Drugs acting on uterus Oxytocic and Tocolytic Drugs

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UGS

Faculty of Medicine

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 hemorrhage

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

   Ergometrine (Ergonovine)
3. **PROSTAGLANDINS**

   a) PGE2

   b) PGF2α

OXYTOCIN (Syntocinon®)

Synthesis

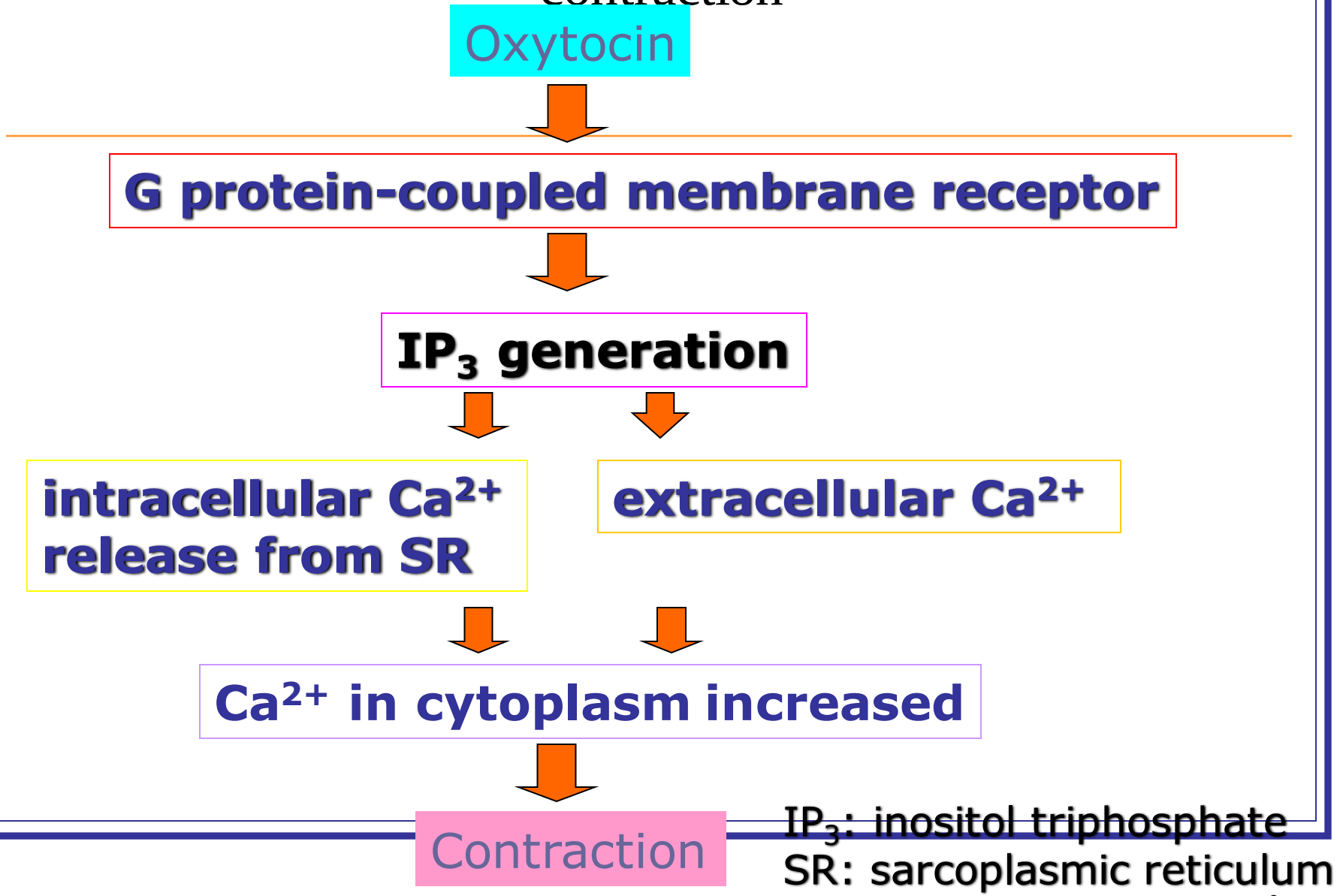
- **Is a posterior pituitary hormone secreted by the posterior pituitary gland.**

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

Mechanism of action

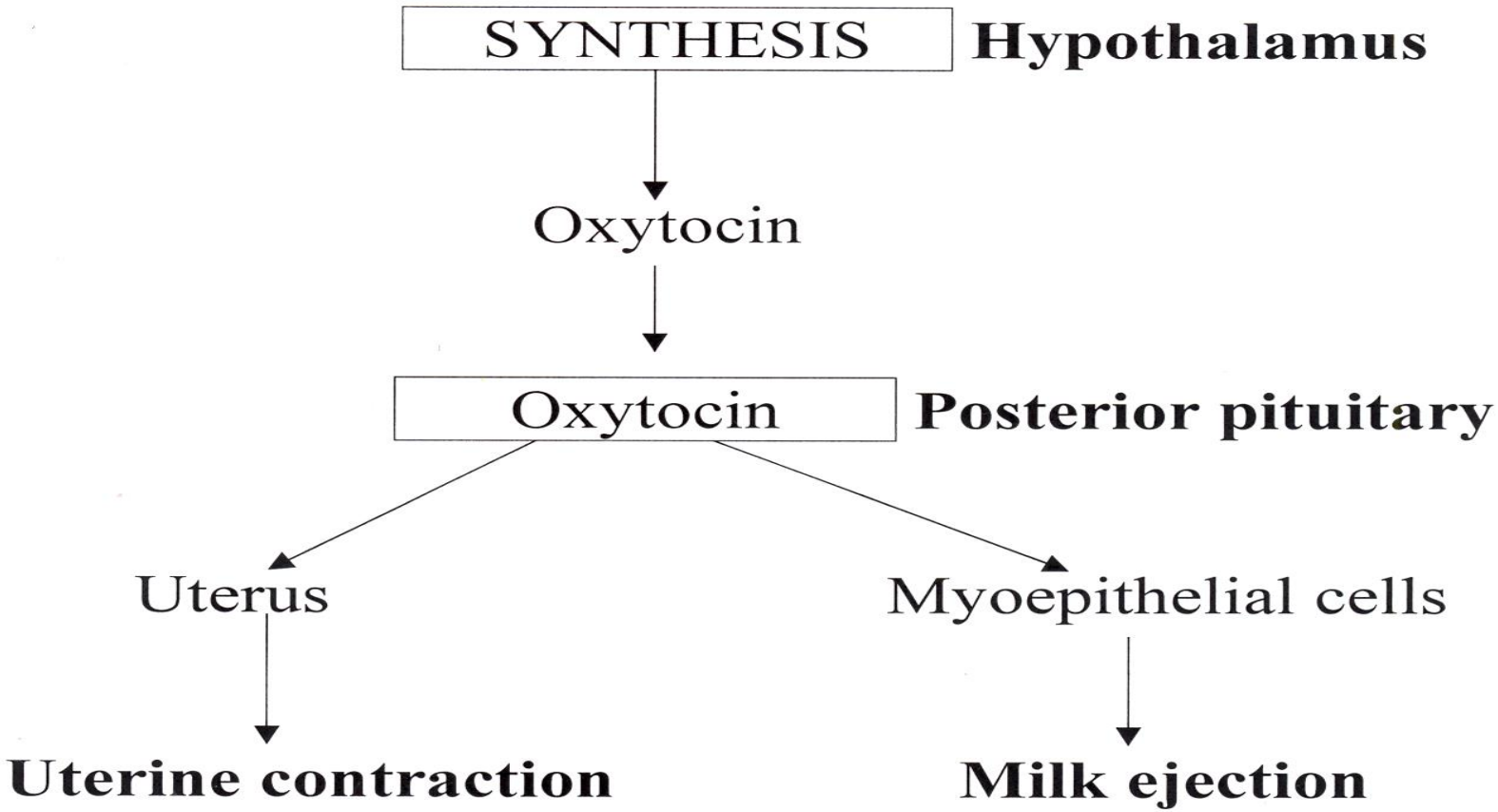
- **The interaction of endogenous or administered oxytocin , with myometrial cell membrane receptor promotes the influx of ca ++ from extra cellular fluid and from S.R in to the cell , this increase in cytoplasmic calcium ,stimulates uterine contraction .**

Mechanism of stimulation of uterine smooth muscle contraction



IP_3: inositol triphosphate
SR: sarcoplasmic reticulum

OXYTOCIN


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

Oxytocin

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

Pharmacokinetics of oxytocin

Absorption ,Metabolism and Excretion

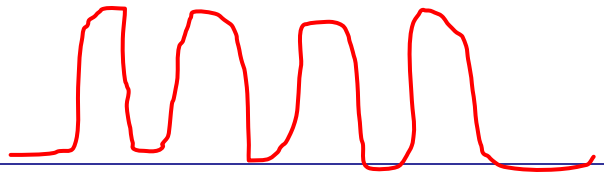
- Not effective orally
- Administered intravenously
- Also as nasal spray
- Not bound to plasma proteins
- Catabolized by liver & kidneys
- Half life = 5 minutes

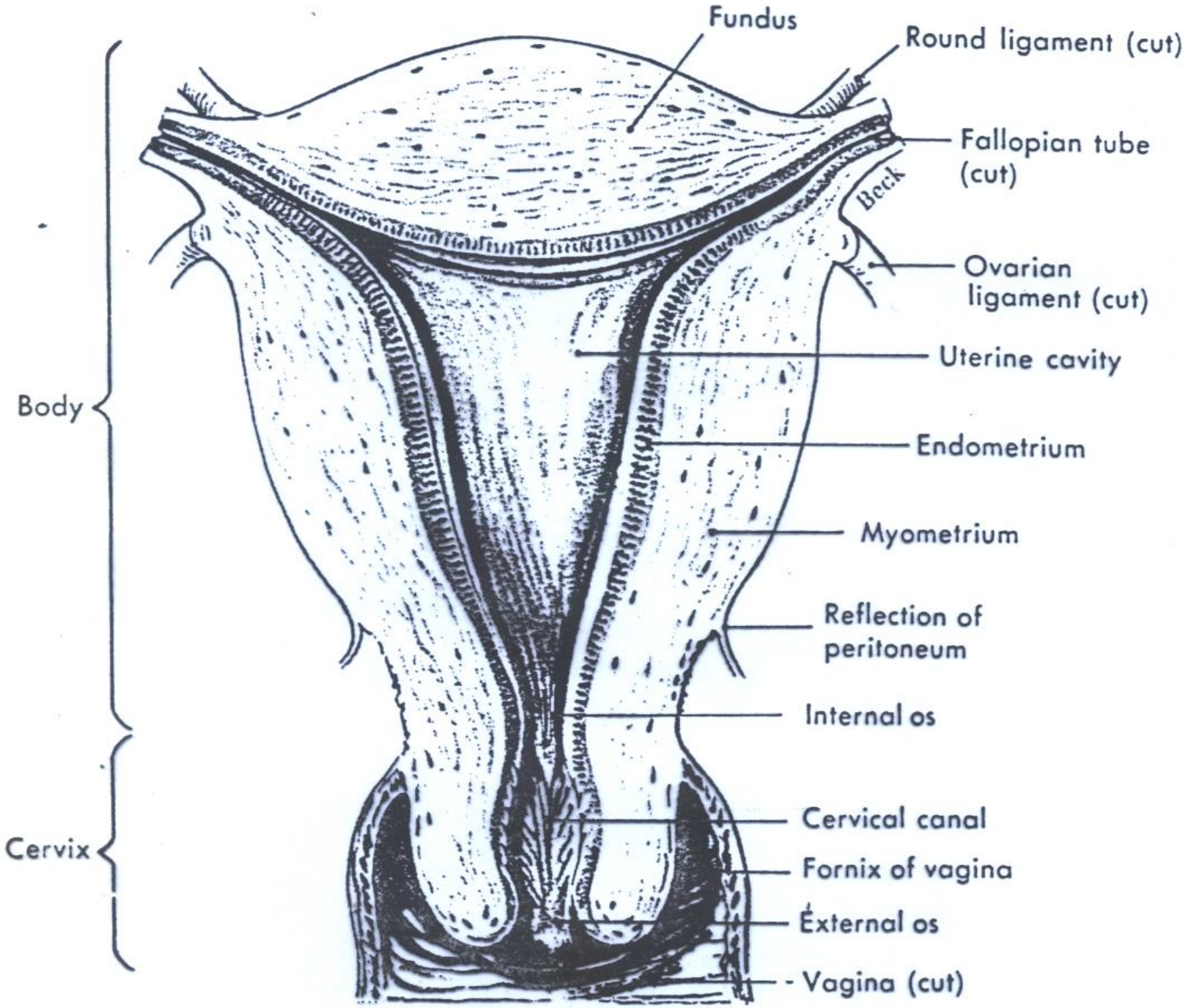
Role of oxytocin

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

- 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 labor.
- Clinically oxytocin is given only when uterine cervix is soft and dilated.

Oxytocin Uses

- Induction/augmentation of labor

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

- Management of incomplete abortion
- Control postpartum bleeding and hemorrhage **(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

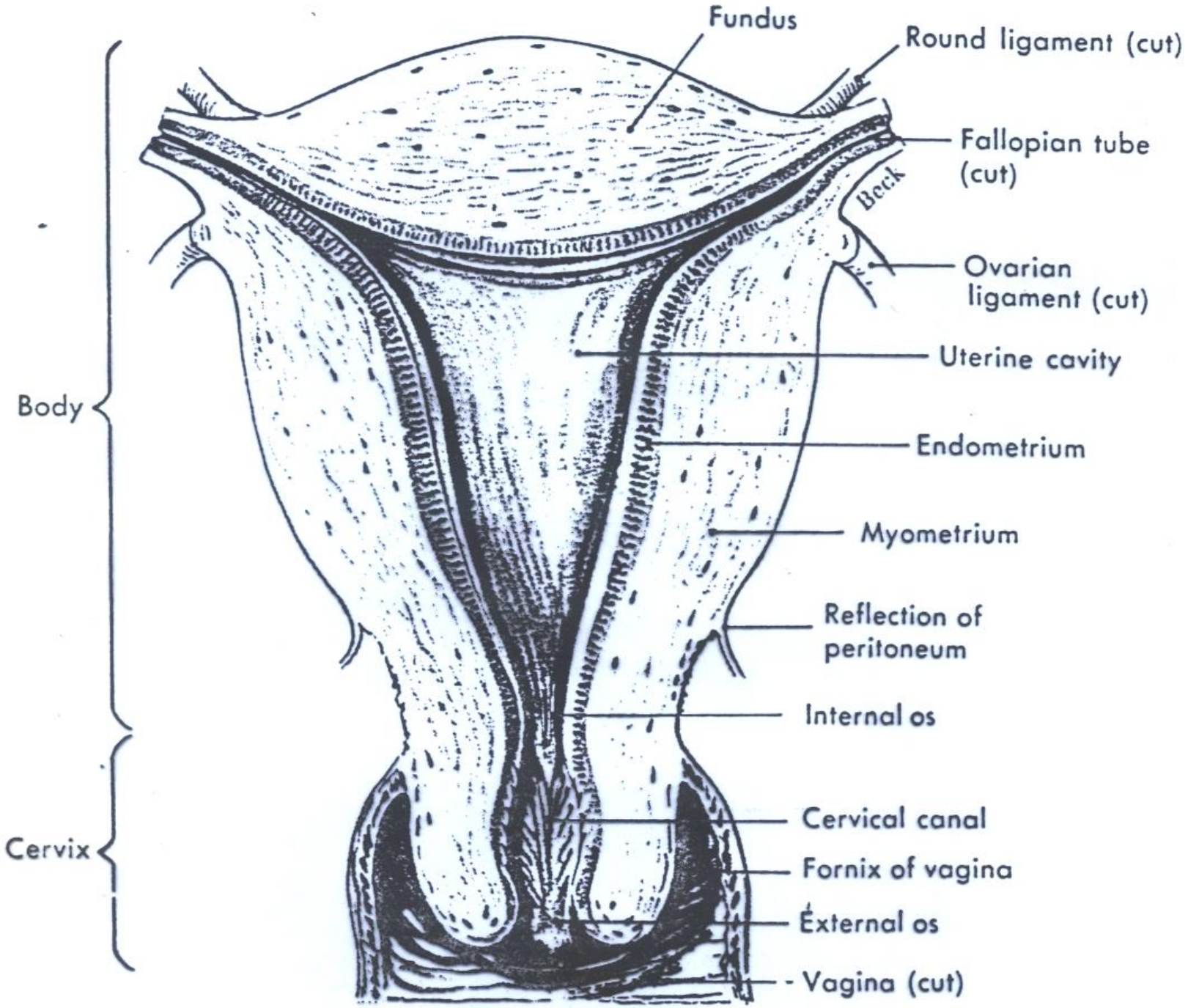
Ergot Alkaloids

- 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??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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**
-

Clinical uses

- **When to give it?**
- **Post partum hemorrhage (3rd stage of labor)**

Preparations

Syntometrine(ergometrine 0.5 mg

+ oxytocin 5.0 I.U), I.M.

Side effects

a) Nausea, vomiting, diarrhea

b) Hypertension

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

c) Gangrene

Ergot alkaloids

* **Contraindications:**

a) 1st and 2nd stage of labor

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 hemorrhage

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)

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 soften the cervix; whereas oxytocin does not.
- PGS have longer duration of action than oxytocin.

Prostaglandins
(PGE2 & PGF2α)

- **Therapeutic uses**

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

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 labor and post partum hemorrhage**	**Used for 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 P.partum hemorrhage
Onset and Duration	Rapid onset Shorter duration of action	Moderate onset Long duration of action

UTERINE RELAXANTS

Tocolytic Drugs

Drugs Producing Uterine Relaxation (Tocolytic Drugs).

Action and Uses

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

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 Dydrogesterone

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