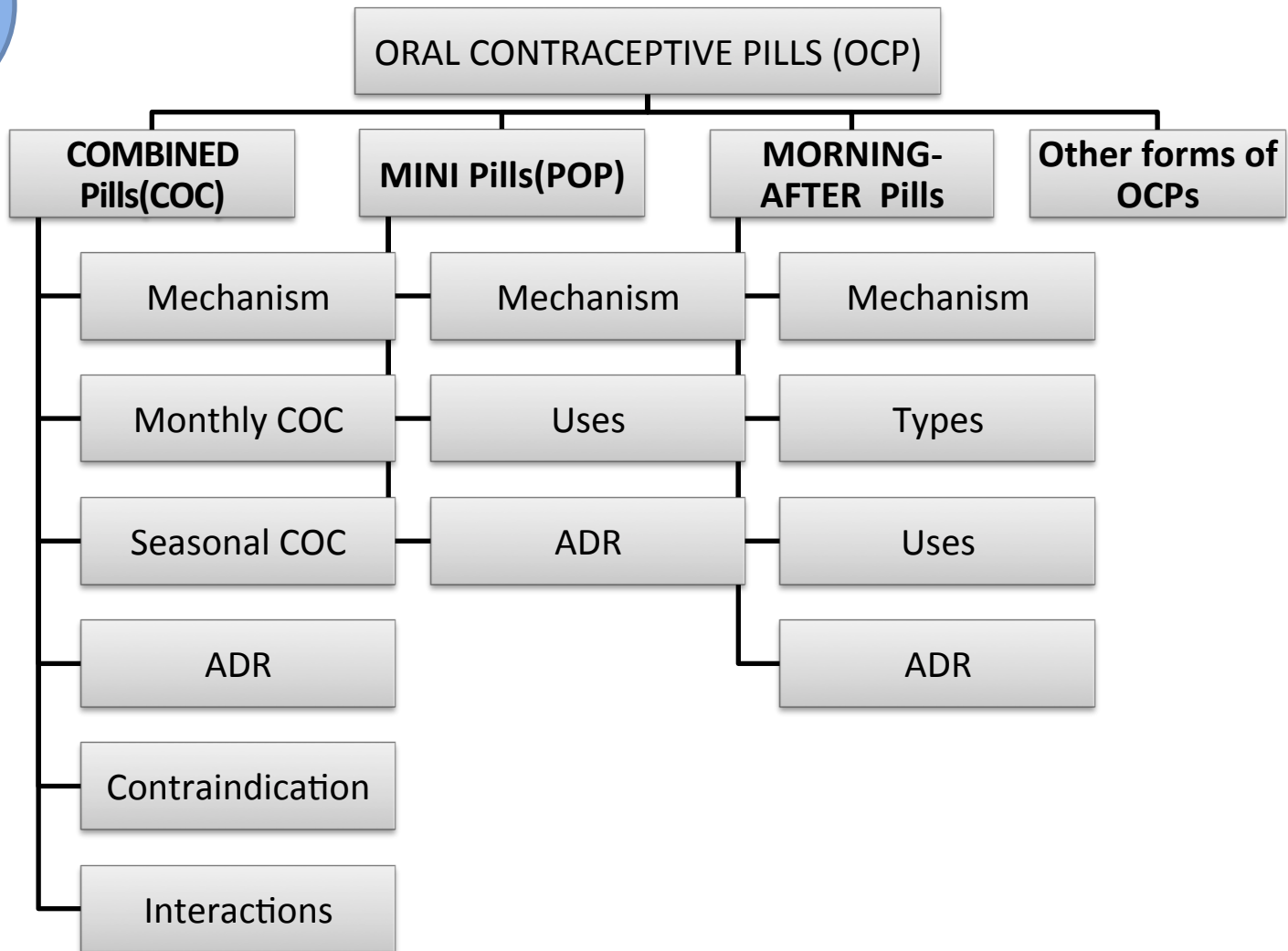
Female side

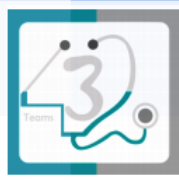
Male side

Explanation



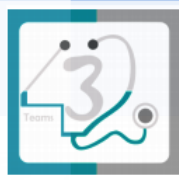
Mind map





- **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 :

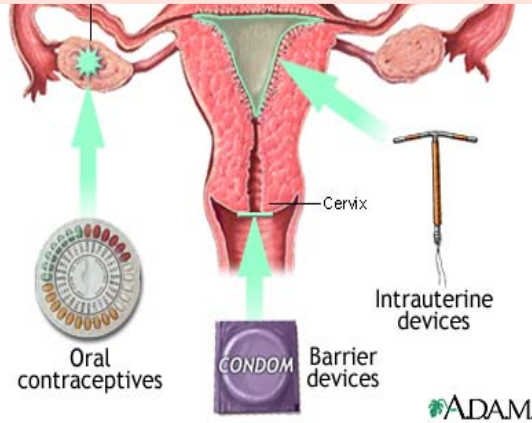
<p><b>1- Normal process of ovulation</b> (HORMONAL THERAPY)</p>	<ul style="list-style-type: none"> <li>• <b>Oral Contraceptives</b> ( most common method)</li> <li>• Contraceptive Patches</li> <li>• Injectable</li> <li>• Implants</li> <li>• Vaginal rings</li> <li>• IUD (with hormone)</li> </ul>	
<p><b>2- Implantation</b> <u>Note</u> : Here fertilization happened but you're preventing the Implantation.</p>	<ul style="list-style-type: none"> <li>• <b>IUD</b> (intra uterine devises) (copper T)</li> </ul>	
<p><b>3- Prevents sperm from fertilizing the ovum</b> <u>Note</u> : normally 90% of the sperm dies in its journey to fertilize the ovum this method further destroy it.</p>	<p><b>A-Killing the sperm:</b></p> <ul style="list-style-type: none"> <li>• Spermicidals</li> <li>• Jells</li> <li>• Foams</li> <li>• Ovules.....</li> </ul>	<p><b>B-Interruption by a barrier:</b></p> <ul style="list-style-type: none"> <li>• Condoms → For Males</li> <li>• Cervical caps</li> <li>• Diaphragms</li> <li>• Thin films</li> </ul> <p style="text-align: right; color: green;">} For Females</p>



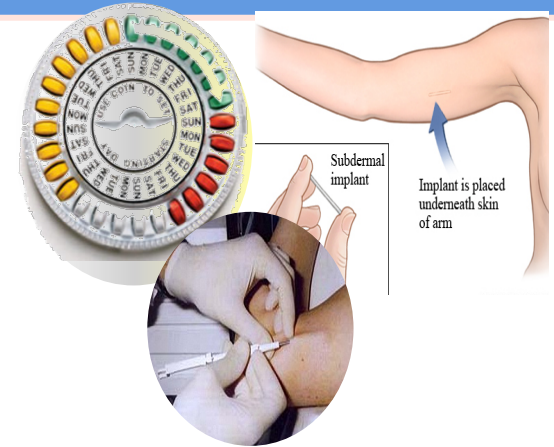
### CONTRACEPTIVE UTILITIES AVAILABLE



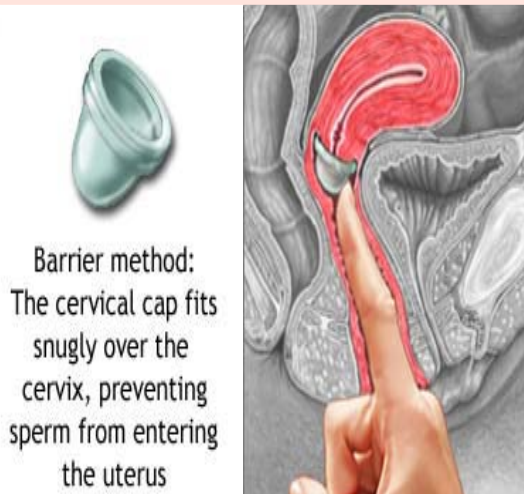
### SITE OF ACTION OF CONTRACEPTIVES



### Interruption of normal process of ovulation

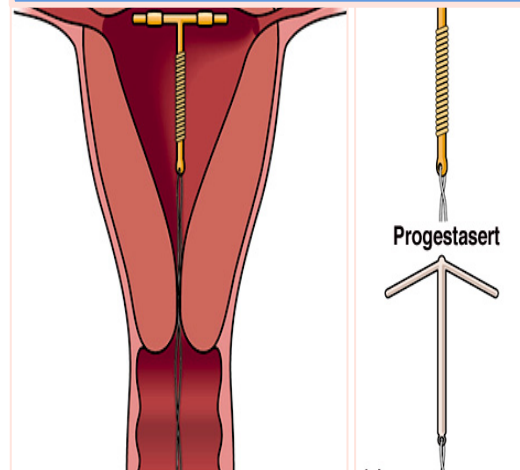


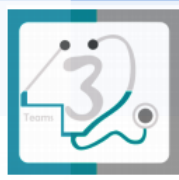
### Interruption by a barrier



Barrier method:  
The cervical cap fits snugly over the cervix, preventing sperm from entering the uterus

### Interruption of Implantation by IUD





# ORAL CONTRACEPTIVE PILLS

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

## **1-COMBINED Pills(COC):**

Contain **estrogens & progestin**

### A-ESTROGENS

Ethinyl estradiol (EE) or mestranol [a “prodrug” converted to ethinyl estradiol]

Currently concentration used now is very low to minimize estrogen hazards

B-PROGESTINS : ( not natural progesterone because 1- very short acting 2- oral route destroys it )

### 1- Old generation

- Norethindrone (oral)
- Levonorgestrel (Norgestrel ) (oral)
- Medroxyprogesterone acetate (IM)

} **Show systemic androgenic effects; acne, hirsutism, weight gain, & deleterious effects on lipid & CHO metabolism.**

### 2- 2nd generation ( currently used)

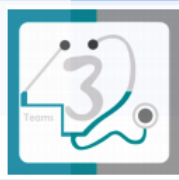
- Norgestimate
- Desogestrel
- Drospirenone

- **All Have no systemic androgenic effects**
- **Drospirenone : Has also anti mineralocorticoid activity ( they have a spironolactone like action ; which antagonizes aldosterone and so the edema side effect wont occur )**

**2-MINI Pills(POP):** Contain only a progestin

## **3-MORNING-AFTER Pills:**

- Contain both hormones
- Each one alone (high dose)
- **Mifepristone + Misoprostol**



# COMBINED Pills [COC]

- by **Preventing OVULATION** by **SUPPRESSING GONADOTROPHINS** → through 2 ways:
- **Inhibit IMPLANTATION** by → ↓ endometrial proliferation → no ovum can be embedded + ↓ secretion & peristalsis in fallopian tubes → hinder transport
  - **Inhibit FERTILIZATION** → ↑ viscosity of cervical secretion → no sperm pass

## MOA:

## Monthly pills:

- **mimic the natural** on going changes in hormonal profile → **PHASE FORMULATIONS**
- **Monophasic** (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)
- **Multiphasic** (fixed amount of estrogen [ or variable] + amount of progestin ↑ [ in second half or 3 successive phases of cycle)
- **Methods of administration:** formulation of **28 pills**
  - Pills are better taken **same time of day**
  - **21 pill** For **21 days**; starting **on day 5** / ending at **day 26**.
  - **This is followed by a 7 day pill free period (placebo) → TO IMPROVE COMPLIANCE**

## Seasonal pills:

- **Continuous / Extended cycle** → Cover 91 days schedule Taken continuously for 84 days, break for 7 days
- **Benefit;** It lessens menstrual periods to **4 times a year'** useful in those who have pre-menstrual or menstrual disorders, and in perimenopausal women with vasomotor symptoms on pill free days.
- **Disadvantages;** Higher incidence of breakthrough bleeding & spotting during early use.

## Indications:

- **As a contraceptive;** In women seeking; a reliable, reversible, coitally-independent method of contraception. **Effective 99%**
- **Other indications:** As a **HRT+ Endometriosis;** specially the extended cycle pills.

# COMBINED Pills [COC]

## Cont.

### ADRs

#### A. Estrogen Related

1. Nausea and breast tenderness
2. Headache
3. **↑ Skin Pigmentation**
4. Impair glucose tolerance
5. **↑ incidence of breast, vaginal & cervical cancer**
6. **Cardiovascular** - major problem
  - a. **Thromboembolism**
  - b. **Hypertension**
7. **↑** frequency of gall bladder disease

#### B. Progestin Related

1. Nausea, vomiting
2. Headache
3. **Fatigue, depression of mood**
4. Menstrual irregularities
5. **Weight gain**
6. **Hirsutism, masculinization**
7. **Ectopic pregnancy.**

### contraindications

- **Thrombophlebitis / thromboembolic disorders**
- CHF or other causes of edema
  - **Vaginal bleeding of undiagnosed etiology**
- Known or suspected **pregnancy**
- Known or suspected **breast cancer, or estrogen-dependent neoplasms**
- Impaired hepatic functions
- **Fibroid tumors – use mini pill**
  - Dyslipidemia, diabetes, hypertension, migraine.....
- **Lactating mothers – use mini pill**
- **N.B. Females that are obese, smokers, Females > 35 years = use mini pill**

### interactions

#### A. Medication that cause contraceptive failure

- **Impairing absorption:**

**Antibiotics** that interfere with normal GI flora → ↓ absorption & ↓ enterohepatic recycling → ↓ its bioavailability

- **CYT P450 Inducers:**

**Microsomal Enzyme Inducers** → ↑ catabolism of OC Phenytoin, Phenobarbitone, Rifampin.

#### B. Medications that ↑ COC toxicity

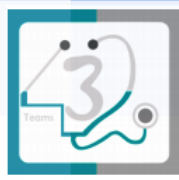
CYT P450 Inhibitors

**Microsomal Enzyme Inhibitors**  
↓ metabolism of OC → ↑ toxicity  
Acetaminophen, Erythromycin, SSRIs

#### C. Medications that is altered in clearance by COC

↑ toxicity

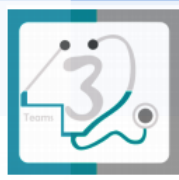
**WARFARIN**, Cyclosporine, Theophylline



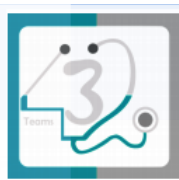
**MINI Pills**  
**Progestin-Only Pills (POP)**

Mechanisms	Indications	Method of administration	ADRs & Contraindications
<p>The main mechanism of action → increase cervical mucous plug → no sperm penetration → <b>inhibit FERTILIZATION</b> .</p>	<ul style="list-style-type: none"> <li>• <b>Are alternative when estrogen is contraindicated</b> specially in cardio-vascular, hepatobiliary, cancer and some metabolic disorders).</li> <li>• Are used with no age limits, in smokers &amp; during lactation.</li> </ul>	<p>Should be taken every day, the same time, better in evenings, all year round</p>	<p><b>That related to progestins only.</b></p>
<p><b>Contains only a progestin</b> as norethindrone or desogestrel....</p>	<p>N.B. They became popular because no worry of estrogenic side effects &amp; are better tolerated</p>	<p>timing is very important in this group</p>	<p><b><u>N.B.</u></b> There is slightly higher contraception failure rates when used.</p>





Mechanisms	Indications	ADRs & Contraindications
<p>Exact mechanism(s) is questionable depending on the time it is taken in relevance to the menstrual cycle.</p>	<p><b>When desirability for avoiding pregnancy is obvious :</b></p> <ul style="list-style-type: none"> <li>➤ Inevitable ↓ efficacy of other forms of contraception:                     <ul style="list-style-type: none"> <li>▪ Unsuccessful withdrawal before ejaculation</li> <li>▪ <b>Torn, leaking condom</b></li> <li>▪ <b>Missed pills</b></li> <li>▪ Detached contraceptive patch.....etc</li> </ul> </li> <li>➤ <b>Medico-legal insult: Rape</b></li> </ul>	<p>Depending on formulations used.</p> <p>If <b>Mifepristone</b> → <b>uterine bleeding</b> could be problematic must be under medical supervision .</p>
<p><b>N.B. Mifepristone</b> → is a <b>competitive progesterone antagonist</b> → luteolytic → abortifaciant → potentiated by addition of <b>Misoprostol</b></p>	<ul style="list-style-type: none"> <li>• <b>Emergency Hormonal Contraception [EHC].</b></li> <li>• <b>Post Coital Contraception.</b></li> </ul>	<p>Contraception on instantaneous demand, 2ndry to unprotected sexual intercourse</p>



MORNING-AFTER Pills

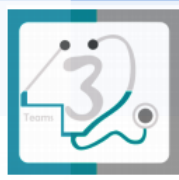
Composition	Method of Administration	Timing of 1st dose After Intercourse	Reported Efficacy (no one going to ask u about this)
Ethinyl estadiol + Levonorgestrel	2 tablets twice with 12 hrs in between	Better within 12 hrs only up to 72hrs	75%
High-dose only Ethinyl estadiol	Twice daily for 5 days	Better within 12 hrs only up to 72hrs	75 - 85%
High dose only levonorgestrel	Twice daily for 5 days	Better within 12 hrs only up to 72hrs	70 – 75%
Mifepristone ± Misoprostol	A single dose ↑Tendency of uterine bleeding.	Within 120 hrs	85 - 100%



Composition	Method of Administration	Timing of 1st dose After Intercourse	Reported Efficacy (no one going to ask u about this)
<b>Patch (Transdermal System)</b>	Like COC, having both hormones	On same day every week for three weeks, 1 week free	99%
<b>Injectable (given IM)</b>	Depot medroxyprogesterone acetate	Every three month	99.7%
<b>Implant ( 6 rods)</b>	Levonorgestrel	Every three –five years	98-99%
<b>Vaginal Ring</b>	Releases a continuous low dose of hormones	Worn for 3 weeks, one week free to get the cycle	85 - 100%
<b>IUR</b>	Levonorgestrel	Regular contraception Worn for 5 years	97%
	Levonorgestrel	For EHC → Worn for a week / within 5 days	

# Summary

- **Oral OC are divided into three types :**
- 1-COMBINED Pills(COC) :**Contain estrogens & progestin**
- 2-MINI Pills(POP):**Contain only a progestin**
- 3-MORNING-AFTER Pills:
  - **Contain both hormones**
  - **Each one alone (high dose)**
  - **Mifepristone + /-Misoprostol**
- **Mini pills** contain only progestin and used when estrogen is contraindicated .
- **Morning after pills** an emergency hormonal contraception. Composed of (progestin +estrogen )or(high dose estrogen only)or (high dose progestin only) or (anti-progestin + prostaglandin analogue)



1. **Which method of these oral contraceptives mimic the natural cycle (period):**
  - A. Monthly pills COC
  - B. Seasonal pills COC
  - C. Morning pills
  - D. Mini pills
  
2. **One of these is a side effect of excess progestin:**
  - A. Skin Pigmentation
  - B. Hirsutism
  - C. Thromboembolism
  - D. incidence of breast cancer

Answers: 1. A 2. B



- 3. MINI Pills (Progestin-Only Pills) work by which one of the following mechanisms :**
  1. Inhibit Implantation
  2. Inhibit Fertilization
  3. increase cervical mucous plug
  4. Both (B-C)
  
- 4. Using Warfarin along with contraceptive pills could lead to:**
  1. Impairing absorption of oral contraceptive pills
  2. Increasing Toxicity by inhibiting CYT P450 enzymes
  3. Decreasing Toxicity by inducing CYT P450 enzymes
  4. Increasing Toxicity by altering the clearance of contraceptive pills
  
- 5. Mifepristone is used when desirability for avoiding pregnancy is obvious, which of the following side effects could accompany the use of Mifepristone :**
  1. Skin Pigmentation
  2. uterine bleeding
  3. Thromboembolism
  4. Weight gain



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**PHARMACOLOGY**  
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**Pharmacology Leaders**

**Tuqa Al-Kaff & Abdullah Al-Anzi**

**Pharmacologyteam1@gmail.com**