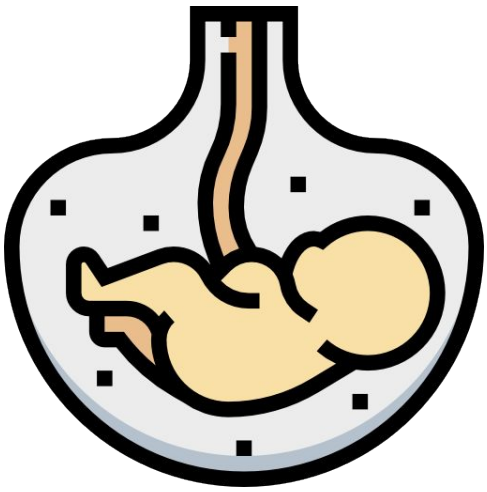
Pharmacology 439

MED439

Revised & Approved

Bassam Alasmari
Rania Almutiri



Editing File

Reproduction Block

Pharmacology team 439

Oxytocin & Tocolytics

Objectives:

By the end of the lecture , you should know:

- Drugs used to induce & augment labor.
- Drugs used to control postpartum hemorrhage.
- Drugs used to induce pathological abortion.
- Drugs used to arrest premature labor.
- The mechanism of action and adverse effects of each drug.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only

Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)

Green: Dr. notes (438)

Drugs Producing Uterine Contractions (oxytocics)

- **Oxytocin**
  - **Syntocinon And pitocin**
- **Prostaglandins**
  - **Synthetic PGE1:** Misoprostol
  - **PGE2:** Dinoprostone
  - **PGF2α:** Dinoprost, Carboprost
- **Ergot alkaloids**
  - **Natural:** Ergometrine (Ergonovine)
  - **Synthetic:** Methyl ergometrine (Methyl ergonovine)

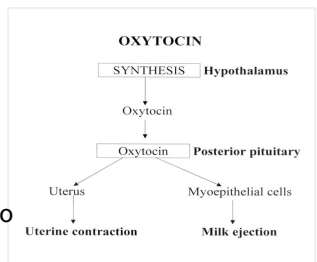
Induce vasoconstriction

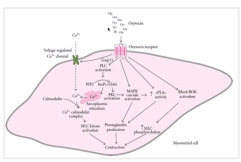
Drug: Oxytocin (Syntocinon)

Male's doctor: I'll not ask you about this cascade (pic), you're just required to know whats written.

MOA

- 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^{2+} (which plays an imp role in contractility)** from extracellular fluid and from sarco endoplasmic reticulum into the cell, this increase in cytoplasmic calcium → **stimulates uterine contraction**





Action

Dr: You should know it (first two points in red)

1- Effect on uterus:

- Stimulates **both the frequency** (no. of contractions) **and force** (↑ amplitude) of uterine contractility **particularly of the fundus segment** → to expel the baby out of the uterus.
- These contractions resemble the **normal** physiological contractions of uterus **(contractions followed by relaxation)** Due to the refractory period of smooth muscle cells, only a strong stimulus can cause continuous (tetanic) contractions and diminish the refractory periods, this can happen with ergot drugs (discussed in next page) and very high oxytocin concentration. Which may lead to uterine rupture and fetal ischemia due to compression of endometrial arteries.
- **Immature** uterus is **resistant** to oxytocin. (if immature uterus exposed to oxytocin, there is no effect as a result of low oxytocin receptors and gap junctions due to low estrogen/progesterone ratio) In this case we do obstetric surgery.
- ★ Contract uterine smooth muscle **only at term**. So we only use it at term, if taken earlier it will not work.
- Sensitivity **increases** to 8 fold **in last 9 weeks** and 30 times **in early labor**.(so keep in mind that expression of oxytocin receptors increase whenever we reach the last months)
- ★ Clinically oxytocin is given only when uterine cervix **is soft and dilated** (through PE)

2- Effect on Myoepithelial cells: (when the mother breastfeeds, suckling sends a positive feedback which increases the production of oxytocin. At the same time, the mother experiences uterine contractions due to increased oxytocin, which helps returning the uterus to its normal size postpartum)

- Oxytocin contracts myoepithelial cells surrounding mammary alveoli (around nipples) in the breast & leads to **milk ejection**.

P.K

- Not effective orally as it is destroyed in GIT
- Administered **I.V.** to augment labor, given when the mother exceeds her due date and "the baby does not want to come to the world
- Also as **nasal spray in impaired milk ejection**
- Not bound to plasma proteins
- Catabolized by liver & kidneys
- $T_{1/2}$ = **5 min**

Uses

Synthetic preparations of oxytocin e.g. syntocinon (also pitocin) are preferred.

- ★ **Induction & augmentation of labor (slow I.V infusion):**
  - Induction is the starting of labor, augmentation is when there are signs of labor but there's no enough contractions to make the labor successful
    - Mild preeclampsia near term (pregnancy complication characterized by high blood pressure and signs of damage to another organ system, most often the liver and kidneys.)
    - Uterine inertia = uterine atony (failure of uterus to contract)
    - Incomplete abortion (abortion w/ some reminants inside like the placenta and other contents)
    - Post maturity, the mother completed 9 months but there is no delivery yet so it's better to start inducing the labor to avoid complications like macrosomia)
    - **Maternal diabetes** (diabetes insipidus), as it may cause preeclampsia and macrosomia so we deliver the baby at 38 weeks (early delivery).
- Postpartum uterine hemorrhage (I.V drip): **ergometrine** is often used? When it's normal delivery , oxytocin wasn't used.
  (postpartum hemorrhage happens due to loss of the normal involution of the uterus which to atomic bleeding due to dilated blood vessels. We give a combo of ergometrine and oxytocin to increase contractions and "squeezes" the blood vessels)
- **Impaired milk ejection**: One puff in each nostril 2-3 min before nursing
  (now it's given in the pharmacies if the mother with normal production of milk but impaired ejection of milk)

Drug	Oxytocin (Syntocinon)
ADR	• Maternal death due to hypertension, can cause severe hypotension and tachycardia as well and that's why we give it in small doses + the mother's BP and the sensitivity of the uterus should be measured. • Uterine rupture, especially if there previous c-section and when administered continuously (overdose) , and when given on closed cervix • Fetal death (ischemia).as a result of high pressure because of the contractions continuous monitoring of heart sounds and rate for the baby is required to avoid fetal distress. But once fetal distress happen, oxytocin should be discontinued and the mother should deliver rapidly (whether normally or by c-section if needed). ★ **Water intoxication:** if oxytocin is given with relatively large volumes of electrolyte-free aqueous fluid intravenously. Oxytocin has ADH-like effect. it is released from posterior pituitary gland & is similar to ADH structurally, in could decrease diuresis and lead to water retention When administered with electrolytes free solution it could lead to severe hypervolemia and (more importantly) hyponatremia, thus possibly leading to convulsion, coma, and death.
C.I	• Hypersensitivity. Measure myometrial contraction • Prematurity of the uterus. Resistant to oxytocin (contraction against closed cervix) leading to compression of fetus. • Abnormal fetal position may lead to ischemia and fetal death (baby should be in cephalic position before administration.) • Evidence of fetal distress. • **Cephalopelvic** disproportion Fetal head is large & doesn't fit the pelvis • **Incompletely dilated cervix**
Caution	Multiple pregnancy & previous C-section (increased risk of uterine rupture), hypertension (it causes vasoconstriction)

Ergot Alkaloids it's a plant

Drug	Natural: E.g. Ergometrine (Ergonovine)	Synthetics: E.g. Methyl ergometrine (Methylergonovine)
Info	A fungus that grow on rye & contains pharmacologically active substances.	
MOA	• Ergot alkaloids induce **Tetanic contraction of uterus without relaxation** in between (not like normal physiological contraction) ★ It causes contraction of uterus **as whole** i.e. fundus and cervix **(tend to compress rather than to expel the fetus)** → **NEVER** used to induce labor 	
P.K	• Can be given orally & absorbed from GIT (tablets) • Usually given I.M • Extensively metabolized in liver • 90% of metabolites are excreted in bile	
Uses	★ **Postpartum hemorrhage** (third stage of labor) Because of its direct action on blood vessels (vasoconstrictor) ○ **When to give ? immediately after the labor** (sometimes used when the placenta is not expelled fully (can lead to infections if not removed). ○ **Preparation**: syntometrine (ergometrine 0.5mg + oxytocin 5.0 I.U) , I.M	
ADR	★ Vasoconstriction of peripheral blood vessels (toes & finger). Shown as blue color ★ Severe hypertension, gangrene (it's partial alpha adrenergic receptors agonist so leading to prolonged vasoconstriction and therefore hypertension. Also blood flow is halted so cause gangrene) • Nausea, vomiting, diarrhea (Binds to dopaminergic receptors in chemoreceptor trigger zone. Ergometrines have dopaminergic, adrenergic, and serotonergic action.)	
C.I	★ **Induction of labor → first and second stage of labor** • Vascular diseases • Severe hepatic and renal impairment • Severe hypertension	

Oxytocin VS Ergometrine

Male's doc: These differences are IMP

	Oxytocin	Ergometrine
Type of contraction	• Resemble **normal physiological** contraction	• **Tetanic contraction**,does not resemble normal physiological contraction
Uses	• To induce & augment labor • Postpartum hemorrhage	★ **Only in postpartum hemorrhage as a combination with oxytocin**
Onset & Duration	• Rapid onset • Shorter duration of action	• Moderate onset • Long duration of action

Prostaglandins

(PGF2α, Thromboxane A2, PGE2 and PGE1 are the main prostaglandins that cause uterine contraction, PGI2 (prostacyclin) causes uterine relaxation)

Drug	Synthetic PGE1 E.g. Misoprostol	PGE2 E.g.Dinoprostone	PGF2α E.g.Dinoprost Carboprost
Admin.	It was used in the beginning as a protector to stomach from ulcers which induced by NSAIDs	• Vaginal suppository/gel • **Extra**-amniotic solution (injected by a catheter to the extra-amniotic fluids.) - Extra-amniotic is a space between the fetus and endometrium	• **Intra**-amniotic injection
Uses	★ Induction of **abortion** (pathological) • Induction of labor (first line: Oxytocin) **when fetal death in utero occur** • Postpartum hemorrhage (rarely) (first line: Ergometrine)		
ADR	• Nausea, vomiting • Abdominal pain due to contraction of abdominal muscles • Diarrhea		
	—	★ Flushing	★ Bronchospasm
C.I	• Mechanical obstruction of delivery, such as when we have birth defects of mother's pelvis so it's C.I to induce labor because it will lead to complications even if fetus died • Fetal distress, like fetus it's not feeling well or O2 isn't enough • Predisposition to uterine rupture		
Pre-caution	• Asthma, especially in PGF2α • Multiple pregnancy • Uterine rupture • Glaucoma ↑ IOP		

Oxytocin VS Prostaglandins

Male's doc: These differences are IMP

	Oxytocin	Prostaglandins
Type of contraction	• Contraction only at term	• Contraction throughout pregnancy not only at term
Cervix	★ **Does not soften the cervix**	★ **Soften the cervix**
	Cervical smooth muscle play almost no role in softening the cervix, therefore oxytocin (its action is mainly on myometrium) plays almost no role in softening. It is PGs that cause uterine softening, this happens because they degrade the collagen within the cervix and increase the synthesis of glycosaminoglycans (make the cervix more flexible), so that the head of the fetus can easily dilate the cervix helped by the intrauterine pressure from uterine contractions.	
Uses	• To induce & augment labor & postpartum hemorrhage	• Induce abortion in second trimester of pregnancy • Used as vaginal suppository for induction of labor (to augment oxytocin's effects)
Duration of action	• **Shorter** 5 min	• **Longer**

Uterine Relaxants (tocolytic)

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

- **β2-Adrenoceptor agonists** → Ritodrine (1st choice)
- **Calcium Channel Blockers** → Nifedipine (2nd choice)
- **Oxytocin Antagonists** → Atosiban

Drugs	β2-Adrenoceptor agonists (Ritodrine)	Calcium Channel Blockers (Nifedipine)	Oxytocin Antagonists (Atosiban)
MOA	• **Selective β2 receptor agonist used specifically as a uterine relaxant.** • Bind to β-adrenoceptors → **activate enzyme Adenylate cyclase** → increase in the level of **cAMP** → reducing intracellular calcium level → Smooth muscle relaxation.	• Calcium channel blocker • Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions • Causes relaxation of myometrium	• **Compete with oxytocin at its receptors on the uterus.** • Relatively New tocolytic agent
Pharmacokinetics	IV drip	-	Given by IV infusion for 48hrs, to block the effect of oxytocin
Action	Relax the uterus		
Uses	• Arrest threatened abortion • Delay premature labor, for example the pregnant in the 7th month but she started to feel of contractions • Severe Dysmenorrhea		
ADR (due to general stimulation of the β2-Adrenoceptor)	• Hyperglycemia (glycogenolysis) • Hypokalemia (induce the movement of potassium from blood to get into cells) R/O arrhythmia and heart problems • Tremor • Nausea, vomiting • Flushing (vasodilation) • Sweating (vasodilation) • **Tachycardia(high dose** can effect β1**)** and as reflex to hypotension • **Hypotension** due to smooth muscle relaxation	• **Ankle edema** (Calcium channel blockers usually cause arteriolar dilation without venodilation, and since capillaries lie in-between arterioles and venules, this increases hydrostatic pressure leading to edema) • **Flushing** • **Constipation** • Headache, dizziness • Hypotension • Coughing • Wheezing • Tachycardia as reflex to hypotension	–

Quiz

MCQ

Q1- in case of impaired milk ejection which of the following we should use?

A- Oxytocin I.V B- Oxytocin I.M C- Oxytocin nasal spray D- none of the above

Q2- which of the following is a contraindication of Oxytocin?

A- Incompletely dilated cervix B- Abnormal fetal position
C- Multiple pregnancy D- A&B

Q3- Oxytocin-induced uterine contraction resemble which one of the following?

A- physiological contractions B- tonic contractions C- A&B D- none of the above

Q4- which of the following is a property of Ergometrine?

A- To induce or augment labor. B- only in Postpartum hemorrhage
C- Rapid onset of action D- Shorter duration of action than oxytocin

SAQ

- A diabetic pregnant women her cervix is soft and dilated.

Q1- Name a Drug can be used to induce labor especially her case
Q2- what's the M.O.A of the drug?

Q3- List two ADR of Ergot Alkaloids
Q4- Name two Uterine Relaxants (tocolytic) drugs

Answers:

MCQ

Q1	C
Q2	D
Q3	A
Q4	B

SAQ

Q1	IV Syntocinon
Q2	interaction of oxytocin with myometrial cell membrane receptor promotes the influx of Ca2+ this increase in cytoplasmic calcium → stimulates uterine contraction .
Q3	1- Vasoconstriction of peripheral blood vessels (toes & finger) 2- Gangrene
Q4	1- Ritodrine 2- Nifedipine

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

This amazing work was originally done by (Team438):

Team Leaders:

May Babaeer (رحمها الله) Zyad Aldosari

Team members:

Khalid Aldossari, Naif Aldossari, Abdullah Alnuwaybit

Note writers:

Raghad AlKhashan, Nayef Alsaber

Quiz writers:

Khalid Aldossari

edited by (Team439):

Team Leaders:

Banan AlQady Ghada AlOthman Nawaf Alshahrani

Organizer:

Ghada AlOthman

Team members:

Sarah Alaidarous

Note writers:

Norah almassad, Yasmine alqarni

Reviser:

Sarah AlQuwayz