



PT 431 Team Pharmacology

Reproductive Block

Lecture 1

Oral and other form of contraception

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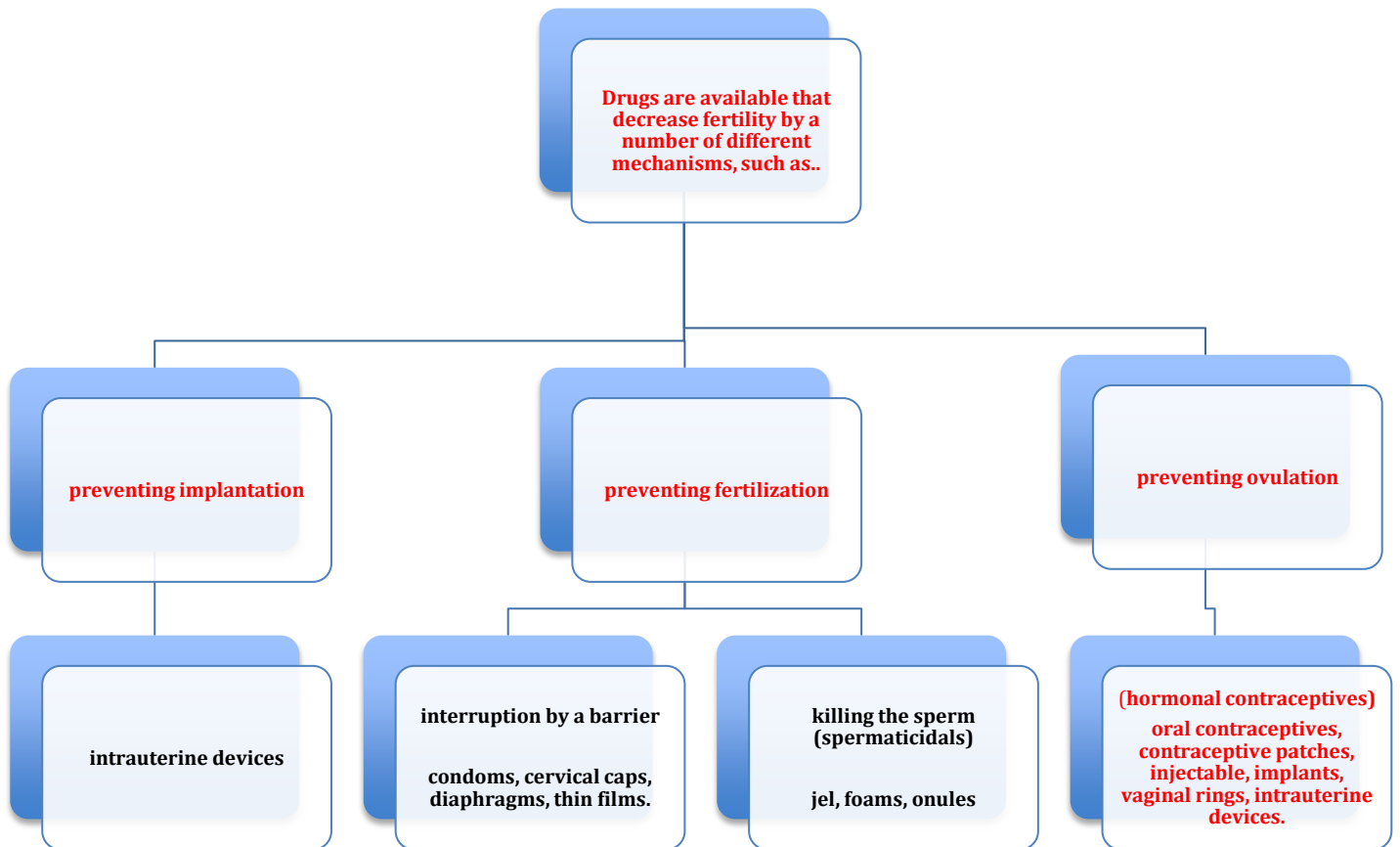


CONTRACEPTION

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

IN CONTRACEPTION → we are preventing this fusion to occur.

How do we achieve contraception pharmacologically...???



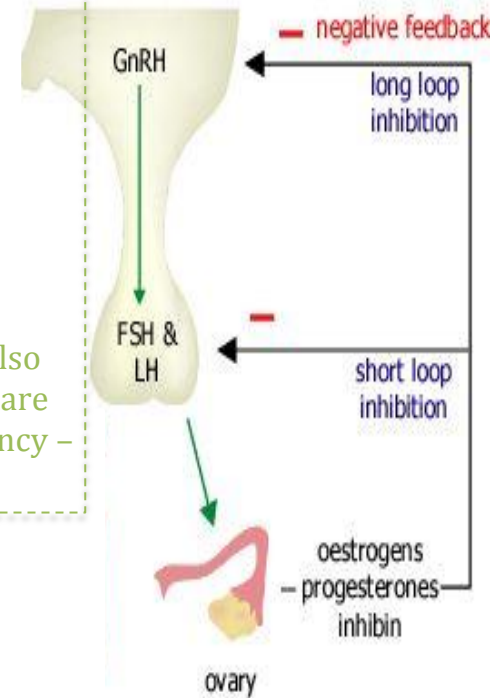
Hormonal contraception:

- hormonal contraception refers to birth control methods that act on the endocrine system.
- there are two main types of hormonal contraceptive formulations:
 - Combined methods :which contain both an estrogen and a progestin,
 - Progestogen-only methods: which contain only progesterone or one of its synthetic analogues (progestins).
- Combined methods work by suppressing ovulation and thickening cervical mucus; while with progestogen-only methods, most of them rely more **heavily on thickening cervical mucus.**

MOA:

The estrogen provide a **negative feedback on the release of LH and FSH by pituitary gland, thus, preventing ovulation.** The progestin also inhibits LH release and thickens cervical mucus, thus hampering the transport of sperm.

Birth control is a way for men and women to prevent pregnancy. There are many different methods of birth control; some types also protect against sexually transmitted diseases or STDs. Condoms are one type of birth control that -- in addition to preventing pregnancy -- also prevent the spread of STDs.



Oral Hormonal contraception:

Classified according to composition and intent of use:

- I- **Combination Oral contraceptives (COC) = combined pills :**
(contain estrogens and progestin)
- II- **Progestin Only Pills. (POP). = mini pills:**
(contain only progestin)
- III- **Postcoital contraception (PCC) = morning after pills = Emergency hormonal contraception = EHC:**
(Contain both hormones or each one alone in high dose or Mifepristone)

Estrogen preparations:

- Ethinyl estradiol
- mestranol

Mestranol: is a "prodrug" converted to ethinyl estradiol in vivo

The estrogen concentration must be kept very low to minimize the side effects & Prevent and lower the chances of having tumors.

Progestins preparations:

Progestin can stimulate both progesterone receptors and androgen receptors.

Non selective:

- Norethindrone
- Levonorgestrel (Norgestrel)
- Medroxyprogesterone acetate

Selective: (stimulate progesterone receptors only)

- Norgestimate
- Desogestrel
- Drospirenone

- Non selective drugs : **have androgenic effects:** acne, hirsutism, weight gain, & deleterious effects on lipid & CHO metabolism.

What is the difference between progesterone and progestin?
Progesterone → Natural (protects against breast cancer)
Progestin → Synthetic (significantly increase the risk of breast cancer)

Further differences....

[Click Here](#)

OR:

[Click Here](#)

Combination Oral contraceptives(COC)

- They are essentially designed to mimic the menstrual cycle by producing a monthly withdrawal bleeding.
- Currently, their formulation were more improved to also mimic the natural on going changes in hormonal profile.
- Products containing a combination of an estrogen and a progestin are the most common type of oral contraceptives.
- Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 days.
- Triphasic oral contraceptive products **attempt to mimic the natural female cycle** and contain a constant dose of estrogen with increasing doses of progestin given over three successive 7-day periods. With either type of combination oral contraceptives, active pills are taken for 21 days followed by 7 days of placebo.
- Withdrawal bleeding occurs during the hormone-free interval.

Formulations:

- Monophasic → a fixed amount of estrogen & a fixed amount of progestin
- Biphasic → a fixed amount of estrogen, & progestin increases in the second half of the cycle
- Triphasic → a fixed amount of estrogen & amount of progestin increases in 3 successive phases

(In Triphasic →estrogen can also be variable)

MOA:

- **Mainly** → Estrogen will lead to negative feedback on FSH and LH → suppressing the release of gonadotropins → low levels of LH → no ovulation
- Inhibit implantation by decreasing endometrial proliferation; therefore, no ovum can be embedded
- Less secretion & peristalsis in fallopian tubes, which hinders the transport of ovum.
- Progestin will increase cervical secretions → no sperm pass → Inhibit fertilization

Indications:

As a **contraceptive** → for any woman seeking a reliable, reversible, coitally*-independent method of contraception.

Other uses → to delay menstruation.

*Coitus = sexual intercourse

Administration:

- Day 1 is the first day where bleeding occurs
- Pills are taken for 21 days, starting on day 5 & ending at day 26. This is followed by a 7-day pill free period
- To improve compliance → there exist a formulation of 28 pills that resemble the biphasic or triphasic formulation, but the last 7 pills of these 28 pills are actually placebo.
- 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:

A. Estrogen Related

1. Nausea and breast tenderness
2. Headache
3. ↑ Skin Pigmentation
4. Impair glucose tolerance
5. **Cardiovascular - major problem**
 - a. Thromboembolism
 - b. Hypertension
6. ↑ frequency of gall bladder disease
7. **cancer**
8. **prolactin inhibition** + breast tissue growth (tenderness)

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.

The most serious adverse effects of oral contraceptives is cardiovascular disease, including: (thrombophlebitis, thromboembolism, hypertension, increased incidence of myocardial infarction and cerebral and coronary thrombosis)

Contraceptives and neoplasms:

Contraceptives increase the risk of → Breast, vaginal, cervical cancer + benign liver tumors
Contraceptives reduce the risk of → endometrial and ovarian cancer

Contraindications:

- **Thrombophlebitis / thromboembolic disorders**
- Congestive heart failure 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**
- Dyslipidemia, diabetes, hypertension, migraine...
- **Lactating mothers** (because estrogen inhibit prolactin)

- >35yrs, smoker, obese
 - Fibroid tumors
 - Lactating mothers
- 
- AVOID ESTROGEN → Use mini pills (Progestin only pills)**

Interactions:

1) Medications that cause contraceptive failure → by either A- impairing absorption or B- inducing CYT P450

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

B- Microsomal Enzyme Inducers → ↑ catabolism of COC → Phenytoin, Phenobarbitone, Rifampin

2) Medications that increase COC toxicity → by inhibiting CYT P450 → ↓ metabolism of COC → ↑ toxicity → Acetaminophen, Erythromycin, SSRIs

3) COC can alter and decrease the clearance of other drugs and lead to their toxicity: WARFARIN, Cyclosporine, Theophylline

Progestin Only Pills. (POP):

Are taken daily on a continuous schedule. These are less effective than COC. Thus, **There** is a slightly higher contraception failure rates when used.

MOA:

Increase cervical mucous secretion → plug formation → no sperm penetration → inhibit fertilization

Indications:

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

administration:

Should be taken every day, all the year round

ADRs & Contraindications:

Progesterone related.

Postcoital contraception(PCC)

For maximum effectiveness, **emergency contraception should be taken as soon as possible after unprotected sex**

types:

- a. Estrogen and progestin → Ethinyl estradiol + Levonorgestrel
- b. High dose estrogen only → Ethinyl estradiol
- c. High dose progestin only → Levonorgestrel
- d. **Mifepristone +- Misoprostol → a progesterone antagonist → endometrium can not be prepared for implantation (most successful)**

a+b+c administered within 72 hrs of unprotected sex. A second dose should be taken 12 hrs after the first dose.

d → a single dose within 120 hrs .

MOA: not clearly understood

Indications:

- Unsuccessful withdrawal before ejaculation
- Torn, leaking condom
- Missed pills
- Detached contraceptive patch
- Medico-legal insult: Rape

ADRs:

With Mifepristone → uterine bleeding could be problematic → must be under medical supervision
→ patient must be admitted

Other forms of hormonal contraceptives: (Patches and injectable forms are IMP)

Transdermal patches: an alternative to COC containing ethinyl estradiol and the progestin norelgestromin. One contraceptive patch is applied each week for 3 weeks to the abdomen, upper torsi, or buttock. Week 4 is patch-free, and withdrawal bleeding occurs. The transdermal patch has efficacy and adverse effects similar to that of COC. However, it has been shown to be less effective in women weighing greater than 90 kg (too much fat under the skin).

Vaginal rings: an additional contraceptive option is a vaginal ring containing ethinyl estradiol and the progestin etonogestrel. The ring is inserted into the vagina and is left in place for 3 weeks. It releases a continuous low dose of hormones. Week 4 is ring-free, and withdrawal bleeding occurs. The vaginal ring has efficacy and adverse effects similar to that of COC. One extra problem with the vaginal ring is that it may slip or be expelled accidentally.

Progestin implants: a subdermal implant containing the progestin levonorgestrel offers long-term contraception. A capsule is placed subcutaneously in the upper arm and provides contraception for approximately 3 years. The effect is totally reversible when surgically removed. Once the progestin-containing capsule is implanted, this method of contraception does not rely on patient compliance.



Progestin intrauterine device: a levonorgestrel-releasing intrauterine system offers a highly effective method of long-term contraception for up to 5 years. It is a suitable method of contraception for women who already have at least one child and do not have a history of inflammatory diseases or ectopic pregnancy. There is another type IUD that can be worn for a week after unprotected sex to prevent pregnancy.



Injectable Hormones (given IM): Depot medroxyprogesterone acetate, injected every 3 months.

MCQs:

1- An obese diabetic woman. Takes oral contraceptives. What would be the major concern side effect caused by combined oral contraceptives:

- a) Thromboembolic disorders
- b) Skin pigmentation.
- c) Depression of mood
- d) Breast tenderness

2- A women using Phenytoin. She got married before 3 months. She used oral contraceptive. And now she is pregnant. Which of the following would explain her case?

- a) Phenytoin suppresses bioavailability
- b) Phenytoin increase renal clearance
- c) Phenytoin increase catabolism of COC

3- A 22-year-old female who requests a postcoital contraceptive after being raped would best be treated with which of the following?

- a) Mifepristone
- b) Spironolactone
- c) Aminoglutethimide
- d) Leuprolide

4- All of the following are side effects of estrogen therapy except :

- a) weight gain
- b) breast tenderness
- c) Spotting or darkening of skin
- d) Weight loss

5- Regarding COC (combined oral contraceptive) :

- a) They contain only estrogen
- b) they contain only progesterone
- c) they contain both estrogen and progesterone
- d) they don't contain neither estrogen nor progesterone

6- Regarding MINI pills:

- a) They contain only estrogen
- b) they contain only progesterone
- c) they contain both estrogen and progesterone
- d) they don't contain neither estrogen nor progesterone

7- The "minipill" containing only a progestin, rather than a combination: estrogen-progestin oral contraceptive, was developed because progestin alone:

- a) Results in less depression and cholestatic jaundice
- b) Is a more effective contraceptive agent than the two combined
- c) Results in a more regular menstrual cycle
- d) Is thought to be less likely to induce endometriosis
- e) Is thought to be less likely to induce cardiovascular disorders

1:A, 2:C, 3:A, 4:D, 5:C, 6:B, 7:E