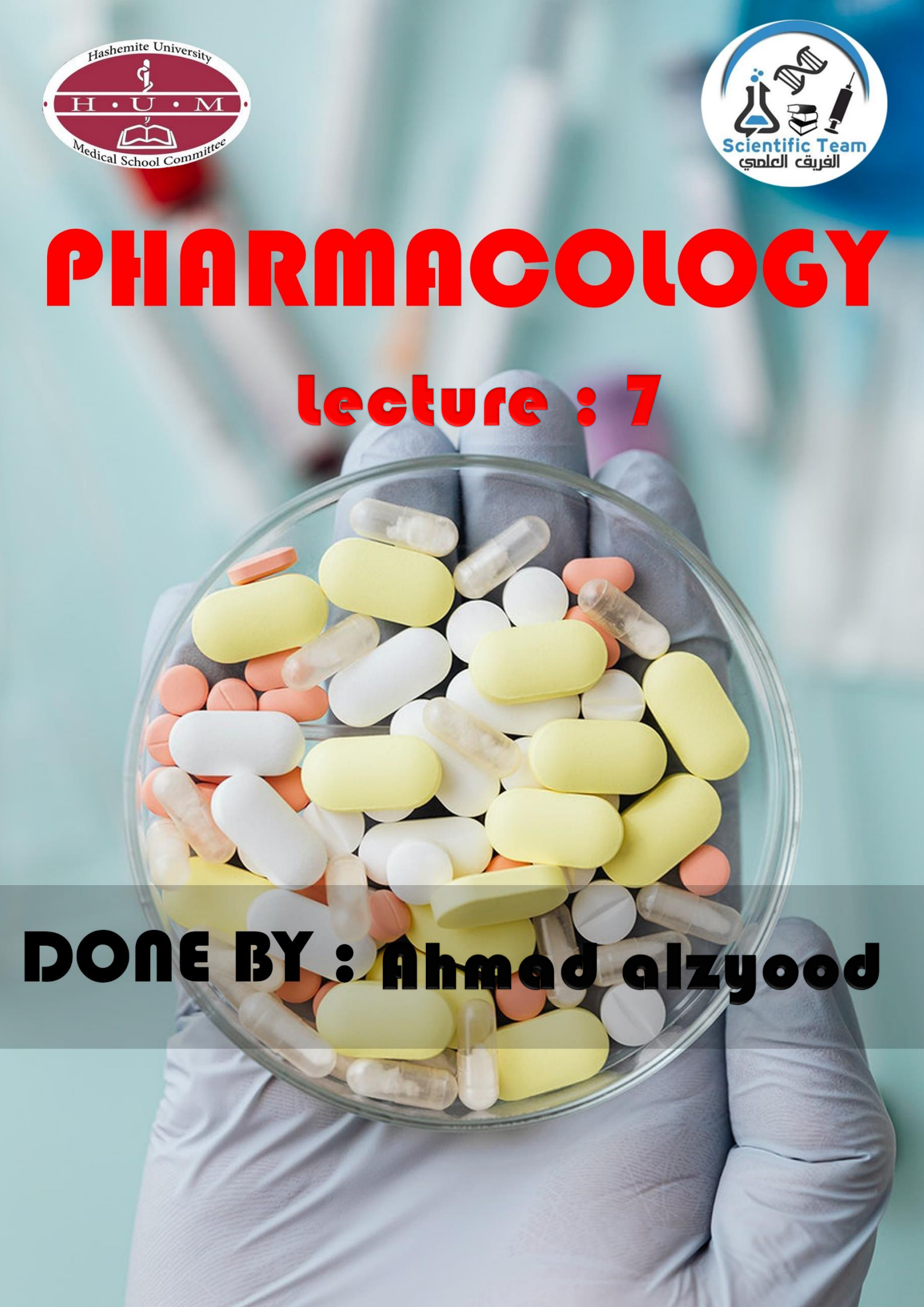
Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

lecture : 7



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Hormonal contraception

Methods of contraception are:

1- mechanical

2- physiological

3- chemical

4- hormonal

in this lecture, we will talk about hormonal contraception.

Hormonal Contraceptives

1. Combined oral contraceptives.

this type of drug is taken orally and has both estrogen and progestin(combined). MOA is mainly by negative feedback to hypothalamus, inhibiting FSH and LH. the drug is taken in the 5th cycle and for 21 days then is omitted for 7 days (along with estrogen and progestin that are released during the cycle)

Mechanism of Action

1. Suppression of ovulation: inhibit FSH & LH.

2. Change cervical mucosa (thick & more acidic) ⍰ inhibit sperm

penetration.

3. ↓ Endometrial glycogen deposition ↓ inhibit implantation.

Preparations: Combined contraceptive Pills

- They contain estrogen and progestin .
- They are taken for 21 days starting from the 5th day of the cycle and are omitted for 7days.

الجرعات مش مطلوبه

Indications

1. Contraception.

2. Regulation of menstrual cycle. some women have irregular cycle due to irregular release of the hormones, a cycle is 20 days then the next cycle is 30 days

3. To postpone menstruation e.g. during pilgrimage.

تأخير النزيف (الحيض) لكي تبقى على طهارة خوفا من حرمانها من الحج لانه في وقت محدد وقد يوافق ايام الحيض

4. Dysfunctional uterine bleeding.

this because of progestin action

Adverse Effects & Contraindications (CI) of Combined Pills

AE is mainly of estrogen so modern preparation contain less estrogen

* the AE is same AE of both estrogen and progestin so we will not discuss in details.

I. Minor Risks

1. Nausea, vomiting, headache.

2. Breast tenderness.

3. Edema.

II. Intermediate Risks

1. Bleeding (low dose), amenorrhea (large dose).

2. Acne, hirsutism, skin pigmentation.

III. Major Risks: mostly from estrogen. Modern preparations contain low dose estrogen→↓risks.

1. Cardiovascular: ↑ in females over 35 & smokers:

a. Thromboembolism - pulmonary embolism.

b. Hypertension - stroke - myocardial infarction.

CI: myocardial infarction and cerebrovascular disorders.

2. Carcinogenic

↑ Risk of endometrial & breast cancer (estrogen): ↓ by adding progestins.

CI: 1. Estrogen-dependent tumors of breast & uterus.

2. Undiagnosed vaginal bleeding.

3. Cholecystitis - gall stones – jaundice → CI in liver disease.

4. Hyperglycemia

5. Depression: by progesterone.

2. Progestin-Only Preparations

As in previous lecture, progestin is taken orally or parenteral. This type has not AE of estrogen (only progestin). The progestin increase viscosity of cervical mucus and inhibit ovulation as a negative feedback.

A. Oral preparations (Minipills)

B. Parenteral Preparations

1. Implants → **5 years**.
   - Biodegradable: do not need to be removed on expiry.
   - Non-biodegradable: be removed on expiry
2. Depot injections (medroxyprogesterone acetate) →**3 months**.

Mechanism of action:

1- Inhibition of ovulation

2- Inhibition of sperm penetration in the uterus due to increase viscosity

of cervical mucous.

Advantages:

1. Useful in patients with hepatic disease, hypertension, thromboembolism

2. They do not suppress lactation. → used in lactating women

Disadvantages:

1. Less effective than combined preparations

2. Long term progestin injections are not desirable for women planning a

pregnancy soon after cessation of therapy because ovulation suppression can sometimes persist for as long as **18 months** after the last injection. The effect still persist as long as 1 year after cessation.

3. Unpredictable spotting and bleeding, particularly during the first year of use.

3. Other hormonal preparations:

A. Transdermal patch

- contains synthetic estrogens and the progestins.

B. Vaginal ring

- contains synthetic estrogens and the progestins.

- The ring is inserted into the vagina and left in place **for 3 weeks**

C. Progestin intrauterine device اللولب

- levonorgestrel-releasing intrauterine devices → highly effective(due to actions of both the device and levonorgestrol)

Levonorgestrel(progestin) → prevent bleeding (action of the device)

method of contraception for **3 to 5 years**.

D. Postcoital contraception يعني بعد العلاقة الجنسية العابرة ومش مخطط الها ويستخدم بكثرة في الغرب

- Postcoital or emergency contraception reduces the probability of pregnancy after intercourse without effective contraception

- The most common method: a single high dose of levonorgestrel

→ should be taken as soon as possible after unprotected intercourse and preferably within **72 hours**.

High dose of levonorgestrel causes rapid maturation of endometrium and inhibit ovulation (decrease progesterone) so this make more potent shedding of endometrium (remove the implanted zygote)

- An alternative: ulipristal: progesterone agonist/antagonist(modulator) → within **5 days** of unprotected intercourse.

UTERINE STIMULANTS

(Oxytocic, Abortifacients)

This type are called oxytocic (oxytocin like action) → causes uterine contraction

And any pregnant women takes this drug → will lead to abortion

- These drugs increase uterine contraction, especially at term.

1. Posterior pituitary hormone: Oxytocin, Desamino-oxytocin, Carbetocin

2. Ergot alkaloids: Ergometrine, Methylergometrine

3. Prostaglandins (E2, F2α) analogues: Dinoprostone, Dinoprost, Misoprostol

1. OXYTOCIN

- Secretion by the posterior pituitary increase in (↑ coitus, parturition, suckling)

- Actions:

1. Uterus: - ↑ force and frequency of uterine contractions.

- Estrogens sensitize the uterus to oxytocin by ↑its receptors while progestins ↓ the sensitivity,

- Mechanism of action:

a- G-protein coupled oxytocin receptors → ↑ DAG, IP3 → ↑ intracellular Ca2+ & depolarization of muscle fibers.

b. Oxytocin ↑PGs synthesis and release → contractile response.

2. Breast: contracts the myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids → 'milk ejection reflex' is initiated by suckling so that it may be easily sucked by the infant.

3. Kidney: high doses exerts → ADH-like action → ↓ urine output:

[pulmonary edema can occur if large amounts of IV fluids and oxytocin are infused together].

- Pharmacokinetics: inactive orally (peptide)- by IM or IV routes,

- Uses:

1. Induction of labor: in case of toxemia of pregnancy, diabetic mother, ruptured membranes or placental insufficiency.

2. Uterine inertia: uterine contractions are feeble and labour is not progressing satisfactorily.

3. After Caesarean section to prevent uterine atony.

4. Postpartum hemorrhage.

- Adverse effects:

1. Too strong uterine contractions → force the presenting part through incompletely dilated birth canal → maternal & fetal soft tissue injury, rupture of uterus, fetal asphyxia and death.

2. Water intoxication: if large doses given along with IV fluids, especially in toxemia of pregnancy and renal insufficiency.

Desamino-oxytocin buccal formulation; action is similar to injected oxytocin, but less consistent and used for → Induction of labor- Uterine inertia (buccal tablet repeated every 30 min)- Breast engorgement (before breast feeding)

Carbetocin: long-acting analogue of oxytocin used for → prevention of uterine atony after caesarean section - control PPH.

2. Ergometrine, methylergometrine

- Actions:

1. Uterus: ↑ force, frequency and duration of uterine contractions.

Mechanism of action: partial agonist on serotonin (5-HT2) and α-adrenergic receptors.

2. GIT: High doses ↑ peristalsis.

- Methylergometrine is more potent than ergometrine on the uterus

- Pharmacokinetics: rapid and nearly complete absorption from the oral route.

- Adverse effects :- Nausea, vomiting and ↑BP occur occasionally.

- High doses for many days → ↓ milk secretion (due to inhibition of

prolactin release).

- Uses:

1. The main indication: control and prevent postpartum hemorrhage (PPH) only in those expected to bleed more e.g. grand multipara, uterine inertia. A combination of ergometrine with oxytocin may be used in severe bleeding.

2. After caesarean section to prevent uterine atony.

3. Prostaglandins

- PGE2, PGF2α are potent uterine stimulants, & cause ripening of cervix.

- Dinoprostone & Dinoprost and Misoprostol are PGs analogues used in:

1. Induction of labor (especially in toxemic and renal failure patients as an alternative to oxytocin because PGs do not cause fluid retention)

2. Therapeutic abortion (proceeded 2 days by Mifepristone)

3. Postpartum hemorrhage

UTERINE RELAXANTS

(Tocolytics)

- These drugs ↓ uterine contractions.

- Uses: 1. Delay or postpone labor,

2. Arrest threatened abortion

3. Dysmenorrhea.

4. Prevention of premature labour (to allow the foetus to mature, to allow time for initiating glucocorticoid therapy for foetal lung maturation or to transfer the mother in labour to a centre with proper facilities)

1- Adrenergic agonists: Ritodrine, Terbutaline

→ They are β2-selective agonists

- Adverse effects:

1. Tremors of skeletal muscle, Tachycardia.

2. Hypokalemia and muscle cramps, Hypoxemia, Hyperglycemia

2- Calcium channel blockers

Nifedipine →↓influx of Ca2+ ions →↓ uterine contractions, can postpone labor if used early enough.

- Adverse effects: Tachycardia, hypotension

3- Oxytocin antagonist:

Atosiban acts as antagonist at the oxytocin receptors.

- postpone preterm labor with fewer cardiovascular and metabolic complications than β2 adrenergic agonists.

4- Magnesium sulfate IV infusion

→ **first line drug for prevention & treatment of seizures in preeclampsia and eclampsia.**

- It acts as a tocolytic by competing with Ca2+ ions for entry into myometrium at Ca2+ channels (both voltage gated & ligand gated).