



Oxytocics & Tocolytics

Objectives:

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

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Drug's name | **Doctors' notes** | **Important** | **Extra**

« قل سيروا في الأرض فانظروا كيف بدأ الخلق »

Mind Map

Drugs producing uterine **contractions** (oxytocic drugs)

oxytocin

Syntocinon

Very famous

promotes the influx of calcium from extra cellular fluid and from S.R. into the cell and stimulates uterine contraction (frequency and force) particularly of the fundus

ergot alkaloids

Ergometrine

Methyl ergometrine

Ergot alkaloids induce tetanic contraction of uterus as a whole without relaxation in between

prostaglandins

PGE2, PGF2 α

PGE1 (misoprostol)

contraction of uterine smooth muscle not only at term but throughout pregnancy. PGs also soften the cervix

Drugs producing uterine **relaxation** (tocolytic drugs)

β -adrenoceptor agonists

Ritodrine

Activate Adenylate cyclase and increase in the level of cAMP which reduce intracellular calcium level.

calcium channel blockers

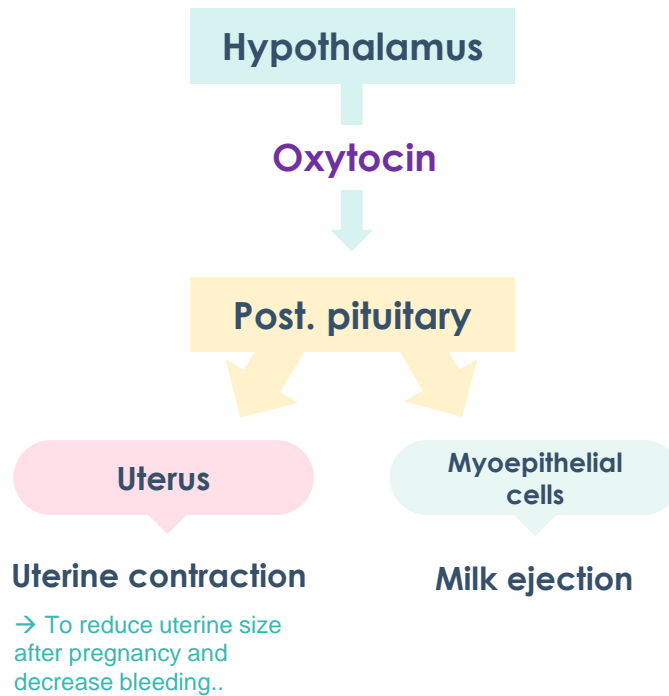
Nifedipine

Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions

Atosiban

Compete with oxytocin at its receptors on the uterus.

To Understand Better



Role of **oxytocin** “physiological”:

uterus

- Stimulates both the **frequency** and **force** of uterine contractility particularly of the **fundus** segment of the uterus. Contract **the fundus only, not the cervix**. If it is not followed by relaxation? Will lead to **abortion!**
- These contractions resemble the normal physiological contractions of uterus (**contractions followed by relaxation**)



زي ما نعرف بشكل طبيعي، الأوكسيتوسين يصير تأثيره واضح لما تدخل المرأة مرحلة الولادة عشان ال up-regulation of its receptors in the uterus .. سو يعني لما اليوترس لسه ما وصل لمرحلة الولادة، مراح يصير عندي تأثير الأوكسيتوسين عشان ما فيه رسيترز كافية على الرحم تستقبله.

- Immature uterus is **resistant** to oxytocin.
- Contract uterine smooth muscle only at term. **Induction of labor + last week of pregnancy**
- Sensitivity increases to 8 folds in last 9 weeks and 30 times in early labor.
- **Clinically oxytocin is given only when uterine cervix is soft and dilated.**

Myo-epithelial cells

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

Oxytocic drugs

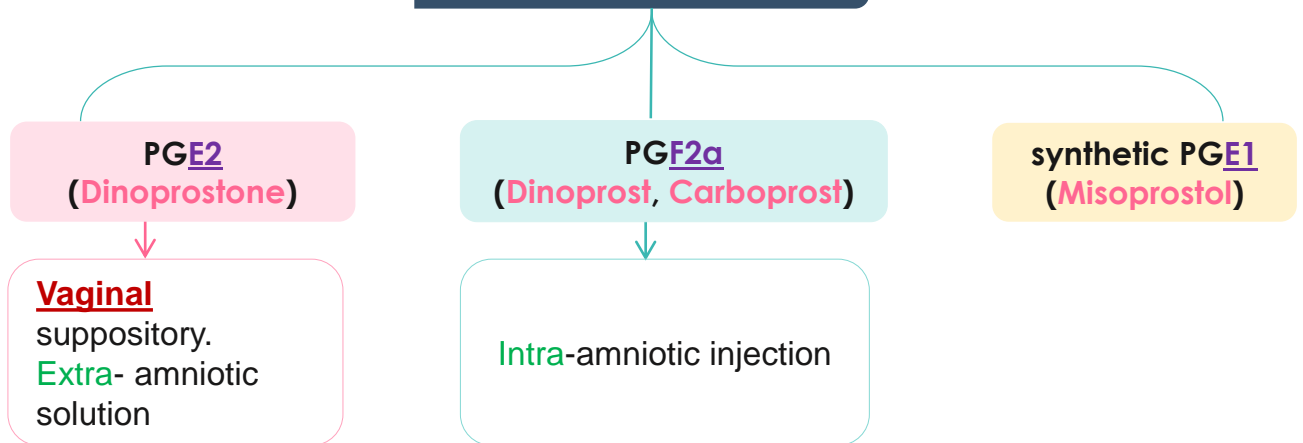
Drug	1- Oxytocin (syntocinon)	
MOA	<ul style="list-style-type: none"> The interaction of endogenous or administered oxytocin, with <u>myometrial cell</u> membrane receptor promotes the influx of Ca^{++} from extra cellular fluid and from S.R. into the cell , this increase in cytoplasmic calcium, stimulates uterine contraction. 	
P.K	<ul style="list-style-type: none"> <u>Not effective orally</u> (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 (short, other drugs in this lec have longer $T_{1/2}$) 	
Indications	<p>Synthetic preparations of oxytocin; e.g. syntocinon are preferred.</p> <ol style="list-style-type: none"> Induction + augmentation of labor (slow IV) <ul style="list-style-type: none"> Mild pre-eclampsia near term Uterine inertia <small>خمول الرحم، الرحم ضعيف ما عنده كونتراكشن كافية</small> Incomplete abortion <small>ينزل بقايا الجنين</small> Post maturity <small>يصير الجنين كمل ٩ شهور ودخل أسبوعين زيادة ومش عايز ينزل</small> Maternal diabetes <small>عشان ما تحصل مضاعفات للبيبي</small> Post partum uterine bleeding (in 3rd stage) (I.V drip) ergometrine is often used Impaired milk ejection (1 puff in each nostril, 2-3 min before nursing) <p style="text-align: right;"><small>فيه شيء لازم نتفق عليه، الأوكسيتوسين ما نعطيه للي ناوين يولدون بالعملية cesarean !!! بس نعطيهم للي بيولدون طبيعي</small></p>	
ADRs	<ol style="list-style-type: none"> Maternal death due to hypertension <small>Bc oxytocin has anti-diuretic effect, salt & water retention</small> Uterine rupture → <small>Excessive stimulation of uterine contractions before delivery can cause fetal distress, placental abruption, or uterine rupture.</small> Fetal death (ischemia) → <small>During the antepartum period, oxytocin induces uterine contractions that transiently reduce placental blood flow to the fetus.</small> Water intoxication if oxytocin is given with relatively large volumes of <u>electrolyte-free</u> aqueous fluid intravenously → <small>High concentrations of oxytocin with activation of vasopressin receptors can cause excessive fluid retention, or water intoxication.</small> 	
C.I	<ol style="list-style-type: none"> Hypersensitivity Prematurity (it is used only in mature & dilated cervix) Abnormal fetal position Evidence of fetal distress Cephalopelvic disproportion <small>لما يصير الرأس كبير، بيصير فرصة الولادة طبيعي أقل، فلجأ للعملية على طول بدون ما أتعب نفسي وأعرض البيبي للخطر</small> <u>In</u>completely dilated cervix 	<p style="text-align: center;">Precautions</p> <ol style="list-style-type: none"> Multiple pregnancy → rupture of uterus Previous c- section Hypertension

Oxytocic drugs (cont.)

Drug	2- Ergot alkaloids
MOA	<ul style="list-style-type: none"> ❖ Effects on the Uterus: <ul style="list-style-type: none"> ○ 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) لو أعطيته للأم ولسه البيبي جواتها، كذا كأتك تعصر الرحم وتعصر البيبي معاه ☺ .. لذلك ممنوع نعطي الأم ولسه البيبي جواتها!!! ○ Main differences between oxytocin & ergots? 1. Type of contraction: <ul style="list-style-type: none"> ▪ Oxytocin: contraction followed by relaxation ▪ Ergot: contraction <u>without</u> relaxation 2. Place of contraction: <ul style="list-style-type: none"> ▪ Oxytocin: only fundus. ▪ Ergot: the whole uterus.
P.K	<ul style="list-style-type: none"> ○ Natural <ul style="list-style-type: none"> • Ergometrine (Ergonovine) ○ Synthetic <ul style="list-style-type: none"> • Methyl-ergometrine (Methylergonovine) ○ Usually given I.M ○ Extensively metabolized in liver ○ 90% of metabolites are excreted in bile
Indications	<ul style="list-style-type: none"> ○ Post-partum hemorrhage (3rd stage of labor) بعد الولادة، السنت بتصير تنزف في هذا السنج <ul style="list-style-type: none"> • When to give it? After birth, 3rd stage of labor ○ Preparations: <ul style="list-style-type: none"> • Syntometrine (ergometrine 0.5 mg + oxytocin 5.0 I.U) , I.M.
ADRs	<ul style="list-style-type: none"> ○ Nausea, vomiting, diarrhea ○ Hypertension ○ Vasoconstriction of peripheral blood vessels (toes & fingers) → Gangrene
C.I	<ul style="list-style-type: none"> ○ Induction of labor in case of: <ol style="list-style-type: none"> A. 1st and 2nd stage of labor B. Vascular disease C. Severe hepatic and renal impairment D. Severe hypertension

Oxytocic drugs (cont.)

3- Prostaglandins



Therapeutic uses:

- 1. Induction of abortion** (pathological) + زي ما قلنا في الأورال كونتراسيبتف (morning-after pills) نستخدم misoprostol to induce abortion
- 2. Induction of labor** (fetal death in utero) → Used in both; to induce normal labor with live fetus, or died fetus in the uterus + استخدامه الأساسي للإجهاض في جميع مراحل الحمل
- 3. Postpartum hemorrhage**

ADRs	Contraindications	Precautions
<ul style="list-style-type: none"> Nausea, vomiting, Diarrhea Abdominal pain Bronchospasm (PGF2α; Dinoprost, Carboprost) Flushing (PGE2; Dinoprostone) 	<ul style="list-style-type: none"> Mechanical obstruction of delivery. e.g. placenta previa Fetal distress <small>هنا أحول على العملية بسرعة</small> Predisposition to uterine rupture 	<ul style="list-style-type: none"> Asthma Multiple pregnancy Uterine rupture Glaucoma (↑ IOP)

Difference between PGs & Oxytocin:

Important

Character	Oxytocin	Prostaglandins
Contraction	○ Only at term (time of delivery)	○ Contraction through out pregnancy (in anytime of preg)
Cervix	○ Does not soften the cervix	○ soften the cervix
Duration of action	○ Shorter	○ Longer
Uses	<ul style="list-style-type: none"> ○ Induce and augment labor (at time of delivery, not before (bc of oxytocin Rs) ○ Post partum hemorrhage <small>* الأوكسيتوسين ما يستخدم في ال induction of abortion ..ليه؟ لأن زي ما قلنا إن ال ريسيتورز حقت الراكسيتوسين ما تطلع إلا وقت الولادة، فحتى لو عطيت اوكسيتوسين في أول أو وسط الحمل ما راح يقع لأنه ما فيه ريسيتورز تستقبلهم</small>	<ul style="list-style-type: none"> ○ Induce <u>abortion</u> in 2nd trimester of pregnancy. ○ Used as vaginal suppository for induction of <u>labor</u>

Oxytocic drugs (cont.)

Difference between **Oxytocin** & **Ergometrine**:

Character	Oxytocin	Ergometrine
Contraction	<ul style="list-style-type: none"> Resembles normal physiological contractions (contraction then relaxation) 	<ul style="list-style-type: none"> Tetanic contraction; doesn't resemble normal physiological contractions (without relaxation)
Uses	<ul style="list-style-type: none"> To induce & augment labor. Post partum hemorrhage 	<ul style="list-style-type: none"> Only in post-partum hemorrhage
Onset and Duration	<ul style="list-style-type: none"> Rapid onset, I.V Shorter duration of action 	<ul style="list-style-type: none"> Moderate onset, I.M Long duration of action

Tocolytic Drugs (uterine relaxation)

Action and uses:

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

1- β -Adrenoceptor agonists

Imp, MCQs ☺

- Ritodrine**, I.V. drip → the cheapest & commonly used.
- Selective **β_2 receptor agonist** used specifically as a **uterine relaxant**.

❖ Mechanism of action

- Bind to β -adrenoceptors, **activate enzyme Adenylate cyclase**, **increase in the level of cAMP** **reducing intracellular calcium level**.

❖ Side effects

- | | | |
|---|---|--|
| <ul style="list-style-type: none"> Tremor Nausea , vomiting Flushing | <ul style="list-style-type: none"> Sweating Tachycardia (high dose) | <ul style="list-style-type: none"> Hypotension (vasodilation) Hyperglycemia Hypokalemia |
|---|---|--|

2- Calcium channel blockers (**Nifedipine**)

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

❖ Side effects

- **Hypotension**
- Flushing
- **Constipation**
- **Ankle edema**
- Coughing, Wheezing → be careful with asthmatic pts.
- **Tachycardia**
- Dizziness, Headache

3- **Atosiban:**

- New tocolytic agent, *expensive, not used widely.*
- **Compete with oxytocin at its receptors on the uterus.**
- Given by **IV** infusion for 48 hrs (*long*)
- May be **less effective** as tocolytic than β_2 agonists.
- It is **better tolerated than β_2 agonists**, especially with regards to **cardiovascular side effects** and may be useful alternative.

Summary-2

Dru g	3- Prostaglandins:		
Types	PGE2 – Dinoprostone Vaginal suppository. Extra- amniotic solution.	PGF2α- Dinoprost, Carboprost intra-amniotic injection	Misoprostol (synthetic PGE1)
AD Rs	a) Nausea, vomiting. b) Abdominal pain. c) Diarrhea. d) Bronchospasm (PGF2α) . e) Flushing (PGE2) .		
Prec. & C.I	C.I.: a) Mechanical obstruction of delivery. b) Fetal distress. c) Predisposition to uterine rupture.		
	Prec.: a) Asthma . b) Multiple pregnancy. c) Glaucoma. d) Uterine rupture.		
Uses	a) Induction of labor & abortion. b) Postpartum hemorrhage		

B- Drugs that produce uterine relaxation.

Dru g	Tocolytic Drugs		
Acti on	Relax the uterus and arrest threatened abortion or delay premature labor.		
Types	1.B-adrenoceptor agonists Ritodrine , I.V. Drip selective B2 receptor agonist used specifically as a uterine relaxant.	2. Calcium channel blockers e.g: Nifedipine	3. Atosiban
Mech. of action	Bind to β-adrenoceptors , activate enzyme Adenylate cyclase , increase in the level of cAMP reducing intracellular calcium level.	-Causes relaxation of myometrium -Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions.	- Compete with oxytocin at its receptors on the uterus. -Given by IV infusion for 48 hrs. -Better tolerated than β2 agonists, especially with regards to CVS ADRs.
ADR	<ul style="list-style-type: none"> Tremor. Nausea, vomiting. Flushing. Sweating. Tachycardia (high dose). Hypotension. Hyperglycemia. Hypokalaemia. 	<ul style="list-style-type: none"> Headache, dizziness Hypotension Flushing Constipation Ankle edema Coughing Wheezing Tachycardia 	-

Character	Oxytocin	Prostaglandins
Contraction	Only at term	Contraction through out pregnancy
Softening the cervix	X	✓
Duration of action	Shorter	Longer
Uses	Induce and augment labor and post partum hemorrhage.	-Induce abortion in 2 nd trimester of pregnancy. -Used as vaginal suppository for induction of labor.

Character	oxytocin	Ergometrine
Contractions	Resembles normal physiological contractions	Tetanic contraction ;doesn't resemble normal physiological contractions
Uses	Induce and augment labor and post partum hemorrhage.	Only in postpartum hemorrhage
Onset and Duration	Rapid onset Shorter duration of action	Moderate onset Long duration of action

MCQs

1- which one of the following is the clinical use of ergot alkaloids?

- A. Induction of birth
- B. Postpartum bleeding
- C. Both

2- The effect of oxytocin on the uterus is?

- A. Increase ca influx
- B. Increase k influx
- C. Decrease ca influx

3- Which one of the following consider as a side effect of oxytocin?

- A. Vaginal bleeding
- B. Hypertension
- C. gangrene

4- A 29-year-old pregnant lady came to the clinic complaining of ankle edema that she noticed 5 days ago. After taking the history she said that she is taking a drug for premature labor but she forgot the name of the drug. Which one of the following drugs she most likely uses?

- A. Ergometrine
- B. Misoprostol
- C. Nifedipine
- D. Ritodrine

5- A 16-year-old pregnant girl came to the ER with severe vaginal bleeding. After doing routine procedures it is learned that the baby is dead. While taking the history the patient told the doctor that her friend gave her a suppository to induce abortion. Which one of the following drugs she most likely took?

- A. Dinoprost
- B. Dinoprostone
- C. Carboprost
- D. Oxytocin

6- A 36-year-old multiparous pregnant lady (who had cesarean sections for all her previous pregnancies) is now 10 months pregnant, her obstetrician decides to induce labor so he gave her an intra-amniotic injection. After giving birth to a healthy baby the patient complained of abdominal pain and died of a hypovolemic shock a few hours later. Which one of the following drugs did the doctor give her?

- A. Carboprost
- B. Dinoprostone
- C. Oxytocin
- D. Ergometrine

7- The drug of choice for controlling postpartum Hemorrhage is:

- A. Oxytocin
- B. Methylergometrine
- C. Dihydroergotamine
- D. Prostaglandin E2

8- Ergometrine is contraindicated in the following conditions except:

- A. Multiparity
- B. Toxaemia of pregnancy
- C. Pelvic sepsis
- D. Peripheral vascular disease

9- Select the drug that has been used to suppress Labor:

- A. Atropine
- B. Ritodrine
- C. Prostaglandin E2
- D. Progesterone

10- Use of ritodrine to arrest premature labor can cause the following complications except:

- A. Tachycardia
- B. Fall in blood pressure
- C. Hypoglycaemia
- D. Pulmonary edema

Thank you for checking our team!



Pharmacology 435

 @ pharmacology435

Sources:

1. 435's slides.