DRUGS ACTING ON THE UTERUS

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Objectives

- 1- Uterine contractions
- 2- Drugs affecting uterine contractions
- 3- Oxytocin: actions, mechanism of action, kinetics, indications, side effects , precautions and contraindications
- 4- Ergometrine: mechanism of action, uses, side effects and contraindications
- 5- Prostaglandins PGs: dinoprostone, gemeprost, misoprostol and dinoprost
- 6- prostaglandin receptors
- 7- Tocolytic drugs
- 8- Contraindications of tocolytics
- 9- Other Agents Affecting the Uterus

Uterine contractions

•**Uterine smooth muscle** is characterized by high level of **spontaneous contractile activity**.

• It is innervated by autonomic nervous system

• Uterine contractions are muscle contractions of the uterine smooth muscle that occur **during:**

•Menstrual cycle

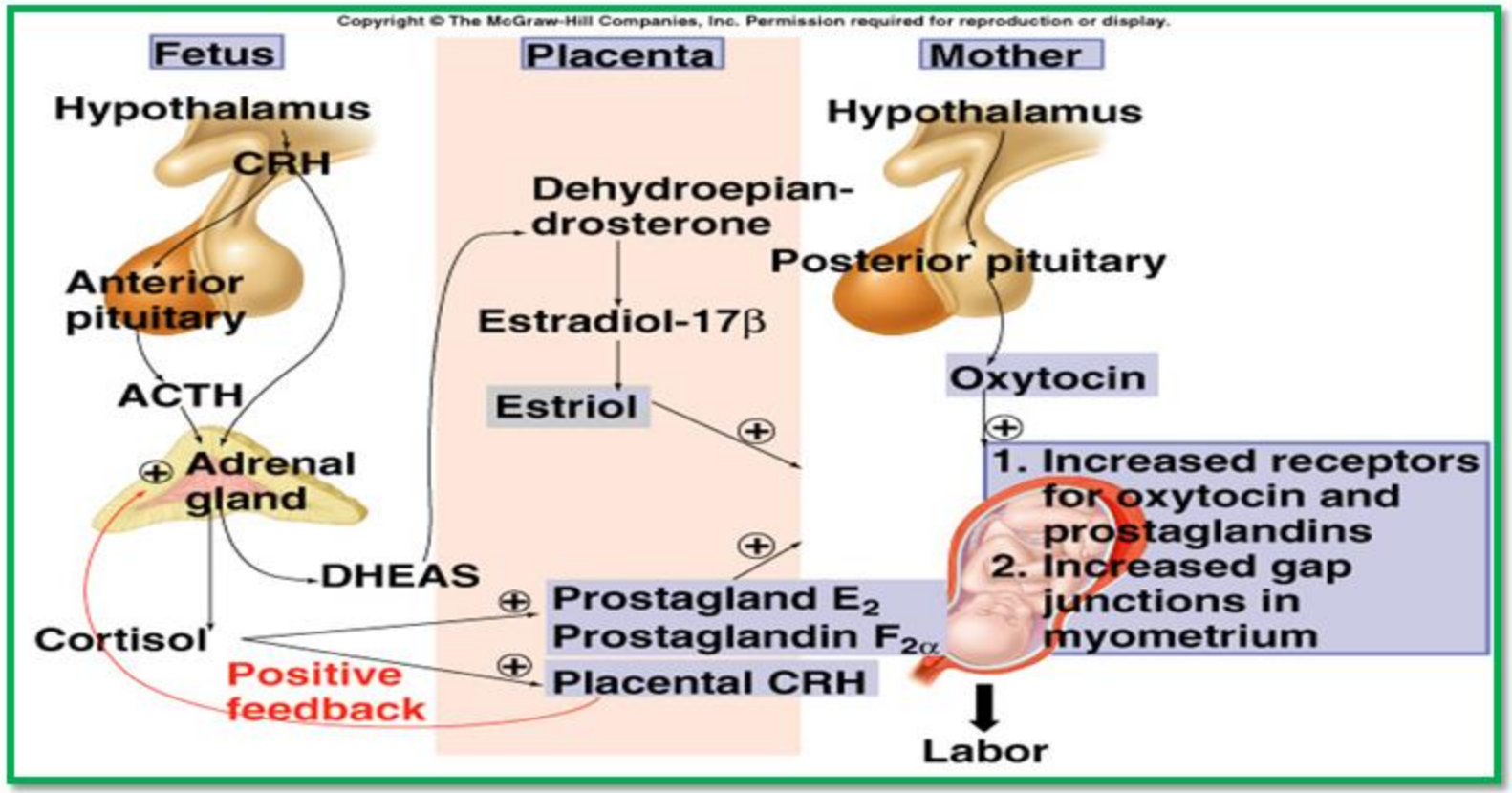
•Ovulation

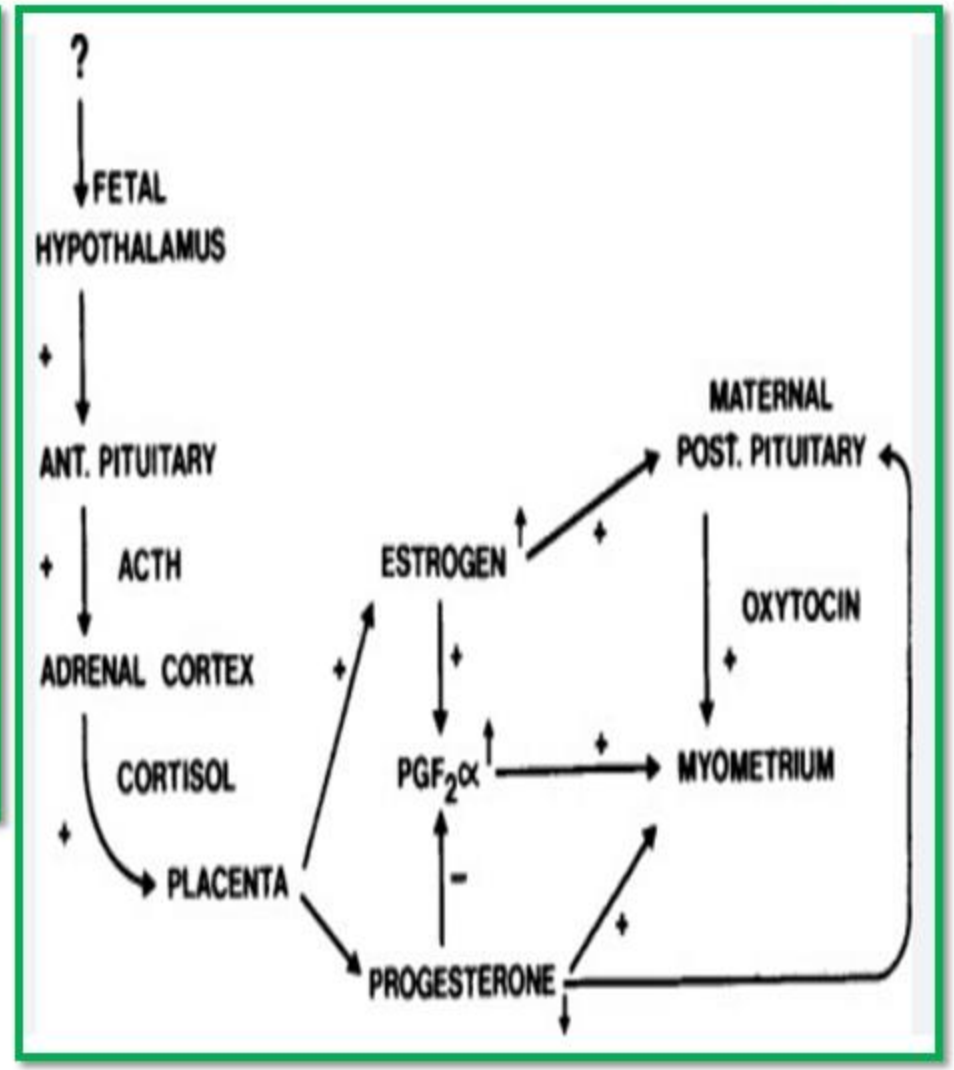
•Pregnancy

•Labor

•Sexual stimulation & during lactation: due to oxytocin (love hormone)

Parturition





Drugs acting on uterus

- Drugs acting on the uterus target the **myometrium** to either stimulate (oxytocics) or relax (tocolytics) uterine muscle.

Stimulatory: oxytocics (uterotonics) (abortifacients)

- **The main drugs used clinically to increase uterine contractility:**
- Oxytocin
- $Alph_1$- Adrenoceptor agonists (ergot derivatives)
- PGE_2 or $PGF_{2\alpha}$

- **Inhibitory: tocolytics**
- B2- adrenoceptor agonists
- Calcium channel blockers
- Atosiban
- **Indications:**
- Prevention of preterm labor

Indications of uterine stimulants

- Uterine stimulants are agents that induce or increase the frequency and strength of uterine contractions.
- **1- Induction and Augmentation of Labor: Initiating or increasing contractions to progress childbirth:**
- **Pre-term**: diabetic mother- pre-eclampsia- Rh negative fetus
- **Incomplete abortion**
- **At-term:** uterine inertia (atony)
- **Late or Post-term:** delayed labor
- **2- Prevention of postpartum hemorrhage**
- **3- Induction of abortion**

Uterine stimulants:
1. Oxytocin

- **1. Oxytocin (Pitocin, Syntocinon) :**
- Oxytocin and vasopressin are **nonapeptide hormones**, synthesized in **hypothalamus**, then transported to **posterior pituitary** where they are stored and released.
- **Pharmacological actions of oxytocin :**

1. Contraction of myoepithelial cells surrounding secretory alveoli of breast leading to **milk ejection in lactating females**.

2. Induction of intermittent uterine contractions and maintenance of labor:

- It contributes to initiation of parturition.
- Reaches peak during pushing phase of labor
- Oxytocin-induced contractions can be inhibited by: B2-adrenoceptor agonists or by general anesthetics.

3. Uterine involution: Uterine involution is the natural, six-week process where the uterus contracts and shrinks from about 1000g to its pre-pregnancy size 60g after childbirth

4. Oxytocin has weak antidiuretic or pressor activity.

❑**Mechanism of action:**

❑Oxytocin binds to specific G-protein coupled receptors in the uterine smooth muscle, increasing intracellular calcium levels and stimulating contractions.

❑Increasing PGs levels intrauterine

PKs of oxytocin

- **It is not given orally** since it is destroyed by proteolytic enzymes (nonapeptide) of stomach and intestine (trypsin and chymotrypsin).
- It is **NOT** bound to plasma proteins
- **Rapid** onset of action
- Eliminated by liver and kidney (plasma $t_{1/2}$~ 5 min):
- IV infusion

Indications of oxytocin

1- Induction of labor: given by IV infusion in:

1- Conditions requiring early vaginal delivery at 37-38 weeks: maternal diabetes, pre-eclampsia, Rh-iso-immunization

2- Primary uterine inertia, and to enhance uterine contractions in **incomplete abortion** and **full-term labor**

3- Delayed onset of labor at term: post-maturity

2- Postpartum hemorrhage

Control of post-partum hemorrhage (PPH): first line (by IV infusion or IM injection with ergonovine)

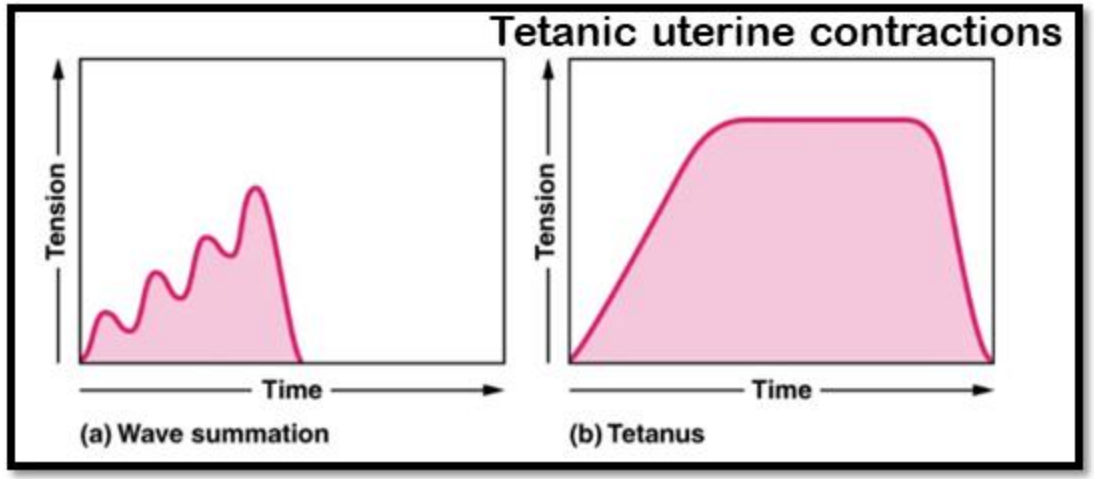
3- To induce milk let-down after labor: by nasal spray.

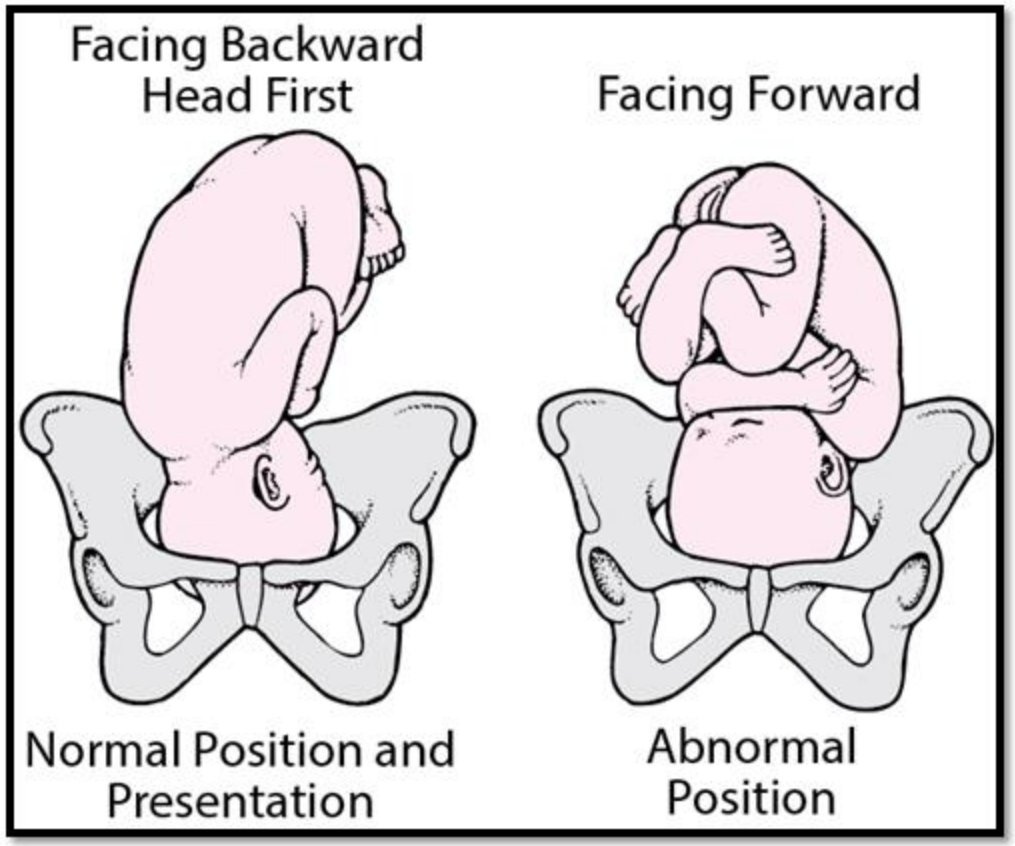
Precautions:

- **Requires close monitoring of both fetal and maternal conditions during administration.**
- **Clinically oxytocin is given only when uterine cervix is soft and dilated (ripened)**
- **Multiple pregnancy**
- **Previous c- section**
- **Hypertension**

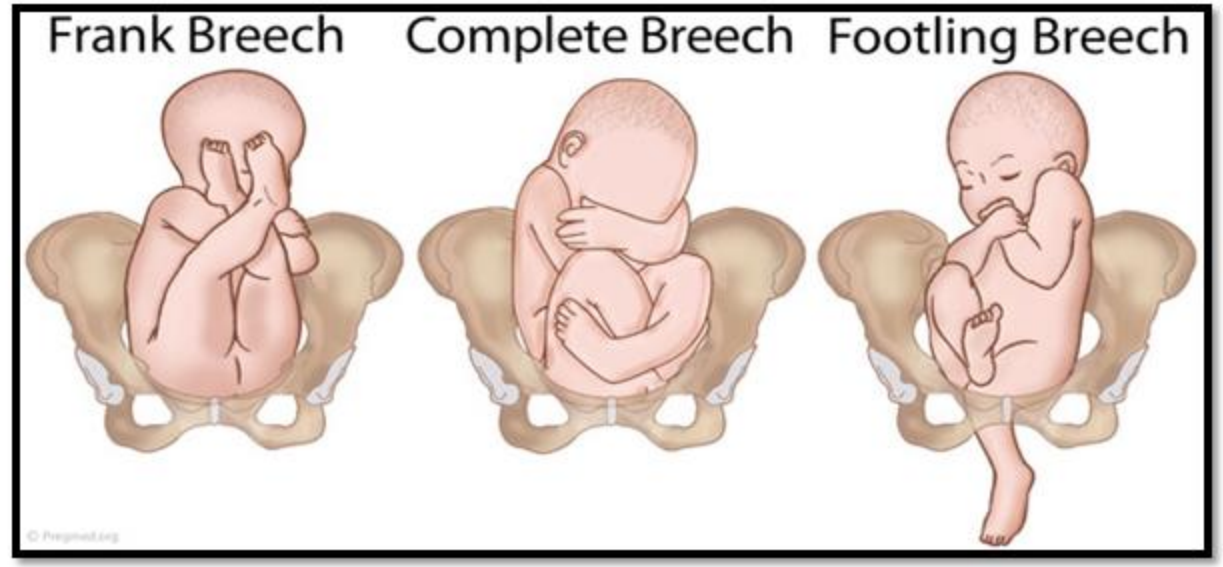
Adverse effects & contraindications of oxytocin

- **Adverse effects are rare with proper monitoring**
- 1-With **large IV infusion doses, tetanic uterine contractions** can occur which obstructs intramural uterine blood flow causing:
- fetal distress or death.
- Uterine rupture may occur esp. with obstructed labor.
- 2- With large doses , blood pressure increases due to vasoconstriction (pressor effect)
- **3-Water intoxication**: can rarely occur due to high infused doses of oxytocin with large volumes of electrolyte-free fluids, (structural similarity to vasopressin).
- (may be fatal)
- Mechanism: Oxytocin acts on the kidneys to reduce water excretion, which, when combined with high-volume intravenous fluid (like 5% dextrose), leads to dilution of serum sodium (hyponatremia) and water intoxication.
- Ends in cerebral edema and coma
- Use electrolyte-containing solutions (e.g., Ringer's lactate) instead of 5% dextrose.
- **4- Increased incidence of neonatal jaundice**: due to increased osmotic fragility of RBC
- **Contra-indications:**
- 1- Fetal distress
- 2- Prematurity of fetus
- 3-Fetal-malpresentation e.g. breech presentation & Cephalopelvic disproportion i.e. contracted pelvis: both predispose to uterine rupture.
- 4- Prolapse of umbilical cord following rupture of fetal membranes





Fetal malpresentations



2. Ergonovine (Ergometrine) and methylergonovine

- **More selective than other ergot alkaloids in stimulating the uterus and is the ergot alkaloid of choice in obstetrics.**
- **Mechanism of action:**

1. Powerful **direct action** on uterine muscles
2. Possibly other actions (5-HT_2, αlpha$_1$-adrenoceptor agonist actions).

- **It helps to prevent postpartum hemorrhage by causing powerful , sustained uterine contraction.**
- **Route of administration:**
- IV or IM at time of delivery of placenta or after delivery of fetus but never before.
- Oral tablets (3–4 times daily for up to a week).
- **Adverse effects:**
- **Common:** headache, nausea, vomiting, and dizziness.
- **Serious risks:** hypertension, chest pain, and severe allergic reactions.
- **Contraindications**
- Hypertension as in pre-eclampsia
- Peripheral vascular disease
- Angina

3. Prostaglandins (PGs)

- **Mechanism of action as uterine stimulants:**
- **1- Direct action**: : PGs activate FP, EP1, and EP3 receptors to cause direct muscle contraction.
- **2- Indirect action**:
- Upregulation of oxytocin receptors
- Increase the sensitivity of the uterus to other stimulants like oxytocin
- **3- Cervical Ripening: PGs (especially PGE2) act directly on the cervix to break down collagen and make it softer.**

❑ **PGE2 (Dinoprostone): It is commonly used vaginal**

- **A. To stimulate uterine contractions for:**
- **Induction of labor** given as **vaginal gel or insert**
- Note: If oxytocin is needed for induction of labor, it is given after 6 hours have passed after PG use to avoid excessive uterine contractions.
- **Induction of abortion**: **vaginal suppository** is used.

- **B. For softening the cervix** (ripening) **at term**: This shortens time to onset of labor and labor time.

3. Prostaglandins (PGs)

❑ **Gemeprost: PGE1 analogue**

- used as **vaginal suppository** to induce early medical abortion during first trimester.

❑ **Misoprostol: PGE1 analogue**

- oral or vaginal supp.:

used for induction of medical abortion in first trimester or when gemeprost is not available.

❑ **PGF2α (Dinoprost) : less commonly used**

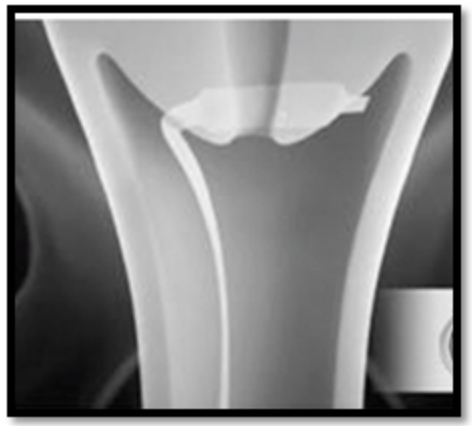
- May be given vaginally, intra-amniotically, or IV for induction of abortion in second trimester, PPH
- Intra-amniotic PGF2α has up to 100% success rate with fewer and less sever adverse effects than IV.

3. Prostaglandins (PGs)

❖**Adverse Effects:**

- excessive contractions, nausea, vomiting, diarrhea, and fever.
- PGF2α causes more G.I. side effects (vomiting, diarrhea) than PGE2.
- **Contraindications:**
- Previous cesarean section or uterine surgery (risk of uterine rupture)
- Hypertension

3. Prostaglandins (PGs)



Dinoprostone vaginal insert

Vaginal suppositories

Tocolytics

Tocolytics

- Drugs that inhibit (reduce) uterine contractions
- **Indications:**
- 1- Delay, inhibit or prevent premature labor (< 37 weeks of pregnancy).
- 2- Usually for (48 hours) to allow for corticosteroid administration, which promotes fetal lung maturity
- **Corticosteroids are given IV to mother** or **into cord blood** to stimulate maturation of fetal lung (by enhancing surfactant formation)
- **Betamethasone and dexamethasone** are preferred due to high potency, placental transfer, and lack of mineralocorticoid activity.
- **Dexamethasone** is preferred because it is bound less to plasma proteins.
- **Clinical hint:**
- Usually, regular uterine contractions can stabilize on bed rest & local warmth.
- When this is insufficient, then a tocolytic drug is used.
- Tocolytic therapy is generally limited to between 24 and 34 weeks of gestation

Beta-2 Adrenergic Receptor Agonists

- **Ritodrine, Terbutaline, salbutamol**
- **Mechanism of action: increasing cAMP in myometrium which leads to phosphorylation and inactivation of myosin light-chain kinase, causing smooth muscle relaxation.**
- **Route of administration:**
- oral or IV infusion in 5% dextrose
- **Adverse effects:**
- 1. Tachycardia
- 2. Sometimes acute left ventricular failure in mother occurs due to overload of infusion fluid and marked tachycardia.
- 3. Hypokalemia
- 4. Hyperglycemia

2. Calcium channel blocker CCBs

- The short acting Nifedipine or Nicardipine
- Highly effective, first-line tocolytic agents
- **They are preferred over other tocolytics due to:**
- 1- Low incidence of maternal side effects
- 2- Oral administration
- 3- Improved neonatal outcomes, such as reduced risk of respiratory distress syndrome
- **Mechanism of action:**
- Block L-type calcium channels on myometrial smooth muscle cells, reducing intracellular calcium inhibiting contractions.
- **Route of administration**: oral
- **Adverse effects**:
- The most common adverse effects are well-tolerated and include:
- Hypotension, headache, flushing, and tachycardia due to vasodilation.

3- Atosiban

- **Analogue of oxytocin:**
- **Mechanism of action:**
- Synthetic peptide acting as competitive antagonist on oxytocin receptor, which decreases uterine contractions.
- **Administration:**
- IV to delay imminent preterm labor (24–33 weeks).
- **Adverse Effects**: Generally well-tolerated
- Reported adverse effects are rare: nausea, headache, dizziness, and hypotension

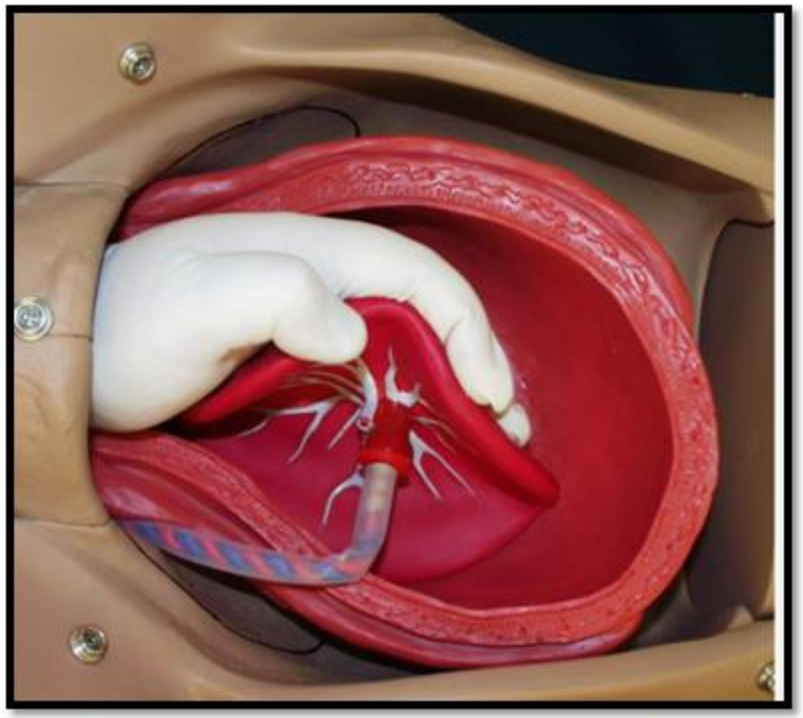
4- Miscellaneous drugs

- **Progesterone:**
- **Myometrial Relaxation via receptors**: relaxes the myometrium throughout pregnancy to accommodate the growing fetus.
- **Blocking Contractions**: It suppresses contraction-associated proteins (such as oxytocin receptors and connexin 43).
- **Ion Channel Modulation**: increase the expression of potassium channels, which reduces electrical activity in the uterus
- **Halothane:**
- A potent halogenated inhalation anesthetic
- **Mechanism of action**: direct smooth muscle relaxant.
- **Clinical Use**:
- Emergency situations, such as retained placenta or intrauterine manipulation, to achieve rapid uterine relaxation

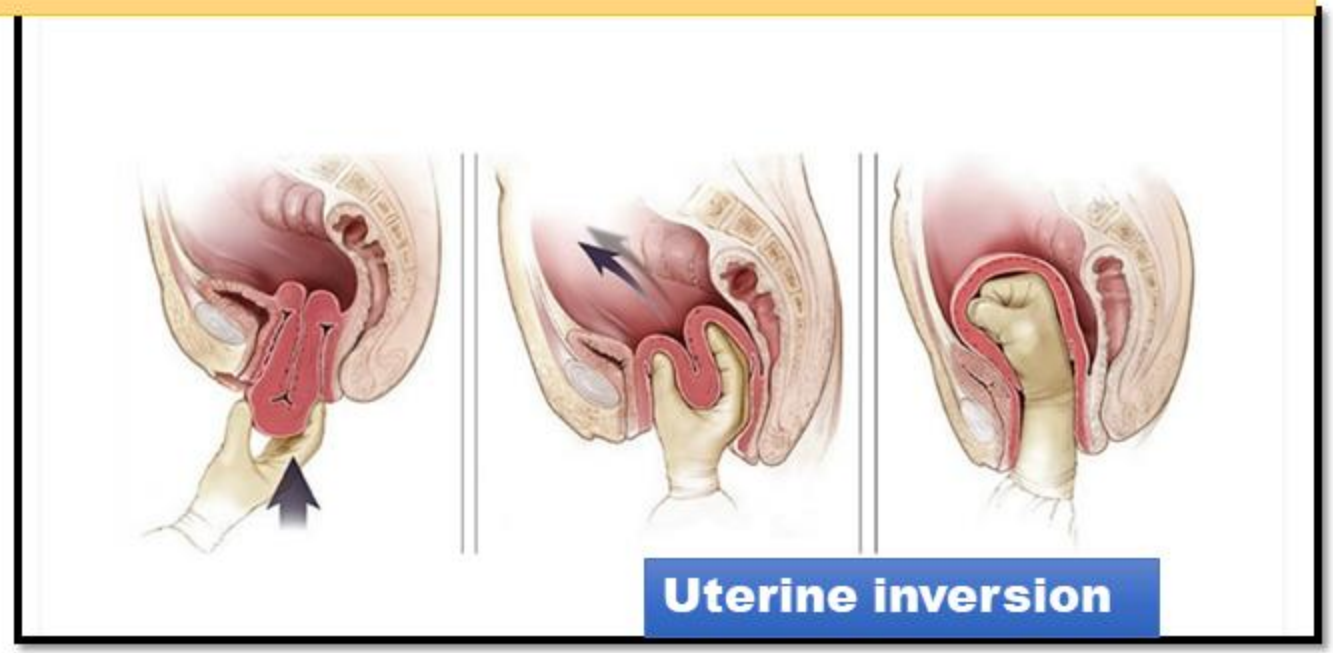
4- Miscellaneous drugs

- **Nitroglycerine:**
- **Mechanism of action**: NO donor: increasing cGMP in myometrium: uterine smooth muscle relaxation
- **Indications:**
- Effective, fast-acting, short-term tocolytic in obstetric emergencies:
- Retained placenta (manual removal), uterine inversion (Immediate manual repositioning) , or fetal head entrapment (tocolytic to reduce cervical spasm).
- Transdermal patches can effectively prolong pregnancy in preterm labor
- Nitroglycerin is **NOT** considered first-line for long-term tocolysis due to potential adverse effects

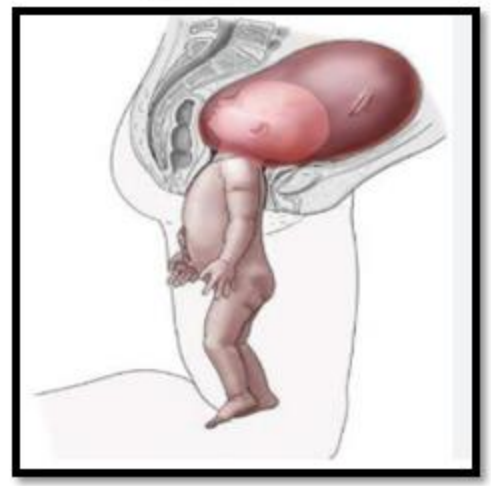
4- Miscellaneous drugs



Retained placenta



Uterine inversion



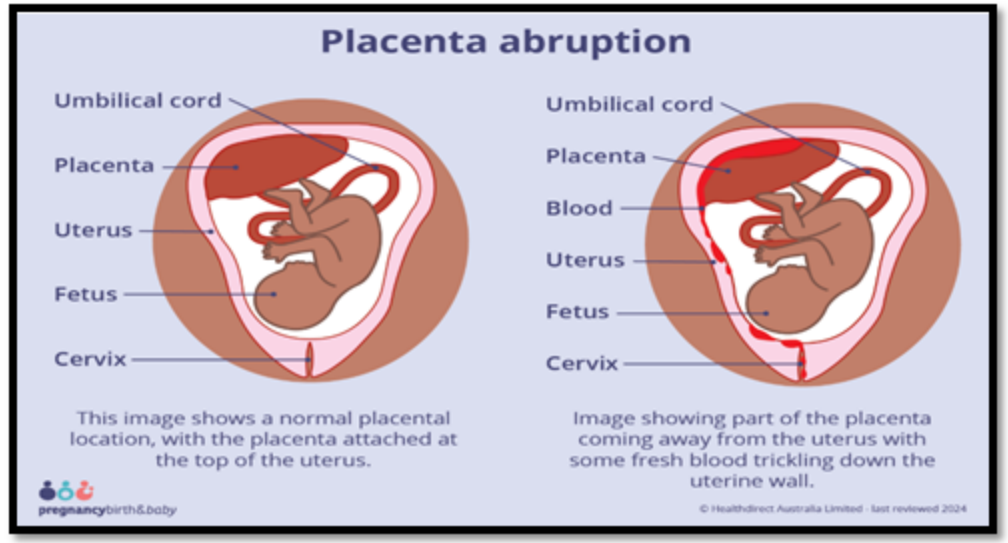
Fetal head entrapment

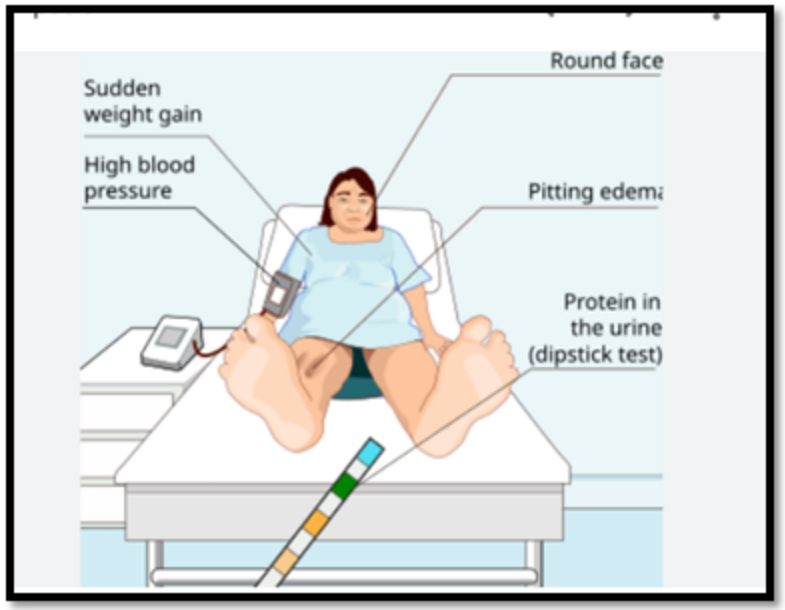
4- Miscellaneous drugs

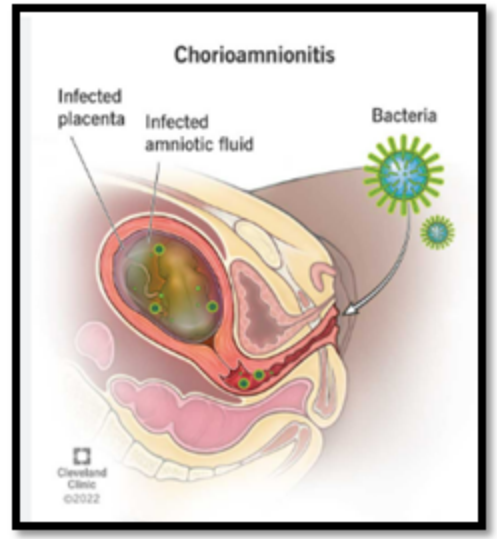
- **Indomethacin:**
- Non selective COX inhibitor
- Indomethacin is an effective, off-label drug (NSAID) used as a tocolytic
- **Indication:** to suppress preterm labor by inhibiting uterine prostaglandins, typically between 24 and 34 weeks of gestation.
- It is often considered **first-line** for early preterm labor to delay delivery for 48 hours, allowing for steroid administration.
- **Magnesium sulphate**:
- Competes with calcium at the cellular level, restricting its availability for muscle contraction
- Its primary established benefit in obstetrics is fetal neuroprotection (reducing the risk of cerebral palsy) when birth is imminent before 32-34 weeks gestation, rather than inhibiting labor itself.
- Preventing the over-activation of neurotransmitter receptors that can damage nerve cells

Contraindications of tocolytics

- 1- Chorioamnionitis: infection of fetal membranes
- 2- Congenital anomalies
- 3- Late pregnancy: more than 34 weeks
- 4- Placenta abruption
- 6- Pre-eclampsia







Other Agents Affecting the Uterus

- **Danazol:** a synthetic androgen
- Used for endometriosis and menorrhagia
- **Mechanism of action:**
- 1- Suppression of the Hypothalamic-Pituitary-Ovarian Axis: decreasing (FSH) and (LH): inhibiting ovulation and regression of endometriosis endometrial tissue.
- 2- Androgen and Progestogen Receptor Activity:
- A weak androgen, it binds to androgen receptors, creating an environment unfavorable to endometriotic growth.
- It also has weak progestogenic activity.
- 3- Inhibition of Steroidogenesis:
- directly inhibits enzymes responsible for producing estrogen and progesterone in the ovaries, adrenal glands, and peripheral tissues.

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THANK YOU