King Saud University

College of Medicine

2nd Year,

Reproduction Block

PHARMACOLOGY 433

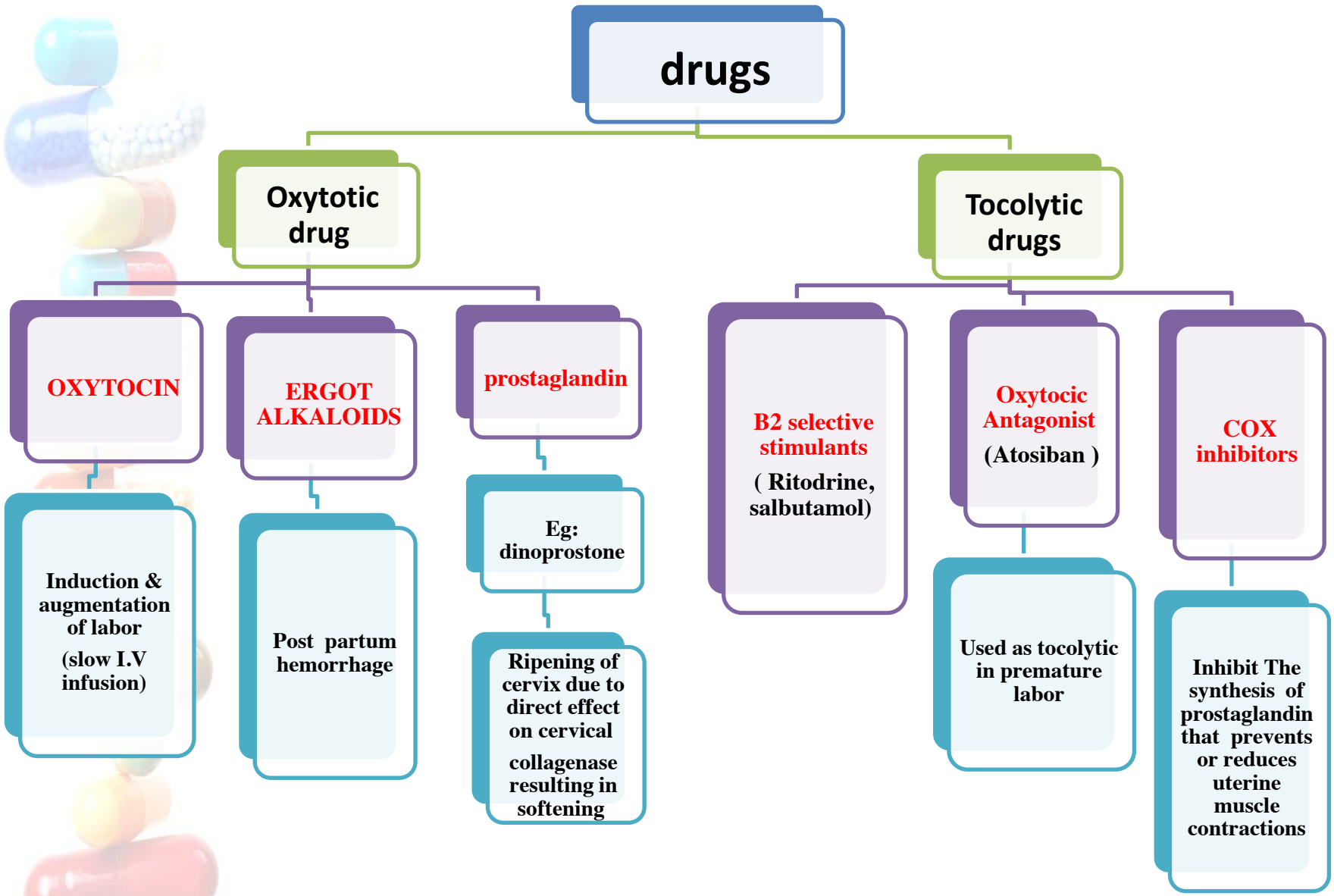
MED 433 Teams

L5- Drugs affecting uterine motility

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.

Mind Map


drugs
Oxytotic drug
Tocolytic drugs
OXYTOCIN
ERGOT ALKALOIDS
prostaglandin
B2 selective stimulants
(Ritodrine, salbutamol)
Oxytocic Antagonist
(Atosiban)
COX inhibitors
Induction & augmentation of labor
(slow I.V infusion)
Post partum hemorrhage
Eg: dinoprostone
Ripening of cervix due to direct effect on cervical
collagenase resulting in softening
Used as tocolytic in premature labor
Inhibit The synthesis of prostaglandin that prevents or reduces uterine muscle contractions

Drugs affecting uterine contractility

1- OXYTOCIC DRUGS

Drugs stimulate uterine smooth muscles during pregnancy , produce contraction that promotes rapid labor (uterine stimulant or abortifacients)

Oxytocin	Ergot alkaloids	Prostaglandines	Miscellaneous
▪ posterior pituitary Hormone ▪ Syntocinon	▪ Ergotamine ▪ Ergonovine ▪ Methyl ergometrine	▪ PGE2 ▪ PGF2α ▪ Misoprostol	▪ Quinine ▪ Emetine ▪ Alcohol

2- TOCOLYTICS

Drugs relax uterine smooth muscles & inhibit uterine contractions

B2 selective stimulants	Oxytocic Antagonist	COX inhibitors
▪ Ritodrine ▪ salbutamol	▪ Atosiban	▪ Celecoxib ▪ Indomethacin ▪ Aspirin ▪ Ibuprofen

Oxytocin

Oxytocin secretion occurs by sensory stimulation from cervix ,vagina , and from suckling at breast.

Syntocinon (Synthetic is preferred)	
PHARMACOKINETICS	▪ **Not effective orally** (Destroyed in GIT) ▪ **Given IV(LABOR) or nasal spray (in cases of impaired milk ejection)** ▪ **Not bound to plasma proteins** ▪ **Eliminated by liver & kidneys** ▪ **Onset = seconds** ▪ **Half life = 5 minutes**
MECHANISM OF ACTION	**Acts through GPCR ➔ activation of phospholipase C ➔ production of IP3 ➔ mobilization of calcium from its stores (SR)** **Also, activates voltage sensitive calcium channels causing an increase in cytoplasmic calcium level that stimulates uterine contraction .**
USES	**1-Facilitation of labor at term Ivinfusion (Reinforcement of labor)** **2- Induction of labor for conditions requiring early vaginal delivery (I.V infusion)** e.g. a) Placental insufficiency b) Uterine inertia (no contraction) d) Post maturity f) Premature rupture membranes **3- Post partum uterine hemorrhage (ergometrine replaced it)** **4- Impaired milk ejection: One puff in each nostril 2-3 min before nursing** **5- Incomplete abortion**

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Oxytocin

Uterus

Small dose:	Large dose:
Small doses stimulates both the frequency and force of uterine contractility particularly of the fundus segment of the uterus. These contractions resemble the normal physiological contractions of uterus (contractions followed by relaxation)	Large doses causes sustained contractions Immature uterus 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.

Mammary glands:

Stimulate myoepithelial cells surrounding mammary alveoli produce milk production
Without oxytocin induced contraction lactation can not occur.

At high doses it has antidiuretic (water retention) activity due to action on **vasopressin receptors.**

Oxytocin

Syntocinon (Synthetic is preferred)	
ADVERSE EFFECTS	**FETAL**: ▪ Distress, placental abruption , death **MATERNAL**: ▪ Uterine rupture ▪ Fluid retention, ▪ water intoxication ▪ Hyponatremia, ▪ heart failure ▪ Seizures ▪ Death (Bolus injection can produce hypotension, so used as infusion at a controlled rate)
CONTRAINDICATIONS	▪ Hypersensitivity ▪ Prematurity ▪ Abnormal fetal position ▪ Evidence of fetal distress ▪ Cephalopelvic disproportion
PRECAUTIONS	▪ Multiple pregnancy (afraid of uterine rapture due to weakness of muscles) ▪ Previous c- section ▪ Hypertension

Ergot Alkaloid

Ergometrine

Preparations	▪ Natural: Ergonovine ▪ Semisynthetic : Methyl ergonovine ▪ Synthetic: Methyl ergometrine *Syntometrine(ergometrine 0.5 mg + oxytocin 5.0 I.U), I.M.
Effects on the uterus	Alkaloid derivatives 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)
Pharmacokinetics	▪ Absorbed orally from GIT(tablets) ▪ Usually given I.M ▪ Extensively metabolized in liver. ▪ 90% of metabolites are excreted in bile
Clinical uses	**1-Post partum hemorrhage** **(3rd stage of labor)** **very strong contraction of smooth muscles and closure of blood vessels** **2-Hastens involution of the uterus**
Side effects	▪ Nausea, vomiting, diarrhea ▪ Hypertension ▪ Vasoconstriction of peripheral blood vessels (toes & fingers) ▪ Gangrene
Contraindications	▪ Induction of labor: (1st and 2nd stage of labor) ▪ vascular disease ▪ severe hepatic and renal impairment Severe hypertension

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Prostaglandins

Drug one	**Dinoprostone** (synthetic PGE2)		
Pharmacological action	▪ Given intravaginally as a gel or tablet. ▪ Given extra-amniotically as a solution. ▪ 1st metabolism in lung (95%) ▪ Metabolized in local tissues. ▪ Metabolites excreted in urine. ▪ Some absorption directly through cervix & lymphatics into maternal circulation. ▪ Half-life 2.5- 5 min.		
Effects	Stimulation of G protein coupled PGE2 receptors ➔ contraction of myometrium . Ripening of cervix due to direct effect on cervical collagenase resulting in softening . Has natriuretic effect Superior to oxytocin for women with pre-eclampsia , as no fluid retention		
Therapeutic uses	1-Abortifacients 2-Induction of labor	3-Facilitate labor at term 4-Used as vaginal suppositories alone or with oral misoprostol	
Adverse effects	1-Nausea, vomiting, diarrhea 2-Incomplete abortion	3-Increase blood loss	

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Prostaglandins

Drug two	**Carboprost** (15 methyl PGF2α Analog)
Therapeutic uses	1- Abortion 2- Induction of labor 3- To control PPH IMI
Adverse effects	1- Vomiting, diarrhea 2-Transient rise of temperature 3-Bronchoconstriction 4-Fetal toxicity uncommon

Drug three	**Misoprostol** (synthetic PGE1)
ROA	intravaginally as a gel or tablets

Contraindications of prostaglandins	Precautions of prostaglandins
1 -Mechanical obstruction of delivery 2-Fetal distress 3 -Predisposition to uterine rupture	1- Asthm 2- Multiple pregnancy 3- Glaucoma 4- Uterine rupture

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Difference B/w Oxytocin and Prostaglandins and Ergometrine

Character	Oxytocin	Prostaglandins	Ergometrine
Contraction	-Only at term . -Resembles normal physiological contractions	-Contraction through out pregnancy	-Tetanic contraction ; doesn't resemble normal physiological contractions
Cervix	-**Does not** soften the cervix	-soften the cervix	
Duration of action and onset of action	-Rapid onset Shorter duration of action	-Longer duration of action	-Moderate onset Long duration of action
Uses	-Induce and augment labor post partum hemorrhage	-Induce abortion in 2nd trimester of pregnancy. -Used as vaginal suppository for induction of labor	-Only in postpartum hemorrhage

1-Oxytocin = induce labor
2-Ergometrine = used in Post partum hemorrhage
3-Prostaglandins = Induce abortion

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2- Tocolytic drugs

Drugs relax uterine smooth muscles & inhibit uterine contractions

Uses	▪ To arrest premature labor. ▪ Treatment of dysmenorrhea . ▪ Delay delivery for 48 hrs , this time can be used to administer glucocorticoids (Injection betamethasone) to mother for maturation of the fetal lung. ▪ To make it possible that baby is born where facility of neonatal ICU is available .		
Classification	**B2 selective stimulants** 1-Ritodrine 2- salbutamol	**Oxytocic Antagonist** 1-Atosiban	**Other dugs** Used in treatment of dysmenorrhea COX inhibitors

COX inhibitors

Drugs (NSAID,s)	**Non-selective Cox inhibitors** 1- Indomethacin 2- Aspirin 3- Ibuprofen	**Selective COX2 inhibitors** celecoxib
Mechanism of action	Inhibit The synthesis of prostaglandins that prevents or reduces uterine muscle contractions	
Uses	clinically in treatment of dysmenorrhea	
Adverse effects	1- ulceration (Gastric) 2- premature closure of ductus arterious	

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2- Tocolytic drugs

B2 selective stimulants	
Drugs	Ritodrine (β- adrenoceptor agonist)
Mechanism of action	Bind to β-adrenoceptors activate Adenylate cyclase increase in the level of cAMP reducing intracellular calcium level
Adverse effects	1-Anxiety, Restlessness, Headache 2-Pulmonary edema 3-Flushing 4-Sweating 5-Tachycardia (high dose) 6- Hypotension 7- Hyperglycemia

Oxytocic Antagonist	
Drugs	Atosiban
Mechanism of action	Antagonizes the effects of oxytocin at its receptors
Uses	tocolytic in premature labor
ROA	IV infusion for 48 hrs

SUMMARY

Drugs induced uterine contraction				
Drug	**MOA**	**Uses**	**Side Effect**	**Contraindication**
OXYTOCIN Post. Pituitary Hormone	↑Intracellular Ca+2 By GPCR → activation of phospholipase C → production of IP3 → mobilization of calcium from its stores (SR)	IV infusion → *Facilitation of labor at term. *Induction of labor for conditions requiring early vaginal delivery : •Placental insufficiency (mild preeclampsia, maternal diabetes) •Post maturity •Premature rupture membranes •Uterine inertia Nasal spray →in case of Impaired milk ejection Incomplete abortion	-Fetal Distress,death -Maternal Uterine rupture Fluid retention, water intoxication Hyponatremia, heart failure Seizures,Death	a)Hypersensitivity b)Prematurity c)Abnormal fetal position d)Evidence of fetal distress e)Cephalopelvic disproportion Precautions a) Multiple pregnancy b) Previous csection c) Hypertension
Ergot Alkaloids **Natural** Ergonovine **Synthetic** Methyl ergometrine Methyl ergonovine 90% of metabolites are excreted in bile		•Post partum hemorrhage •Hastens involution of the uterus	• Nausea, vomiting, diarrhea. Hypertension. • Vasoconstriction of peripheral blood vessels (toes & fingers). • Gangrene.	a)Induction of labor b)1st and 2nd stage of labor c)vascular disease d)Severe hepatic and renal impairment e)Severe hypertension

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SUMMARY

Drugs induced uterine contraction				
Drug	**MOA**	**Uses**	**Side Effect**	**Contraindication**
Prostaglandins				
Dinoprostone (synthetic PGE2) 1st metabolism in lung (95%)	*Stimulation of G protein coupled PGE2 receptors ➔ contraction of myometrium. *Ripening of cervix due to direct effect on cervical collagenase resulting in softening. *Has natriuretic effect	Medical Abortifacient	•Incomplete abortion •Increase blood loss	a)Mechanical obstruction of delivery b)Fetal distress c)Predisposition to uterine rupture Precautions: a)Asthma* b)Multiple pregnancy c)Glaucoma d)Uterine rupture
Carboprost: 15 methyl PGF2α Analog		*Used as vaginal suppository for induction of labor *To control PPH, IMI *For 2nd trimester abortion , single intra-amniotic injection	•Transient rise of temperature •Bronchoconstriction*	
Misoprostol (synthetic PGE1)				

Group	Duration of action	Cervix	Contraction	
OXYTOCIN	Short (5 minutes)	Does not soften the cervix	Only at term	Resembles normal physiological contractions
Prostaglandins	Long	soften the cervix	Contraction through out pregnancy	
Ergot	Long			Tetanic contraction ; doesn't resemble normal physiological contractions

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SUMMARY

TOCOLYTIC DRUGS

Drugs relax uterine muscles & inhibit uterine contractions

Uses

- To arrest premature labor.
- Delay delivery for 48 hrs , this time can be used to administer glucocorticoids (Injection betamethasone) to mother for maturation of the fetal lung.

Drug	MOA	Side Effect
B2 selective stimulants (Ritodrine, salbutamol)	Bind to β-adrenoceptors , activate Adenylate cyclase , increase in the level of cAMP reducing intracellular calcium level	Anxiety, Restlessness, Headache. Pulmonary edema. Flushing, Sweating. Tachycardia. (high dose). Hypotension. Hyperglycemia.
Oxytocic Antagonist Atosiban	Antagonizes the effects of oxytocin at its receptors Used as tocolytic in premature labor	
Ca channel blockers (Nifedipine)	Causes relaxation of myometrium. Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions.	Headache, dizziness Hypotension ،Flushing Ankle edema،Tachycardia
COX inhibitors Indomethacin, Aspirin ,Ibuprofen	The depletion of prostaglandins prevents stimulation of uterus	Ulceration. premature closure of ductus arterious.

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Quiz yourself

1-which one of the following is the effect of oxytocin on the uterus?
A-relaxatoin
B-contraction
C-dilation
D-no effect

2-clinically,oxytocin is given only when cervix is ?
A-soft
B-dilated
C-soft and dilated
D-contracted

3-oxytocin is contraindicated in which one of the following :
A-cevalopelvic disproportion
B-prematurity
C-abnormal fetal position
D-all

4-which one of the following is the effect of ergots on uterus?
A-tetanic contraction
B-physiological contraction
C-tetanic relaxatoin
D-no effect

5-a pregnant woman who had post partum hemorrhage ,which one is the *drug of choice*:
A-oxytocin
B- Misoprostol
C-ergotes
D- b-agonist

6-ergote is contraindicated in which stage of labor?
A-first stage
B-second stage
C-third stage
D-first and second stages

7-prostaglandin induced abortion in which trimester:
A-first
B-second
C-third
D-all

8-which one is b-agonist and used as tocolytic drug?
A-ritonide
B- Atosiban
C- Aspirin
D- celecoxib

Answers: 1-b , 2-c , 3-d ,4-a , 5-c , 6-d , 7-b , 8-a

Done by

PHARMACOLOGY 433

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