

King Saud University
College of Medicine
2nd Year,
Reproduction Block




PHARMACOLOGY
433



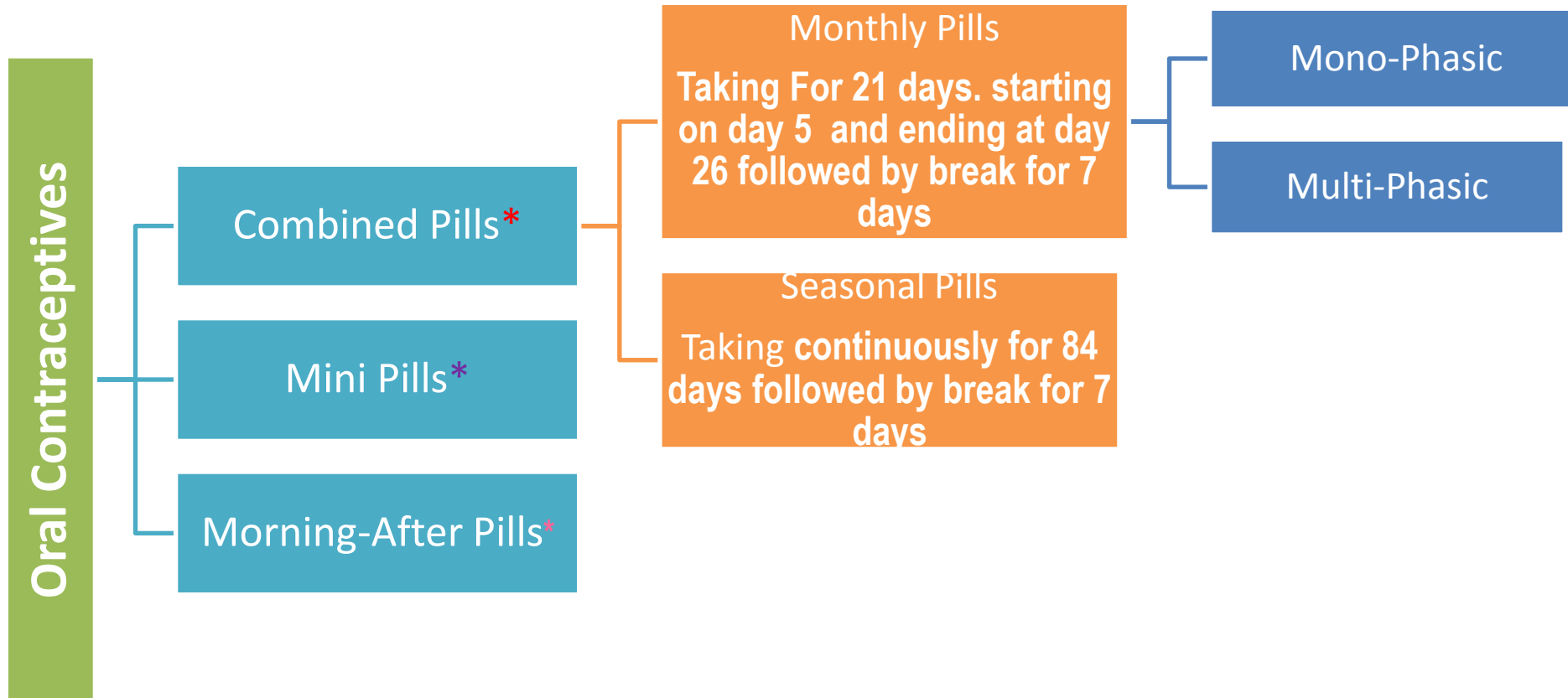
L4- Pharmacology of Contraception

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**

Mind Map



* Have side effects which are related to Estrogen and progesterone together because it is combination between them.

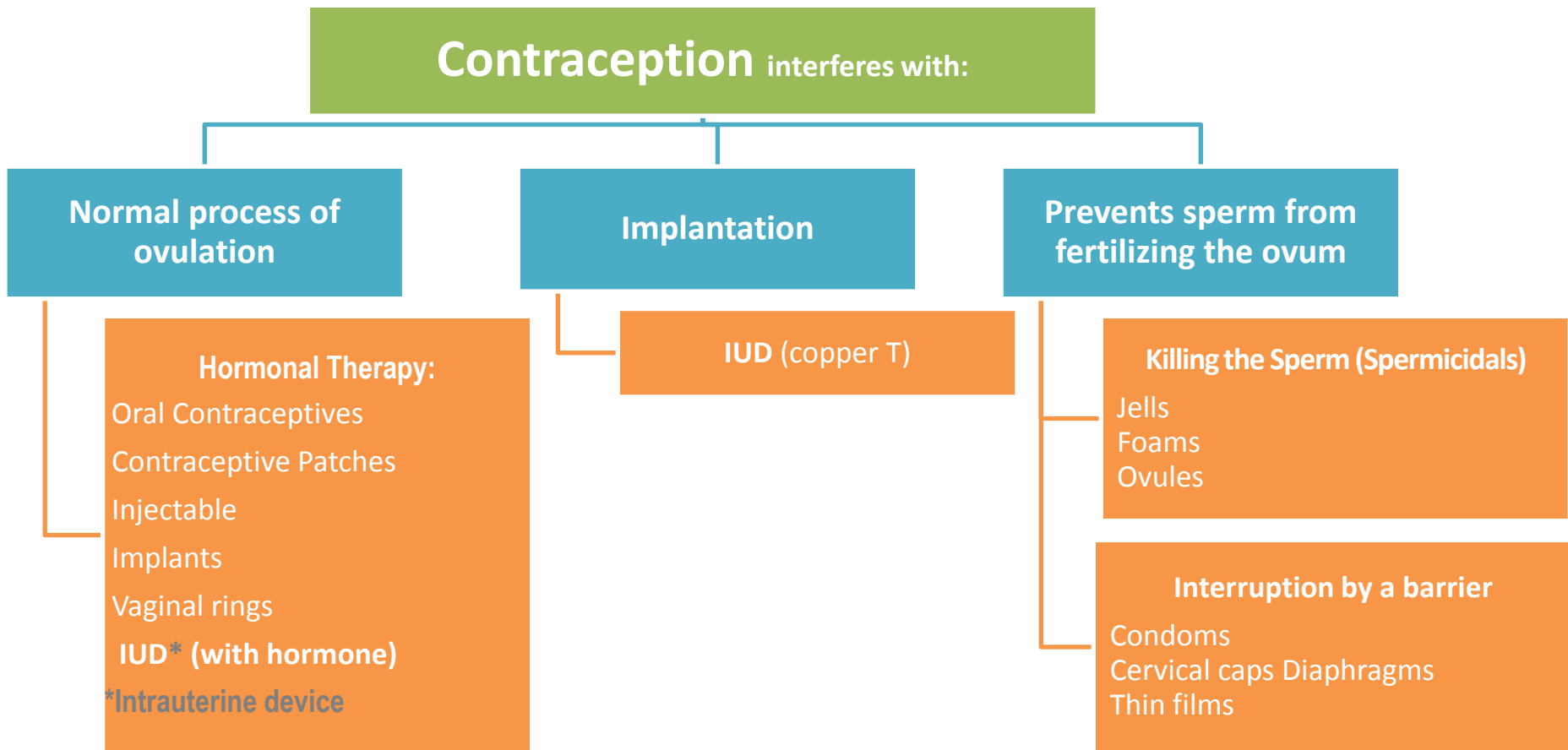
* Have side effects which are related to Progesterone only. + should be taken everyday all year round.

* Contraception on instantaneous demand. 2ndry to unprotected sexual intercourse

Introduction

In Conception: there is fusion of the sperm & ovum to produce a new organism.

In Contraception: we are preventing this fusion to occur.



Types of OC

According to composition & intent of use

Combined Pills (COC)

Contain estrogens & progestin

Mini Pills (POP)

Contain only a progestin

Morning-After Pills

Contain both hormones or each one alone (high dose) or Mifepristone + Misoprostol



Estrogens

• Ethinyl estradiol or mestranol [a “prodrug” converted to ethinyl estradiol].
Currently concentration used now is very low to minimize estrogen hazards. •

Progestins

Norethindrone, Levonorgestrel (Norgestrel), Medroxyprogesterone acetate. •
Show systemic androgenic effects; acne, hirsutism, weight gain, & deleterious •
effects on lipid & CHO metabolism.

Currently

Norgestimate & Desogestrel: has no systemic androgenic effects. •
Drospirenone: has also antimineralocorticoid activity •



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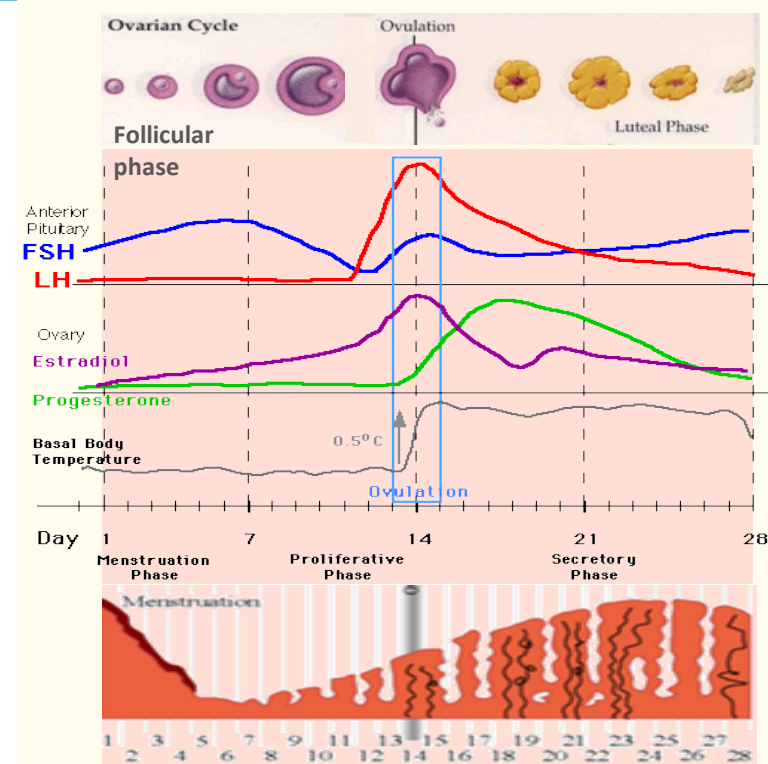
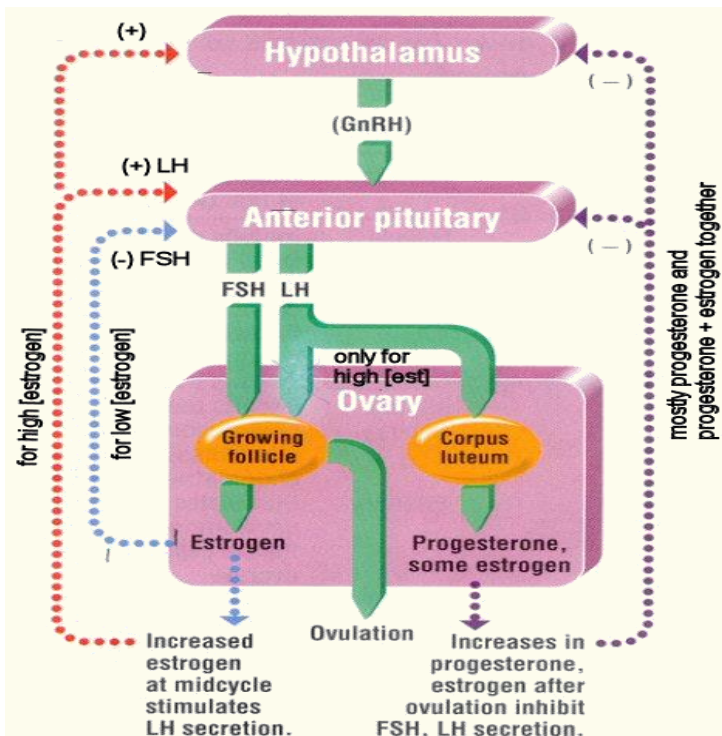
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Combined Pills (COC)

Mechanism of Action of Combined Pills (COC)

COC act mainly by **preventing ovulation** by suppressing the release of gonadotrophins. Yet, by doing so they also:

- **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



Combined Pills (COC)

Monthly Pills

They were essentially designed to mimic the menstrual cycle by producing a monthly withdrawal bleeding.

Formulation

Currently, their formulation were more improved to also mimic the natural on going changes in hormonal profile → **PHASE FORMULATIONS.**

1. **Monophasic** (fixed amount of estrogen & progestin).
2. **Multiphasic** (fixed amount of estrogen (or variable) + amount of progestin ↑↑ (in 2nd half or 3 successive phases of cycle)). (Mimic the natural cycle)

Methods of Administration

- Pills are better taken same time of day.
- For **21 days**; starting on day 5 / ending at day 26.
- This is followed by a **7 day pill free period.**

To Improve Compliance

A formulation of **28 pills**:

- The **first 21 pills** are of **multiphasic formulation.**
- Followed by the **last 7 pills** are actually **placebo.** (contain sugar)

Seasonal Pills

- Are known 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 progestins.
- Also useful in some cases such as anemia, sever cycle pain.

Benefits

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.

Combined Pills (COC)

Indications	<ul style="list-style-type: none"> • As a contraceptive; In women seeking; a reliable, reversible, coitally-independent method of contraception. Efficacy reach up to (99.9%) in preventing pregnancy if a woman is compliant. • Other indications; <ul style="list-style-type: none"> • As a HRT. • Endometriosis; specially the extended cycle pills. 		
Adverse Effects	<table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> A. Estrogen Relate: <ol style="list-style-type: none"> 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 <ul style="list-style-type: none"> • Thromboembolism • Hypertension 7. ↑ frequency of gall bladder disease. </td> <td style="width: 50%; vertical-align: top;"> B. Progestin Related: <ol style="list-style-type: none"> 1. Nausea, vomiting. 2. Headache. 3. Fatigue, depression of mood. 4. Menstrual irregularities. 5. Weight gain. 6. Hirsutism , masculinization. 7. Ectopic pregnancy. </td> </tr> </table>	A. Estrogen Relate: <ol style="list-style-type: none"> 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 <ul style="list-style-type: none"> • Thromboembolism • Hypertension 7. ↑ frequency of gall bladder disease. 	B. Progestin Related: <ol style="list-style-type: none"> 1. Nausea, vomiting. 2. Headache. 3. Fatigue, depression of mood. 4. Menstrual irregularities. 5. Weight gain. 6. Hirsutism , masculinization. 7. Ectopic pregnancy.
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Contraindications	<ul style="list-style-type: none"> • 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 		

Note: Females that are obese, smokers & Females > 35 years are better given the mini pills.

Combined Pills (COC)

Interactions

A. Medications that cause contraceptive failure: (i.e. **impairing absorption & CYT P450 Inducers**)

- Antibiotics that interfere with normal GI flora → ↓absorption & ↓ enterohepatic recycling → ↓ its bioavailability.
- Microsomal Enzyme Inducers → ↑ catabolism of OC. (**Phenytoin , Phenobarbitone, Rifampin**)

B. Medications that ↑ COC toxicity: (i.e. **CYT P450 inhibitors**)

- Microsomal Enzyme Inhibitors; ↓ metabolism of OC → ↑ toxicity. (**Acetaminophen, Erythromycin, SSRIs.**)

C. Medications of altered clearance (↓) by COC: ↑ toxicity

- **WARFARIN, Cyclosporine, Theophylline.**

Mini Pills

Progestin-Only Pills (POP)

Contains only a progestin → as norethindrone or desogestrel....

Mechanisms

- The main mechanism of action:
increase cervical mucous plug → no sperm penetration → **inhibit fertilization.**

Indications

- Are alternative when oestrogen is contraindicated (specially in cardio-vascular, hepatobiliary, cancer and some metabolic disorders)
- Are used with no age limits, in smokers & during lactation.

Methods of Administration

Should be taken **every day**, the **same time**, better **in evenings**, **all year** round.

ADRs & Contraindications

That related to progestins only.

Note:

- They became popular because no worry of estrogenic side effects & are better tolerated.
- There is slightly higher contraception failure rates when used.

Morning-After Pills

Emergency **Hormonal** Contraception [EHC]

- **Post Coital Contraception.**
- 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	Better within 12 hrs only up to 72hrs	75%
High-dose only Ethinyl estadiol	Twice daily for 5 days		75 - 85%
High dose only levonorgestrel			70 – 75%
Ethinyl estadiol + Levonorgestrel	2 tablets twice with 12 hrs in between		75%
Mifepristone ± Misoprostol	A single dose	Within 120 hrs	85 - 100%

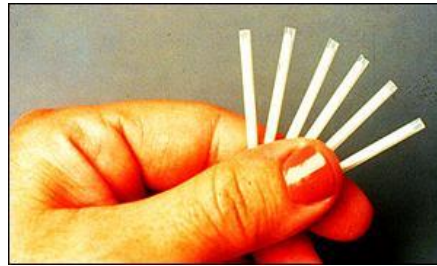
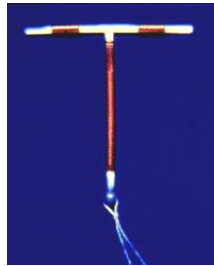
Note: Misoprostole = prostaglandin

Morning-After Pills

Mechanism	<ul style="list-style-type: none">• Exact mechanism(s) is questionable depending on the time it is taken in relevance to the menstrual cycle.• N.B. Mifepristone: is a competitive progesterone antagonist → luteolytic → abortifacient → potentiated by addition of Misoprostol.
Indications	<p>When desirability for avoiding pregnancy is obvious:</p> <p>A. Inevitable \square efficacy of other forms of contraception:</p> <ul style="list-style-type: none">• Unsuccessful withdrawal before ejaculation• Torn, leaking condom• Missed pills• Detached contraceptive patch.....etc <p>B. Medico-legal insult:</p> <ul style="list-style-type: none">• Rape
ADRs	<p>Depending on formulations used.</p> <p>If Mifepristone:</p> <ul style="list-style-type: none">- Uterine bleeding could be problematic.- Must be under medical supervision.

Other Hormonal Contraceptive Modalities

Other Application MODALITIES	Hormonal Content Within	Dosing Frequency	Reported Efficacy
Patch (<i>Transdermal System</i>)	Like COC, having both hormones	On same day every week for three weeks, 1 week free	99%
Injectable (given IM)	Depot medroxyprogesterone acetate	Every three month	99.7%
Implant (6 rods)	Levonorgestrel	Every three –five years	98-99%
Vaginal Ring	Releases a continuous low dose of hormones	Worn for 3 weeks, one week free to get the cycle	85 - 100%
IUR	Levonorgestrel	Regular contraception Worn for 5 years	97%
	Levonorgestrel	For EHC → Worn for a week / within 5 days	



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explanation

SUMMARY

Drug	MOA	Method of administration	ADRs	Contraindications	Interactions
COC (combined pills) (100% effective) Estrogen - Ethinyl estradiol - mestranol (prodrug) Progesterone : -Norgestimate -Desogestrel -Drospirenone	-inhibit ovulation by suppressing the release of gonadotropins (FSH and LH). -Inhibit implantation by causing abnormal contraction of the fallopian tubes & uterine. -Increase viscosity of the cervical mucus making it so viscous → no sperm pass.	For monthly pills : -take it same time of the day. -for 21 days : Start on day 5 stop on day 26 then 7 days free of pills. (to not forget , there are 7 placebo pills taken in this period) ----- ----- for seasonal pills : (91 days) use it continuously for 84 days then stop it for 7 days. Advantage : - 4 menstrual periods annually. -better in women who have pre-menstrual or menstrual disorders and vasomotor symptoms on pill free days. disadvantage : higher incidence of breakthrough bleeding and spotting during pregnancy.	A.Estrogen Related : 1.Nausea , breast tenderness 2. Headache 3. ↑Skin Pigmentation 4. hyperglycemia 5. ↑ incidence of breast, vaginal & cervical cancer. 6.CVS : a. Thromboembolism b. Hypertension 7. ↑ frequency of gall bladder disease ----- - B. Progestin Related : 1. Nausea, vomiting, headache 2. Slightly higher failure rate 3. Fatigue, depression of mood 4. Menstrual irregularities 5. Weight gain 6. Hirsutism 7. Masculinization (Norethindrone) 8. Ectopic pregnancy.	-Thrombophlebitis / thromboembolic disorders - CHF or other causes of edema - Vaginal bleeding of undiagnosed etiology - pregnancy - breast cancer, or estrogen-dependent neoplasms - Impaired hepatic functions -Dyslipidemia, diabetes, hypertension, migraine..... - Lactating mothers – use progestin - only pills(mini pills) (obese , smoker , female>35 = progestin only pills better)	- Medications cause contraceptive failure : 1- Antibiotics that interfere with normal GI flora 2- Microsomal Enzyme Inducers → Phenytoin , Phenobarbitone, Rifampin Medications that increase toxicity Microsomal Enzyme Inhibitors; Acetaminophen, Erythromycin. Medications decreased clearance (↓) by COC; → ↑ in their toxicity : WARFARIN, Cyclosporine, Theophylline

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SUMMARY

Drug	MOA		Method of administration		Indication
MINI Pills (Progestin-Only Pills (POP)) norethindrone desogestrel	increase cervical mucus, so no sperm penetration & therefore, no fertilization.		- should be taken every day at same time during all year . -For. medroxy progesterone acetate , I.M injection , 150 mg every 3 months..		When oestrogen is contraindication : (during breast feeding, hypertension, cancer, smokers over the age of 35) ADRs : that related to Progesterone in previous slide
Morning after pills : (use on instantaneous demand, 2 nd ry to unprotected sexual intercourse)	Composition	Method of Administration	Timing of 1st dose After Intercourse	Reported Efficacy	-Unsuccessful withdrawal before ejaculation -Torn, leaking condom -Missed pills -Exposure to teratogen e.g. Live vaccine -Rape
	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%	ADRs : <u>Mifepristone</u> uterine bleeding could be problematic must be under medical supervision
	High dose only levonorgestrel	Twice daily for 5 days	0- 72hrs	70 – 75%	
	Mifepristone ± Misoprostol	A single dose	0- 120 hrs	85 - 100%	

Quiz yourself



Q1: 39 year old Depressant women was taking Fluoxetine. 6 months ago she start OC. And she developed Thromboembolism. Which of the following is the most likely cause?

- A) Drug toxicity related to Estrogen.
- B) Drug toxicity related to Progesterone.
- C) Drug toxicity related to Fluoxetine.
- D) Old Age complication only.

Q2: A women was using Oral Contraceptives went for regular checkups and found out that she has Ectopic pregnancy. Which of the following is the most likely cause ?

- A) Estrogen.
- B) Mestranol.
- C) Mini Pills.
- D) None of the above.

Q3: 37 year old obese smoker women came to the clinic and asked for Oral contraceptives. Which of the following is the most suitable drug for her ?

- A) Mestranol.
- B) Combined Pills.
- C) Estrogen.
- D) Mini Pills.

Q4: which of the following we should avoid in treating women with Migraine ?

- A) Drospirenone.
- B) Desogestrel
- C) Combined Pills
- D) Mini Pills.

Q5: 38 year old women was on Oral Contraceptives. 6 months later she developed Cervical Cancer. Which of the following is the most likely cause for her cancer ?

- A) Norgestimate.
- B) Drospirenone.
- C) Combined Pills.
- D) Mini Pills.

Q6: Women was taking OC and she developed Nausea, weight gain, depression. Which of the following is the most likely cause ?

- A) Estrogen Side Effect.
- B) Estrogen toxicity.
- C) Mestranol Side Effect.
- D) Mini Pills Side Effect.

Q7: Recently married women went to the doctor and asked for oral contraceptives. She has no CVS abnormalities but she has fibroid tumors. Which of the following OC is suitable for her ?

- A) Combined Pills.
- B) Mini Pills " POP " .
- C) Mestranol.
- D) Estrogen.

Q8: women with Edema and water retention and she want to take contraceptive which of the following is the best for her case ?

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

Answers Q1: A. Q2: C. Q3: D. Q4: C. Q5: C. Q6: D. Q7: B. Q8: B.

Done by



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