Drugs Affecting Uterus
Oxytocin

Oxytocin (Pitocin, Syntocinon) is a cyclic 8–amino acid peptide that is synthesized in the paraventricular nucleus of the hypothalamus and transported within hypothalamic neurons (in association with neurophysin) to the posterior pituitary for storage.

- Its mechanism of action involves the direct stimulation of oxytocin receptor found on the myometrial cells.
- Oxytocin circulates unbound in the plasma, where it has a half-life of approximately 15 minutes.
- It is primarily inactivated in the kidneys and liver.

Oxytocin is generally considered to be the drug of choice for inducing labor at term.

- In combination with amniotomy, oxytocin is highly successful in inducing and augmenting labor.
- When given oxytocin, approximately 80% of patients with documented labor disorders progress into labor and deliver vaginally.
• It has also been used following incomplete abortion after 20 weeks of gestation (although use of prostaglandins may be preferred in this instance), and it may be used after fullterm delivery to prevent or control uterine hemorrhage.

• Oxytocin in high doses is used to induce abortion.

• An oxytocin challenge test (an assessment of the fetal heart rate in response to oxytocin-induced contractions) can be performed in certain high-risk (e.g., those with hypertension, diabetes, preeclampsia) obstetrical patients as a measure of fetal well-being
• Inappropriate use of oxytocin can lead to uterine rupture, anaphylactoid and other allergic reactions, and possibly maternal death.

• Prolonged stimulation of uterine contractions can result in the following fetal adverse reactions:
  ✓ persistent uteroplacental insufficiency,
  ✓ sinus bradycardia,
  ✓ premature ventricular contractions,
  ✓ Other arrhythmias, and fetal death.
  ✓ Prolonged use of oxytocin can lead to water intoxication secondary to the antidiuretic hormone–like effects of oxytocin.
  ✓ Maternal and fetal cardiovascular parameters should be monitored during oxytocin administration.
Oxytocin may be given by:

- Intravenous infusion (e.g., Labor induction).
- Intramuscular injection (e.g., Control of postpartum bleeding).
- Nasal spray (e.g., to promote milk ejection).
**Ergonovine Maleate and Methylergonovine Maleate**

- **Ergonovine** *(Ergotrate)* and **methylergonovine** *(Methergine)* are compounds obtained either directly or semisynthetically from **ergot**, a fungus that grows on rye and other grains.

- ✓ These compounds stimulate uterine smooth muscle directly, thereby increasing muscular tone and enhancing the rate and force of rhythmical contractions.

- ✓ **Ergonovine** also stimulates cervical contractions.
• These drugs are capable of inducing a **sustained tetanic contraction**, which can shorten the final stage of labor and aid in the reduction of postpartum blood loss.

• Both are commonly used for the **routine expulsion of the placenta after delivery** and in postpartum and postabortal atony and hemorrhage.
Both drugs are partial agonists at α-adrenergic receptors and at some serotonin and dopamine receptors; they also can inhibit the release of endothelial-derived relaxation factor.

They may induce arterial vasoconstriction and have minor actions on the central nervous system.

Their α-adrenergic blocking activity is relatively weak compared with those of other ergot alkaloids.
• Absorption is rapid and largely complete after oral administration, and onset of action occurs in 5 to 15 minutes and lasts about 3 hours.

• Both ergonovine and methylergonovine can be given intramuscularly or intravenously, although intravenous administration can be associated with transient but severe hypertension.

• These compounds undergo hepatic metabolism, with elimination primarily by renal excretion of metabolites.
• They also can be found in breast milk, and therefore, neither drug should be administered longer than necessary, since prolonged use can lead to ergot poisoning (**ergotism**), including gangrene, in the nursing infant.

• Adverse reactions associated with their administration include hypertension, headache, and possible seizures.

• Nausea, vomiting, chest pains, difficulties in breathing, and leg cramps also have been reported.

✓ These alkaloids should not be used in cases of threatened spontaneous abortion or in patients with known allergies to the drugs.

• **Contraindications** generally include angina pectoris, myocardial infarction, pregnancy, and a history of a cerebrovascular accident, transient ischemic attack, or hypertension.
Dinoprostone, Carboprost Tromethamine, and Misoprostol

• Dinoprostone (Prostin E2) is a naturally occurring prostaglandin E2 found in mammalian tissues, human seminal plasma, and menstrual fluid.

• Carboprost tromethamine (Hemabate, Prostin/15M) is a synthetic analogue of the naturally occurring prostaglandin PGF2.

• Both drugs stimulate uterine smooth muscle contractions and can be used to induce abortion during gestation weeks 12 to 20.
• Abortion was successful in 96% of the cases in which these agents were used, with complete passage of fetal products occurring more than 75% of the time without surgical intervention.

• The mean time to abortion after drug administration was 16 hours.

• The prostaglandins are more effective stimulants of uterine contraction through the second trimester of pregnancy than is oxytocin.

• Inhibition of endogenous prostaglandin synthesis with a nonsteroidal antiinflammatory agent, such as aspirin or ibuprofen, can increase the length of gestation, prolong spontaneous labor, or interrupt premature labor.
- **Dinoprostone** is slowly absorbed from the amniotic fluid into the systemic circulation.
- It and its metabolites readily cross the placenta and can concentrate in the fetal liver.
- **Dinoprostone** is primarily metabolized in the maternal lungs and liver and has a half-life in plasma and amniotic fluid of less than 1 minute and 3 to 6 hours, respectively.
- **Carboprost** also is metabolized in maternal lung and liver but somewhat more slowly than dinoprostone.
- It is primarily eliminated by renal excretion of its metabolites, with small amounts appearing in the feces.
• Because dinoprostone produces cervical ripening along with stimulation of the uterus, it has been used as an alternative to oxytocin for the induction of labor.
• Preparations of dinoprostone can be placed in either the cervix or the posterior fornix.
• Carboprost has been used successfully to control postpartum bleeding that was secondary to loss of uterine tone and where the myometrium was unresponsive to oxytocin, ergonovine, or methylergonovine.

• Given intramuscularly, carboprost causes an almost immediate and sustained uterine contraction.

• Clinical experience has shown that the use of this agent has saved many women from operative interventions (including hysterectomy) to control postpartum hemorrhage.
• **Misoprostol** *(Cytotec)* *is a prostaglandin E1 analogue* that is being evaluated as a cervical ripening agent.

• It also is used in the treatment and prevention of peptic ulcer disease.

• Clinical trials show that misoprostol is an effective agent for both cervical ripening and labor induction.

✓ It appears to be as effective as dinoprostone and is much less expensive.
• While adverse reactions are common following the use of abortion-inducing doses of the prostaglandins, most are not serious.
• Gastrointestinal disturbances include nausea, vomiting, and diarrhea.
• Transient fever, retained placental fragments, excessive bleeding, decreased diastolic blood pressure, and headache also have been noted.
• These drugs should be used with caution in patients with asthma, cervicitis, vaginitis, hypertension or hypotension, anemia, jaundice, diabetes, or epilepsy
• They should not be used in patients with acute pelvic inflammatory disease, drug hypersensitivity, or an active renal, hepatic, or cardiovascular disorder.

• Since prostaglandins are potentially carcinogenic, if pregnancy is not effectively terminated following their use, another method should be used.

✓ The prostaglandins are not generally used concomitantly with oxytocin because of the possibility of uterine rupture.
Uterine Relaxants

• Many risk factors are associated with the triggering of premature labor, that is, labor that begins before the end of week 37 of gestation.

• These include maternal smoking or drug abuse, lack of prenatal care, multiple gestation, placental abnormalities, infection of the fetal membranes, cervical incompetence, and previous preterm birth.

• Although most episodes are of unknown origin, premature labor can develop spontaneously or may follow early rupture of fetal membranes, perhaps as a result of a genetically associated abnormality.
• Uterine relaxants (tocolytic drugs) are administered where prolonged intrauterine life would greatly benefit the fetus or would permit additional time to allow treatment with drugs such as corticosteroids, which promote the production of fetal lung surfactant.

• Tocolytics are also used when temporary uterine relaxation is be desirable (e.g., intrauterine fetal resuscitation).

• While hydration, bed rest, and sedation have been used to inhibit uterine contractions, tocolytics are more likely to inhibit labor early in gestation, especially before labor is far advanced.
Agents used in this regard include:

- Magnesium Sulfate
- Alcohol,
- Prostaglandin Inhibitors,
- Calcium Channel Blockers,
- hydroxyprogesterone.
- β2-adrenergic agonists.

All tocolytic agents are powerful drugs that must be used with extreme care, since pulmonary edema, myocardial infarction, respiratory arrest, cardiac arrest, and death can occur during tocolytic therapy.
• Newborns of mothers given tocolytics have had respiratory depression, intraventricular hemorrhage, and necrotizing enterocolitis.

• Absolute contraindications to tocolysis include acute fetal distress (except during intrauterine resuscitation), chorioamnionitis, eclampsia or severe preeclampsia, fetal demise (of a singleton pregnancy), fetal maturity, and maternal hemodynamic instability.
Ethanol

- Intravenous use of ethanol, while once widely employed to inhibit premature labor, is now of historical interest only.
- Ethanol inhibits oxytocin release from the pituitary and thus indirectly decreases myometrial contractility.
- Today, β-adrenomimetics and magnesium sulfate have replaced ethanol for parenteral tocolysis.
β-Adrenoceptor Agonists

• Although β-adrenoceptor agonists are the most commonly used tocolytic agents in the United States, they are not completely successful treating preterm labor.

• Prophylactic administration of these agents to patients at high risk for preterm labor is not always effective.

• There is clear evidence that β-agonists can arrest preterm labor for at least 48 to 72 hours.

• The efficacy of these drugs beyond this time frame is in dispute.

✓ Even a short delay in delivery can be desirable, however, in that at very early preterm gestations (24–28 weeks) a 2-day delay in delivery may mean a 10 to 15% increase in probability of survival for the newborn.

▪ such a delay allows for corticosteroid administration to the mother, which has been shown to decrease the incidence and severity of respiratory distress syndrome of the newborn, decrease the incidence of neonatal intraventricular hemorrhage, and improve survival in the premature newborn.
• These drugs act by binding to β-adrenoceptors on myometrial cell membranes and activating adenylyl cyclase.

• This in turn increases levels of cAMP in the cell activating cAMP-dependent protein kinase, hence decreasing intracellular calcium concentrations and reducing the effect of calcium on muscle contraction.

• β-Adrenergic drugs have many side effects. These result both from their residual β₁ activity and from their ability to stimulate β₂-receptors elsewhere in the body
• The side effects include palpitations, tremor, nausea, vomiting, nervousness, anxiety, chest pain, shortness of breath, hyperglycemia, hypokalemia, and hypotension.

• Serious complications of drug therapy are pulmonary edema, cardiac insufficiency, arrhythmias, myocardial ischemia, and maternal death.
Terbutaline

- Terbutaline (Brethine, Bricanyl) is a relatively specific \( \beta_2 \)-adrenoceptor agonist.
- Terbutaline can prevent premature labor, especially in individuals who are more than 20 weeks into gestation and have no indication of ruptured fetal membranes or in whom labor is not far advanced.
- Its effectiveness in premature labor after 33 weeks of gestation is much less clear.
- Terbutaline can decrease the frequency, intensity, and duration of uterine contractions through its ability to directly stimulate \( \beta_2 \)-adrenoceptors.
- While it appears to be especially selective for \( \beta_2 \)-receptor activation, terbutaline does have some \( \beta_1 \) activity as well.
• Terbutaline should be initially used only in an appropriate hospital setting where any obstetric complications can be readily addressed.

• After initial administration, it can be used in the outpatient setting.

✓ Concomitant use of β2-adrenergic agonists and corticosteroids have additional diabetic effects and may rarely lead to pulmonary edema.

✓ The combination of β2-adrenergic agonists and magnesium sulfate can cause cardiac disturbances, while coadministration of terbutaline with other sympathomimetics can lead to the potentiation of the actions of the latter drugs.
• Terbutaline can cause tachycardia, hypotension, hyperglycemia, and hypokalemia.

• It can be given orally in addition to subcutaneous or intravenous administration.
Magnesium Sulfate

- Magnesium sulfate prevents convulsions in preeclampsia and directly uncouples excitation–contraction in myometrial cells through inhibition of cellular action potentials.
- Magnesium sulfate decreases calcium uptake by competing for its binding sites, activating adenylyl cyclase (thereby reducing intracellular calcium), and stimulating calcium-dependent adenosine triphosphatase (ATPase), which promotes calcium uptake by the sarcoplasmic reticulum.
- Magnesium is filtered by the glomerulus, so patients with low glomerular filtration will have low magnesium clearance.
• Although the compound does have some cardiac side effects, magnesium sulfate may be preferred over - adrenergic agents in patients with heart disease, diabetes, hypertension, or hyperthyroidism.

• There is much debate as to the efficacy of magnesium sulfate.

• For effective inhibition of uterine activity, enough must be given to maintain a blood plasma level of at least 5.5 mEq/L.

• Even at this level, tocolyisis may be hard to achieve.
• Magnesium toxicity can be life threatening.
• Patients given magnesium lose patellar reflexes at plasma levels greater than 8 to 10 mEq/L.
• Respiratory depression can occur at levels greater than 10 to 12 mEq/L, with respiratory paralysis and arrest soon after (e.g., at levels greater than 12–15 mEq/L).
• Higher levels cause cardiac arrest.
• Toxicity can be avoided by following urine output and checking patellar reflexes in patients receiving magnesium.
• Other side effects include sweating, warmth, flushing, dry mouth, nausea, vomiting, dizziness, nystagmus, headache, palpitations, pulmonary edema, maternal tetany, profound muscular paralysis, profound hypotension, and neonatal depression.
Other Agents

• Since certain prostaglandins are known to play a role in stimulating uterine contractions during normal labor, it is logical that inhibitors of prostaglandin synthesis have been used to delay preterm labor.

• **Indomethacin** (*Indocin*) *has been the principal agent for this use*. Indomethacin is given orally or rectally for 24 or 48 hours to delay premature labor.

• A potential worry concerning the use of indomethacin is premature closure of the fetal ductus arteriosus induced by its ability to inhibit prostaglandin synthesis.
• **Indomethacin** use also can decrease amniotic fluid volume and cause oligohydramnios through its ability to decrease fetal urinary output.

• **Long-term use** of maternal indomethacin is associated with primary pulmonary hypertension and an increased incidence of intraventricular hemorrhage in the newborn.
The calcium channel blocking agent nifedipine

• *is one of the more recent* drugs examined as a tocolytic agent.

• It acts by impairing the entry of Ca into myometrial cells via voltage dependent channels and thereby inhibits contractility.

• Although preliminary results appear promising, more studies are needed before its usefulness can be fully assessed.
Hydroxyprogesterone

- *Hydroxyprogesterone has been used prophylactically* for the 12th to 37th week of pregnancy, particularly in women who are in the high-risk category for premature delivery (e.g., those with a history of premature delivery or spontaneous abortion).

- A concern relating to teratogenic potential has limited its use.

- Hydroxyprogesterone as a tocolytic agent requires further evaluation before its routine prophylactic administration can be recommended.
Oxytocin Antagonists

- With the increasing evidence that oxytocin is important in human labor, investigators are studying oxytocin antagonists for the treatment of preterm labor.
- **Atosiban** is an analogue of oxytocin that is modified at positions 1, 2, 4, and 8.
- It is a competitive inhibitor of oxytocin binding.
- Early studies have demonstrated that this drug does decrease and stop uterine contractions.
- Atosiban is not available for use in the United States.