Drugs acting on the Uterus

These are the combination b\w female and male slides,
Our notes are in green

Done by

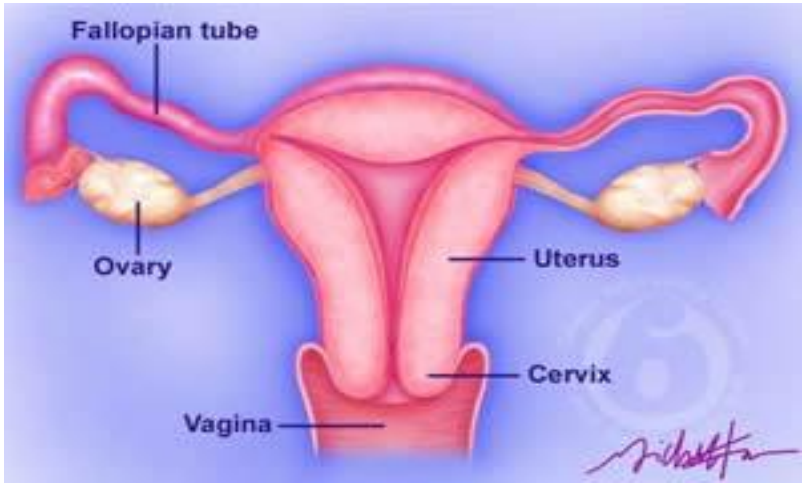
Eman Alrashidi ,Shoog Alageel, Reham Alhenaki , Sarah Bin-Hussain

Ismail Raslan

plz note that doses of drugs are not for memorization

if you have any comments or suggestions kindly contact us by
pharma.team29@gmail.com

Objectives



At the end of the lectures, students should be able to know and understand the:

1. Drugs used to induce & augment labor.(oxytocin)
2. Drugs used to control post partum haemorrhage.(Ergot)
3. Drugs used to induce pathological abortion.(PG)
4. Drugs used to arrest premature labor.(tocolytic)
5. The mechanism of action and adverse effects of each drug.

Neurosecretory cells produce releasing and release inhibiting hormones.

These hormones are secreted into a portal system.

Each type of hypothalamic eighter stimulates or inhibits production or secretion of another pituitary hormone.

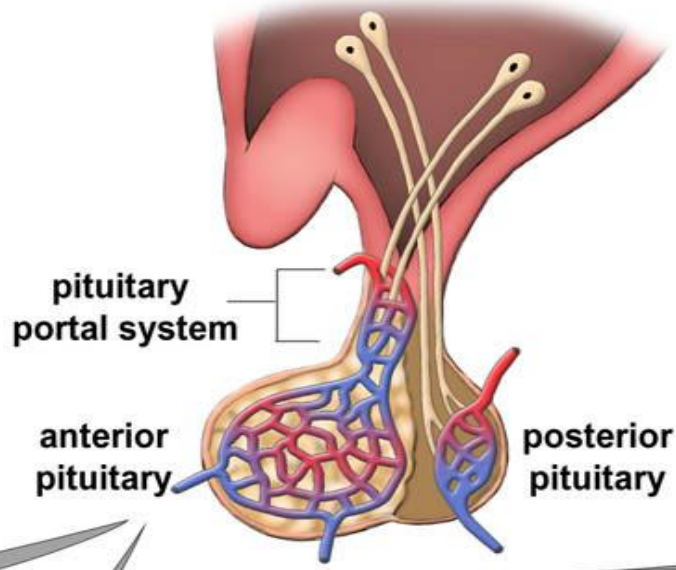
The anterior pituitary secretes its hormones into a blood stream.

Hypothalamus

Neurosecretory cells produce ADH and oxytocine.

These hormones move down axons to axon endnes.

When appropriate, ADH and oxitocine are secreted from the axon endnes into the blood stream.



gonadotropins (FSH & LH)

ovaries, testes

growth hormone (GH)

bones, tissues

prolactin (PRL)

Mammary glands

adrenocorticotropic hormone (ACTH)

adrenal cortex

thyroid stimulating hormone (TSH)

thyroid gland

antidiuretic hormone (ADH)

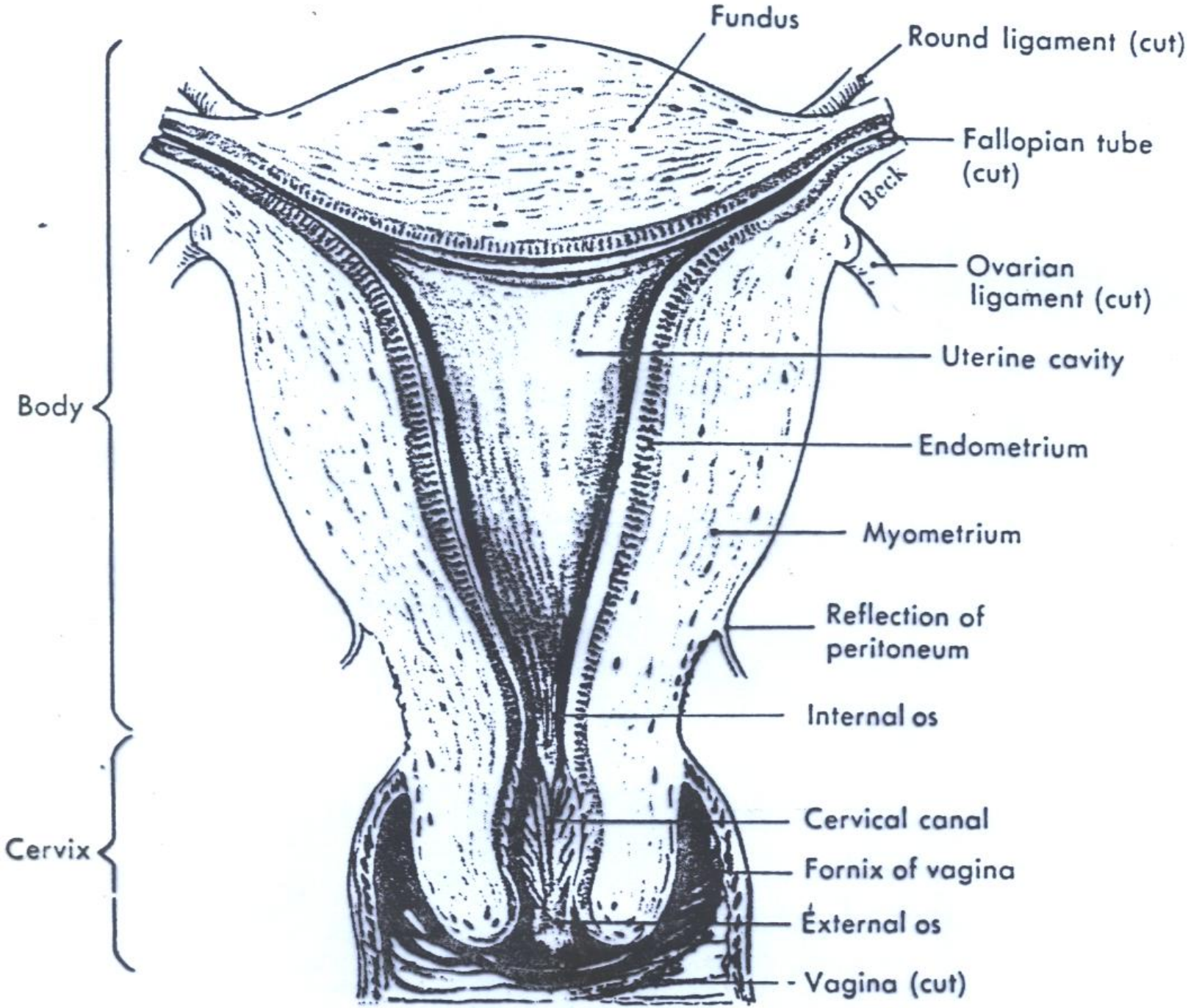
kidney tubules

oxytocin (OT)

Mammary glands

oxytocin (OT)

smooth muscle in uterus


Fundus
Round ligament (cut)
Fallopian tube (cut)
Beck
Ovarian ligament (cut)
Uterine cavity
Endometrium
Myometrium
Reflection of peritoneum
Internal os
Cervical canal
Fornix of vagina
External os
Vagina (cut)
Body
Cervix

Introduction: Uterine control

- During the 1st 2 trimesters of pregnancy, the uterus is controlled by the inhibitory action of high circulating levels of progesterone.
- During the final trimester, uterine smooth muscle becomes increasingly excitable, start with mild muscle **contractions**, which gradually increase in strength & frequency.
- High level of estorgen increase receptor conc. of oxytocin, which increase response to plasma oxytocin.
- Increase in the number of α-adrenergic receptors also increase muscle contractions.
- Release of oxytocin at labor promotes PGs (E & F) production, which are powerful myometrial stimulants
- For contraction, Actin & Myosin interact thru phosphorylation by **myosin light chain kinase** (MLCK) that requires Ca^{2+}.

Uterine Relaxation is controlled by:

- Inhibition of MLCK
- Stimulation of myometrial β–adrenoceptors
- Activation of cAMP mediated protein kinase
- Accumulation of Ca^{2+} in the SR
- Decrease in cytoplasmic Ca^{2+}.

DRUGS PRODUCING UTERINE CONTRACTIONS

{oxytocics}

- **Drugs & hormones used clinically to <u>enhance</u> uterine contractions are used to:**

❖ **Augment contractions during labor & delivery**

❖ **Limit an extended pregnancy**

❖ **Prevent postpartum hemorrhage.**

➢ **e.g.**

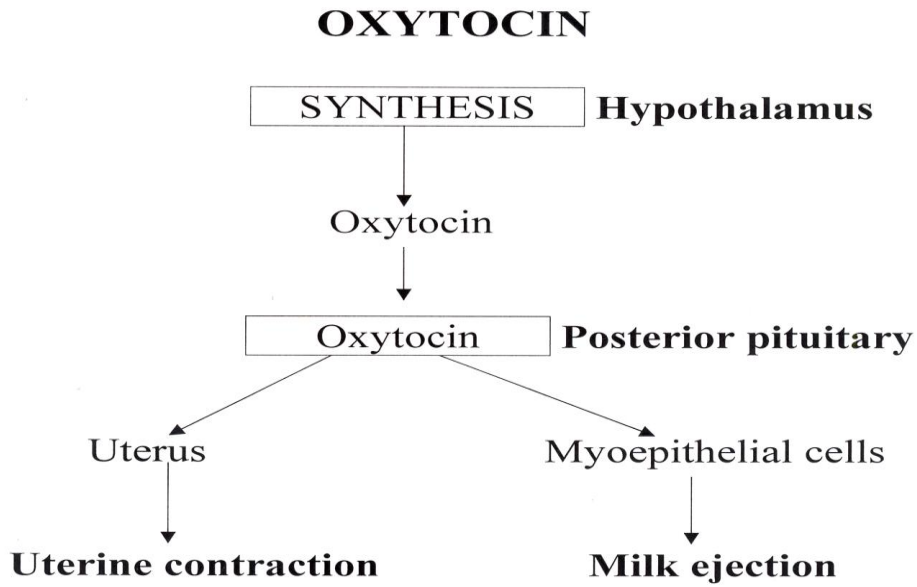
1. **Oxytocin (Syntocinon)**
2. **Ergot alkaloids (Ergometrine (Ergonovine))**
3. **Prostaglandins PGE2, PGF2, & PGE1 (Misoprostol).**

1- Oxytocin (Pitocin® / Syntocinon®)

❖ Synthesis

- Is a posterior pituitary hormone synthesized in the hypothalamus & secreted by the posterior pituitary gland.
- Oxytocin secretion occurs by sensory stimulation from cervix ,vagina , and from suckling at breast.

✓For milk production mothers need the hormone : prolactin
✓For milk ejection from the breast mothers need the hormone : oxytocin .why?
Induces myopepethelial contraction



❖Role of oxytocin

- At term (at delivery) ,the uterus is highly sensitive to oxytocin. Sensitivity increases to 8 fold in last 9 weeks and 30 times in early labor.
- Oxytocin stimulates both the frequency & amplitude of uterine contractility (both are related to the dose).
- These are highly dependent on **estrogen** & antagonized by progesterone
- Oxytocin causes regular coordinated contractions resemble (look like) **the normal physiological** contractions of uterus that travel from fundus to cervix. Then contraction is followed by relaxation.

❖Mechanism of action

- The interaction of endogenous or administered oxytocin with myometrial cell membrane, oxytocin receptor promotes :

  influx of Ca^{2+} from extra cellular fluid & from S.R in to the cell , this increase in cytoplasmic calcium,stimulates uterine contraction by activation of MLCK.

❖Other actions of oxytocin:

- Oxytocin contracts myoepithelial cells in the mammary gland → breast feeding, (Letdown /milk ejection)
- Weak antidiuretic action.

PK

- Not absorbed orally
- Administered by i.v, i.m, & most often given by i.v. infusion to induce labor.
- Not bound to plasma proteins
- $t_{1/2}$: 5- 15 minutes
- Metabolized in liver & kidney & by placental oxytocinase.

❖ Clinical Uses of oxytocin:

- !!!! Considered the drug of choice to induce or augment labor at term when the uterine muscle is not functioning adequately. Clinically oxytocin is given only when uterine cervix is soft & dilated.
- Postpartum uterine hemorrhage
- Following incomplete abortion (but PGs are preferred).

❖ Uses cont'd

1. Induction of labor

- Intrauterine growth retardation
- Placental insufficiency as in (diabetes, pre -eclampsia)
- Uterine inertia uterus is not responsive
- Incomplete abortion to clean the remaining debris
- Post maturity.

Dosage:

Slow I.V infusion 1-2 mU /min then gradually increase the dose to 5-30 mU/min.

2. Postpartum uterine hemorrhage

- Given slow I.V injection 5 units followed by I.V infusion of 5-200 in severe cases.

3. Impaired milk ejection

- One puff in each nostril 2-3 min before nursing.

❖ Side Effects: (with over dose mainly)

- Maternal death
- Uterine rupture
- Fetal death {due to Ischemia >> due to the blood vessel constriction }
- Water intoxication (weak anti-diuretic effect see next slide) & hyponatremia
- Hypertension (due to water retention)
- Allergic reactions.

Overdose:

Rupture of the uterus, fetal distress, & maternal injury.

N.B: for reading

- Because oxytocin is a posterior pituitary hormone , when extracted some of it is mixed with ADH (anti diuretic hormone) which is also a posterior pituitary hormone
- So when using oxytocin mixed with some ADH >> ADH will cause water retention >> leading to water intoxication
- Also because the use of IV > leads to intoxication

Imp . MOA & their uses

Uterine contraction (fundus)

Used for augmenting or inducing labour

Can lead to uterine rupture

With over dose

Myoepethelial contraction

Used to help mothers in lactation

(nasal spray)

blood vessel constriction

Treat post partum haemorrhage

Can lead to hypertension and ischemia

With over dose

❖ Contraindications:

- Hypersensitivity
- Prematurity
- Placental abnormalities
- Abnormal positioning of the fetus {**to prevent rupture of uterus** }
- Cephalopelvic disproportion {**head of baby is larger than pelvis of the mother .. If given can lead to compression of fetus and uterine rupture**}
- Incompletely dilated cervix

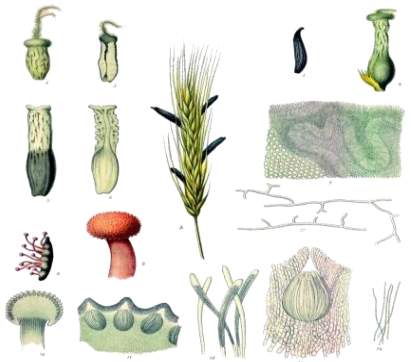
❖ Precautions:

- Monitor mother & fetus, bec over stimulation interferes with blood flow thru the placenta & causes fetal distress/ death.
- previous uterine surgery (Previous c- section)
- Multiple pregnancy
- Hypertension

✓Oxytocin receptor antagonist: ATOCIBAN
{ used in case when over dose is given }

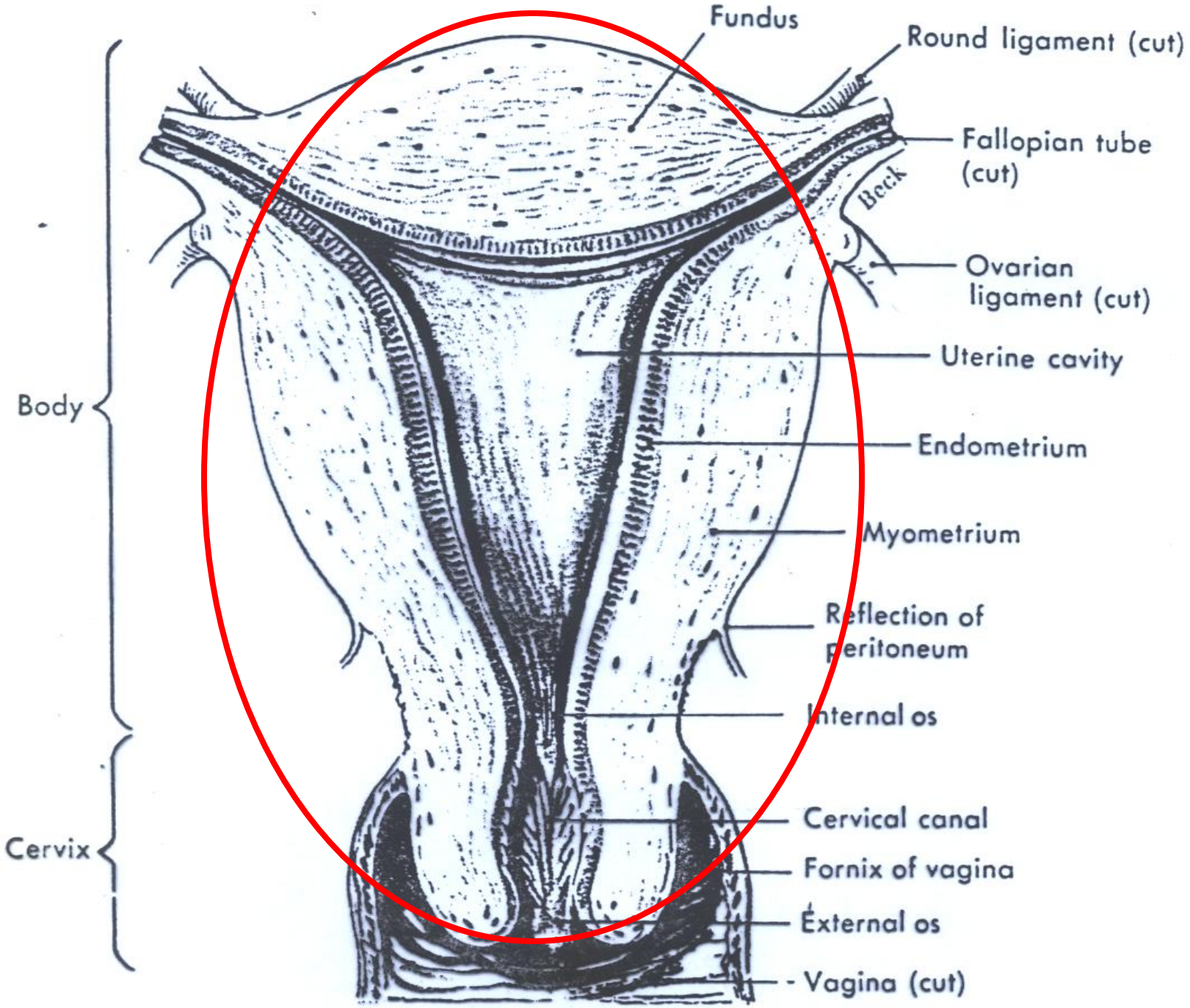
2-ERGOT ALKALOIDS

- Ergometrine (Ergonovine)
- Dihydroergotamine
- Methylergonovine



- Alkaloid derivatives induce **TETANIC CONTRACTION** **{sever contraction}** of uterus with OUT relaxing in between; NOT like the normal physiological contractions **{contraction followed by relaxation}.**

✓ It causes contractions of uterus as a whole i.e. fundus & cervix. (tend to compress rather than to expel the fetus)


Fundus
Round ligament (cut)
Fallopian tube (cut)
Beck
Ovarian ligament (cut)
Uterine cavity
Endometrium
Myometrium
Reflection of peritoneum
Internal os
Cervical canal
Fornix of vagina
External os
Vagina (cut)
Body
Cervix

❖PK:

- Rapid oral absorption
- both ergonovine & methylergonovine can be given im / iv. "fast"
- Duration of action 24 hrs with half life: 2hrs
- Metabolized extensively in liver
- 90% metabolites are excreted in bile.

Has a moderate onset of action (10 minutes) but long duration of action > opposite of oxytocin

❖THERAPEUTIC USES

- Post partum hemorrhage **{ 1st choice b/c it cause very sever contraction}**
- Administered immediately postpartum to obtain marked uterine response.
- (3rd stage of labor)**

When to give it?
3rd stage of labor is when the placenta is expelled after the baby is delivered

❖Preparations

- Syntometrine(ergometrine 0.5 m + oxytocin 5.0 I.U), I.M.

This preperation:
✓ allows it to have a fast onset of action because ergots need around 10 minutes to work
✓It gives it a long duration of action

❖ Adverse effects:

- Nausea, vomiting & diarrhea
- Hypertension {due to the blood vessel constriction, it is the most important side effect }
- Vasoconstriction of peripheral blood vessels
- Gangrene
- Headache.

❖ Contraindications:

- 1st and 2nd stage of labor { b/c the baby still inside }
- Induction of labor {never used to induce labor! Because of its strong and aggressive contraction of the whole uterus }
- vascular disease, HTN," toxemia"{sever hypertension in pregnancy " due to its side effects on the circulatory system}
- impaired hepatic functions. {excreted via liver and kidney , if it is impaired it will stay in the blood for a long time causing more side effects }

N.B:

- what is the drug of choice for treatment of post partum haemorrhage ?

  Answer : ergot alkaloids

- If patients has sever hypertension , what is the drug of choice in post partum haemorrhage ?

  Answer : oxytocin

3-PROSTAGLANDIS

❖Mechanism of action :

➢ **Endogenous:**

- **They are significantly synthesized in endometrium & myometrium**
- **They cause contraction of both the non-pregnant & pregnant uterus but sensitivity increases with gestation.**
- **They play a significant role in:**
  + dysmenorrhea = pain full menstruation &
  + Menorrhagia = hypermenrrhea

➢ **Exogenous:** **{ Dinoprostone (PGE_2) & Carboprost (PGF_2) }**

- **They promote a series of coordinated contraction of body of organ along with relaxation of cervix**
- **Increase uterine tone**
- **Can expel uterine content in early pregnancy.**

❖ THERAPEUTIC USES

1. Oxytocic use for inducing abortion, missed abortion, repining (softening) of cervix {1 choice **imp***}

✓They can work throughout pregnancy (at any stage of pregnancy) (can be used for abortion) unlike oxytocin(only at term)
✓(Oxytocic use or Oxytocic effect = uterine contraction)

- ✓ Stimulate uterine contraction in the 2nd trimester of pregnancy, administered iv, extra –amniotic & vaginal. Initiation to abortion time is 12 to 23 hours
- ✓ for softening of the cervix at term single vaginal insert or jell is administered every 6 hours.

2. For induction & augmentation of labor administered as vaginal tablets & vaginal jell, or as controlled release formulation. **To dilate the cervix PGE2 is used as a gel or suppository preparations**

3. In post partum hemorrhage : It is administered by I.V infusions

❖ Adverse effects:

- Nausea , vomiting & diarrhea
- Abdominal pain
- Bronchospasm
- Flushing.

PGE2 in the periphery causes → vasodilation (flushing)
PGE2 in the uterus causes → vasoconstriction

❖ Contraindications:

- Mechanical obstruction to delivery
- Fetal distress
- Predisposition to uterine rupture (**like c-section)**

❖ Precautions:

- Asthma {**due to bronchospasm }**
- Multiple pregnancy
- Glaucoma {**can raise intraoccular pressure }**
- Uterine rupture

N.B: imp !!

If the mother is at term :

- If the cervix is dilated , but there is no contraction we use **oxytocin** to induce labor
- If the cervix is not dilated and there is contraction we use **PGE2** as gel **or suppository** to dilate cervix

imp!!!! Difference between Oxytocin & PGs

Character	Oxytocin	Prostaglandins
Contraction	Only at term	Contraction through out pregnancy
Effect at myoepithelium	Only in lactating mothers	Contraction in both pregnant & non pregnant woman
Cervix	Does not soften the cervix	Does soften the cervix

Difference (cont'd)

Character	Oxytocin	Prostaglandins
Duration of action	Shorter	Longer
uses	Not used for abortion Used for induction & augmentation of labor & post partum hemorrhage	Used for abortion in 2nd trimester of pregnancy. Used as vaginal suppository for induction of labor

Imp !!!Difference between Oxytocin & Ergometrine

Character	Oxytocin	Ergometrine
Contractions	Resembles normal physiological Contractions {contraction followed by relaxation}	Tetanic contraction ; not similar to normal physiological contractions {continuous contraction}
Uses	To induce labor To Augment labor In post partum hemorrhage	Only in postpartum hemorrhage
Onset Duration	Rapid onset Shorter duration of action	Rapid onset Long duration of onset

UTERINE RELAXANTS

{ Tocolytic Drugs }

Toco= childbirth , **lytic=** inhibition

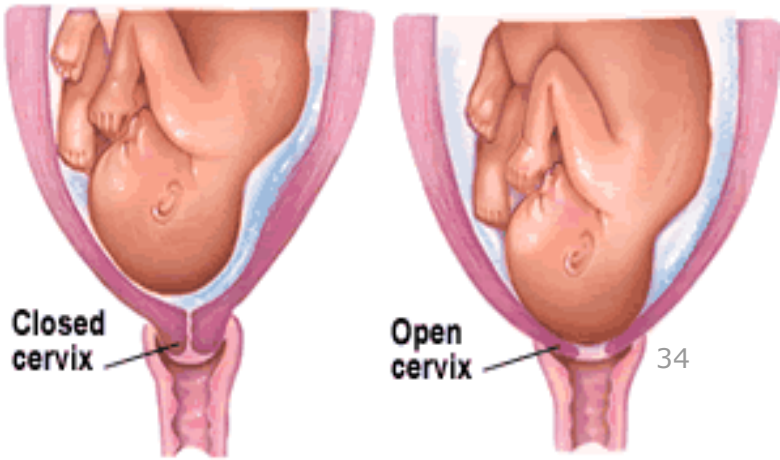
Introduction: Preterm Labor:

abnormal time of delivery

- Cervical changes & uterine contractions that occur before 37 weeks' of gestation.

- **Risk factors for preterm delivery:**

- Previous preterm delivery
- Bacterial infection in (vagina, urinary tract) or sexually transmitted infection.
- Multiple gestation,,,or any other complication.
- Management: tocolytic therapy.



❖ Major Risks Of Preterm Delivery

- Death
- Respiratory distress syndrome
- Hypothermia
- Hypoglycaemia
- Jaundice
- Infection

❖Goal of tocolytics:

- Is to postpone/ delay delivery long enough to reduce the incidence of problems associated with prematurity.

Relax the uterus and arrest susceptible abortion or delay premature labor.

- Allow sufficient time for the administration of antenatal corticosteroids to improve pulmonary maturity

- For transportation of the mother to a facility equipped to deal with high-risk deliveries.

❖ Tocolytics should NOT be used in

- Intrauterine infection
- Fetal distress
- Severe preeclampsia
- Vaginal bleeding
- Maternal hemodynamic instability

All of these situations need to expel the fetus so no relaxation is needed

❖ Tocolytics can be started if

- Regular uterine contraction with cervical change.
- Tocolytics are less effective if cervical dilatation is > 3 cm.

Uterine Relaxants (Tocolytics)

1. **β_2 Adrenergic agonists** **(most commonly use as uterine relaxants) !!!**
2. Ca^{++} channel blockers
3. Magnesium sulfate
4. Nonsteroidal antiinflammatory agents.
5. Magnesium sulfate (i.v. infusion)

دكتور الأولاد قال مو معاكم والبنات تقول معاكم فخليناها احتياط ..

!! These drugs can prolong pregnancy **(delay preterm labor)** from 48 hr- one week. (short period only not for months)

1- β- adrenoceptor agonists

- **E.g.** Ritodrine & terbutaline

❖Mechanism of action :

✓ Bind to β-adrenoceptors → activate enzyme Adenylate cyclase→increase in the level of cAMP → reducing intracellular calcium level & the level of sensitivity of actin myosin contractile unit. → Relaxing the uterus

❖ Adverse effects:

- Nervousness, headache
- Nausea, vomiting
- Flushing
- Sweating
- Tremors : (all beta blockers cause tremor)
- Tachycardia, arrhythmia (it can lose its selectivity to B2 and affect B1 " heart")
- Hypotension : vasodilatation
- Hyperglycemia
- Hypokalaemia

❖ USES :

- To prevent Premature labor (To delay labour)
  I.v infusion 50µg/min

❖ CI: Heart disease, diabetes, on beta blockers.

2- Calcium channel antagonists

- **E.g.** Nifedipine.

❖ **MOA:** Reduce Ca entry→ Reduced tone & Cause relaxation of myometrium

✓ Markedly inhibits the amplitude of spontaneous & oxytocin-induced contractions

3- Prostaglandin synthesis inhibitors=NSAIDs

- The depletion of prostaglandins prevents stimulation of uterus.

e.g.

- Aspirin
- Indomethacin
- Ibuprofen

✓ Given orally /rectally.

4- Magnesium sulfate (i.v. infusion)

❖ Mechanism of action

- It competes with calcium & antagonize intracellular Ca^{2+}

- Higher doses are required to inhibit contractions.

Questions

Q1. A healthy pregnant woman admitted to the hospital for labor and she was about 10 days post term. After examination, the uterine cervix was soft. Which one of the following drugs is to be selected to induce labor?

a) Ergonovine
b) Prostaglandin E2
c) Oxytocin ←
d) Prostaglandin F2 alpha

Q2. Which one of the following drugs is clinically used to delay preterm labor?

a) Syntocinon
b) Ritodrine ←
c) Prostaglandin E2
d) Ergonovine

Q3. Which one of the following statements regarding ergometrine (ergonovine) is correct?

a) It is commonly used to induce abortion in 2nd trimester of pregnancy.
b) It is used as vaginal suppositories to dilate the cervix.
c) It is used only to control post partum haemorrhage. ←
d) It is used to induce labor only at term.