DRUGS AFFECTING UTERINE MUSCLE CONTRACTILITY

Objectives

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

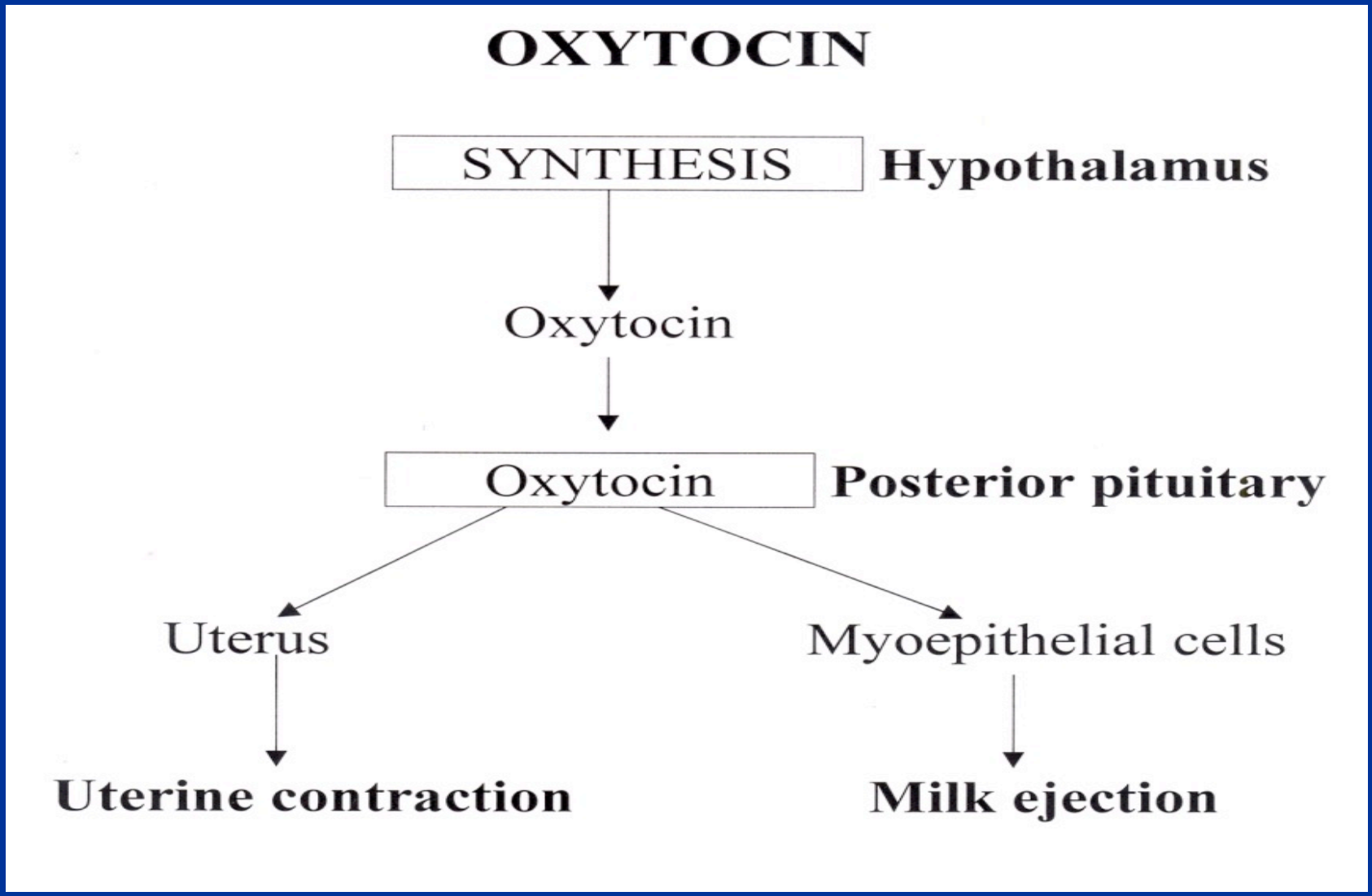
1. Drugs used to induce & augment labor.
2. Drugs used to control post partum hemorrhage.
3. Drugs used to induce pathological abortion.
4. Drugs used to arrest premature labor.
5. The mechanism of action and adverse effects of each drug.

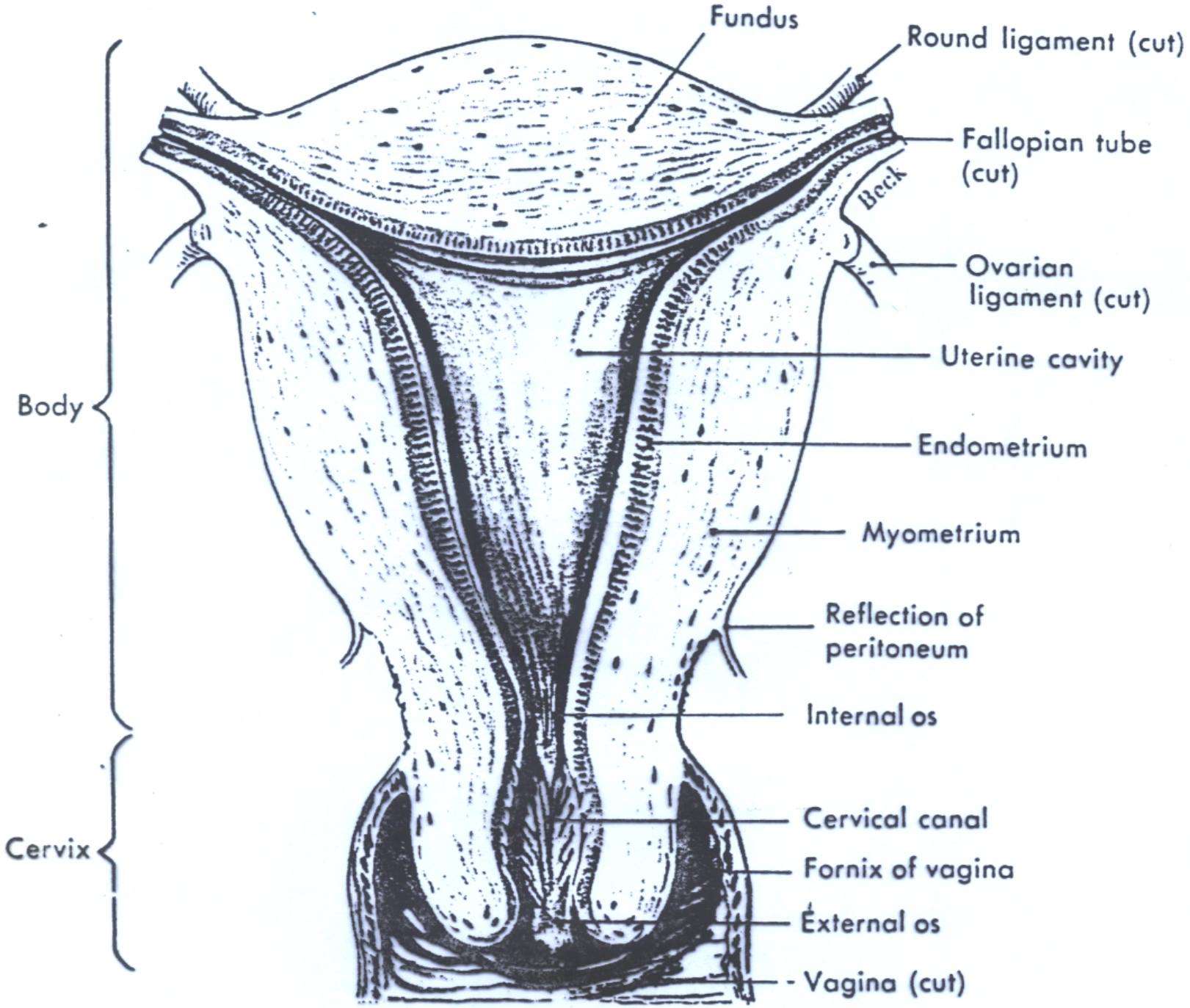
DRUGS PRODUCING UTERINE CONTRACTIONS (Oxytocic Drugs)

1. **OXYTOCIN**
   - Syntocinon

2. **ERGOT ALKALOIDS**
   - Ergometrine (Ergonovine)
   - 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

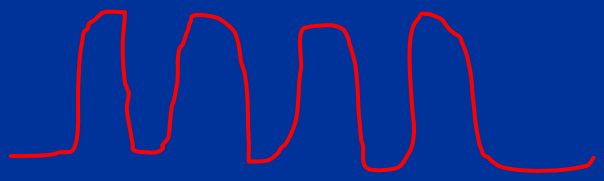

Fundus
Round ligament (cut)
Fallopian tube (cut)
Beck
Ovarian ligament (cut)
Uterine cavity
Endometrium
Myometrium
Reflection of peritoneum
Internal os
Cervical canal
Fornix of vagina
External os
Vagina (cut)
Body
Cervix

Role of oxytocin

1. 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)**



- **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.**

2. 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
- Catabolized by liver & kidneys
- Half life = 5 minutes

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. into the cell , this increase in cytoplasmic calcium , stimulates uterine 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 (continue)

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

Side Effects:

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

Contraindications

a) Hypersensitivity
b) Prematurity
c) Abnormal fetal position
d) Evidence of fetal distress
e) Cephalopelvic disproportion
f) Incompletely dilated cervix

Precautions

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

Ergot Alkaloids

Natural

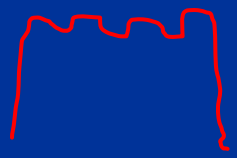
- Ergometrine (Ergonovine)

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**

- **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?

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)

c) Gangrene

- **Contraindications:**

  1) Induction of labour

  a) 1st and 2nd stage of labor

  b) vascular disease

  c) Severe hepatic and renal impairment

  d) Severe hypertension

PROSTAGLANDINS

PGE2 – Dinoprostone

Vaginal suppository.

Extra- amniotic solution

PGF2α- Dinoprost, Carboprost

intra-amniotic injection

Misoprostol (synthetic PGE1)

Therapeutic uses

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

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.**

- **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
  - b) Multiple pregnancy
  - c) Glaucoma
  - 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	Induce and augment labour and 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 p.partum 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.

1. 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.

Side effects

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

2. CALCIUM CHANNEL BLOCKERS
e.g., Nifedipine

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

- **Unwanted effects**

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

3. Atosiban

-New tocolytic agent

-Compete with oxytocin at its receptors on the uterus.

-Given by IV infusion for 48 hrs