





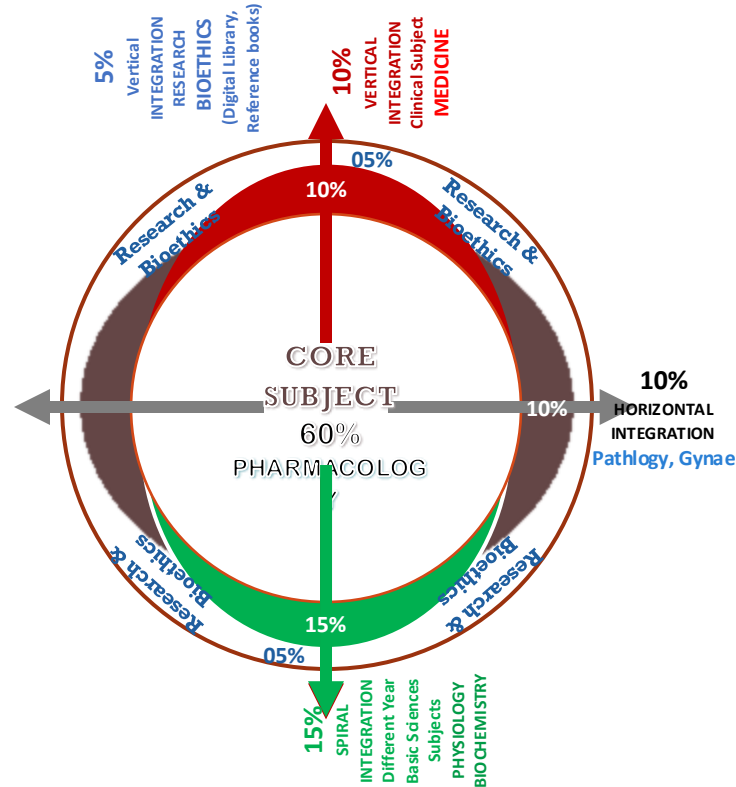
# MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine





# PROFESSOR UMAR'S CLINICALLY ORIENTED INTEGRATION MODEL FOR BASIC SCIENCES INTERACTIVE LECTURES



## 4th Year Pharmacology LGIS(33 slides)

**Core Subject – 17slides (62%)**

**Horizontal Integration (anatomy/physiology)–  
(2 slide) (7%)**

**Vertical integration (Clinical Subjects) • (Medicine) –  
2 slides (7%)**

**Research & Bioethics 4 slide(14%)**



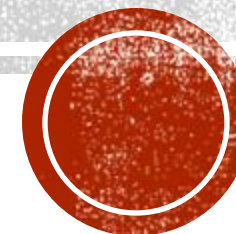


# UTEROTONICS & TOCOLYTIC DRUGS

DR MEMUNA KANWAL

**Sources:**

- **Bertram G. katzung Basic & Clinical Pharmacology 14th Edition**
- **Goodman and Gilman's The Pharmacological Basis of Therapeutics 13<sup>th</sup> edition. Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan - (2017)**





# LEARNING OBJECTIVES

- Describe actions of oxytocin
- Describe uses and adverse effects of oxytocin
- Elaborate clinical uses of prostaglandin
- Enlist ergot alkaloids, their uses and adverse effects
- Classify Tocolytics
- Describe the pharmacodynamics of tocolytic agents
- Discuss their uses & adverse effects







# DRUGS ACTING ON UTERUS

- **Endometrium:** affected by estrogen, progesterone and their antagonists
- **Myometrium:** innervated by sympathetic and parasympathetic system, drugs that act on myometrium are
  - Autonomic drugs
  - Uterotonics
  - Tocolytics
- Response of myometrium to drugs is determined by
  - Hormonal status of body
  - Gestational age



## Posterior Pituitary Hormones

Oxytocin

## Ergot Alkaloids

Ergometrine

Methylergometrine

## Prostaglandins

PGE<sub>2</sub>, Misoprostol

PG F<sub>2</sub> Alpha

CORE SUBJECT

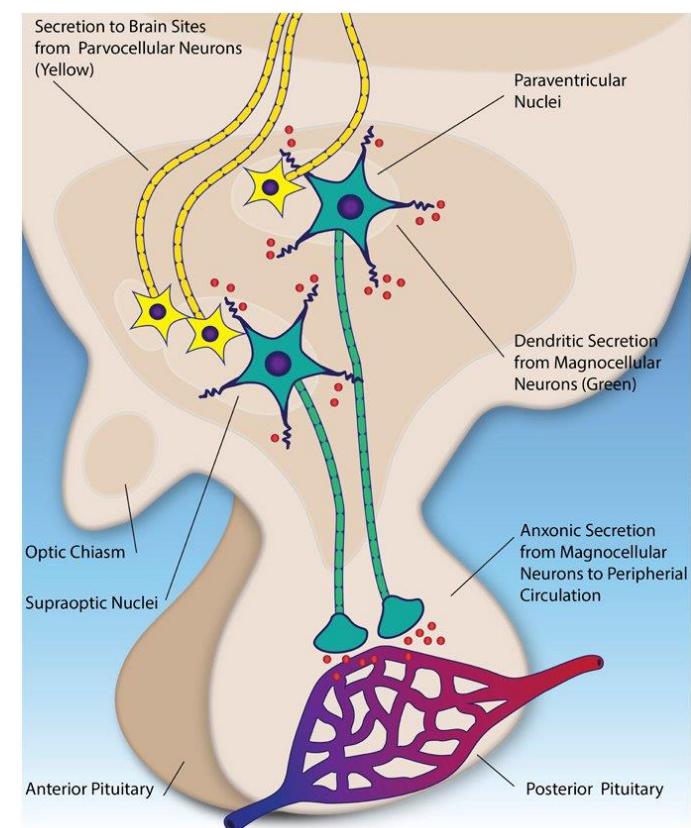
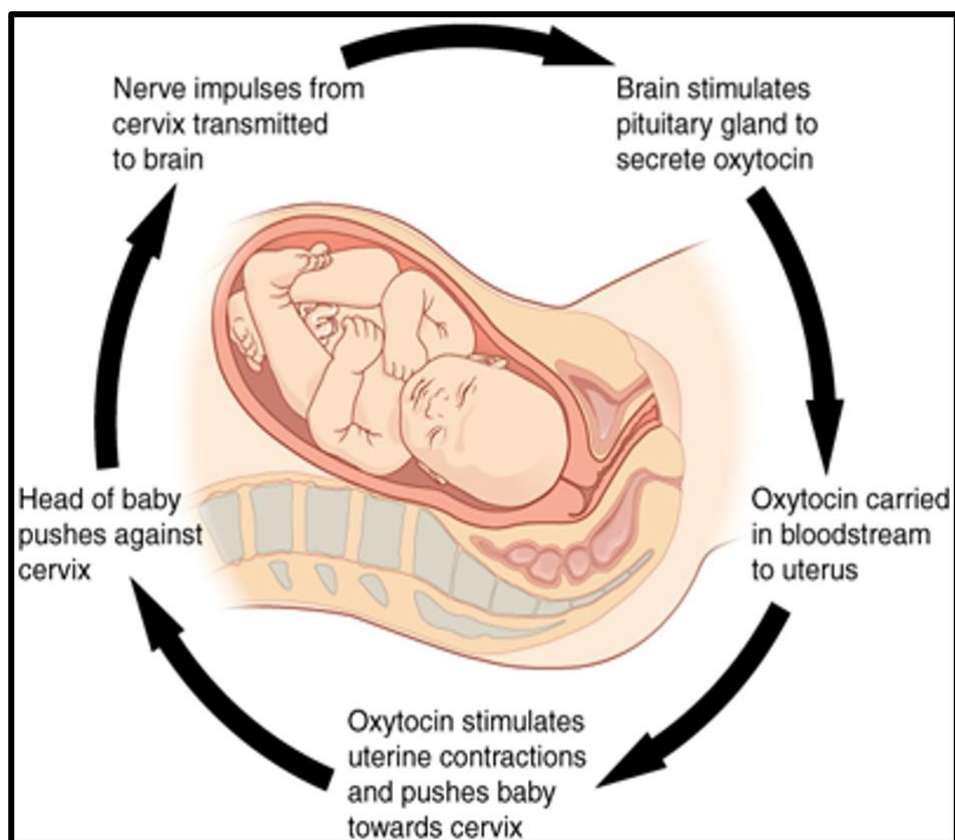


## CLASSIFICATION

- Also called oxytocics
- Have power to stimulate uterine contractions



# OXYTOCIN SYNTHESIS

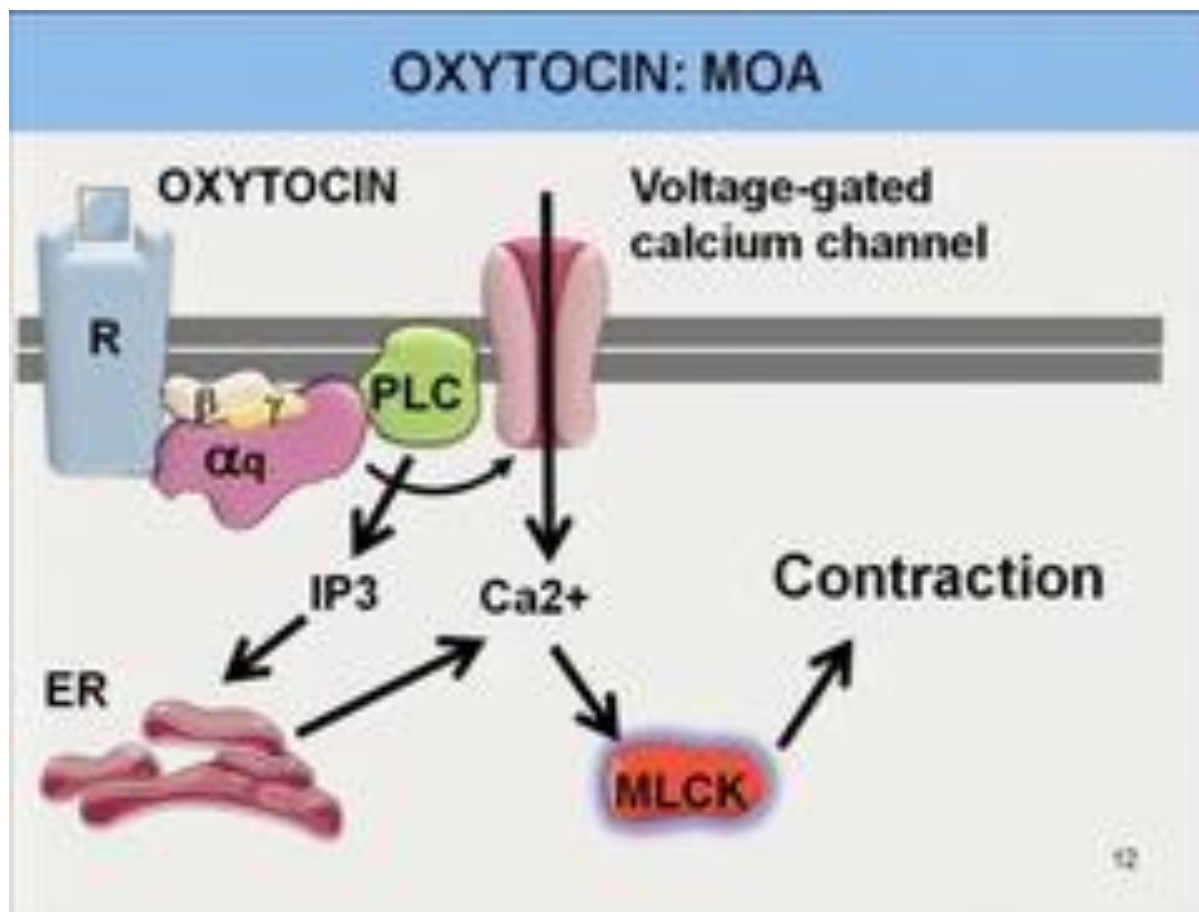


VERTICAL INTEGRATION





# MECHANISM OF ACTION OF OXYTOCIN



- Half life 3-4 minutes
- Duration of action 20 minutes
- IV, IM, Buccal tablets, Nasal spray
- IV Infusion: Start with low dose 1-2mU/min, increase 1-2mIU/min every 20 minutes if needed
- Bolus dose can be given in 3rd stage of labour
- Milk let down Reflex





# PHARMACOLOGICAL ACTIONS OF OXYTOCIN

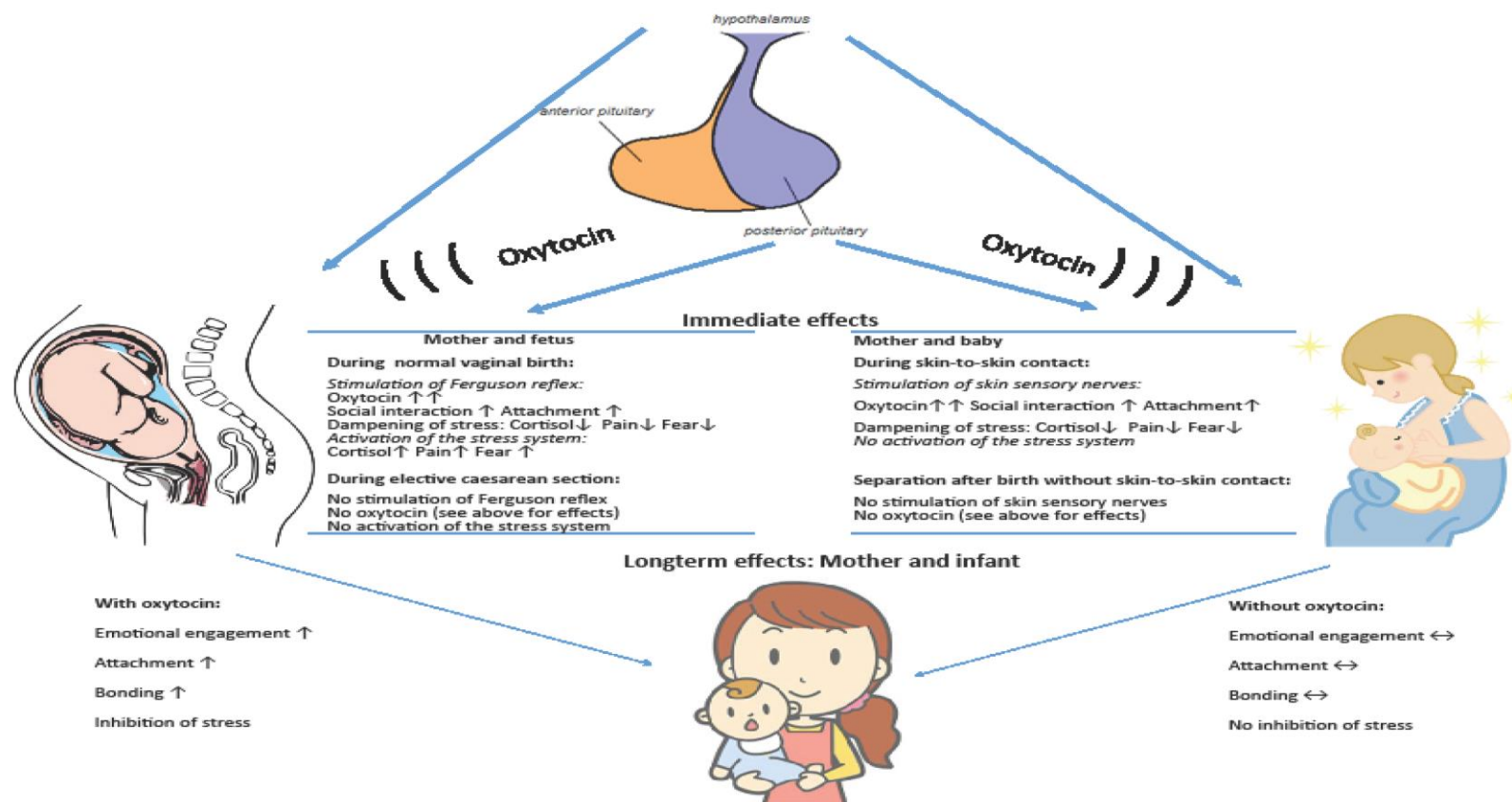
- On uterus: low dose, high dose
- On breast
- CVS
- Kidneys

- Concentration of oxytocin receptors
- Sensitivity of oxytocin receptors
- Sensitivity increases and decreases by?



# CLINICAL USES OF OXYTOCIN

- Induction of labour
- Augmentation of labour
- Active management of 3rd stage of labour





# ADVERSE EFFECTS OF OXYTOCIN

- Inappropriate administration
  - Uterine hyperstimulation
  - Uterine rupture
  - Nausea, Vomiting
  - Asphyxia for fetus
  - Placental abruption
- Water intoxication: hyponatremia, seizures
- Bolus injection: hypotension







# CONTRAINDICATIONS

■

Grand  
multipara

CPD

Previous  
C/Section

Fetal distress

Placenta previa

Malpresentation

CORE SUBJECT





# ERGOMETRINE

- Amine ergot alkaloid
- Partial agonist at adrenergic and 5-HT<sub>2</sub> receptors
- Pharmacological actions
  - on uterus
  - CVS
  - CNS
  - GIT





# PHARMACOKINETICS

- Oral Route: Ergometrine and methylergometrine are rapidly & completely absorbed
- I/M or I/V route
- Metabolized: liver
- Excretion : Renal
- Plasma  $t_{1/2}$  : 1–2 hours





# ERGOMETRINE

## CLINICAL USES

- To control & prevent PPH
- After caesarean section/instrumental delivery—to prevent uterine atony

## ADVERSE EFFECTS

- Nausea vomiting
- Rise in BP
- Decrease milk secretion if higher doses are used for many days postpartum...due to inhibition of prolactin release (dopaminergic action).

CORE SUBJECT+VERTICAL  
INTEGRATION







# CONTRAINDICATIONS

- **Ergometrine Should Be Avoided In:**
  - Patients with vascular disease, hypertension, toxemia
  - Presence of sepsis—may cause gangrene
  - liver and kidney disease
  
- **CONTRAINDICATED**
  - During pregnancy and
  - before 3rd stage of labour





# OXYTOCIN VS ERGOMETRINE

- Oxytocin is the drug of choice and is preferred over Ergometrine and prostaglandins
  - Its short  $t_{1/2}$  and slow I/V infusion
  - Intensity of action....controlled and action can be quickly terminated
  - Low concentrations allow normal relaxation in between contractions—foetal oxygenation does not suffer
  - Lower segment is not contracted foetal descent is not compromised
  - Uterine contractions are consistently augmented





# PROSTAGLANDINS

- PG E1: Misoprostol
  - PG E2: Dinoprostone
  - PG F2 alpha: Carboprost
  - 15-methyl PGF2 alpha
- 
- During early pregnancy uterus is more sensitive to prostaglandins than oxytocin





# PHARMACOLOGICAL ACTIONS ON FEMALE REPRODUCTIVE SYSTEM

- Myometrial contraction
- Softening and dilatation of cervix
- Inhibition of secretion of progesterone by corpus luteum
- Response of the uterus to PGs is maximum in the middle trimester (13th to 20th weeks)







# CLINICAL USES OF PROSTAGLANDINS

- **1<sup>ST</sup> & 2<sup>ND</sup> TRIMESTER ABORTIONS:**
  - Misoprostol(PGE<sub>1</sub>): Early abortion
  - Dinoprotone(PGE<sub>2</sub>): 2<sup>nd</sup> Trimester abortion
  - Carboprost(15-Methyl-PGF<sub>2α</sub>)
- **INDUCTION/FACILITATION OF LABOUR:**
  - Dinoprostone(PGE<sub>2</sub>)
  - Carboprost(15-Methyl-PGF<sub>2α</sub>)





# ADVERSE EFFECTS

- Nausea , vomiting
- Abdominal pain
- Uterine rupture
- Diarrhoea
- Bronchospasm ( $\text{PGF}_2\alpha$ )
- Flushing:  $\text{PGE}_2$  causes vasodilation of the mother's vessels thus leading to cutaneous flushing



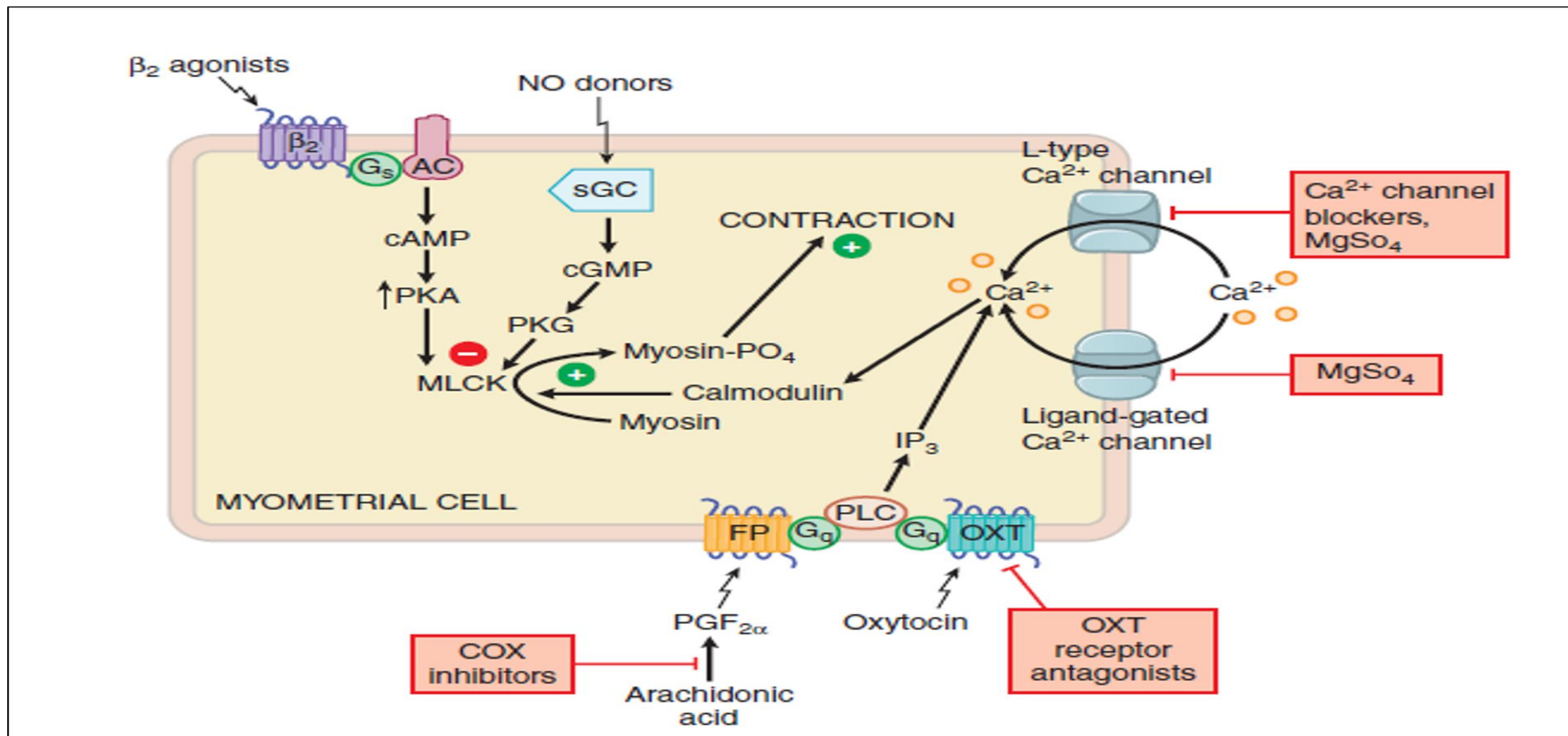


# TOCOLYTICS

- Beta 2 agonists: Terbutaline, Ritodrine
- Calcium channel Blockers: Nifedipine
- Magnesium Sulphate
- Prostaglandins synthetase inhibitors: Indomethacin, Aspirin
- Oxytocin receptor antagonist: Atosiban
- Nitrous oxide donors: Nitroglycerine
- Halothane



# MECHANISM OF ACTION

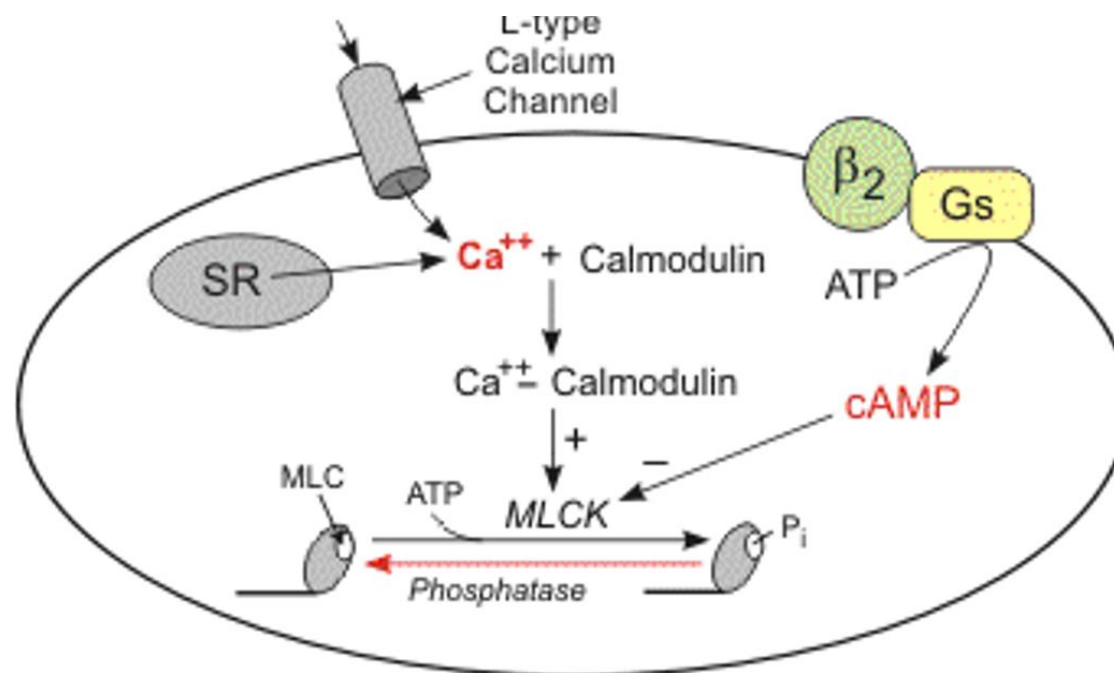




# BETA 2 AGONISTS

- **ROA:** terbutaline S/C
- **SIDE EFFECTS:**
  - Anxiety, Restlessness
  - Headache
  - Pulmonary edema
  - Sweating
  - Tachycardia (high dose)
  - Hypotension
  - Hyperglycemia

## MECHANISM OF ACTION



Abbreviations: SR, sarcoplasmic reticulum; Gq, Gs-protein; MLC, myosin





# MAGNESIUM SULPHATE

- **Exact mechanism not known**
  - Compete with  $\text{Ca}^{++}$  for entry into the cell at the time of depolarization at the motor end of cell membrane so there is decrease intracellular  $\text{Ca}^{++}$
  - Direct depressant action on uterine muscle
- **USES:** Used for prevention of seizures in eclampsia, not used for arrest of preterm labour for its toxicities





# ADVERSE EFFECTS OF MGS04

- **Maternal**
  - Flushing
  - Headache
  - Perspiration
  - Muscle weakness
  - Respiratory depression
- **Fetal**
  - Lethargy
  - Hypotonia
  - Respiratory depression

## CONTRAINDICATIONS

- Myasthenia gravis
- Renal failure





# CALCIUM CHANNEL BLOCKERS

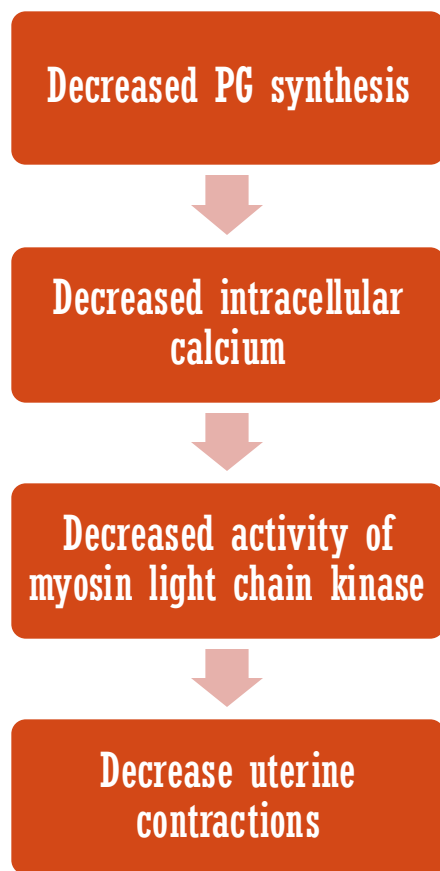
- Nifedipine
- MOA: Blockage of voltage dependant calcium channels in myometrium
- ROA: sublingual or oral

- ADVERSE EFFECTS
  - Reflex tachycardia
  - Maternal palpitations
  - Headache





# INDOMETHACIN



CORE SUBJECT

## ADVERSE EFFECTS

- **MATERNAL**
  - Heartburn
  - Asthma
  - GIT bleeding
  - Renal injury
- **FETAL**
  - Oligohydramnios
  - Closure of ductus arteriosus
  - IUGR

## CONTRAINDICATIONS

- Active peptic ulcer
- Hepatic disease
- coagulopathies





# ATOSIBAN

## ■ **MECHANISM OF ACTION :-**

- Blocks myometrial oxytocin receptors
  - Inhibits intracellular production of inositol triphosphate (IP3)
  - reduce concentration of intracellular calcium in the myometrial cells & blocks release of prostaglandins
- 
- Adverse effects: Nausea, Vomiting





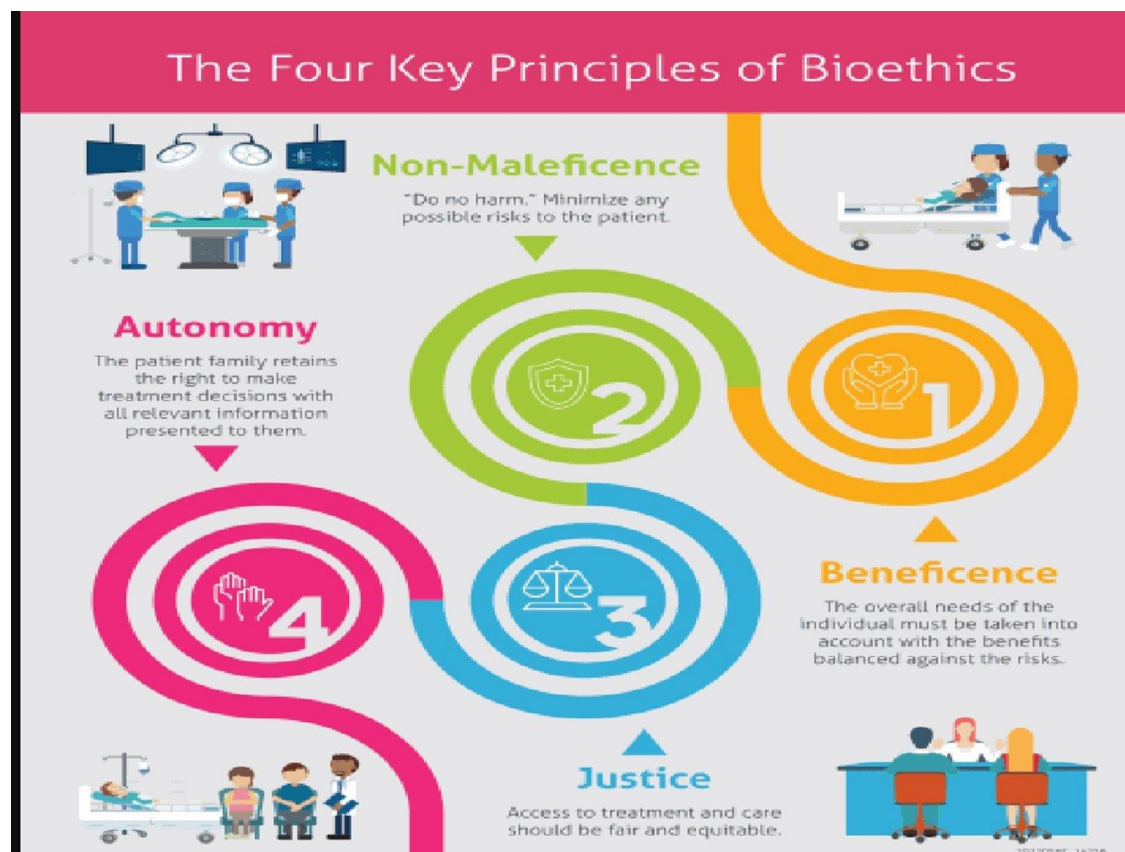


# NO DONORS

- Glyceryl trinitrate
- Smooth muscle relaxant
- Nitroderm patch
  
- Adverse effects: headache, cervical ripening



# BIOETHICS





# HOW TO ACCESS DIGITAL LIBRARY

- Go to the website of HEC National Digital Library.
- On Home Page, click on the INSTITUTES.
- A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
- Select your desired Institute.
- A page will appear showing the resources of the institution
- Journals and Researches will appear
- You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.





## **FURTHER READING**

- Knoll W, Phelan R, Hopman WM, Ho AM, Cenkowski M, Mizubuti GB, Ghasemlou N, Klar G. Retrospective review of time to uterotonic administration and maternal outcomes after postpartum hemorrhage. *Journal of Obstetrics and Gynaecology Canada*. 2022 May 1;44(5):490-5.
- Yamaji N, Suzuki H, Saito K, Swa T, Namba F, Vogel JP, Ramson JA, Cao J, Tina L, Ota E. Tocolytic therapy inhibiting preterm birth in high-risk populations: a systematic review and meta-analysis. *Children*. 2023 Feb 24;10(3):443.





# END OF LECTURE ASSESSMENT

- A uterine stimulant derived from membrane lipid in the endometrium is
  - a. Angiotensin II
  - b. Ergotamine
  - c.  $\text{PGF}_2\alpha$
  - d. Prostacyclin
  - e. Thromboxane





Thank you.

