Tocolytics and Oxytocin

Lecture

By

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Objectives

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

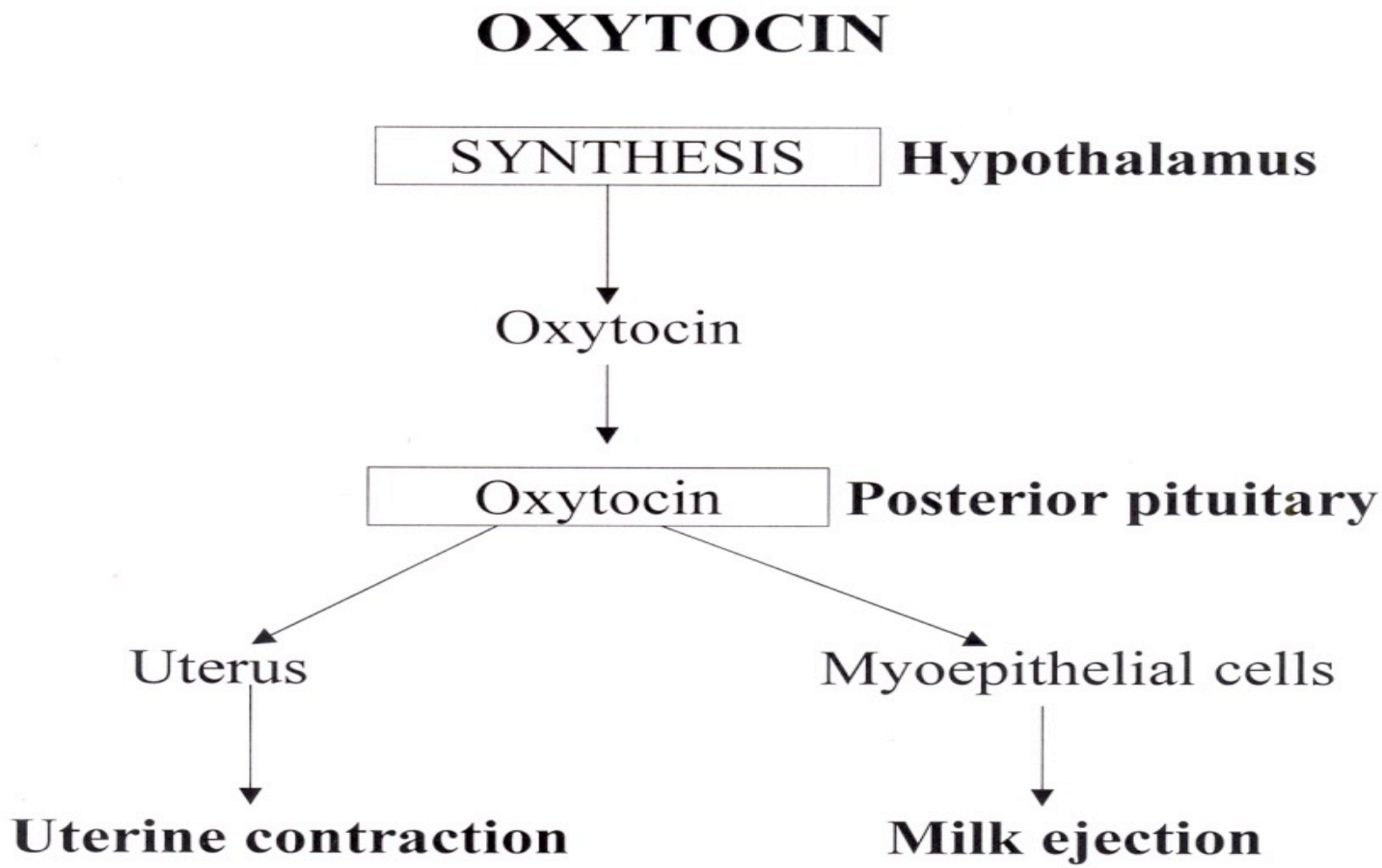
1. Drugs used to induce & augment labor
2. Drugs used to control post partum hemorrhage
3. Drugs used to induce pathological abortion
4. Drugs used to arrest premature labor
5. The mechanism of action and adverse effects of each drug.

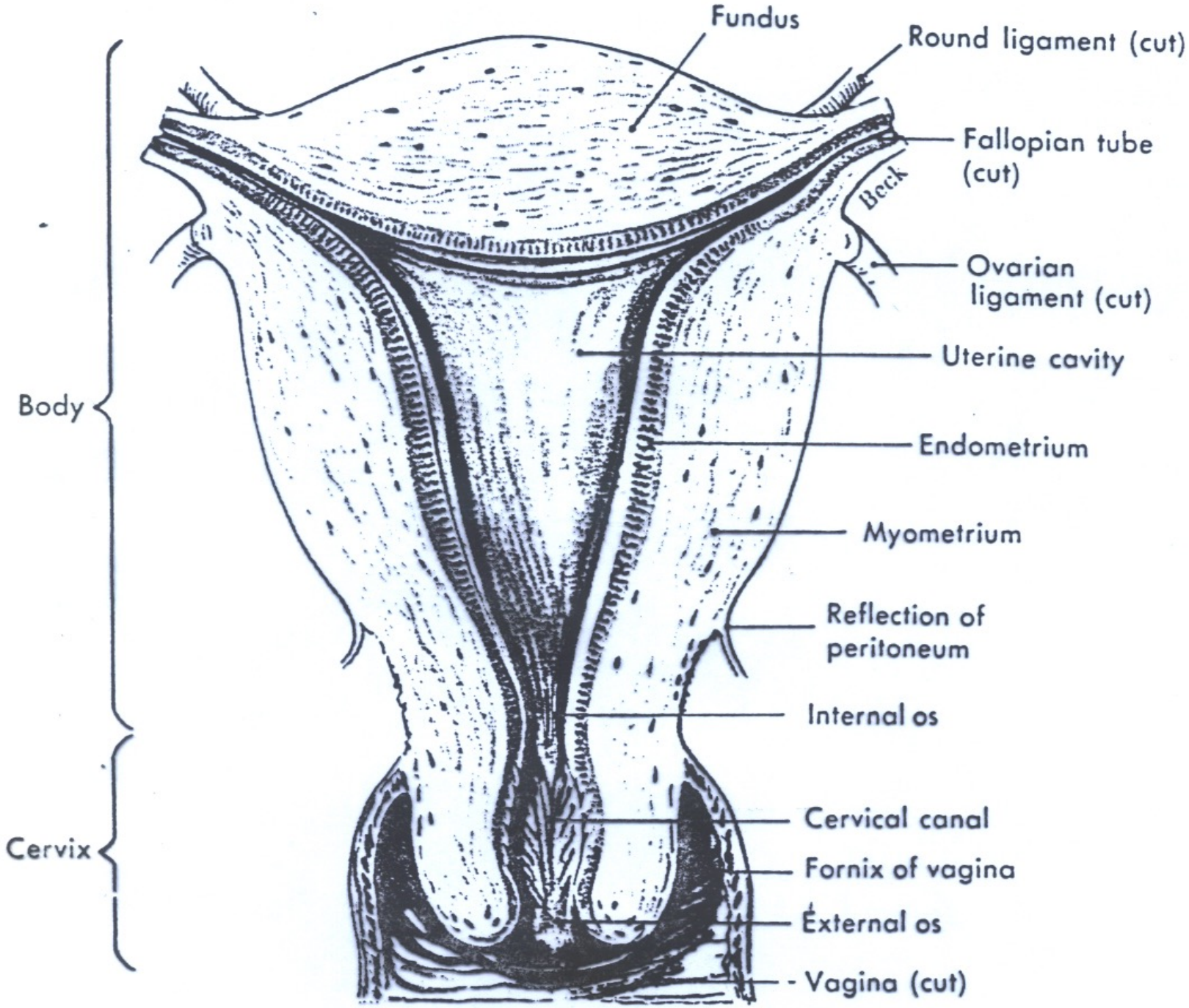
DRUGS PRODUCING UTERINE CONTRACTIONS (Oxytocic Drugs)

1. OXYTOCIN
   a) Syntocinon

2. ERGOT ALKALOIDS
   a) Ergometrine (Ergonovine)
   b) Methyl ergometrine (methyl ergonovine)

3. PROSTAGLANDINS
   a) PGE2
   b) PGF2α
   c) PGE1 (misoprostol).


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

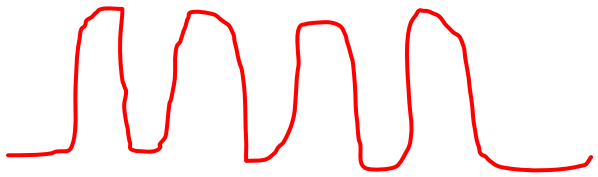

Fundus
Round ligament (cut)
Fallopian tube (cut)
Beck
Ovarian ligament (cut)
Uterine cavity
Endometrium
Myometrium
Reflection of peritoneum
Internal os
Cervical canal
Fornix of vagina
External os
Vagina (cut)
Body
Cervix

Role of oxytocin

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)**.



Role of oxytocin (cont.)

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

Role of oxytocin

Myo-epithelial cells

Oxytocin contracts myoepithelial cells surrounding mammary alveoli in the breast & leads to milk ejection.

Pharmacokinetics of oxytocin

- **Absorption, Metabolism and Excretion**

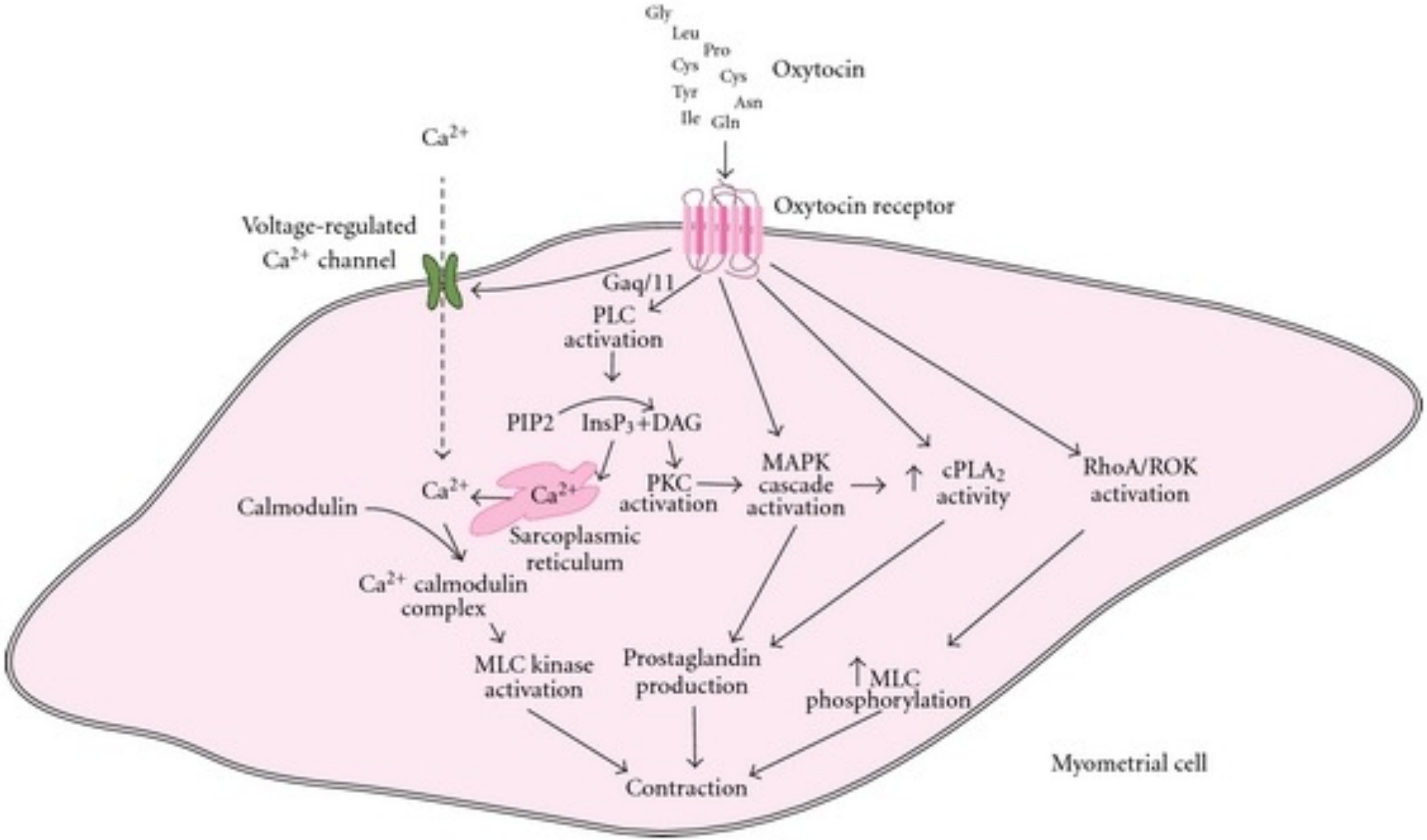
- **Not effective orally (destroyed in GIT)**
- **Administered i.v. (augment labor)**
- **Also as nasal spray (impaired milk ejection)**
- **Not bound to plasma proteins**
- **Eliminated by liver & kidneys**
- **Half life = 5 minutes.**

Mechanism of action

- **Oxytocin acts through G protein-coupled receptors & the phosphoinositide-calcium 2nd-messenger system to contract uterine smooth muscle**
- **The interaction of endogenous or administered oxytocin with myometrial cell membrane receptor promotes :**

the influx of Ca^{++} from extra cellular fluid & from S.R. into the cell, this increase in cytoplasmic Ca^{++} , stimulates uterine contraction.

S.R. Sarcoplasmic Reticulum


Gly
Leu
Pro
Cys
Cys
Oxytocin
Tyr
Asn
Ile
Gln
Ca^{2+}
Oxytocin receptor
Voltage-regulated
Ca^{2+} channel
Gaq/11
PLC
activation
PIP2
$InsP_3$+DAG
Ca^{2+}
Ca^{2+}
PKC
activation
MAPK
cascade
activation
↑ $cPLA_2$
activity
RhoA/ROK
activation
Calmodulin
Sarcoplasmic
reticulum
Ca^{2+} calmodulin
complex
MLC kinase
activation
Prostaglandin
production
↑MLC
phosphorylation
Myometrial cell
Contraction

Therapeutic Uses of Oxytocin

- **Synthetic preparations of oxytocin; e.g. syntocinon are preferred.**

1. Induction & augmentation of labor* (slow I.V infusion)

a) **Mild preeclampsia near term**
b) **Uterine inertia**
c) **Incomplete abortion**
d) **Post maturity**
e) **Maternal diabetes**

Therapeutic Uses of Oxytocin

2. **Post partum uterine hemorrhage (I.V drip)**

   (ergometrine is often used ??)

3. **Impaired milk ejection**

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

Oxytocin Side Effects

- **Maternal death due to hypertension**
- **Uterine rupture**
- **Fetal death (ischemia)**
- **Water intoxication if oxytocin is given with relatively large volumes of electrolyte-free aqueous iv fluid.**

Oxytocin Contraindications

- Hypersensitivity
- Prematurity
- Abnormal fetal position
- Evidence of fetal distress
- Cephalopelvic disproportion
- Incompletely dilated cervix.

Oxytocin Precautions

- **Multiple pregnancy**
- **Previous c- section**
- **Hypertension.**

Ergot Alkaloids

Natural

- Ergometrine (Ergonovine)
- Is a fungus that grow on rye & contains pharmacologically active substances.

Synthetic

- Methyl ergometrine (Methylergonovine)

Effects on the Uterus

- **Ergot alkaloids induce TETANIC CONTRACTION of uterus without relaxation in between (not like 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??**

Ergot alkaloids (pharmacokinetics)

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

Clinical uses

- **Post partum hemorrhage (3rd stage of labor)****

  When to give it?

- **<u>Preparations</u>:**

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

Ergot alkaloids Side effects

- **Nausea, vomiting, diarrhea**
- **Hypertension**
- **Vasoconstriction of peripheral blood vessels (toes & fingers)**
- **Gangrene.**

Ergot Contraindications:

1. **Induction of labor**

   a) 1st and 2nd stage of labor
   b) vascular disease
   c) Severe hepatic and renal impairment
   d) Severe hypertension

PROSTAGLANDINS

- PGE2 – Dinoprostone
  - Vaginal suppository/gel
  - Extra- amniotic solution

- PGF2α- Dinoprost, Carboprost
  - Intra-amniotic injection

- Misoprostol (synthetic PGE1).

Prostaglandins therapeutic uses

- **Induction of abortion in early & late pregnancy (pathological)****
- **Induction of labor (fetal death in utero)**
- **Postpartum hemorrhage.**

Difference between PGs and Oxytocin:

- PGs promote coordinated contraction of uterine smooth muscle not only at term (as with oxytocin), but throughout pregnancy
- PGs soften/relax the cervix; whereas oxytocin does not
- PGs have longer duration of action than oxytocin.

Prostaglandins side effects

- **Nausea , vomiting**
- **Abdominal pain**
- **Diarrhea**
- **Bronchospasm (PGF2α)**
- **Flushing (PGE2).**

Prostaglandins

- **Contraindications:**
  - **Mechanical obstruction of delivery**
  - **Fetal distress**
  - **Predisposition to uterine rupture**

- **Precautions:**
  - **Asthma**
  - **Multiple pregnancy**
  - **Glaucoma**
  - **Uterine rupture**

Difference between 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	• Induce and augment labor & post partum hemorrhage	• Induce abortion in 2nd trimester of pregnancy • Used as vaginal suppository for induction of labor.

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 labor • Post partum hemorrhage	• Only in postpartum hemorrhage
Onset and Duration	• Rapid onset • Shorter duration of action	• Moderate onset • Long duration of action

UTERINE RELAXANTS

DRUGS PRODUCING UTERINE RELAXATION (Tocolytic Drugs)

- **Action and Uses:**

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

- **β-Adrenoceptor agonists****
  - **Ritodrine, i.v. drip**
  - **Selective β_2 receptor agonist used specifically as a uterine relaxant.**

β- adrenoceptor agonists

- **Mechanism of action**

- **Bind to β-adrenoceptors , activate enzyme Adenylate cyclase, increase in the level of cAMP reducing intracellular calcium level.**

β- adrenoceptor agonists Side Effects

- Tremor
- Nausea , vomiting
- Flushing
- Sweating
- Tachycardia (high dose)
- Hypotension
- Hyperglycemia
- Hypokalemia.

CALCIUM CHANNEL BLOCKERS

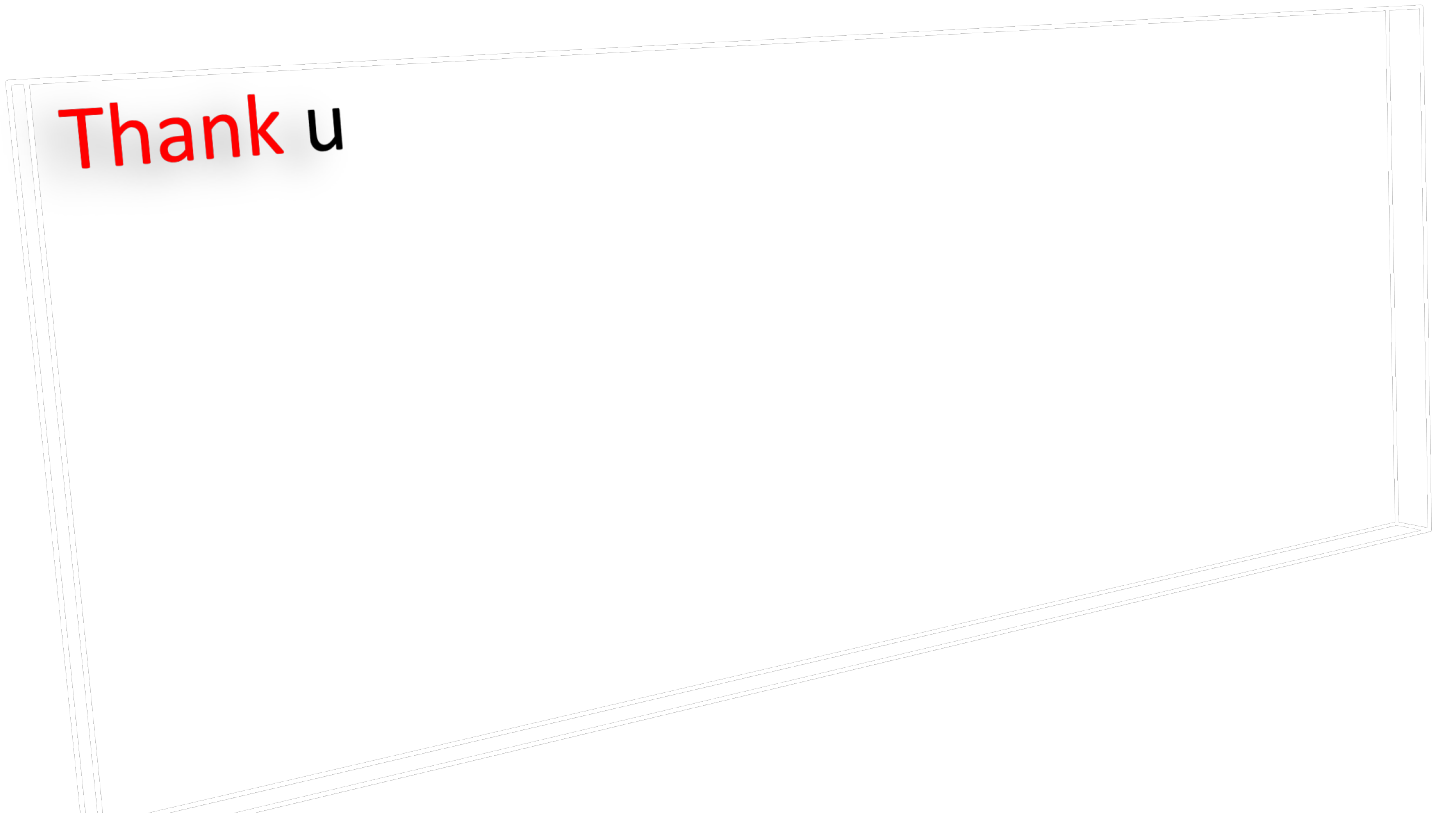
- **Nifedipine**
- **Causes relaxation of myometrium**
- **Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions.**

CALCIUM CHANNEL BLOCKERS Side effects

- Headache, dizziness
- Hypotension
- Flushing
- Constipation
- Ankle edema
- Coughing
- Wheezing
- Tachycardia.

Atosiban

- **New tocolytic agent**
- **Compete with oxytocin at its receptors on the uterus.**
- **Given by IV infusion for 48 hrs**


Thank u