Drugs Acting On Uterus

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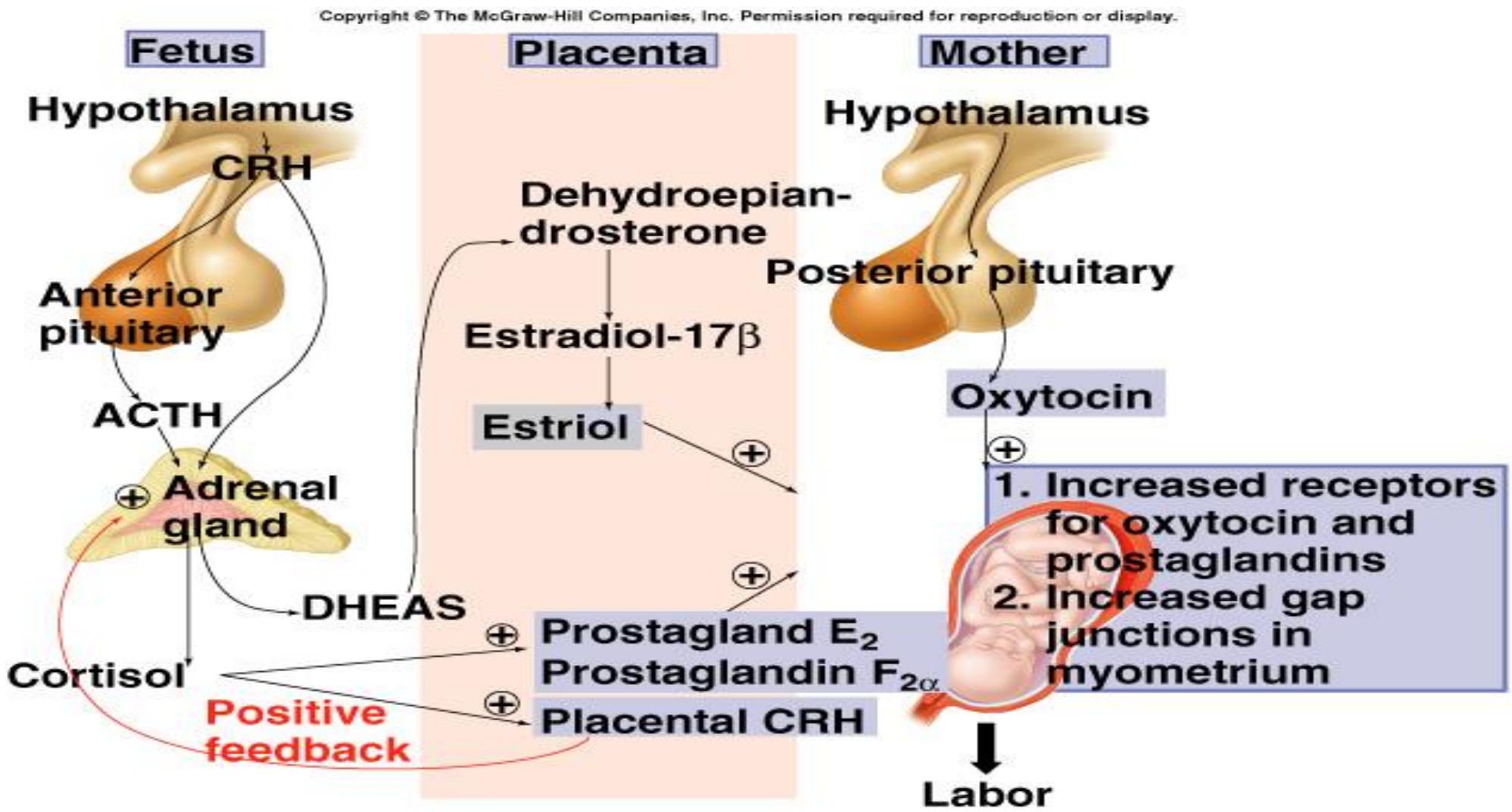
Objectives

- 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- Tocolytic drugs

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 affecting uterus

Stimulatory

The main drugs used clinically to increase uterine contractility:

- Oxytocin
- $Alph_1$- Adrenoceptor agonists (ergot derivatives)
- PGE_2 or $PGF_{2\alpha}$

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

Indications of uterine stimulants

- **1- Induce or facilitate labor:**
- **Pre-term**: diabetic mother- pre-eclampsia- Rh negative fetus
- **Incomplete abortion**
- **At-term:** uterine inertia
- **Post-term:** delayed labor
- **2- Prevention of postpartum hemorrhage**
- **3- Induction of abortion**

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 maintainance of labor:

- It contributes to initiation of parturition.
- Reaches **peak** during **pushing phase of labor**
- **Oxytocin-induced contractions can be inhibited by:**
- B_2-adrenoceptor agonists or by general anesthetics.

3. Uterine involution

4. Oxytocin has weak antidiuretic or pressor activity.

Mechanism of action:

1. Stimulation of oxytocin receptors
2. Increasing PGs levels intrauterine

PKs of oxytocin

- **It is not given orally** since it is destroyed by proteolytic enzymes of stomach and intestine (trypsin and chymotrypsin).
- It is **NOT** bound to plasma proteins
- Eliminated by liver and kidney (plasma t½~ 5 min): IV infusion.

Therapeutic uses of oxytocin

Induction of labor: given by IV infusion in:

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

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

Postpartum hemorrhage

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

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

N.B. **Clinically oxytocin is given only when uterine cervix is soft and dilated**

Adverse effects:

Rare with proper supervision

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

3- Water intoxication can rarely occur due to large volume of IV infused fluid. (may be fatal)

4- Increased incidence of neonatal jaundice: due to increased osmotic fragility of RBC

Contra-indications:

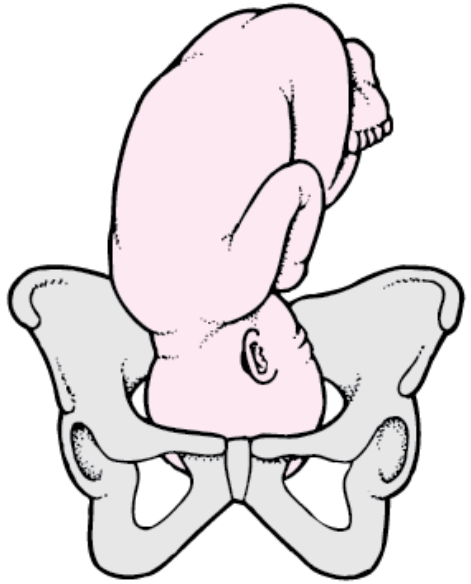
1- Fetal distress

2- Prematurity of fetus

3-Fetal-malpresentation e.g. breech presentation & **Cephalopelvic disproportion** i.e. contracted pelvis: both predispose to uterine rupture.

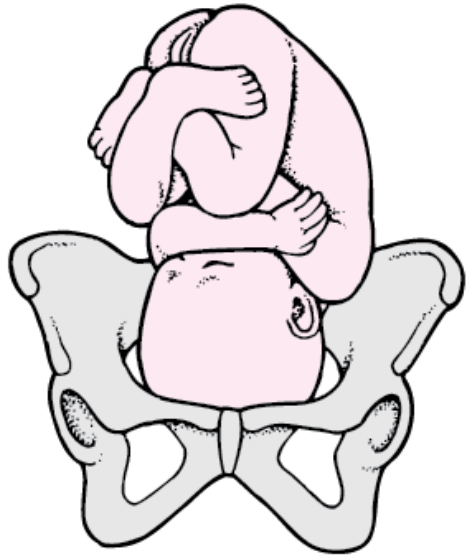
4- Prolapse of umbilical cord following rupture of fetal membranes.

Facing Backward
Head First



Normal Position and Presentation

Facing Forward



Abnormal Position

Frank Breech

Complete Breech

Footling Breech

Precautions to oxytocin use

- Multiple pregnancy
- Previous c- section
- Hypertension

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.**

Side effects: Increased B.P

Contraindications

1. Hypertension as in pre-eclampsia
2. Peripheral vascular disease
3. Angina

3. Prostaglandins (PGs)

- **Mechanism of action as uterine stimulants:**
- **1- Direct action**: via receptors
- **2- Indirect action**: upregulation of oxytocin receptors

❑**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 at term: This shortens time to onset of labor and labor time.

PGE2 **directly affects collagenase of cervix that breaks down the collagen network and softens it.**

- **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 second trimester or when gemeprost is not available.

$PGF_{2\alpha}$ (Dinoprost) : less commonly used

May be **given vaginally, intra-amniotically, or IV** for **induction of abortion in second trimester**.

Intra-amniotic $PGF_{2\alpha}$ has up to 100% success rate with fewer and less severe adverse effects than IV.

Side effects:

$PGF_{2\alpha}$ causes more G.I. side effects (vomiting, diarrhea) than PGE_2.

Tocolytics

What are tocolytic drugs?

- Drugs that inhibit uterine contractions

Indications:

- Delay, inhibit or prevent **premature labor** (< 37 weeks of pregnancy).

- **Clinical hint:**

• Usually, regular uterine contractions can stabilize on bed rest & local warmth. **When this is insufficient, then a tocolytic drug is used.**

N.B. **Betamethasone** is given IV to mother or into cord blood to stimulate maturation of fetal lung (by enhancing surfactant formation); it is preferred to **dexamethasone** because it is bound less to plasma proteins.

1. B_2 - adrenoceptor agonists

- **Ritodrine, Terbutaline, salbutamol**
- **Mechanism of action: increasing cAMP in myometrium**
- **Route of administration:**
- oral or IV infusion in 5% dextrose
- **Side 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

- The short acting Nifedipine or Nicardipine
- **Mechanism of action**: inhibition of Ca influx in myometrium
- **Route of administration**: oral
- **Side effects**: hypotension

3- Atosiban

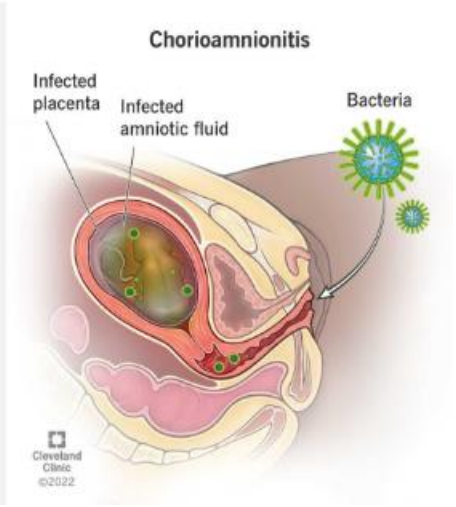
- **Analogue of oxytocin** that act as competitive antagonist, inhibiting oxytocin binding to its receptor.
- Given IV

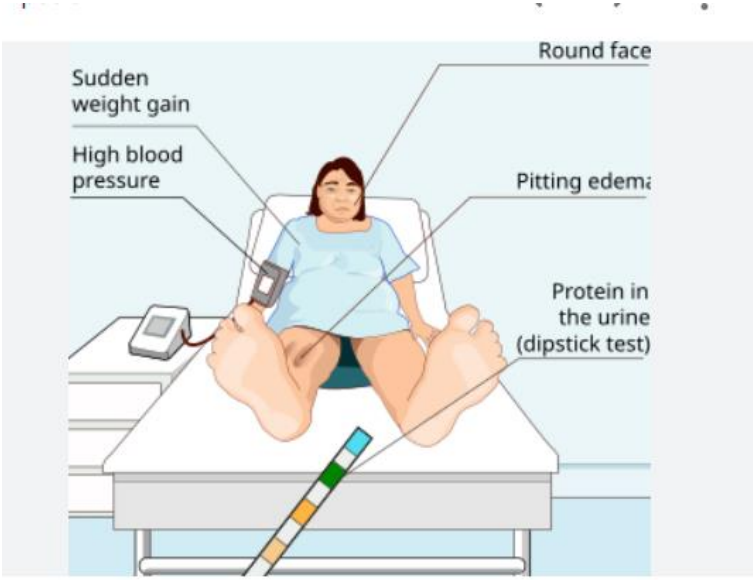
4- Miscellaneous drugs

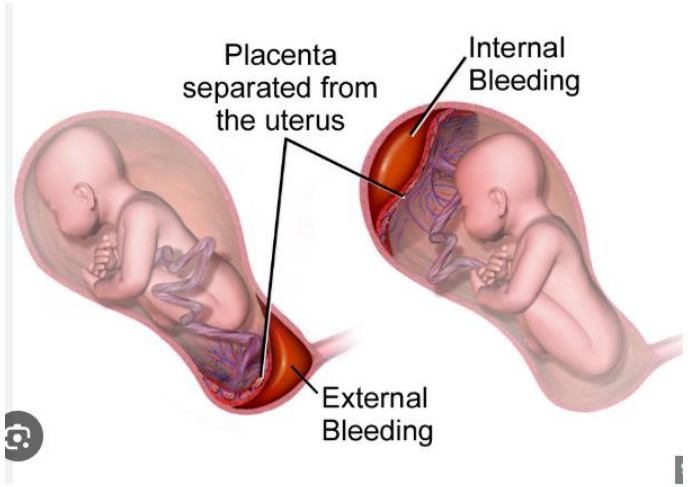
- Progesterone
- Halothane
- Nitroglycerine: NO donor: increasing cGMP in myometrium
- Indomethacin: COX inhibitor

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







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THANK YOU