Reproductive Pharmacology Revision

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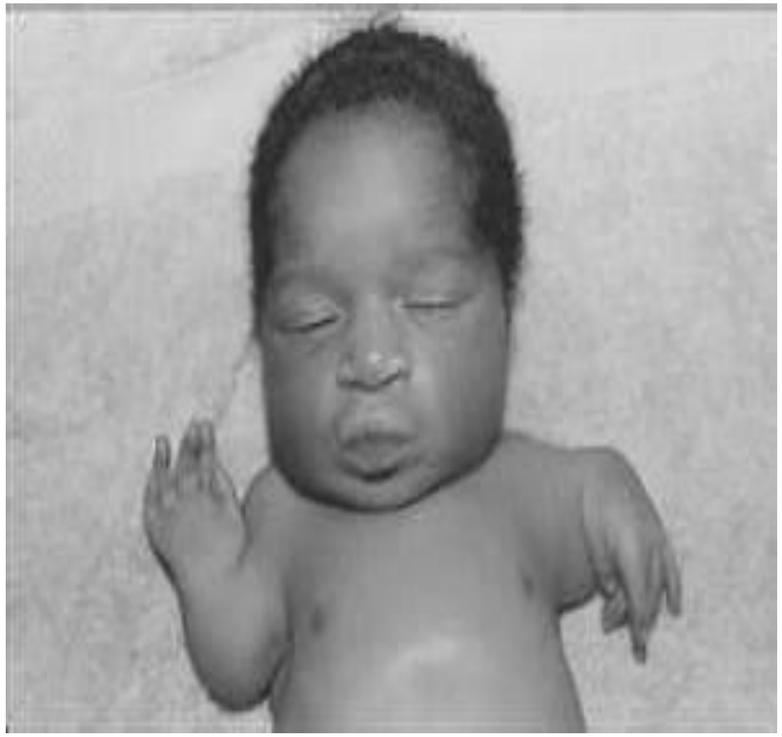
	Estrogen	progesterone	Androgens
Preparations	I. Natural estrogens: ▪ Estradiol ▪ Estrone ▪ Estriol II. Semisynthetic estrogens: Ethinyl estradiol and mestranol. III. Synthetic estrogens: diethyl stilbosterol.	• Natural: progesterone injection ▪ Synthetic: medroxy progesterone acetate	▪ Natural androgens: androsterone and testosterone ▪ Synthetic androgens: testosterone propionate. ▪ Anabolic steroids: nandrolone and stanazol
Therapeutic uses	1) Contraceptive pills. 2) Postmenopausal symptoms e.g. atrophic vaginitis and osteoporosis. 3) Dysfunctional uterine bleeding. 4) Replacement therapy in ovarian hypofunction. 5) Cancer prostate.	1)Contraceptive pills. 2) Dysfunctional uterine bleeding 3) Dysmenorrhea and endometriosis. 4) Threatened abortion.	1) primary hypogonadism or secondary hypogonadism in male (androgens) 2) Chronic wasting associated with human immunodeficiency virus or cancer. (anabolic steroids) 3) to increase muscle bulk and strength in athletes (anabolic steroids)

	Estrogen	progesterone	Androgens
Adverse effects		1)Headache 2) Depression 3) Weight gain 4) Changes in libido 5) Menstrual irregularities	1) Reduction in spermatogenesis. 2) Virilizing effects in females. 3) Precocious puberty and premature closure of epiphysis in children. 4) Cholestatic jaundice. ➢ Contraindications 1) Prostatic tumors (benign and malignant). 2) Liver diseases 3) Children.
Gonadal antagonist	1. Estrogen receptors blockers 2. Selective estrogen receptor modulators (SERMs) 3. Aromatase inhibitors	1. progesterone receptors blocker: Mifepristone	1. 5 α-reductase inhibitors: 2. Testosterone receptor blockers

	Clomiphene citrate (Clomid)	SERMs		Aromatase inhibitors (Anastrazole , letrozole Exemestane)	Mifepristone
		Tamoxifen	Raloxifene		
Mechanism of action	Clomiphene blocks estrogen receptors in hypothalamus and pituitary →↑ FSH and LH → stimulate ovulation.	❑ estrogen antagonist in the breast ❑ an agonist in the uterus and bone.	❑ agonist in bone ❑ no effect on the uterus	inhibitors of aromatase------estrogen synthesis inhibiton	❑ It is a competitive blocker of progesterone receptors.
Therapeutic Uses	▪ stimulate ovulation in infertile women <u>with normal pituitary function</u>	▪ treatment of advanced, estrogen receptor positive breast cancer. ▪ primary prevention of breast cancer in women at high risk	ttt and prevention of postmenopausal osteoporosis	ttt of postmenopausal women with estrogen-receptor positive breast cancer who have received two to three years of tamoxifen.	It is used with misoprostol (PGE1) to induce medical abortion in the first trimester
Adverse effects	▪ Ovarian enlargement ▪ hot flushes	▪ Increases the risk of endometrial cancer ▪ Thrombotic complications	▪ Hot flashes ▪ Thrombotic complications		

	5 α-reductase inhibitors (Finasteride)	Testosterone receptor blockers		
		Cyproterone acetate	Flutamide	Spironolactone
Mechanism of action	It inhibits 5 α-reductase enzyme responsible for conversion of testosterone into the active form dihydrotestosterone (DHT).	a competitive blocker of testosterone receptors	a competitive blocker of testosterone receptors	a competitive blocker of both aldosterone and testosterone receptors
Therapeutic Uses	1) benign prostatic hyperplasia. 2) male baldness. 3) hirsutism in females.	1) male hypersexuality 2) hirsutism in females.	1) cancer prostate	1) hirsutism in females

Examples of drugs with teratogenic effect



Thalidomide-induced Phocomelia

Hare lip ---phenytoin

Antiseizure drugs, valproic acid

FDA(Food &drug administration)- Pregnancy categories of drugs

▪ The FDA(American Committe) has established five drug categories (A,B, C,D & X) to indicate the potential of causing birth defects.

Pregnancy category	Definition
A	▪ Drug proved to be safe in animal and human ▪ e.g. Folic acid.
B	▪ Animal studies have shown a fetal risk, but adequate studies in human have not shown a risk to the fetus. ▪ e. g. paracetamol and penicillin

Pregnancy category	Definition
C	▪ Animal studies have shown a risk to the fetus but there are no adequate studies in humans ▪ e.g. Antihistamines
D	▪ There is evidence of fetal risk, but benefits are thought to outweigh the risks. ▪ e.g. lithium (anti-mania).
X	▪ Studies in animals or humans demonstrate fetal abnormalities. ▪ contra-indicated (should not be used) in pregnancy. ▪ e.g. thalidomide.

A.Mention two Therapeutic uses of Tamoxifen

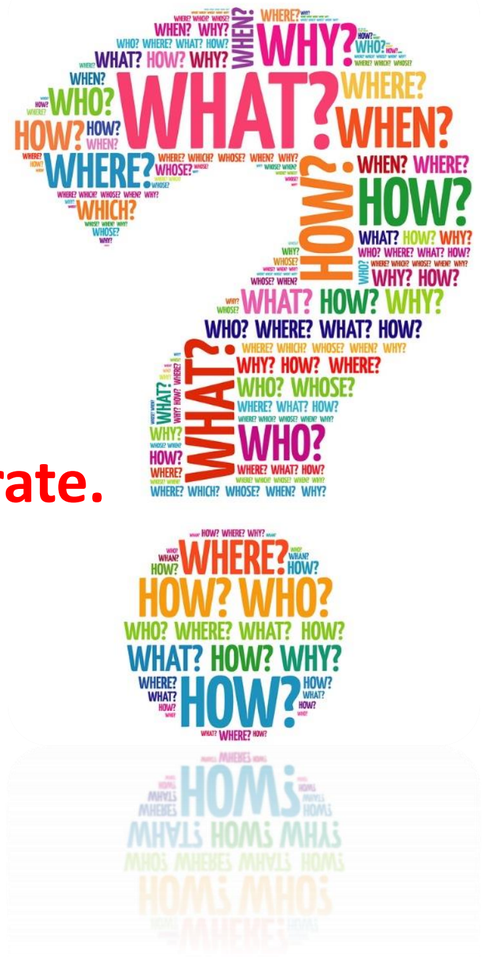
B.Mention therapeutic uses and adverse effects of Raloxifene.

C.Explain the mechanism of action and therapeutic uses of Clomiphene citrate.

D.Mention Mechanism of action of Flutamide.

E.Mention two therapeutic uses of Cyproterone acetate.

F.Mention Contraindications of Anabolic steroids.



Which enzyme does anastrozole inhibit?

A.Aromatase.

B.Desmolase.

C.17α-hydroxylase.

D.17β-hydroxysteroid dehydrogenase.

E.5α-reductase.

Raloxifene is a selective estrogen receptor modulator (SERM). Its characteristic properties make the drug most suitable for treatment of a female patient who:

(a) Decides to start using an oral contraceptive

(b) Has postmenopausal osteoporosis and is at risk for breast cancer

(c) Needs postcoital contraception

(d) Suffers from hirsutism

The drug that causes phocomelia is:

A. Paracetamol

B. Lithium

C. Thalidomide

D. Penicillin

E. Phenytoin

A 65-year-old woman with postmenopausal atrophy and hot flashes is prescribed with estrogen therapy by her primary care physician. She has a family history of endometrial cancer and is concerned about her risk for this condition. Which of the following statements is true?

(A) Breast cancer is unlikely

(B) Postmenopausal bleeding is unlikely

(C) The risk can be offset by adding a progestogen product

(D) Thromboembolic events are unlikely

A 35-year-old woman is experiencing infertility due to anovulation.

Which agent is most appropriate for this patient?

A.Clomiphene

B.Ospemifene

C.Raloxifene

D.Mifepristone

E.Letrozole

A 70-year-old woman is being treated with raloxifene for osteoporosis. Which is a concern with this therapy?

A.Breast cancer

B.Endometrial cancer

C.Venous thrombosis

D.Hypercholesterolemia

A progestin is included in regimens for HRT to prevent which of the following adverse effects?

(A) breast cancer

(B) endometrial cancer

(C) myocardial infarction

(D) stroke

(E) elevated cholesterol levels

A 60-year-old man is found to have a prostate lump and an elevated prostate-specific antigen (PSA) blood test. Magnetic resonance imaging suggests several enlarged lymph nodes in the lower abdomen, and an x-ray reveals 2 radiolucent lesions in the bony pelvis. This patient is likely to be treated with which of the following drugs?

(A) Anastrozole

(B) Desogestrel

(C) Flutamide

(D) Methyltestosterone

(E) Oxandrolone

Benign prostatic hyperplasia (BPH) can be characterized by frequent urinary urgency, diminished urinary stream, urinary retention, and prostate-specific antigen levels within normal limits for age. Finasteride reduces the size of the prostate by:

A. Inhibiting the interaction of the DHT-androgen receptor complex with promoter DNA.

B.Decreasing the formation of gonadotropins.

C. Antagonizing 5α-reductase, reducing formation of DHT.

D.Decreasing gonadal androgen production.

E.Competitively antagonizing the androgen receptor

Antihistamines belong to Pregnancy Category :

A.A

B.D

C.X

D.C

E.B

The most dangerous period of pregnancy for drug adverse effect:

A. 0-14 day

B. 11-20 weeks

C. 3-10 weeks

D. 21-30 weeks

E. 31-40 weeks

Hormonal contraceptives may be:

- **Oral:**

I. Combined regimen type

II. Single entity perpetrations

- **Non – oral:**

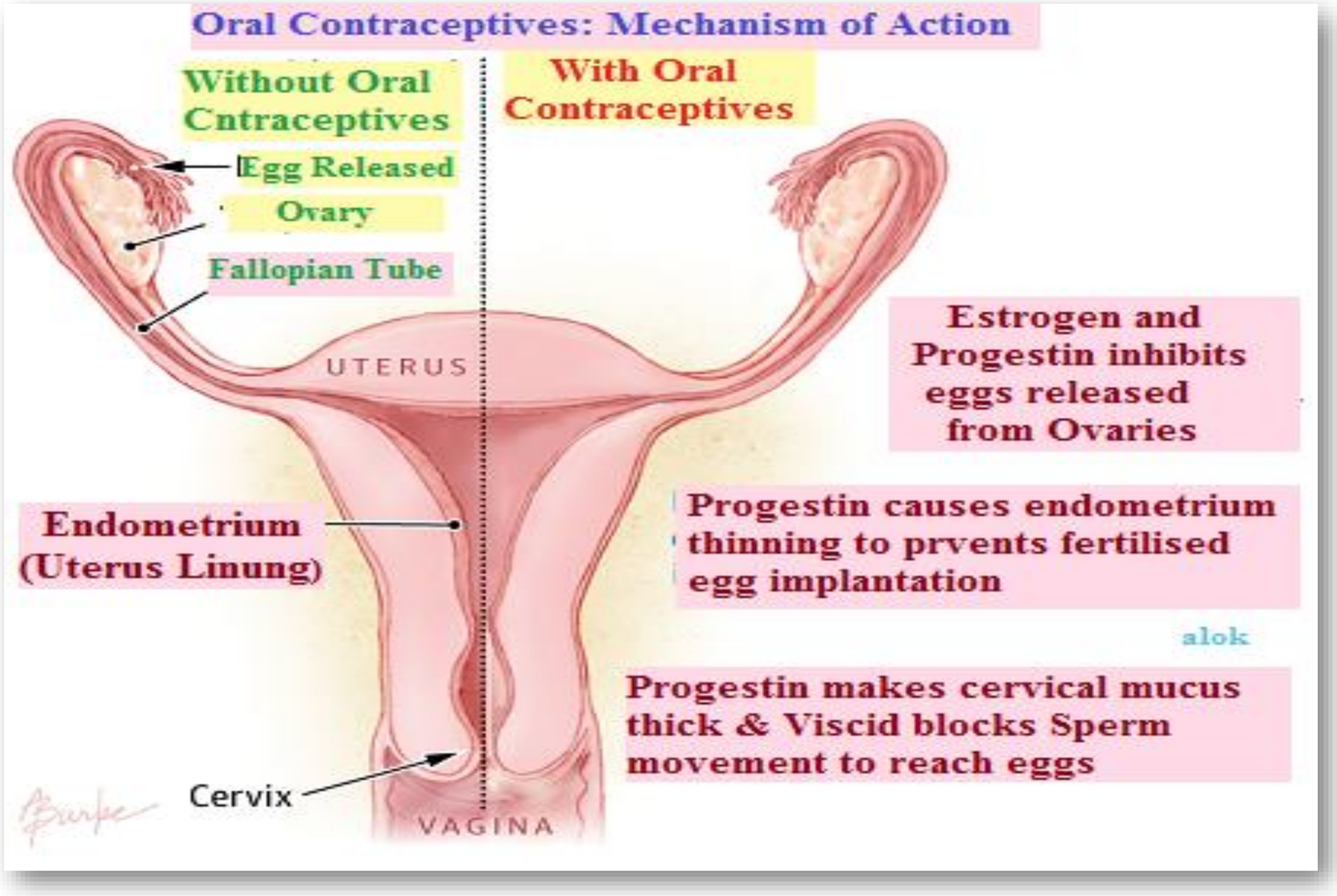
I. Transdermal patch

II. Vaginal ring

III. Injectable progestin

IV. Progestin implants

V. Progestin intrauterine system



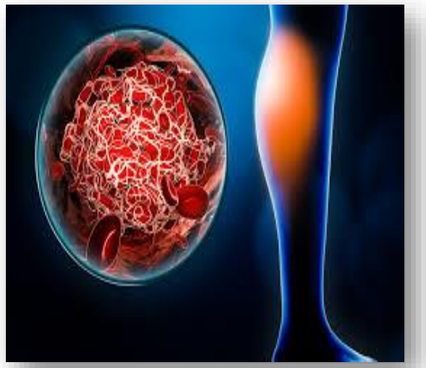
SIDE EFFECTS

- **CVS** (combined hormonal contraceptive):

- The most serious side effects especially in women above 35 years and in women who are smokers:

i. Hypertension

ii. increase risk of myocardial infarction.



iii. Thrombosis and thromboembolic catastrophes.

➢ CNS:

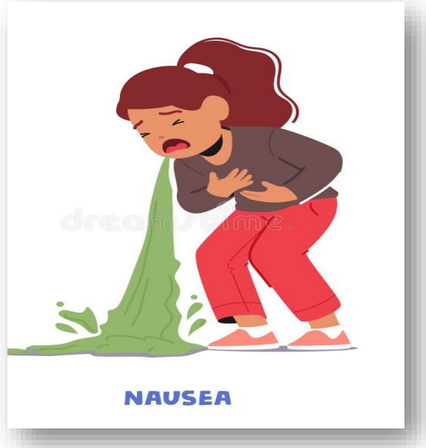
- Migraine headache (combined hormonal contraceptive) .

- Ischemic stroke (combined hormonal contraceptive).

- Mood changes and depression.

➢ GIT:

- Nausea and vomiting.



- Cholecystitis and gall stones.

- Cholestatic hepatitis and hepatotoxicity.

➢ Endocrinal:

- Hyperglycemia and DM.

- Weight gain and edema due to salt and water retention.

- Inhibition of lactation in lactating women (combined hormonal contraceptive).

➢ Endocrinal:

- Menstrual irregularities: spotting bleeding, breakthrough bleeding, amenorrhea, and dysmenorrhoea.
- Acne and hirsutism.

➢ Cancer (combined hormonal contraceptives):

- Increased risk of breast cancer.

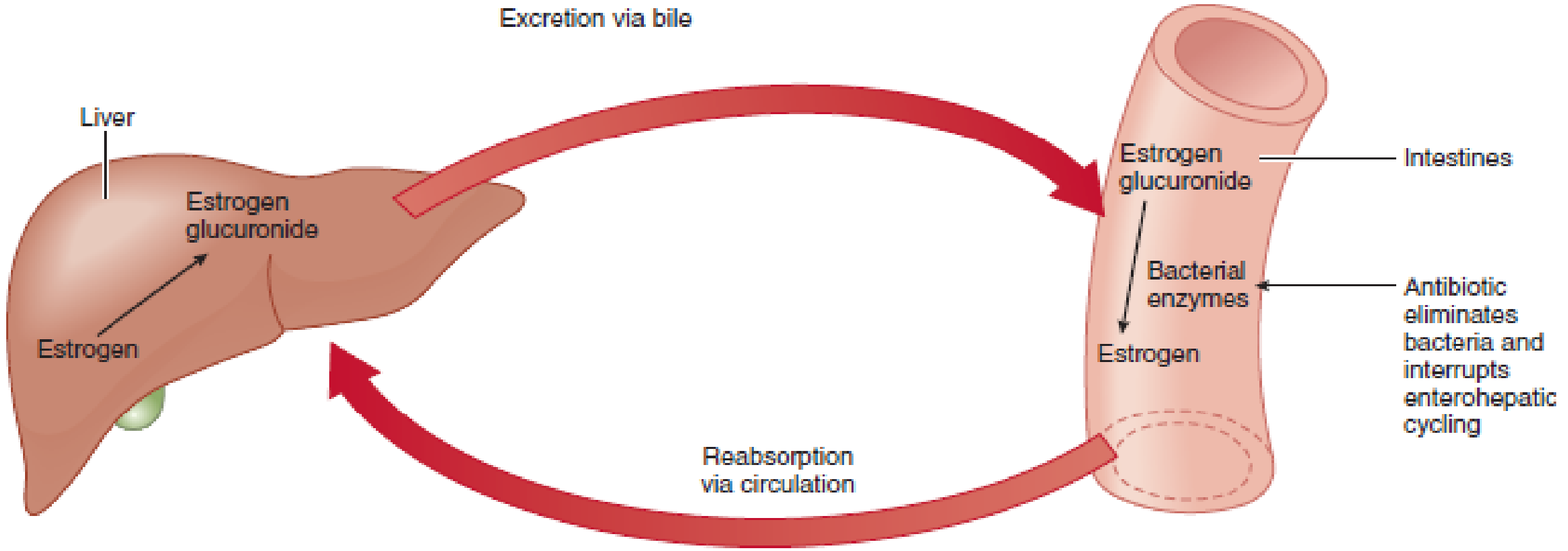
❖ N.B: By contrast, the combined contraceptives reduces the risk of ovarian cancer and endometrial cancer

CONTRAINDICATIONS OF COMBINED CONTRACEPTIVES

- Hypertension or ischemic heart disease (IHD).
- History of embolism, thrombosis or cerebral hemorrhage.
- History of cancer breast or estrogen-dependent neoplasm.
- Migraine headache.
- Chronic liver disease and gall stones.
- Diabetes mellitus.
- Obese, smokers, or women over 35 years.
- Depression.

❑ Drug-interactions that cause failure of contraception:

- If taken with enzyme inducers e.g. rifampin, phenytoin, etc.
- If woman taking broad spectrum antibiotics e.g tetracyclines(kill bacteria flora)
- Paraffin oil (laxative) ↓ intestinal absorption of contraceptive pills.

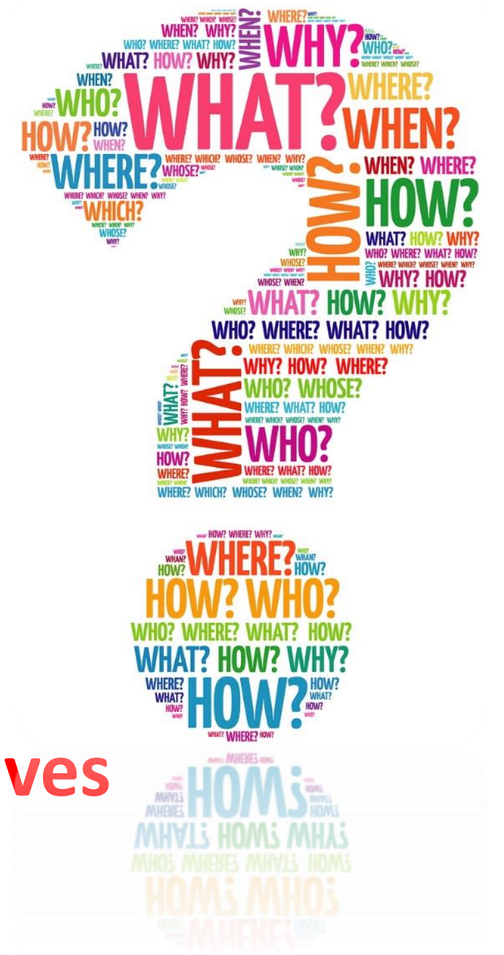


A.Mention Contraindications of **combined hormonal contraceptives**

B.Mention 4 hormonal contraceptives containing **Progestin only.**

C.Mention 2 side effects of **combined hormonal contraceptives** on <u>cardiovascular system</u>.

D.Mention causes of failure of **contraceptive pills**.



A 21-year-old female sees her GP regarding contraception. Which of the following contraindicates the prescription of the combined oral contraceptive pill?

A. Asthma.

B. Hypotension.

C.Hypertension

D. Previous pregnancy.

E. Renal disease.

Which contraceptive method provides long-acting reversible contraception:

A.Contraceptive vaginal ring

B.Progestin implants

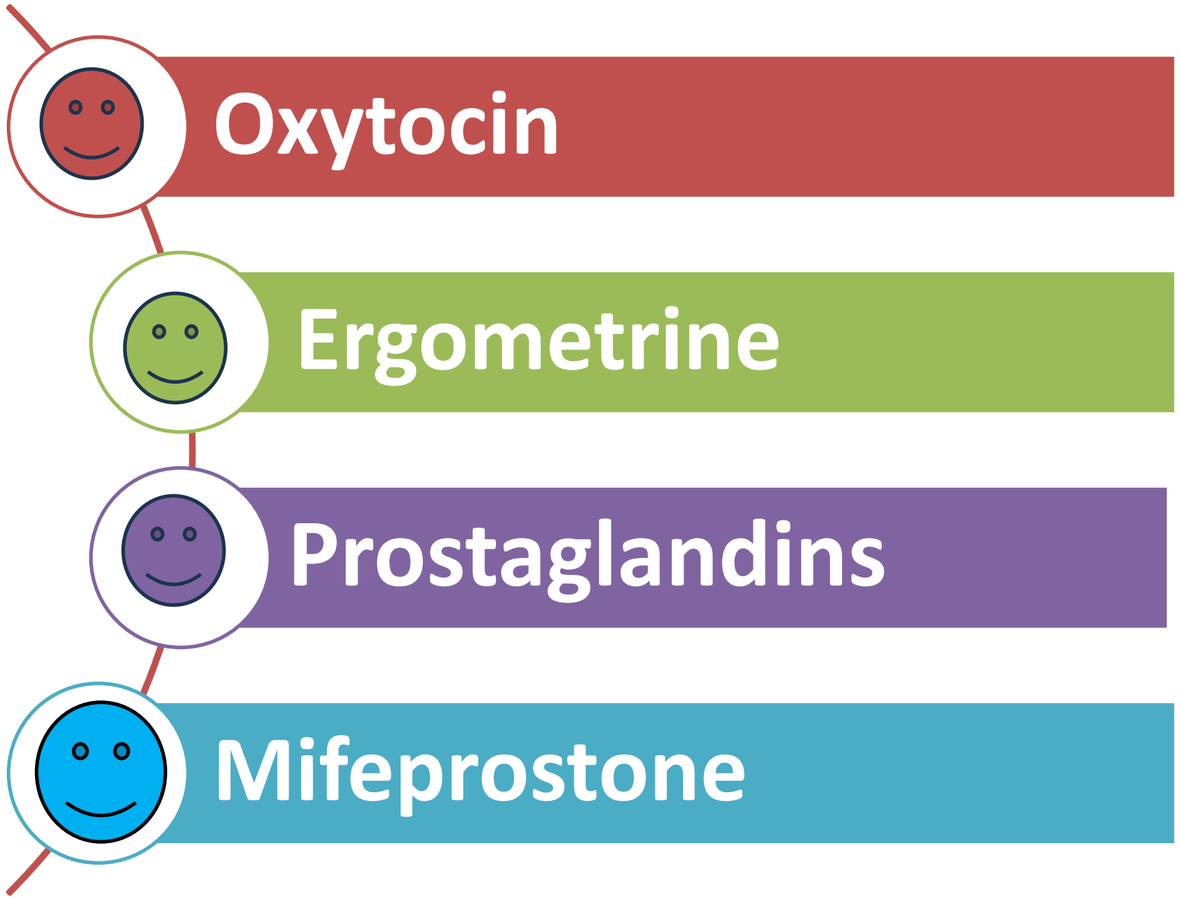
C.Extended-cycle oral contraceptives

D.Transdermal contraceptive patch

E.Injectable progestins

Oxytocic drugs

Drugs that stimulate the pregnant uterus and are important in obstetrics include :



Oxytocin	Ergometrine	Prostaglandins
Oxytocin is a posterior pituitary hormone that acts on uterine muscle to induce powerful contractions	▪ should **not be used to induce labor**. ▪ should be given at the time of placenta delivery never before that. ▪ If it is given before delivery of the placenta, it causes severe spasm of uterine smooth muscles and retained placenta.	e.g. ▪ gemeprost and misoprostol [PGE_1 analogues], ▪ dinoprostone [PGE_2] ▪ carboprost [15-methyl $PGF_2\alpha$]
▪ Oxytocin releases prostaglandins from fetal membranes ▪ acts synergistically with prostaglandins to release Ca^{2+} from intracellular stores in the myometrial cells and promote muscle contraction.	• causes vasoconstriction by α-adrenoceptor stimulation-------limits hemorrhage. • It also causes prolonged and forceful contraction of uterine smooth muscles**.**	▪ The PGs act at PG receptors release Ca^{2+} from intracellular stores in the myometrial cells promote muscle contraction. ▪ prostaglandins ripen and soften the cervix, further aiding the expulsion of uterine contents. ▪ Prostaglandins also upregulate oxytocin receptors. N.B. PGs are contraindicated with uterine scar.

Indications of oxytocics

1- Induction of abortion: **Gemeprost** (intravaginally) or **misoprostol** (following mifepristone) are used.

2- induction of labour : **Oxytocin** and **dinoprostone** are used

3- Bleeding due to incomplete abortion : ***ergometrine*** and ***oxytocin*** (**Syntometrine**) given intramuscularly

4-prevention and treatment of postpartum haemorrhage:

Oxytocin, **ergometrine** and **carboprost** (in those unresponsive to **oxytocin** and **ergometrine**) are used.

Side effects of oxytocics

1. Nausea and vomiting, vaginal bleeding, uterine pain.

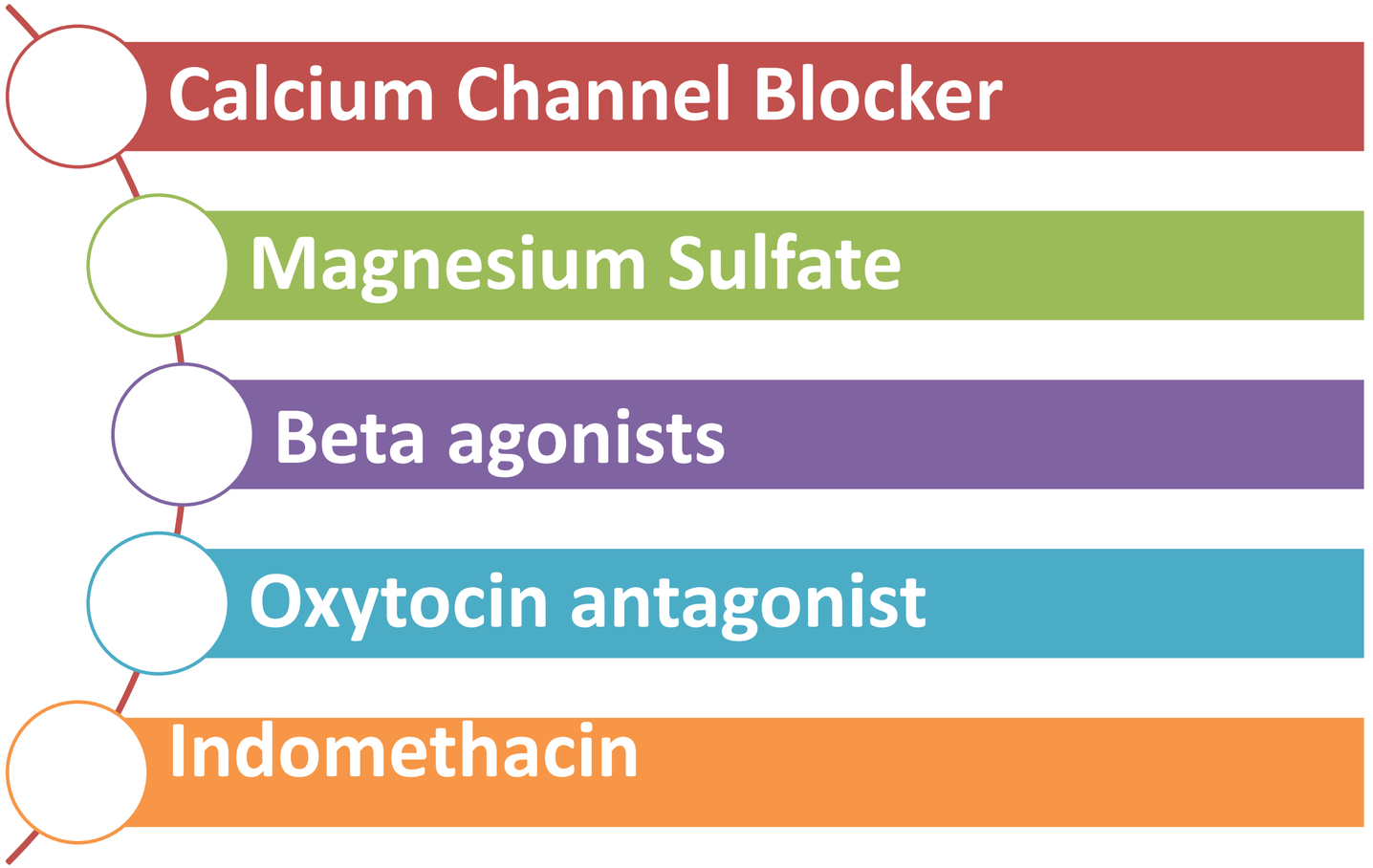
2. **Oxytocin** can cause hypotension and tachycardia. Its antidiuretic hormone-like effect on water excretion by the kidney causes water retention and consequent hyponatraemia.

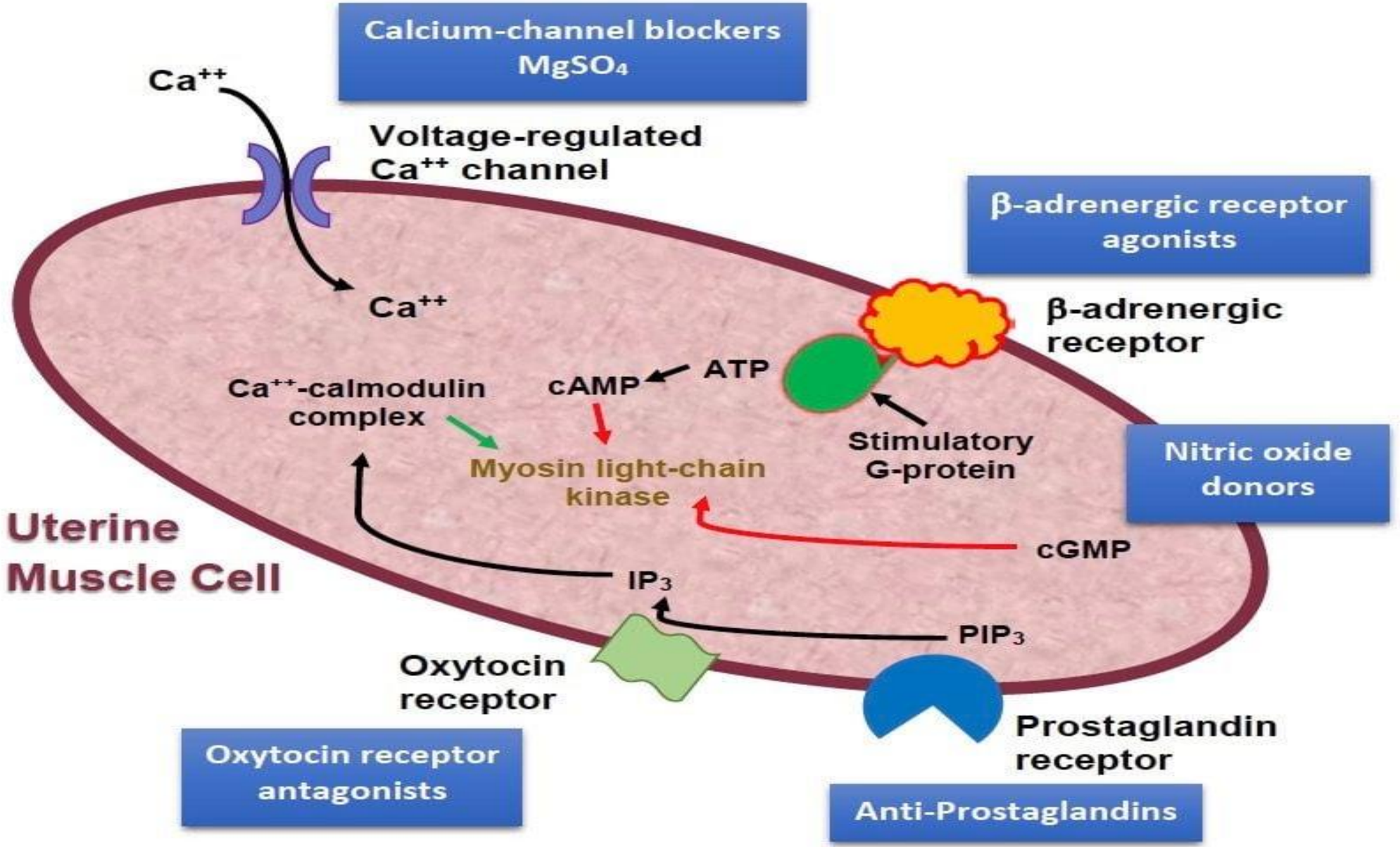
3. **Ergometrine** may cause vasoconstriction with an increase in blood pressure (if vasospasm of the coronary arteries, resulting in angina).

4. **Prostaglandins** may be associated with an increased incidence of uterine rupture during labor in women who have had a previous cesarean section.

Tocolytic drugs

Drugs that inhibit labor or slowdown contractions of uterus are called **tocolytics. They include:**




Calcium-channel blockers
MgSO4
Ca++
Voltage-regulated
Ca++ channel
β-adrenergic receptor
agonists
Ca++
β-adrenergic
receptor
Ca++-calmodulin
complex
cAMP
ATP
Stimulatory
G-protein
Nitric oxide
donors
Myosin light-chain
kinase
Uterine
Muscle Cell
cGMP
IP3
PIP3
Oxytocin
receptor
Prostaglandin
receptor
Oxytocin receptor
antagonists
Anti-Prostaglandins

Side Effects of Tocolytics

All available tocolytic agents cause maternal and/or fetal AEs

1- Maternal adverse effects:

- tachycardia, hypotension, and pulmonary edema (with beta agonists).
- nausea, vomiting and hyperglycemia (with atosiban)
- Hypotension and muscle weakness (with Mg sulfate)

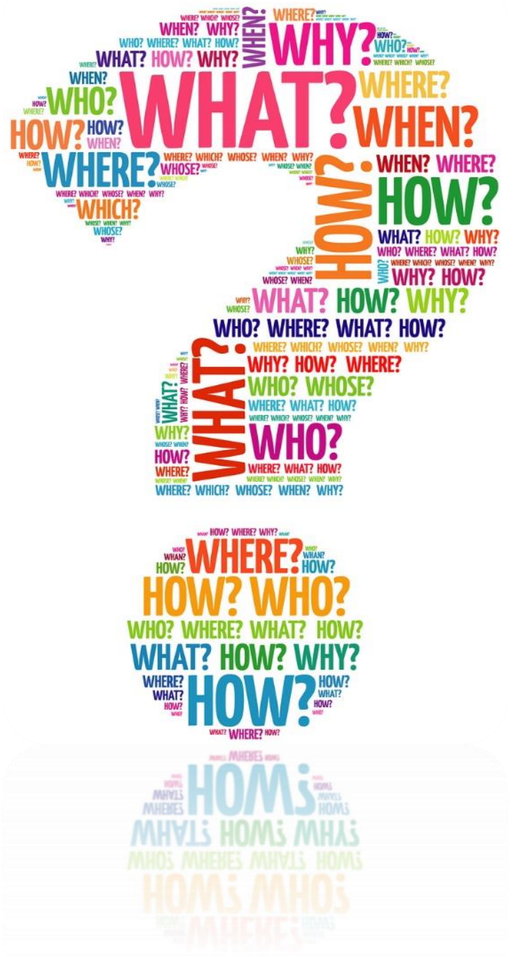
2- Fetal adverse effects:

- renal dysfunction and premature closure of the ductus arteriosus (with indomethacin).

- **Explain: Ergometrine should not be used to induce labor**

- **Enumerate 2 drugs that can be used to delay <u>premature labor</u> and explain their <u>mechanism of action.</u>**

- **Mention <u>4 indications</u> of oxytocic drugs.**



Which class of drugs is commonly used as tocolytics to delay preterm labor?

A.Beta-blockers

B.Calcium channel blockers

C.Diuretics

D.Antihistamines

E.Antidepressants

A pregnant patient at term presents for induction of labor. The best pharmacological approach would be administration of:

A. PGE until the woman is in active labor.

B. PGE with concurrent intravenous infusion of oxytocin.

C. Oxytocin intramuscularly.

D. PGE until the cervix has ripened followed by oxytocin.

E. Ergonovine intramuscularly.


Thank
You