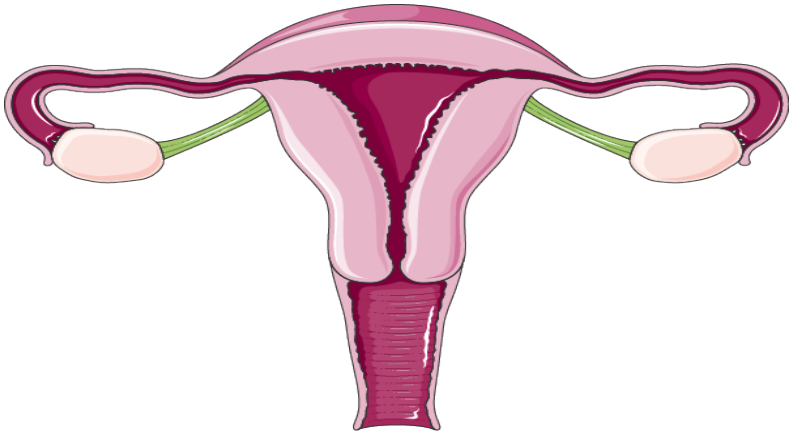
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



4: Drug affecting Uterine Muscle Contractility

Objectives

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.

Color index

- Doctors' notes
- Drugs names
- Extra information and further explanation
- Important
- Mnemonics

تمت المراجعة
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Drugs Producing Uterine Contractions (oxytocic)

Oxytocin	Ergot alkaloids	Prostaglandins
Syntocinon	1. Natural: **Ergometrine** (Ergonovine) 2. Synthetic: **Methyl ergometrine** (Methylergonovine)	1. PGE2: **Dinoprostone** (PGE2- Tone/Tuna = بقيتوا لي تونا) 2. PGF2α: **Dinoprost**, **Carboprost** (F-2-prost = فيه تو بروست) 3. synthetic PGE1: **Misoprostol** (E-1-miso/ E I miss you = إيه آي مس يو)

Role of oxytocin[1]

3:37

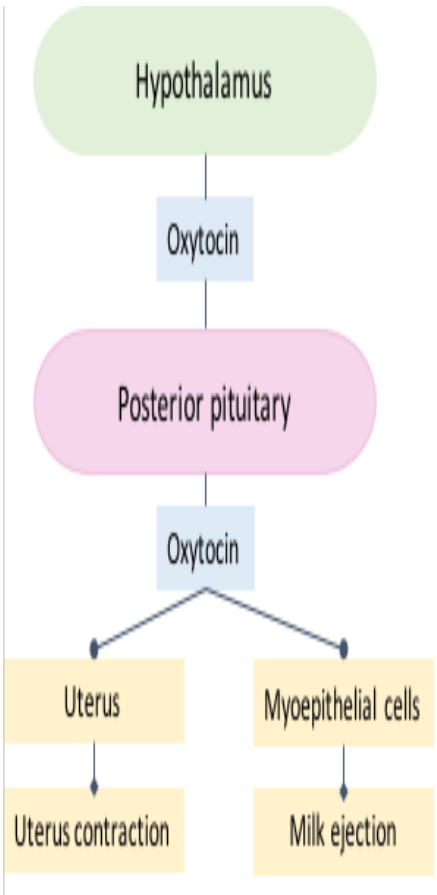
Effect on uterus:

- Stimulates both the **frequency and force** of uterine contractility particularly of the fundus segment of the uterus. (only the fundus not the cervix)
- These contractions resemble the normal physiological contractions of uterus (contractions followed by relaxation)[2]

- Immature uterus[3] 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 (otherwise it may cause rapture)

Effect on Myoepithelial cells:

- Oxytocin contracts myoepithelial cells surrounding mammary alveoli in the breast & leads to milk ejection. Especially for the first neonate if there is insufficient milk production .



[1] Bc oxytocin has effect on uterus and the breast, we can use it to induce labor and lactation
[2] If the drug resemble the normal physiology, it will be very effective drug
[3] Uterus not in labor

Oxytocin

Oxytocin e.g. **Syntocinon**	
M.O.A	The interaction of endogenous or administered oxytocin , with myometrial cell membrane receptor promotes the influx of Ca^{2+} from extra cellular fluid and from sarcoendoplasmic reticulum into the cell , this increase in cytoplasmic calcium → stimulates uterine contraction .
P.K	• Not effective orally (destroyed in GIT) • Administered I.V. (augment labor) then we monitor its effect on the uterus • Also as nasal spray (impaired milk ejection) • Not bound to plasma proteins • Catabolized by liver & kidneys • Half life = 5 minutes
Indications	**Synthetic preparations of oxytocin; e.g. syntocinon are preferred.** Due to ↑ ½ life 1. Induction & augmentation of labor[4] (slow I.V infusion) ✓ Mild preeclampsia near term تسمم الحمل (يجي مع المريضة ارتفاع بالضغط وانتفاخات ونوبات) فعشان نمنع هذي المخاطر نخليها تولد بسرعة ✓ Uterine inertia الرحم ما يستجيب أو ما يظهر أي علامات للطلق (مافيه تقلصات للرحم) ✓ Incomplete abortion (to expel the placenta and the remnant of the baby) ✓ Post maturity (exceed the normal duration of pregnancy 'about 40 weeks') ✓ Maternal diabetes (bc the baby will be huge) 2. Post partum uterine hemorrhage[5] (I.V drip): ergometrine is often used 3. Impaired milk ejection: One puff in each nostril 2-3 min before nursing
Side effects	• Maternal death due to hypertension (rare, specially in good hospitals) • **Uterine rupture** (most dangerous side effect) • Fetal death (ischemia), so whenever we give oxytocin we should monitor the baby, bc the contraction may decrease the blood supply to the baby • Water intoxication[6] if oxytocin is given with relatively large volumes of electrolyte-free aqueous fluid intravenously

[4] It is used to cause contraction of the uterus in order to start labor or increase the speed of labor, and to stop bleeding following delivery.

[5] cuz contraction of the uterus will contract the blood vessels → stop the bleeding

[6] Oxytocin induce short action then it become contaminated with vasopressin (antidiuretic) in other word, oxytocin may cause water intoxication via an anti-diuretic hormone-like activity

Oxytocin

	Oxytocin e.g. **Syntocinon**
C.I	• Hypersensitivity • Prematurity of the uterus (before labor, the cervix is not relax) • Abnormal fetal position • Evidence of fetal distress (we will see the HR of the baby dropping) • Cephalopelvic disproportion رأس البيبي والحوض غير متوافقين يا الراس كبير أو الحوض صغير • Incompletely dilated cervix
Precaution	1. Multiple pregnancy 2. Previous C-section (is the use of surgery to deliver one or more babies.) 3. Hypertension (this kind of drug cause hypertension, why? it causes vasoconstriction)

Ergot Alkaloids

	Natural e.g. **Ergometrine**	Synthetics e.g. **Methyl ergometrine**
M.O.A	• 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). **SO WE DON'T GIVE IT DURING LABOR** • Main differences between oxytocin & ergots? 1. Type of contraction: • Oxytocin: contraction followed by relaxation • Ergot: contraction without relaxation 2. Place of contraction: • Oxytocin: only fundus. • Ergot: the whole uterus.	

Ergot Alkaloids

	Natural e.g. **Ergometrine**	Synthetics e.g. **Methyl ergometrine**
P.K	• Usually given I.M (if we give IV they will cause powerful hypertension) • Extensively metabolized in liver • 90% of metabolites are excreted in bile	
Uses	• Post partum hemorrhage (3rd stage of labor) DON'T inject until you see the head of the baby • **Preparations:** Syntometrine (ergometrine 0.5 mg + oxytocin 5.0 I.U) , I.M.[7] **When to give it?** After birth, 3rd stage of labor	
ADRs	Vasoconstriction of peripheral blood vessels (toes & fingers) Gangrene (due to Vasoconstriction of peripheral blood vessels 'rare') Nausea, vomiting, diarrhea Hypertension (sever) ergometrin cause less hypertension compare to Methyl ergometrine	
C.I	• Induction of labor: 1st and 2nd stage of labor • vascular disease • Severe hepatic and renal impairment • Severe hypertension	

Oxytocin Vs Ergometrine

	Oxytocin	Ergometrine
Contractions	Resembles normal physiological contractions	Tetanic contraction, doesn't resemble normal physiological contractions (without relaxation in between and causes the contraction of the uterus as a whole)
Uses	• To induce &augment labor. • Post partum hemorrhage	Only in Post partum hemorrhage
Onset and Duration	• Rapid onset • Shorter duration of action	• Moderate onset • Longer duration of action

[7] Although ergo have a long duration ,because it is given I.M it will activate after 7 min. which is a very long period for a bleeding women, thus we combine it with oxytocin which has a **faster** but **shorter** duration of action to help in giving a drug that has a fast onset of action (within 2-3 min) and long duration.

Prostaglandins

	PGE2 e.g. **Dinoprostone**	PGF2α e.g. **Dinoprost**	synthetic PGE1 e.g. **Misoprostol**
Admin.	• Vaginal suppository • Extra- amniotic solution	Intra-amniotic injection	
Uses	• Induction of abortion (pathological) إذا كان فيه مرض للطفل أو فيه مرض عند الأم وما يصلح تكمل الحمل • Induction of labor (fetal death in utero) • Postpartum hemorrhage		
ADRs	• Bronchospasm (PGF2α) PGF2a CI in Asthmatic pregnant = Fetus has Asthma • Flushing of the face and chest (PGE2) bc it causes vasodilatation • Nausea , vomiting • Abdominal pain • Diarrhea		
C.I.	• Mechanical obstruction of delivery, e.g. placenta Previa or the umbilical cord surround the baby • Fetal distress • Predisposition to uterine rupture		
Precaution	• Asthma • Multiple pregnancy • Glaucoma (PG increase the formation of aqueous humorous, so increase IOP) • Uterine rupture		
PG vs oxytocin	❖ **Contraction:** • Oxytocin: Only at term • Prostaglandin: Contraction through out pregnancy[8] ❖ **Cervix:** • **Oxytocin:** Does not soften the cervix • **Prostaglandin:** soften the cervix ❖ **Duration of action:** • **Oxytocin:** Shorter • **Prostaglandin:** longer ❖ **Uses:** • **Oxytocin:** Induce and augment labor and post partum hemorrhage • **Prostaglandin:** Induce abortion in 2nd trimester of pregnancy, Used as vaginal suppository for induction of labor and Postpartum hemorrhage		

[8] PGs contract uterine smooth muscle not only at term (as with oxytocin), but throughout pregnancy

Uterine Relaxants (tocolytic)*

β_2-Adrenoceptor agonists	Calcium Channel Blockers	Compete with oxytocin receptors
R look like B To = 2 **Ritodrine** (1st choice)	نيف دا بلين يحب الحليب(كالسيوم) **Nifedipine** (2nd choice)	(At)osiban= Antagonize oxytocin (AT) receptors A(tosi)ban = oxy(toci)n **Atosiban** Ato-siban=ممكن يقرأ عطوا الشيبان

Action and uses

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

	Ritodrine	Nifedipine	Atosiban
Mechanism of action	• Selective β_2 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.	• Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions • Causes relaxation of myometrium	• Compete with oxytocin at its receptors on the uterus. • New tocolytic agent • Given by IV infusion for 48 hrs
Adverse effects	• **Hyperglycemia** • **Hypokalemia** • Tremor • Nausea , vomiting • Flushing • Sweating • Reflex Tachycardia (high dose) • Hypotension	• Ankle edema • Flushing • Headache, dizziness • Hypotension • Constipation • Coughing • Wheezing • Reflex tachycardia	Doesn't have the cardio vascular side affects

* أهم شي تعرفوا الأسماء والميكانزم (اللي موجودة في المربعات هي أهم شي)

Summary

1- OXYTOCIN (Syntocinon)

Role	**On uterus**	Stimulates both the frequency and force of uterine contractility particularly of the fundus segment of the uterus and these contractions resemble the normal physiological contractions of uterus (contractions followed by relaxation) . • Contract uterine smooth muscle only at term. • Clinically oxytocin is given only when uterine cervix is soft and dilated.
	On myoepithelial cells	Oxytocin contracts myoepithelial cells surrounding mammary alveoli in the breast & leads to milk ejection.
Uses	1. Induction & augmentation of labor (slow I.V infusion) . syntocinon are preferred. 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)	

2- ERGOT ALKALOIDS (Ergometrine, Methyl ergometrine)

Role	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) **Preparations:** Syntometrine (ergometrine+ oxytocin IM) give it After birth, 3rd stage of labor
ADRs	• Vasoconstriction of peripheral blood vessels • Gangrene • Hypertension

3-PROSTAGLANDINS

	PGE2 (Dinoprostone)	PGF2α (Dinoprost, Carboprost)	Synthetic PGE1 (Misoprostol)
ADRs	• Bronchospasm (PGF2α) • Flushing (PGE2)	• Nausea, vomiting, diarrhea.	• Abdominal pain
Prec.	• Asthma • Multiple pregnancy	• Glaucoma	• Uterine rupture

Difference b/w Oxytocin , Ergometrine , and Prostaglandins

Character	Oxytocin	Ergometrine	Prostaglandins
Contractions	Only at term and it resembles normal physiological contractions	Tetanic contraction ; doesn't resemble normal physiological contractions	Contraction through out pregnancy
Cervix	Does not soften the cervix	-	soften the cervix
Uses	Induce and augment labor and postpartum hemorrhage	Only in postpartum hemorrhage	Induce abortion in 2nd trimester of pregnancy and used for induction of labor

DRUGS PRODUCING UTERINE RELAXATION(Tocolytic Drugs)

Types	**1.β-adrenoceptor agonists** Ritodrine selective β_2 receptor agonist used specifically as a uterine relaxant.	**2. Calcium channel blockers** e.g: Nifedipine	**3. Atosiban** Compete with oxytocin receptors (oxytocin receptors antagonist)

MCQs

Q1: Syntocinon can be used in which of the following situation ?

A. To induce labor in uterus of pregnant at term. B. To induce milk ejection in breastfeeding women.
C. Pregnant women with soft and dilated cervix. D. All of them

Q2: Which of the following can be used in case of breastfeeding women who can not nursing her newborn due to impaired milk ejection ?

A. Oral Oxytocin. B. Nasal spray Ritodrine . C. Oral Dinoprostone. D. Nasal spray Syntocinon.

Q3: Women finish 42 weeks of pregnancy and does not show any sign of labor. So her doctor decide to induce the labor, which one of the following is drug of choice?

A. IV Syntocinon. B. Nasal spray Atosiban. C. IM methyl-ergometrine. D. Nasal spray Oxytocin.

Q4: Which of the following can be used to induce labor especially in diabetic pregnant and her cervix is soft and dilated ?

A. IV Syntocinon. B. Nasal spray Atosiban. C. IM methyl-ergometrine. D. Nasal spray Oxytocin.

Q5:31 years old women who suffer from Post partum hemorrhage after she deliver her child. Which one of the following can be used to stop the bleeding in her case ?

A. IV Syntometrine. B. Nasal spray Atosiban. C. IM methyl-ergometrine. D. Both A & C.

Q6: A 20 weeks pregnant lady knows recently that she has teratogenic baby, so she and her husband decide to induce abortion and terminate the pregnancy. Which of the following the doctor can use in her case ?

A. IV Oxytocin. B. Oral Misoprostol. C. . Nasal spray Atosiban. D. . IM methyl-ergometrine. .

Q7: Asthmatic pregnant lady want to terminate her 15 weeks pregnancy, which one of the following is highly contraindicated?

A. Dinoprostone. B. Misoprostol. C. . Dinoprost. D. Atosiban

Q8:Which of the following can be used to delay premature labor in pregnant lady ?

A. Dinoprostone. B. Syntocinon. C. . methyl-ergometrine. D. Ritodrine.

Q9: A 35 weeks pregnant lady who has unstable pregnancy and has high risk of abortion. Which of the following the doctor can use in her case to arrest threatened abortion ?

A. Atosiban. B. Syntocinon. C. . methyl-ergometrine. D. Dinoprostone.

Q10: Which one of the following act as beta adrenoceptors agonist to relax uterine muscles and delay premature labor ?

A. Atosiban. B. Syntocinon. C. .Nifedipine. D. Ritodrine.

Q11: Which one of the following act as oxytocin antagonist on its receptors to relax uterus and delay premature labor ?

A. Atosiban. B. Syntocinon. C. .Nifedipine. D. Ritodrine.

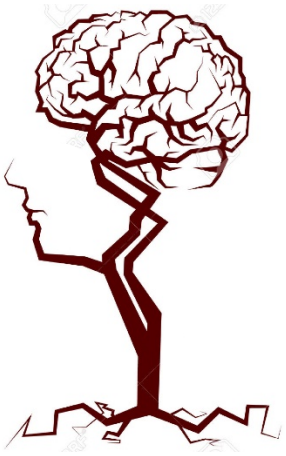
Q12: Which one of the following act as calcium channel blocker to relax uterine muscles and delay premature labor ?

A. Atosiban. B. Syntocinon. C. .Nifedipine. D. Ritodrine.

Q13: Which of the following is the drug of choice to induce labor ?

A. Misoprostol. B. Syntocinon. C. . methyl-ergometrine. D. Ritodrine.

1) D.
2) D.
3) A.
4) A.
5) D.
6) B.
7) C.
8) D.
9) A.
10) D.
11) A.
12) C.
13) B.



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3- The National Center for Biotechnology Information advances science and health

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