YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 5 - Pharmacology

Lec. Title : Drugs acting on uterus

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Drugs acting on uterus Oxytocic and Tocolytic Drugs

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Objectives

- Describe drugs (stimulants and relaxants) of the uterus and their therapeuticuses and adverse effects.

Drugs Producing Uterine Contractions (Oxytocic Drugs)

- Drugs that stimulate the uterus

• Used antepartum to induce uterine contractions

• Used postpartum to prevent haemorrhage

1. **OXYTOCIN**
2. **ERGOT ALKALOIDS**

   Ergometrine (Ergonovine)
3. **PROSTAGLANDINS**
   - **a) PGE2**
   - **b) PGF2α**

Sheet# 1

*the name came from oxytocin because it is the natural contractive for uterus during labour

Antepartum = before labour
Postpartum = after labour --} it prevent haemorrhage due to its vasoconstriction effect

1. **Oxytocin** : it is synthetic compound analogue to our natural oxytocin
2. **ERGOT ALKALOIDS (ergometrine) :** best medication used for postpartum to prevent haemorrhage
3. **Prostaglandins :** uterus contractive stimulus

*we should know the difference between oxytocin and prostaglandin & when to use them

OXYTOCIN (Syntocinon®)

Synthesis

- **Is a posterior pituitary hormone secreted by the posterior pituitary gland.**

- **Oxytocin secretion occurs by sensory stimulation from cervix ,vagina , and from suckling at breast.**

When the secretion of Oxytocin is the most in females during pregnancy ?
Third trimester
*** If women had abortion in first trimester I cant give her oxytocin cause there will be no respond**

Mechanism of action

- **The interaction of endogenous or administered oxytocin , with myometrial cell membrane receptor promotes the influx of ca ++ from extra cellular fluid and from S.R in to the cell , this increase in cytoplasmic calcium ,stimulates uterine contraction .**

Mechanism of stimulation of uterine smooth muscle contraction

important

Oxytocin

↓

G protein-coupled membrane receptor

↓

IP_3 generation

↓ ↓

intracellular Ca^{2+} release from SR

extracellular Ca^{2+}

↓ ↓

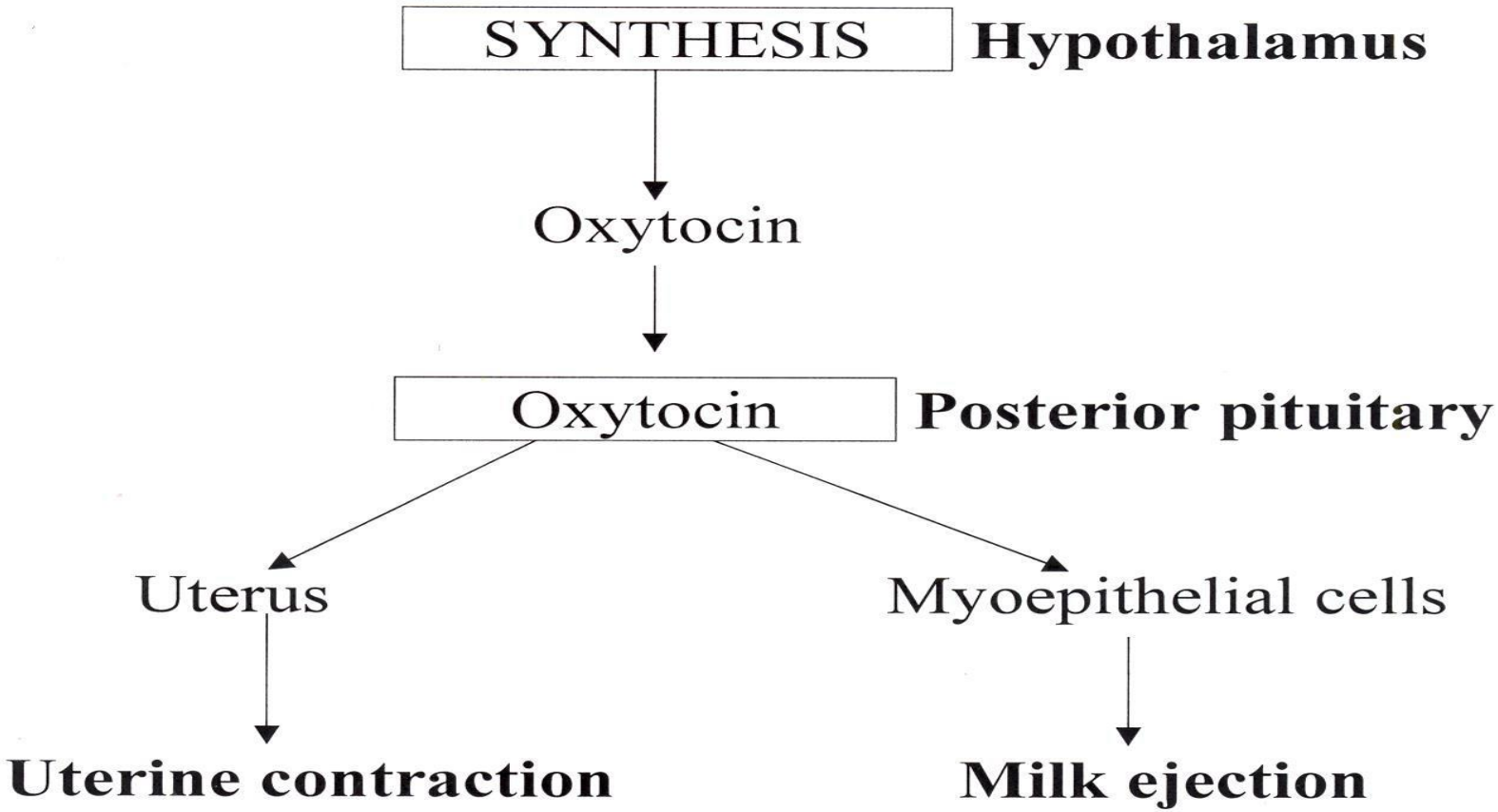
Ca^{2+} in cytoplasm increased

↓

Contraction

IP_3: inositol triphosphate
SR: sarcoplasmic reticulum

OXYTOCIN


SYNTHESIS
Hypothalamus
Oxytocin
Oxytocin
Posterior pituitary
Uterus
Myoepithelial cells
Uterine contraction
Milk ejection

Sheet# 2

When the oxytocin will be secreted ?
1.Cervix or uterus stimulation
2. Sucking breast
Sucking breast make uterus return to normal due to stimulation for oxytocin secretion → contraction of uterus → return to normal size

Oxytocin

- Action
- Stimulates uterine smooth muscle
- Produces contractions similar to those in spontaneous labour
- Stimulates mammary gland smooth muscle
  - Facilitates lactation
- Has vasopressor and antidiuretic effects

Sheet# 3

*lactation happens after delivery because oxytocin stimulation

- If women has decreased lactation we use oxytocin derivatives (intra-nasal spray oxytocin) to stimulate lactation

Vasopressor → increase pressure , decrease postpartum haemorrhage

Pharmacokinetics of oxytocin

Absorption ,Metabolism and Excretion

Increase of oxytocin concentration led to uterus rupture
Nasal spry for stimulate lactation

- Not effective orally
- Administered intravenously
- Also as nasal spray
- Not bound to plasma proteins
- Catabolized by liver & kidneys
- Half life = 5 minutes

Role of oxytocin

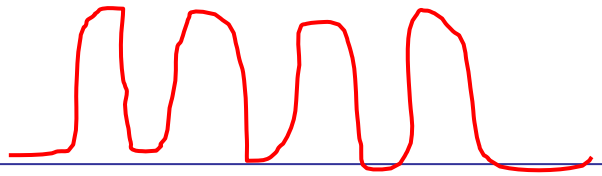
Frequency and force depend on the dose

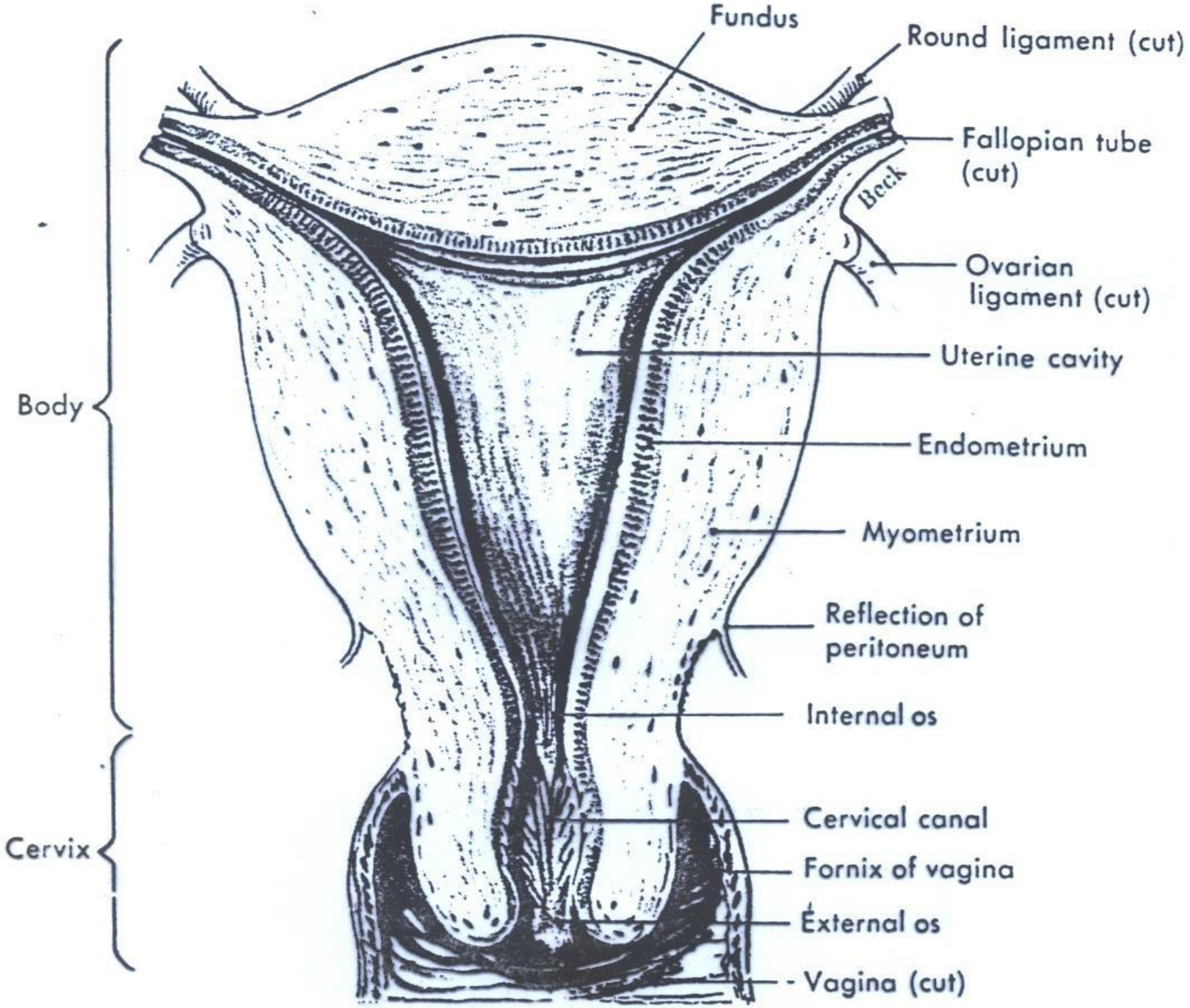
Fundus segment will expel the baby not compress

Uterus

- **Stimulates both the frequency and force of uterine contractility particularly of the fundus segment of the uterus.**

- **These contractions resemble the normal physiological contractions of uterus (contractions followed by relaxation)**




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

Uterus

- As we said we give oxytocin in third trimester
- We can't give oxytocin when the cervix is tough

- **Immature uterus is resistant to oxytocin.**
- **Contract uterine smooth muscle only at term.**
- **Sensitivity increases to 8 fold in last 9 weeks and 30 times in early labour.**
- **Clinically oxytocin is given only when uterine cervix is soft and dilated.**

Oxytocin Uses

- It must be slow infusion because uterus may rupture
- Oxytocin is contraindicated in women with previous C/S

- Induction/augmentation of labour

  (slow I.V infusion) IV 1mU/min initially and increased to 5-20 mU/min gradually

- Management of incomplete abortion
- Control postpartum bleeding and haemorrhage **(I.V drip)**
- Stimulate milk letdown reflex (intranasal)

  One puff in each nostril 2-3 min before nursing

Side Effects:

a) Hypertension due to its ADH-like activity

b) Uterine rupture

c) Fetal death(ischaemia)

d) Neonatal jaundice

Contraindications

a) **Hypersensitivity**
b) **Prematurity**
c) **Abnormal fetal position**

Precautions

a) Multiple pregnancy
b) Previous c- section
c) Hypertension → preeclampsia

Ergot Alkaloids

- Ergometrine (Ergonovine)
- Methylergonovine

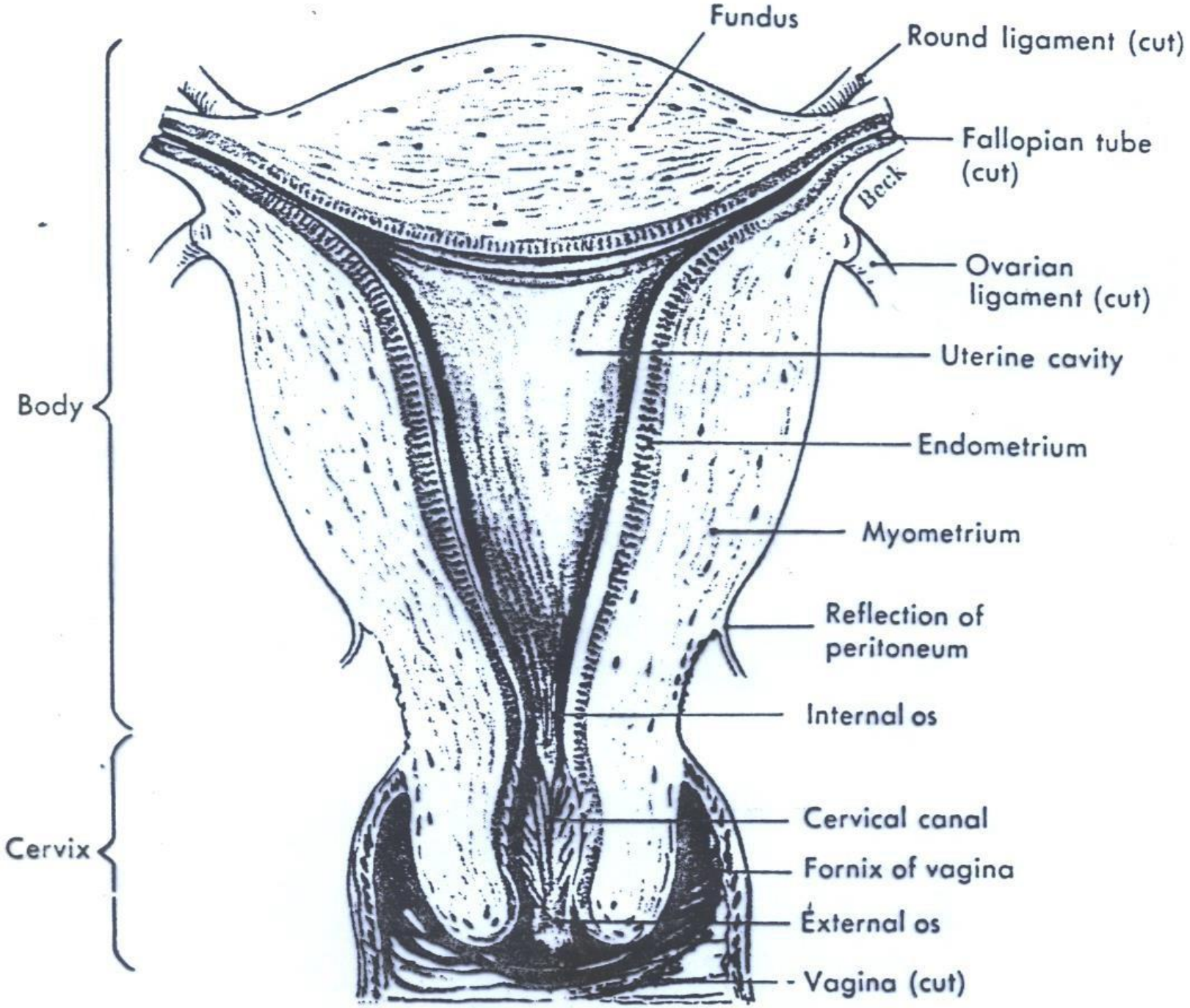
Effects on the Uterus

- **Alkaloid derivatives induce TETANIC CONTRACTION of uterus without relaxation in between. These does not resemble the normal physiological contractions**
- **It causes contractions of uterus as a whole i.e. fundus and cervix(tend to compress rather than to expel the fetus)**

Difference between oxytocin & ergots??

Sheet# 4

* Uterus contraction with out relaxation (not normal) → compress the cervical more than fundus →infant ischemia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Body
Cervix

Ergot alkaloids(pharmacokinetics)

- **Absorption ,fate and excretion**
- **Absorbed orally from GIT(tablets)**
- **Usually given I.M**
- **Extensively metabolized in liver.**
- **90% of metabolites are excreted in bile**
-

Most of the postpartum we give it IM

Clinical uses

- **When to give it?**
- **Post partum haemorrhage (3rd stage of labour)**

Preparations

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

Side effects

- It is stronger vasopressor than oxytocin
- Blockage of a2-adrenoreceptor → inhibit the inhibitory (a1 agonist)

a) Nausea, vomiting, diarrhea

b) Hypertension

c) Vasoconstriction of peripheral blood vessels (toes & fingers) blockade of *α*-adrenoceptor

c) Gangrene

Ergot alkaloids

Contraindication
a) It will cause compression
Severe hyper tension , cardiac disease ,
multiple pregnancy (cause uterine rupture)

* **Contraindications:**

a) 1st and 2nd stage of labour

b) vascular disease

c) impaired hepatic and renal functions

* **Precautions:**

a) Cardiac diseases

b) Hypertension

c) Multiple pregnancy

Remember

Ergot alkaloids remain the drugs of choice to manage postpartum haemorrhage

As compared to oxytocin, ergot alkaloids are more potent, they produce more prolonged and sustained contractions of the uterus and they are less toxic

Ergot alkaloids are contraindicated to be used as inducers to delivery (associated with high incidence of fetal distress and mortality)

Sheet# 5

Drug of choice for induction ,propagation and augmentation in 1st & 2nd stage of labour is **Oxytocin**

- If we give **Ergot alkaloids** in the beginning of labour → the baby will be delivered dead (compression, increased fatality rate, the baby compressed in lateral way)

Prostaglandins
(PGE2 & PGF2α)

- dinoprostone (PGE_2) dinoprost ($PGF_{2\alpha}$)
- **Mechanism Of Action:**
- Contract uterine smooth muscle

Difference between PGS and Oxytocin:

- PGS contract uterine smooth muscle not only at term (as with oxytocin), but throughout pregnancy.
- PGS soen the cervix; whereas oxytocin does not.
- PGS have longer duration of action than oxytocin.

Sheet# 6

- **Prostaglandin are contraindicated in asthma patients**
- Uterus respond to PG in any stage of pregnancy
- **Oxytocin** have shorter duration of action (5min) → giving as drips or even less

Prostaglandins (PGE2 & PGF2α)

- **Therapeutic uses**

1. **Induction of abortion (pathological)**
2. **Induction of labour (fetal death in utero)**
3. **Postpartum haemorrhage**

Side Effects

a) Nausea , vomiting

b) Abdominal pain

c) Diarrhea

d) Bronchospasm (PGF2α)

e) Flushing (PGE2)

- **Contraindications:**
  - a) Mechanical obstruction of delivery
  - b) Fetal distress
  - c) Predisposition to uterine rupture

- **Precautions:**
  - a) Asthma (PGF2α)
  - b) Multiple pregnancy
  - c) Glaucoma (PGE2)
  - d) Uterine rupture

Difference B/w Oxytocin and Prostaglandins

Character	Oxytocin	Prostaglandins
Contraction	Only at term	Contraction through out pregnancy
Cervix	Does not soften the cervix	soften the cervix

Difference (cont'd)

Character	Oxytocin	Prostaglandins
Duration of action	**Shorter**	**Longer**
uses	**Not used for abortion** **Used for induction and augmentation of labour and post partum haemorrhage**	**Used for abortion in 2nd trimester of pregnancy.** **Used as vaginal suppository for induction of labour**

Difference b/w Oxytocin and Ergometrine

Character	Oxytocin	Ergometrine
Contractions	Resembles normal physiological contractions	Tetanic contraction ; doesn't resemble normal physiological contractions
Uses	*To induce &augment labour. *Post partum haemorrhage	Only in P.partum haemorrhage
Onset and Duration	Rapid onset Shorter duration of action	Moderate onset Long duration of action

UTERINE RELAXANTS

Tocolytic Drugs

Drugs that delay labour

Drugs Producing Uterine Relaxation (Tocolytic Drugs).

Action and Uses

- **Relax the uterus and arrest threatened abortion or delay premature labour.**
- **** Major contraindication to tocolytics: fetal distress**

β- adrenoceptor agonists

1.β-adrenoceptor agonists

Ritodrine, i.v. drip

Selective β_2 receptor agonist used specifically as a uterine relaxant.

- **Terbutaline, Oral, S.C, I.V**

Side Effects to β-adrenergics:

Sweating, tachycardia, chest pain…

* Ritodrine & terbutaline also used in asthma

2. Magnesium sulfate

I.V infusion

Activates adenylate cyclase and stimulates Ca^{++} dependent ATPase

Uses: premature delivery and convulsions of pre- eclampsia

Tocolytic Drugs

3. Progesterone

Oral, I.M labour+ vaginal suppository

4.Oxytocin competitive antagonists

Atosiban

5. Prostaglandin synthesis inhibitors

Aspirin, Indomethacin, Meloxicam

6. CCB: Nifedipine

Causes relaxation of myometrium

Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions

Sheet# 7

- **Progesterone** is no.1 because it is the main hormone for endometrial formulation and vascularization
  progesterone vaginal sup: concentration 200 or 400 mg
  Copestone → given twice daily starting from the 2nd month of pregnancy

Atosiban :
for multiple abortion it is very expensive, used from 2nd month of pregnancy till 5th month

Aspirin: (NSAIDS)
there is protocol that pregnant take one pill baby aspirin from the beginning of the 4th month till she gives birth

*aspirin → anticoagulant some abortion cases the umbilical cord blocks and no blood supply reaches the fetus

Nifedipine : oxytocin antagonist → used during premature labour