Oxytocics & Uterine Relaxants

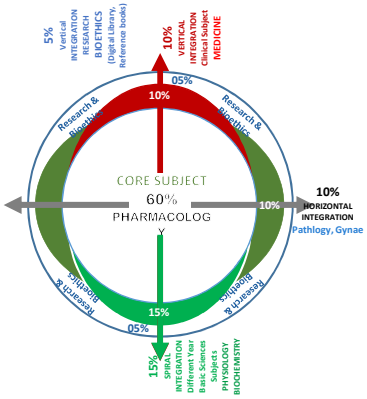
Sources:

- **Bertram G. katzung Basic & Clinical Pharmacology 14th Edition**
- **Goodman and Gilman's The Pharmacological Basis of Therapeutics13th edition. Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan - (2017)**

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

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



4rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Gynae/Obs • Pathology
Vertical Integration – 10%	
Clinical Subjects	• Medicine • Surgery
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Research & Bioethics, Digital library – 05%	

LEARNING OBJECTIVES

➢At the end of the session, the students should be able to:

- 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

Core Subject

DRUGS ACTING ON UTERUS:

- **Endometrium ..Affected by:**
  - Estrogens, Progestins & their antagonists
- **Myometrium…sympathetic and parasympathetic innervation:**
  - Autonomic drugs….affect motility
  - Oxytocics(Abortifacients)
  - Tocolytics

UTERINE STIMULANTS

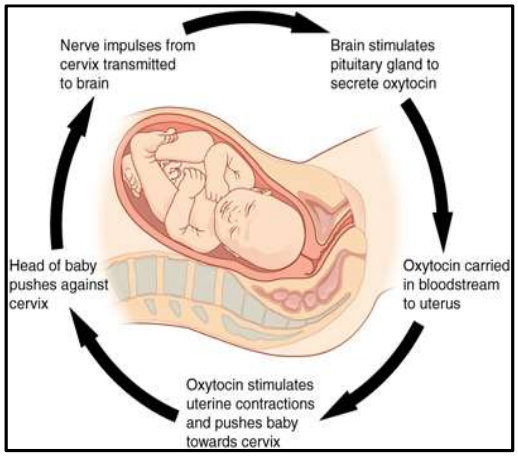
(Oxytocics, Abortifacients)

- Drugs increase uterine motility, especially at term
  - **POSTERIOR PITUITARY HORMONE**
    - Oxytocin, Desamino oxytocin
  - **ERGOT ALKALOIDS**
    - Ergometrine (Ergonovine), Methylergometrine
  - **PROSTAGLANDINS**
    - PGE2, PGF2α, 15-methyl PGF2α, Misoprostol

Spiral integration-Physiology

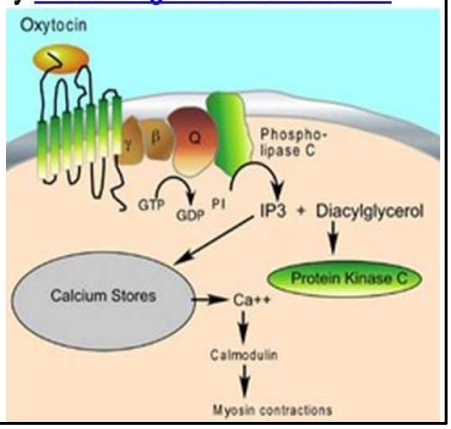
OXYTOCIN

- Released from posterior pituitary along with vasopressin (ADH)
- **MECHANISM OF ACTION**
  - G-protein coupled oxytocin receptors
  - Depolarization & Influx of Ca2+ ions
  - phosphoinositide hydrolysis
  - IP3 mediated intracellular release of Ca2+ ions
  - Also stimulates the release prostaglandins & leukotrienes
- **OXYTOCIN RECEPTORS**
  - Concentration in myometrium is lower in non pregnant state & early pregnancy….Increases markedly as pregnancy advances
  - Sensitivity of receptors to oxytocin..lower in first & second trimester… increases tremendously in late pregnancy & labor

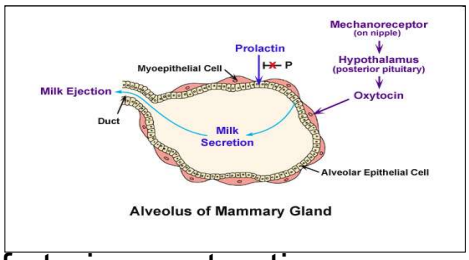


Mechanism of action:

- Bind to specific cell membrane receptors
- Exerts its effects by increasing intracellular Ca++ content.



OXYTOCIN



- **ACTIONS**
- **Uterus :**
- Oxytocin increases the force & frequency of uterine contractions
  - With low doses
    - Full relaxation occurs in between contractions
  - With high doses
    - Basal tone also increases
- **Breast:**
- Milk ejection reflex

OXYTOCIN

- **CVS:**
  - No effect on BP on conventional doses used in obstetrics

- **Kidney:**
  - Oxytocin in high doses exerts ADH-like action

PHARMACOKINETICS:

- Oxytocin…inactive orally
- I/M, I/V , Nasal spray
- Plasma t½ 6–12 min

Vertical integertion- Gynae/Obs

OXYTOCIN

- **USES:**
- Induction of labour, Uterine inertia, Post-partum haemorrhage, Cessarian sections, Breast engorgement(Intra nasal spray)
  - **Induction of labour**, an initial infusion rate of 0.5–2 mU/min is increased every 30–60 minutes(maximum infusion rate is 20 mU/min)
  - **For postpartum uterine bleeding**, 10–40 units are added to 1 L of 5% dextrose, and the infusion rate is titrated to control uterine atony/10 units of oxytocin can be administered by I/M injection

CORE SUBJECT

- **ADVERSE EFFECTS:**
  - Inappropriate administration ……fetal and maternal trauma, fetal asphyxia, placental abruption, uterine rupture, death
  - Water intoxication, hyponatremia, heart failure, seizure
  - Bolus injections….Hypotension

- **CONTRAINDICATIONS:**
- Grand multipara
- CPD
- Placenta previa
- Malpresentation, Previous LSCS, Fetal distress

ERGOMETRINE, METHYLERGOMETRINE

- Amine ergot alkaloid ergometrine (ergonovine) & derivative methylergometrine
- **MECHANISM OF ACTION-**
- Serotonin Receptor (5-HT2) } Partial agonist
  α-adrenoceptor
- **UTERUS:**
- Increase force, frequency & duration of uterine contractions
- Small doses…. rhythmic contraction & relaxation of uterus

ERGOMETRINE, METHYLERGOMETRINE

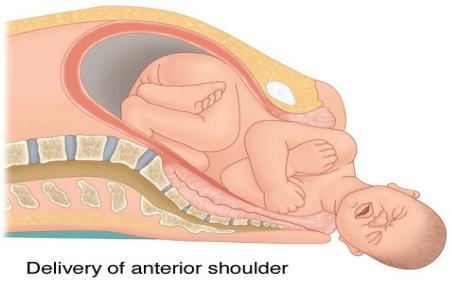
- **CVS:** Weak vasoconstriction…may increase PVR
- **CNS:** Higher Doses can stimulate adrenergic, serotonergic receptors
- **GIT:** Increase peristalsis…..Higher doses

ERGOMETRINE, METHYLERGOMETRINE

- **PHARMACOKINETICS:**
  - Oral Route: Ergometrine and methylergometrine are rapidly & completely absorbed
  - I/M or I/V route
  - Metabolized: liver
  - Excretion : Renal
  - Plasma t½:1–2 hours
- **ADVERSE EFFECTS:**
  - Nausea, vomiting and rise in BP
  - Decrease milk secretion if higher doses are used for many days postpartum

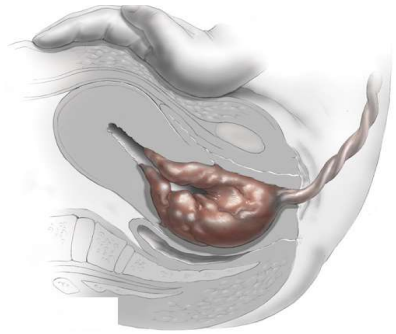
ERGOMETRINE, METHYLERGOMETRINE

- **Ergometrine Should Be Avoided In:**
  - Patients with vascular disease, hypertension, toxaemia
  - Presence of sepsis—may cause gangrene
  - liver and kidney disease
- **CONTRAINDICATIONS**
  - During pregnancy
  - before 3rd stage of labour
- **CLINICAL USES:**
  - To control & prevent PPH
  - After caesarean section
  - To ensure normal involution

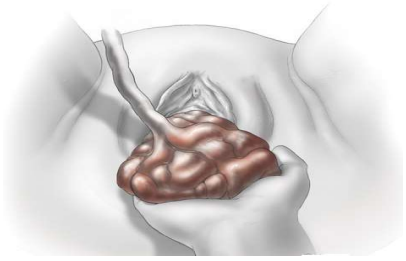


Delivery of anterior shoulder

AFTER DELIVERY OF ANT. SHOULDER/
FOLLOWING DELIVERY OF BABY



at the time of *delivery of the placenta.*



Spiral integeration/ Physiology

PROSTAGLANDINS

- PGE2, PGF2α and 15-methyl PGF2α are potent uterine stimulants
  - Dinoprostone PG E2
  - Misoprostol PG E1
  - Carboprost PG F2 α
- Sensitivity is higher during pregnancy & more with the advance of pregnancy
- During early stages,
  - Uterus is sensitive to PGs (not to oxytocin)

PROSTAGLANDINS

- Effects of PGs on uterus
  - Increase basal tone
  - Increases Amplitude of uterine contractions
  - At term, PGs soften the cervix at low doses and make it more compliant
- In vitro,
  - PGF2α consistently produces contraction
  - PGE2 relaxes non pregnant but contracts pregnant human uterine strips

Core subject

PROSTAGLANDINS

- **Pharmacological effects** are:
  - Contraction of smooth muscles of uterus, blood vessels, GIT and bronchioles

- **Pharmacolgical Effects On Female Reproductive Tract:**
  - 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)

Vertical integeration- Gynae/Obs

PROSTAGLANDINS

- **CLINICAL USES:**

- **1ST & 2ND TRIMESTER ABORTIONS:**
  - Misoprostol(PGE_1)…Early abortion
  - Dinoprotone(PGE_2) 2nd Trimester abortion
  - Carboprost(15-Methyl-$PGF_{2\alpha}$)

- **INDUCTION/FACILITATION OF LABOUR:**
  - Dinoprostone(PGE_2)
  - Carboprost(15-Methyl-$PGF_{2\alpha}$)

Core subject

PROSTAGLANDINS

- **ADVERSE EFFECTS**
  - Nausea , vomiting
  - Abdominal pain
  - Diarrhoea
  - Bronchospasm (PGF2α)
  - Flushing (PGE2) PGE2 causes vasodilation of the mother's vessels thus leading to cutaneous flushing

UTERINE RELAXANTS/TOCOLYTICS

CLASSIFICATION

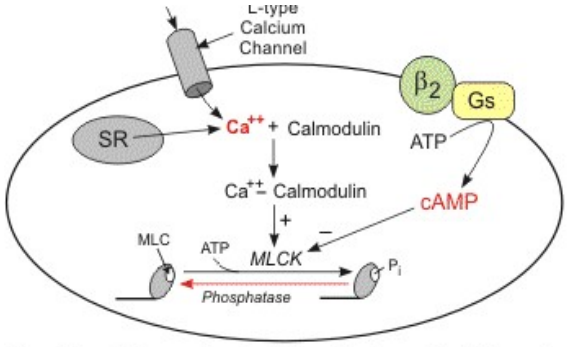
- **B_2 AGONIST**
  - Ritodrine
  - Salbutamol
- **CALCIUM CHANNEL BLOCKERS**
  - Nifedipine
- **OXYTOCIN ANTAGONIST**
  - Atosiban
- **MISCELLANEOUS**
  - Magnesium Sulphate
  - Alcohol
  - Nitric Oxide Donor (Nitroglycerine)
  - Halothane

USES OF TOCOLYTIC AGENTS

- To delay onset of labour in case of premature uterine contractions
- Arrest threatened abortion
- In dysmenorhea
- Increase the time for fetal lungs to get matured- to initiate glucocorticoid therapy, in case of preterm labour

RITODRINE (β-ADRENOCEPTOR AGONIST)

- **MECHANISM OF ACTION**
  - Bind to β-adrenoceptors , activate adenylate cyclase increase in the level of cAMP, dephosphorylation of MLCK
- **SIDE EFFECTS:**
  - Anxiety, Restlessness, Headache
  - Pulmonary edema
  - Sweating
  - Tachycardia (high dose)
  - Hypotension
  - Hyperglycemia



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

MAGNESIUM SULFATE

- **MECHANISM OF ACTION**

- **Exact mechanism not known**
  - Compete with Ca++ for entry into the cell at the time of depolarization at the motor end of cell membrane so there is decrease intracellular Ca^{++}

- **USES:**
  - Used for prevention of seizures in eclampsia

CALCIUM CHANNEL BLOCKER

- **NIFIDIPINE** is a powerful uterine relaxant
- **MECHANISM OF ACTION** :blockade of voltage-dependent calcium channels in myometrial cells
- **ROA**: Sublingual or oral
- **SIDE EFFECTS:**
  - Reflex tachycardia
  - Maternal palpitations, headache

ATOSIBAN

- **MECHANISM OF ACTION :-**
  - Blocks myometrial oxytocin receptors
  - As effective as adrenergic agonist….low incidence of side effects

Research

- Arman BM, Binder NK, de Alwis N, Beard S, Debruin DA, Hayes A, Tong S, Kaitu'u-Lino TU, Hannan NJ. Assessment of the tocolytic nifedipine in preclinical primary models of preterm birth. Scientific reports. 2023 Apr 6;13(1):5646.

- Ibrahim M, Elsenosy E, Mostafa D, Seddik M, Ali M. High Versus Low Dose of Magnesium Sulfate as Initial Tocolytic Agent for Preterm Labour in Symptomatic Placenta Previa. Evidence Based Women's Health Journal. 2023 May 1;13(2):183-91.

Artificial intelligence

- Synan L, Ghazvini S, Uthaman S, Cutshaw G, Lee CY, Waite J, Wen X, Sarkar S, Lin E, Santillan M, Santillan D. First Trimester Prediction of Preterm Birth in Patient Plasma with Machine-Learning-Guided Raman Spectroscopy and Metabolomics. ACS Applied Materials & Interfaces. 2023 Aug 7.

- Diaz-Martinez A, Monfort-Ortiz R, Ye-Lin Y, Garcia-Casado J, Nieto-Tous M, Nieto-Del-Amor F, Diago-Almela V, Prats-Boluda G. Uterine myoelectrical activity as biomarker of successful induction with Dinoprostone: Influence of parity. biocybernetics and biomedical engineering. 2023 Jan 1;43(1):142-56.

Bioethics

- Zhao LR, Lu SJ, Liu Q, Yu YC, Xiao L. Impact of prolonged use of adjuvant tocolytics after cervical cerclage on late abortion and premature delivery. Journal of Obstetrics and Gynaecology. 2023 Dec 31;43(1):2128997.

EOLA

- A uterine stimulant derived from membrane lipid in the endometrium is

a. Angiotensin II
b. Ergotamine
c. PGF2α
d. Prostacyclin
e. Thromboxane

- A 29 year old woman in her 41st week of gestation had been in labour for 12 hours. Although her uterine contraction had been strong and regular initially, they had diminished in force during the past hour. Which drug would be used to facilitate woman's labour and delivery?

a. Dopamine
b. Leuprolide
c. Oxytocin
d. Prolactin
e. Vasopressin