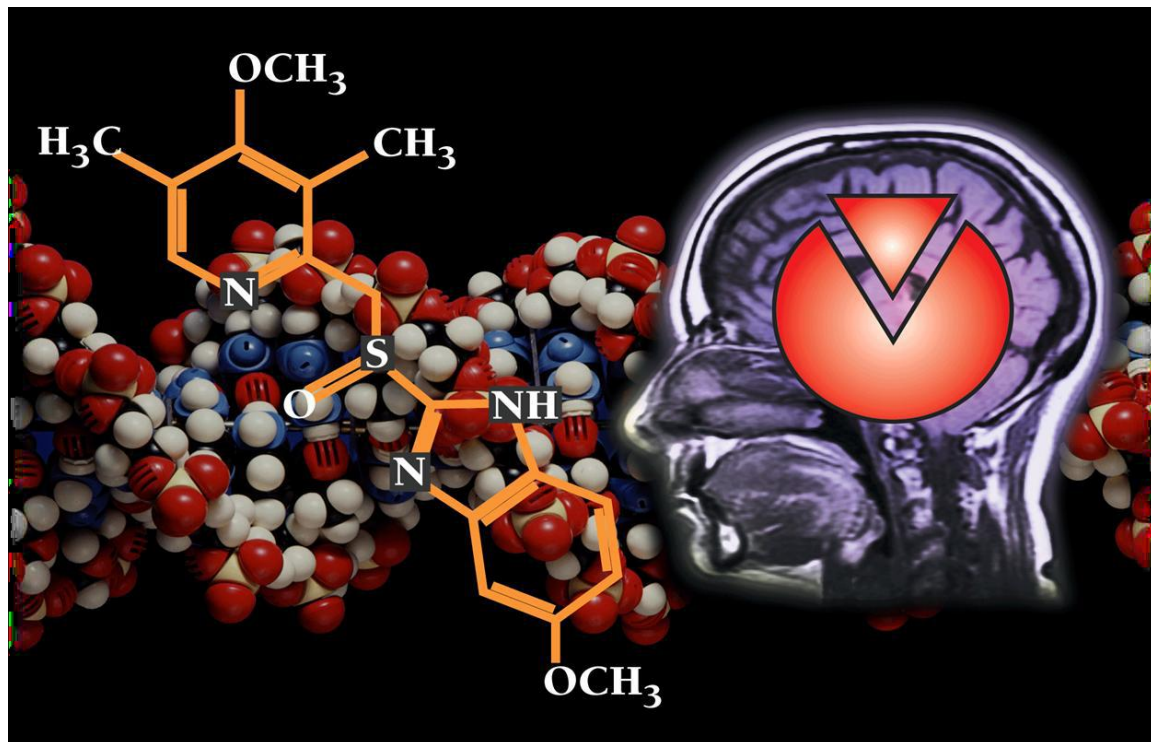


01-Oxytocics & Tocolytics



Note: First page is an introduction, text in blue and textboxes with thick light blue margins are additional info. **Text in red is important.**

Done by:

Mohammed Aldohan

Ayshah al-mahboob

Arwa abudawood

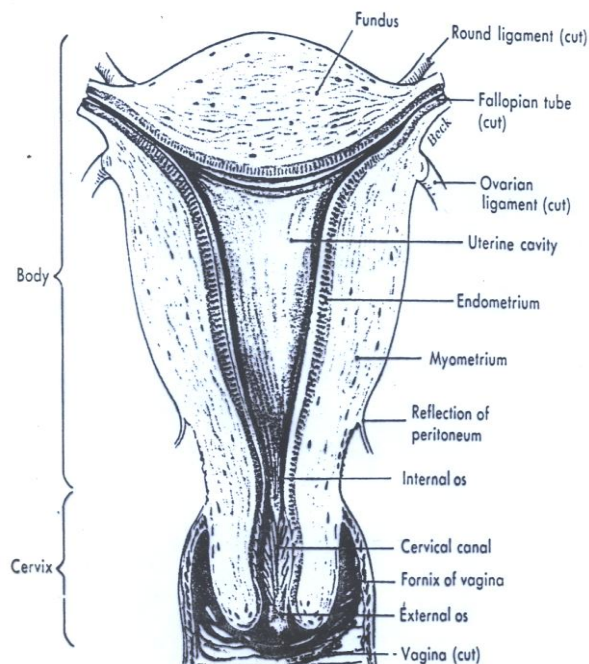
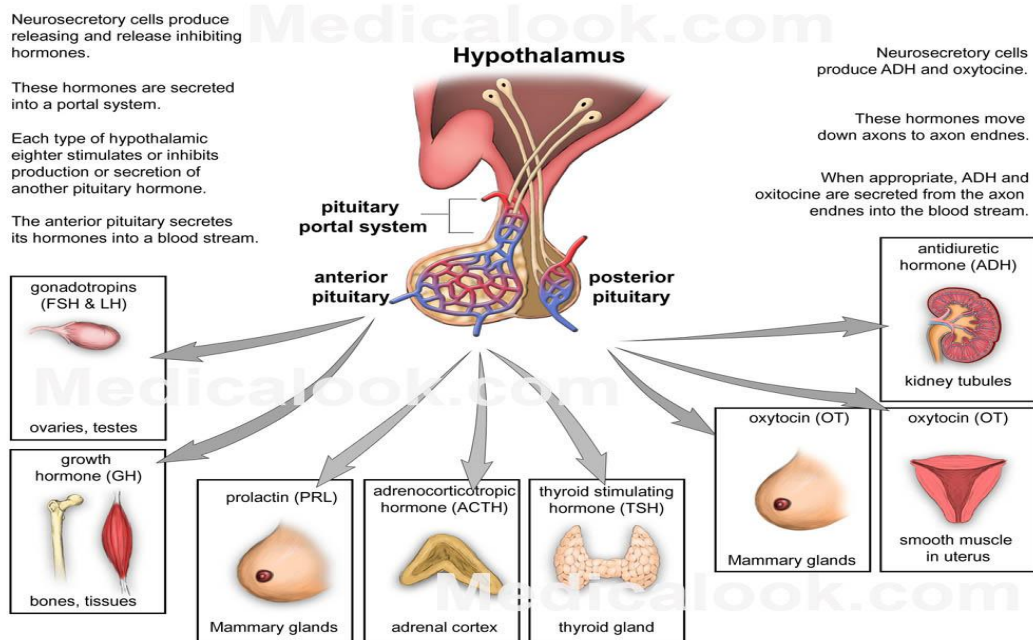
Introduction:

Uterine control

- During the 1st 2 trimesters of pregnancy, the uterus is controlled by the **inhibitory** action of high circulating **levels of progesterone**.
- During the final trimester, uterine smooth muscle becomes increasingly excitable, start with mild muscle **contractions**, which gradually increase in strength & frequency.
- **High level of estrogen** increase receptor concentration of **oxytocin**, which increase response to **plasma oxytocin**.
- Increase in the number of **α -adrenergic receptors** also increase muscle contractions.
- **Release of oxytocin** at labor promotes Prostaglandins (E & F) production, which are powerful myometrial stimulants
- For contraction, **Actin & Myosin** interact thru phosphorylation by **myosin light chain kinase (MLCK)** that **requires Ca^{2+}** .

Uterine Relaxation is controlled by

- Inhibition of **MLCK**
- Stimulation of **myometrial β -adrenoceptors**
- Activation of **cAMP mediated protein kinase**
- Accumulation of **Ca^{2+} in the Sarcoplasmic Reticulum (SR) (Ca trapping)**
- Decrease in **cytoplasmic Ca^{2+}** .



DRUGS PRODUCING UTERINE CONTRACTIONS (oxytocics)

Stimulants: cause uterine contraction

1. Oxytocin

2. Ergot alkaloids (ergometrine)

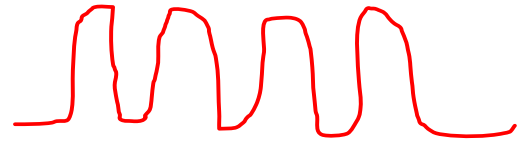
3. Prostaglandins PGE₂, PGF₂,
& PGE₁ (Misoprostol).

**Drugs & hormones that are used clinically to
enhance uterine contractions by:**

- Augmenting contractions during labor & delivery
- Limiting an extended pregnancy
- Preventing postpartum hemorrhage.

1-Oxytocin(Pitocin® / Syntocinon®)

- **Oxytocin** is synthesized in **hypothalamus**, then stored & released from **posterior pituitary gland**.
- **At term**, the uterus is highly **sensitive** to **oxytocin**.
- Oxytocin stimulates both the **frequency & amplitude (force)** of uterine contractility (both are related to the dose).
- These events are highly dependent on **estrogen** & antagonized by **progesterone**
- **Oxytocin** causes **regular coordinated contractions** that resemble the normal physiological contractions of uterus that travel from **fundus to cervix**. Then contraction is followed by relaxation.



MOA

- The interaction of **endogenous or administered oxytocin**, with **myometrial cell membrane oxytocin receptor** promotes :
- **influx of Ca²⁺** from extra cellular fluid & from S.R in to the cell ,
- This increase in **cytoplasmic Ca²⁺**, stimulates uterine contraction **by activation of MLCK**.

Other actions of oxytocin:

- **Oxytocin** contracts myoepithelial cells in the mammary gland → **breast feeding, (Letdown /milk ejection)**
- **Weak antidiuretic action.** (A weak antidiuretic action can result in water retention, which can be problematic in patients with cardiac or renal disease, or preeclampsia.)

Pharmacokinetics

- **Not absorbed orally**
- Administered by i.v, i.m, **& most often given by i.v.** infusion to induce labor.
- **Not bound** to plasma proteins
- t_{1/2}: 5- 15 minutes
- Metabolized in **liver & kidney**



Clinical uses:

- Considered the **drug of choice** to induce or augment labor at term when the uterine muscle is not functioning adequately. **Clinically oxytocin is given only when uterine cervix is soft & dilated.**

Note: Using oxytocin in case of a constricted or an abnormal cervix would lead to potent uterine contraction that will lead to the death of the fetus, and probably the mother as well.

- Following incomplete abortion** (but PGs are preferred).

Note: Incomplete abortion is: An induced abortion in which the contents (remaining fetal or placental) of the uterus are not completely expelled, and this would lead to a septic abortion. It occurs when the tissue from a missed or incomplete abortion becomes infected. The infection of the uterus carries risk of spreading infection (septicemia) and is a grave risk to the life of the woman.

- In Induction of labor in cases of:**

- Intrauterine growth retardation
- Placental insufficiency as in (diabetes, pre-eclampsia-which is severe HTN-)
- Uterine inertia (Failure of the uterus to contract with normal strength and duration and at normal intervals during labor. It is also called uterine atony.)
- Incomplete abortion
- Post maturity.

Dosage : Slow I.V infusion 1-2 mU /min then gradually increase the dose to 5-30 mU/min.

Note: Placental insufficiency is insufficient blood flow to the placenta during pregnancy. It may have an impact upon the CNS. The blood vessels supplying the placenta are constricted in cases such as diabetes and a disorder occurring during late pregnancy or immediately following parturition, characterized by hypertension, edema, and proteinuria.

- Postpartum uterine hemorrhage**

Given **slow I.V injection** 5 units followed by **I.V** infusion of 5-200 in severe cases. (**ergometrine is often used**)

Note: Uterine contractions help the uterine muscle to continue to constrict the uterine blood vessels, and bring about a decrease in the amount of uterine bleeding after delivery.

- Impaired milk ejection: One puff in each nostril 2-3 min before nursing. (Taken in the form of Nasal spray)**

Side Effects:

- Maternal death (**Due to HTN**)
- Uterine rupture
- Fetal death
- Water intoxication (**weak anti-diuretic effect**) & hyponatremia
- Hypertension (**due to water retention**)
- Allergic reactions.

Overdose: Rupture of the uterus, fetal distress, & maternal injury.

Contraindications

- Hypersensitivity
- Prematurity
- Abnormal positioning of the fetus
- **Cephalopelvic disproportion**
- **Incompletely dilated cervix.**

Note: Cephalopelvic disproportion (CPD) occurs when a baby's head or body is too large to fit through the mother's pelvis. It is believed that true CPD is rare, but many cases of "failure to progress" during labor are given a diagnosis of CPD. When an *accurate* diagnosis of CPD has been made, the safest type of delivery for mother and baby is a cesarean.

Precautions:

- Monitor mother & fetus, because over stimulation interferes with blood flow thru the placenta & causes fetal distress/ death.
- previous uterine surgery (C-section)
- Multiple pregnancy
- Hypertension

Note: **Atosiban**, a synthetic peptide, is a **competitive antagonist** of **oxytocin** at **uterine oxytocin receptors** and has been developed as a new tocolytic therapy in the treatment of preterm labour.

2-ERGOT ALKALOIDS

- **Ergometrine (Ergonovine)**
- Dihydroergotamine
- Methylergonovine

- **Alkaloid derivatives** induce **TETANIC CONTRACTION** of **uterus** without relaxing in between;

Note: Ergot (*Claviceps purpurea*) is a fungus that grows on rye and contains a surprising variety of pharmacologically active substances. Ergot poisoning, which was once common, was often associated with abortion. In 1935, **ergometrine** was isolated and was recognised as the oxytocic principle in ergot.



- It causes contractions of uterus as a whole i.e. **fundus & cervix** (Tend to compress rather than expel).

Pharmacokinetics:

- Rapid oral absorption (tablet)
- Both **ergonovine & methylergonovine** can be given im / iv.
- **Duration of action 24 hrs** with half life: **2hrs**
- Metabolized extensively in liver
- 90% metabolites are excreted in bile.

Uses

- **Post partum hemorrhage (3rd stage labor)**
- **Administered immediately postpartum to obtain marked uterine response.**

Note: ergots are not used if the fetus is still in the uterus for two reasons: 1) it leads to a titanic contraction that will harm the fetus. 2) It has a vasoconstricting effect on the blood vessels supplying the placenta.

Preparation:

Syntometrine (ergometrine 0.5 mg + oxytocin 5.0 I.U, IM).

Note: The advantage of using this preparation is a rapid effect (**Oxytocin**), and an effect of long duration (**ergometrine**).

Adverse effects:

- Nausea, vomiting & diarrhea (**ergots has an effect on D2 receptors in chemoreceptor trigger zone**)
- Hypertension
- Vasoconstriction of peripheral blood vessels (toes & fingers)
- Gangrene
- Headache.

Contraindications:

- **1st and 2nd stage of labor**
- **Induction of labor**
- vascular disease, HTN, toxemia (severe HTN)
- Impaired hepatic functions (metabolism site)

3-PROSTAGLANDIS

MECHANISM OF ACTION:

Endogenous:

- They are significantly synthesized in endometrium & myometrium
- They cause contraction of both the non-pregnant (as in menstrual cycle)& pregnant uterus, **but sensitivity increases with gestation.**
- They play a significant role in **dysmenorrhea (painful menstruation) & Menorrhagia (excessive blood loss).**

Note: during pregnancy Progesterone has an inhibitory effect on endogenous PGEs; however, adding **exogenous PGEs** would help overcome the inhibitory action of **progesterone**, thus leading to vigorous contraction of the uterus and eventually to abortion.

Exogenous:

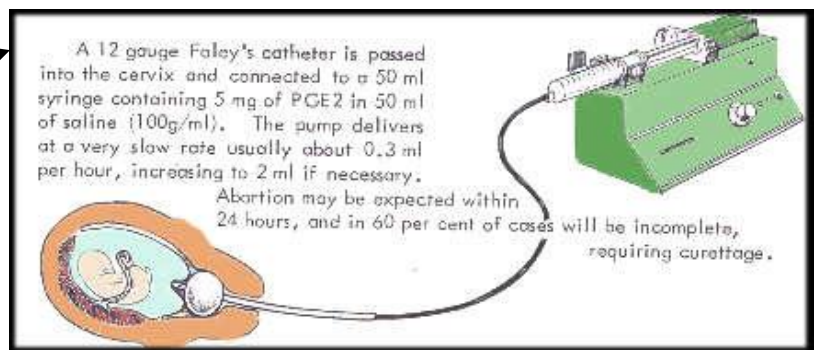
Dinoprostone (PGE₂) & Carboprost (PGF₂)

- They promote a series of coordinated contraction of **body of uterus** along with **relaxation of cervix**
- Increase uterine tone
- **Can expel uterine content in early pregnancy.**
- **PGS** contract uterine smooth muscle not only at term (as with oxytocin), but throughout pregnancy.
- **PGS soften the cervix; whereas oxytocin does not.**
- **PGS have longer duration of action than oxytocin.**

Therapeutic Uses:

1. **Oxytocic use for inducing abortion, missed abortion, repining of cervix** (*the cervix softens and becomes more distensible*)

- Stimulate uterine contraction in the **2nd trimester of pregnancy**, administered **IV, extra amniotic & vaginal**. Initiation to abortion time is **12 to 23 hours**
- **For softening of the cervix at term** single vaginal insert or jell is administered every 6 hours.



2. **For induction & augmentation of labor** (**In case of fetal death in the uterus**) administered as vaginal tablets & vaginal jell, or as controlled release formulation.

3. in post-partum hemorrhage

It is administered by I.V infusion.

ADRs

- Nausea , vomiting & diarrhea (Due to increased contractility of the GIT)
- Abdominal pain
- Bronchospasm (PGF₂ α effect)
- Flushing. (PGE₂)

Contraindications:

- Mechanical obstruction to delivery** (Cephalopelvic disproportion, abnormal pelvis) **in this case a C-section is preformed.**
- Fetal distress** (*The term fetal distress is commonly used to describe fetal hypoxia, which can result in fetal damage or death if it is not reversed or if the fetus is not promptly delivered.*)
- Predisposition to uterine rupture**

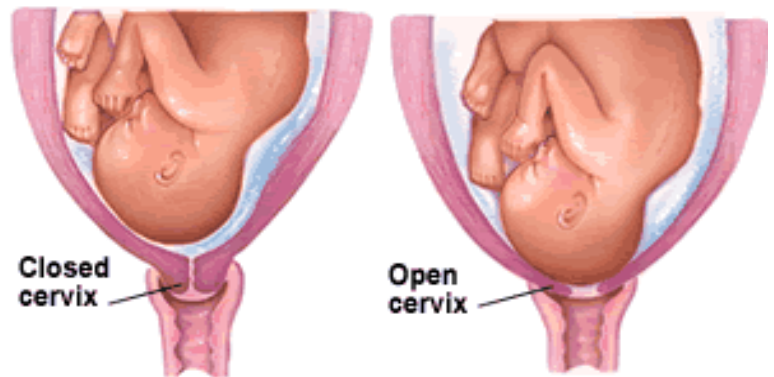
Precautions:

- Asthma** (because it's bronchoconstriction)
- Multiple pregnancy**
- Uterine rupture**
- Glaucoma** (**PGEs increase intraocular pressure**)

DRUGS PRODUCING UTERINE RELAXATION(Tocolytic Drugs).

Preterm Labor:

- Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (between 20 and 37 wk).
- Cervical changes & uterine contractions occur before 37 weeks' of gestation.



Risk factors for preterm delivery:

- ✓ Previous preterm delivery
- ✓ Bacterial infection in (vagina, urinary tract) or sexually transmitted infection.
- ✓ Multiple gestations or any other complication. (normally the uterus restore it's position and active shape after mainly two years from the last delivery so women in risk for preterm if they got pregnant before that)

Major Risks Of Preterm Delivery:

- | | |
|-----------------|---------------------------------|
| ✓ Hypoglycaemia | ✓ Death |
| ✓ Jaundice | ✓ Respiratory distress syndrome |
| ✓ Infection | ✓ Hypothermia |

Management: tocolytic therapy.

Goal of tocolytics:

- To postpone/ delay delivery long enough to reduce the incidence of problems associated with prematurity.
- Allow sufficient time for the administration of antenatal corticosteroids to improve pulmonary maturity
- For transportation of the mother to a facility equipped to deal with high-risk deliveries.

Tocolytics should NOT be used in

- Intrauterine infection
- Fetal distress
- Severe preeclampsia
- Vaginal bleeding
- Maternal hemodynamic instability

Tocolytics can be started if

- Regular uterine contraction with cervical change.
- Tocolytics are less effective if cervical dilatation is > 3 cm.

1. β -ADRENOCEPTOR AGONISTS

E.g. Ritodrine & terbutaline

MOA:

Bind to β -adrenoceptors, activate enzyme **Adenylate cyclase**, increase in the **level of cAMP** reducing **intracellular calcium level**, thus reducing the level of sensitivity of **actin myosin contractile unit**.

Side effects:

- | | |
|---------------------------|--------------------|
| • Tachycardia (high dose) | • Tremor |
| • Hypotension | • Nausea, vomiting |
| • Hyperglycemia | • Flushing |
| • Hypokalaemia | • Sweating |

USES :

To prevent Premature labor (To delay labour)

I.v infusion 50 μ g/min

Contraindications: Heart disease, diabetes, patients on beta blockers.

2. CALCIUM CHANNEL BLOCKERS e.g., Nifedipine

- MOA: Reduce Ca entry \rightarrow Reduced tone & Cause relaxation of myometrium
- Markedly inhibits the amplitude of spontaneous & oxytocin-induced contractions

Clinical uses : To delay or prevent preterm labor.

ADRs:

- | | | |
|---------------|----------------|-----------------------|
| • Ankle edema | • Flushing | • Headache, dizziness |
| • Coughing. | • Constipation | • Hypotension |

3. Prostaglandin synthesis inhibitors

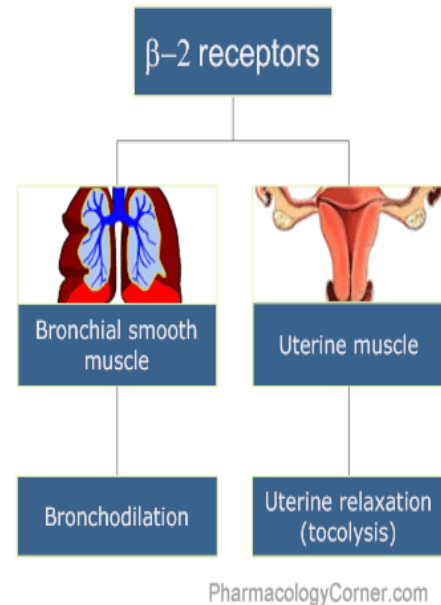
The depletion of prostaglandins prevents stimulation of uterus

e.g.

- Aspirin, indomethacin, ibuprofen
- Given orally /rectally.

Side effects:

- ulceration
- premature closure of ductus arteriosus.



Summary

Character	Oxytocin	Prostaglandins
Contraction	Only at term	Contraction throughout pregnancy
Effect at myoepithelium	Stimulate myoepithelium milk ejection	Does not stimulate
cervix	Does not soften the cervix	Does soften the cervix
Duration of action	Shorter	Longer
Uses	Not used for abortion Used for induction & augmentation of labor & post partum hemorrhage	Used for abortion in 2 nd trimester of pregnancy. Used as vaginal suppository for induction of labor. Dilatation of cervix.

	Oxytocin	Ergometrine
Contractions	Resembles normal physiological contractions	Tetanic contraction ; not similar to normal physiological contractions
uses	To induce labor To Augment labor In post partum hemorrhage	Only in postpartum hemorrhage
Onset/Duration	Rapid onset Shorter duration of action	Rapid onset Long duration of onset

-Oxytocin causes **regular coordinated contractions** that resemble the normal physiological contractions of uterus that travel from **fundus to cervix**.

- **contracts myoepithelial cells** in the mammary gland and have a **Weak antidiuretic** action.
- Administered by **i.v, i.m, & most often given by i.v.** infusion **to induce labor**.
- **Considered the drug of choice to induce or augment labor at term when the uterine muscle is not functioning adequately, but the cervix must be soft and dilated.**
- Taken in the form of **Nasal spray in case of** Impaired milk ejection:
- **ADRs include:** Maternal death ,Uterine rupture ,Fetal death,Water intoxication & hyponatremia ,Hypertension ,Allergic reactions.
- **Contraindicated** in case of Abnormal positioning of the fetus, **Cephalopelvic disproportion**, or **incompletely dilated cervix**.

Ergots (Ergometrine (Ergonovine),Dihydroergotamine ,and Methylergonovine)

- **induce TETANIC CONTRACTION** of uterus without relaxing in between.
- **They are used in Postpartum hemorrhage (3rd stage labor)**
- **Syntometrine (ergometrine 0.5 mg + oxytocin 5.0 I.U, IM) preparation has** The advantage of a rapid effect (**Oxytocin**), and an effect of long duration (**ergometrine**).
- **ADRs include:** Nausea, vomiting & diarrhea ,Hypertension ,Vasoconstriction of peripheral blood vessels (toes & fingers)
- **ergots are not used if the fetus is still in the uterus**

PROSTAGLANDIS (Dinoprostone (PGE₂) & Carboprost (PGF₂))

- promote a series of coordinated contraction of **body of uterus** along with **relaxation of cervix**
- PGS soften the cervix; whereas oxytocin does not.
- PGS have longer duration of action than oxytocin.

It is used for:

- **softening of the cervix at term**
- **For induction & augmentation of labor (In case of fetal death in the uterus)**

Tocolytics are used to To delay or prevent preterm labor. They include:

1. **β-ADRENOCEPTOR AGONISTS** e.g. **Ritodrine & terbutaline**

2. **CALCIUM CHANNEL BLOCKERS** e.g., **Nifedipine**

3. **Prostaglandin synthesis inhibitors (Aspirin, indomethacin, ibuprofen)**

Remember the first choice in:

Induction of labor in pregnant woman (with soft and dilated cervix):

Oxytocin

Induction of abortion:

Prostaglandin

Postpartum hemorrhage:

Ergotamine

Note:

If a pregnant woman exceeds her delivery time (10th month of pregnancy) but have a non dilated cervix (Constricted Cervix):

- **First Prostaglandin → to dilate the cervix (we can't use oxytocin when the cervix is not dilated)**
- **then use oxytocin when it's needed**