62 | Uterine Stimulants and Relaxants

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DRUG LIST

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The physiological processes involved in *parturition* (i.e., labor, delivery, and birth) require a complex interplay of hormonal action, neuronal activity, and uterine smooth muscle contraction. During the first two trimesters of pregnancy, the uterus remains in a relatively quiescent state, demonstrating little or no contraction of the myometrium. This inactivity is largely the result of the inhibitory action of high circulating levels of progesterone on the uterine musculature (see Chapter 63). During the final trimester, however, uterine smooth muscle becomes increasingly excitable, such that mild muscle contractions are seen (Braxton-Hicks contractions); these gradually increase in both strength and frequency, occasionally to the extent that they may even be thought to signal the onset of labor, a phenomenon termed *false labor*. Parturition requires in part the integration of processes that involve cervical canal dilation and uterine smooth muscle contractions that are strong enough to expel the fetus.

Other physiological events must occur at the end of pregnancy to facilitate birth. The cervix begins to soften (*cervical ripening*) as a direct result of connective tissue

dissociation; this process may involve the actions of the peptide hormone *relaxin,* which is produced both in the corpus luteum and in the placenta. Relaxin also aids in the dissociation of the connective tissue between the pelvic bones, a process that also aids in the facilitation of birth. At the true onset of labor, coordinated, rhythmic contractions of the uterus begin, and as labor progresses, the myometrial contractions increase in intensity and strength. These contractions force the fetus against the cervix, further dilating the cervix. Once the cervix has dilated sufficiently, the uterine contractions push the fetus through the birth canal.

A variety of endocrine hormones play a role in initiating the changes in uterine contractility, especially during the final trimester. It is probable that the concentration of receptors responsive to the hypothalamic peptide hormone *oxytocin* (see Chapter 59) increases in the uterine musculature in response to the increasing levels of estrogen during pregnancy. Although circulating blood levels of oxytocin do not change markedly throughout pregnancy, it is likely that the augmented number of oxytocin receptors in the uterus makes the

muscle increasingly responsive to plasma oxytocin. There also is speculation that the uterus itself may be capable of synthesizing oxytocin. If such a synthesis does indeed occur, much higher local concentrations of the peptide will be found than would be predicted strictly on the basis of circulating amounts of the hormone. Increases in the number of myometrial α-adrenergic and angiotensin receptors also will increase the sensitivity of these muscle cells to contractile stimuli. Finally, the possibility of fetal factors playing a role in the initiation of parturition should be considered.

Although, like other smooth muscle, the myometrium is capable of contraction at any time, it is generally quiescent throughout most of pregnancy. As pregnancy progresses, spontaneous repetitive action potentials can be seen, but muscle tension will develop only once these action potentials become synchronized electrical discharges. Contractions do become evident, however, several weeks before labor begins. The contractions of the myometrium progressively increase during the onset of labor, in part through the action of a positive neuroendocrine feedback system that involves both synthesis and release of oxytocin and prostaglandins. The stretching of the softened cervix induced by increasing fetal pressure results in local receptor stimulation and the initiating of a spinal reflex that eventually results in the release of oxytocin from the posterior pituitary. This additional oxytocin will further promote uterine contractions.

Release of oxytocin at this stage of parturition promotes prostaglandin production, particularly of the E and F series, within the decidua; these prostaglandins are powerful myometrial stimulants and thus further enhance uterine contractions. The prostaglandin concentration in maternal serum and amniotic fluid increases with the progression of labor.

Many of the biochemical and molecular events that are responsible for uterine smooth muscle contraction are the same as those that control other smooth muscle tissues (Fig. 62.1). Once uterine smooth muscle sensitivity has been augmented, actin and myosin must interact for contraction to occur. This interaction depends on the phosphorylation of the contractile proteins by the enzyme *myosin light chain kinase* (MLCK). This enzyme requires Ca^{++} and is active only when associated with calmodulin. *Activation of the entire muscle contraction*
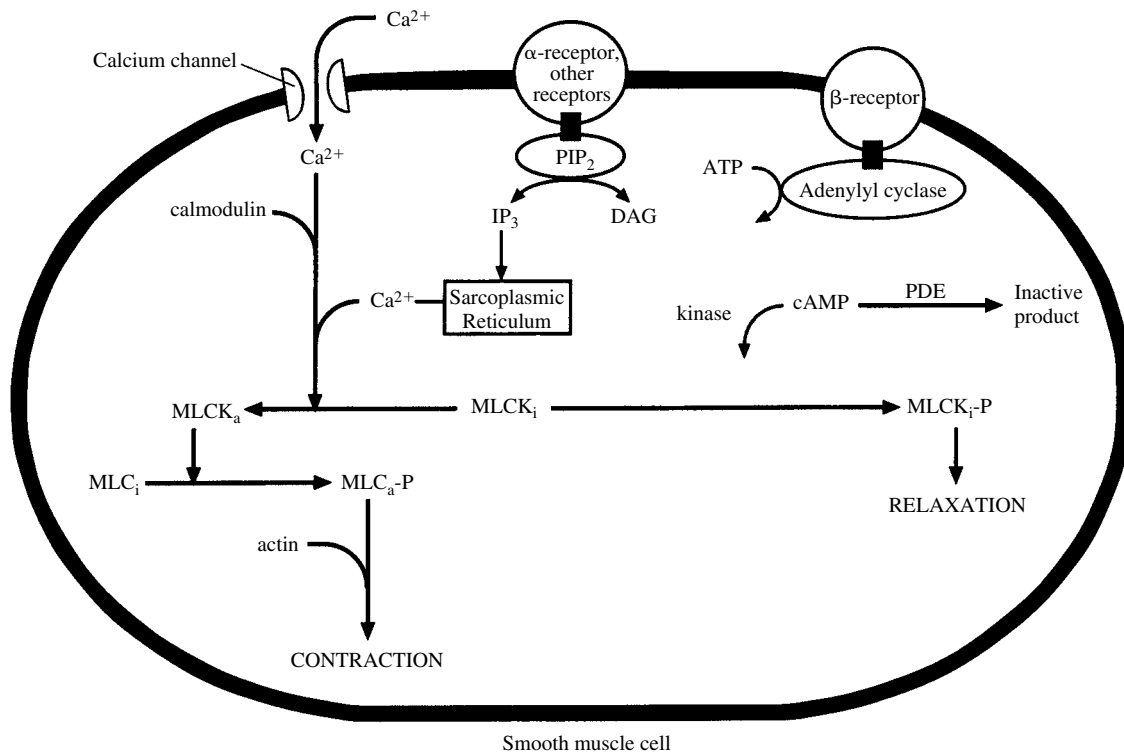
FIGURE 62.1

Major biochemical events of smooth (uterine) muscle contraction and relaxation. Calcium (Ca^{++}) binds to calmodulin and initiates a series of biochemical reactions that ultimately lead to muscle contraction. $MLCK_i$, myosin light chain kinase (inactivated); $MLCK_a$, myosin light chain kinase (activated); MLC_i, inactive myosin light chain; MLC_a-P, phosphorylated active myosin light chain; $MLCK_i$-P, phosphorylated MLCK; PDE, phosphodiesterase; PIP_2, phosphatidylinositol; IP_3, inositol triphosphate; DAG, diacylglycerol.

process involves the receptor binding of estrogen, oxytocin, α_1-adrenergic agonists, and prostaglandins (PGE$_1$ and PGE$_2$). A decrease in the progesterone–estrogen ratio in the myometrium is also an important factor in the timing and initiation of labor; this altered ratio may involve increased fetal estrogen production, particularly in the latter weeks of pregnancy. *Cytokines produced by the fetus* are also thought to be responsible for stimulating uterine contraction.

Uterine relaxation is mediated in part through inhibition of MLCK. This inhibition results from the phosphorylation of MLCK that follows the stimulation of myometrial β-adrenoceptors; relaxation involves the activity of a cyclic adenosine monophosphate (cAMP) mediated protein kinase, accumulation of Ca^{++} in the sarcoplasmic reticulum, and a decrease in cytoplasmic Ca^{++}. Other circulating substances that favor quiescence of uterine smooth muscle include progesterone, which increases throughout pregnancy, and possibly prostacyclin. Progesterone's action probably involves hyperpolarization of the muscle cell membrane, reduction of impulse conduction in muscle cells, and increased calcium binding to the sarcoplasmic reticulum.

Drugs and hormones used clinically to enhance uterine contractions are primarily employed either to induce or to augment contractions during labor and delivery. They have particular value in limiting an extended pregnancy, preventing the early rupture of membranes, or aiding placental insufficiency. Many of these compounds also are useful in limiting postpartum hemorrhage. *The primary use of uterine relaxants (tocolytic agents) is in the prevention of premature labor.* These drugs act either directly to suppress myometrial smooth muscle contraction or indirectly to inhibit synthesis or release of the prostaglandins and/or other endogenous uterine stimulants.

UTERINE STIMULANTS

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 receptors 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 disor-

ders 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 full-term 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), or as a 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 E_2 found in mammalian tissues, human seminal plasma, and menstrual fluid (see Chapter 36). Carboprost tromethamine (*Hemabate, Prostin/15M*) is a synthetic analogue of the naturally occurring prostaglandin $PGF_{2\alpha}$. 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. *Prepidil* is a formulation and delivery system of dinoprostone that delivers a dose of 0.5 mg into the cervix, while *Cervidil* consists of the drug embedded in a plastic matrix. The matrix is designed to deliver a dose of 0.3 mg per hour for 12 hours.

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 E_1 analogue that is being evaluated as a cervical ripening agent. It also is used in the treatment and prevention of peptic ulcer disease (see Chapter 40). 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 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, and β_2-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_2-adrenomimetics and magnesium sulfate have replaced ethanol for parenteral tocolysis.

β_2-Adrenoceptor Agonists

Although β_2-adrenoceptor agonists (see Chapter 10) are the most commonly used tocolytic agents in the United States, they are not completely successful in treating preterm labor. Prophylactic administration of these agents to patients at high risk for preterm labor is not always effective. There is, however, clear evidence that β_2-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. Furthermore, 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. Tocolysis also allows for the transport of the mother to a tertiary center where delivery of the preterm infant often results in its improved survival.

These drugs act by binding to β_2-adrenoceptors on myometrial cell membranes and activating adenylyl cyclase. This in turn increases levels of cAMP in the cell (Fig. 62.1), activating cAMP-dependent protein kinase, hence decreasing intracellular calcium concentrations and reducing the effect of calcium on muscle contraction.

β_2-Adrenergic drugs have many side effects. These result both from their residual β_1 activity and from their ability to stimulate β_2-receptors elsewhere in the body (see Chapter 2). 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 β_2-adrenoceptor agonist (see Chapters 10 and 39). 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 β_2-adrenoceptors. While it appears to be especially selective for β_2-receptor activation, terbutaline does have some β_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 β_2-adrenergic agonists and corticosteroids have additional diabetic effects and may rarely lead to pulmonary edema. The combination of β_2-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 is frequently used in the management of premature labor, although it has not been marketed for such use. Its effectiveness, side effects, precautions, and contraindications are similar to those of all β_2-adrenergic agonists. 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. Furthermore, 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 β-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, tocolysis 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. The fetal ductus is more sensitive to indomethacin beyond 32 weeks of gestation. 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 (*Procardia;* see Chapter 19), 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 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.

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.

Study QUESTIONS

1. Which of the following is the drug of choice for inducing labor?
   (A) Oxytocin
   (B) Misoprostol
   (C) Methyl ergonovine
   (D) Dinoprostone
   (E) Carboprost tromethamine
2. Adverse reactions to the prostaglandin analogue carboprost tromethamine include all of the following EXCEPT
   (A) Diarrhea
   (B) Fever
   (C) Water intoxication
   (D) Nausea
   (E) Dyspnea
3. Carboprost is used primarily to
   (A) Induce labor
   (B) Control postpartum bleeding
   (C) Antagonize effects of dinoprostone
   (D) Inhibit premature labor
   (E) Close the fetal ductus arteriosus
4. All of the following are properties of magnesium sulfate that may be related to its ability to relax uterine smooth muscle EXCEPT
   (A) Uncoupling excitation–contraction in myometrial cells through inhibition of cellular action potentials
   (B) Decreasing calcium uptake by competing for binding sites
   (C) Activating adenylate cyclase

(D) Stimulating calcium-dependent ATPase
(E) Antagonizing prostaglandin action
5. Which of the following is a special concern for the use of indomethacin for inducing labor (tocolysis)?
(A) Fetal cardiac arrest
(B) Fetal gastrointestinal bleeding
(C) Fetal hematuria
(D) Closure of the fetal ductus arteriosis
(E) Fetal muscular paralysis

ANSWERS

1. **A.** Oxytocin is considered the drug of choice for inducing labor. All other methods of labor induction are compared to oxytocin to establish their efficacy. Data demonstrate that oxytocin is highly effective in inducing, establishing, and augmenting labor. Oxytocin is not as effective for labor induction when a woman has a cervix that is not favorable for labor. Another agent, such as misoprostol or dinoprostone, may be better for women with unfavorable cervices. Both misoprostol and dinoprostone are prostaglandin analogues. They cause changes in the substance of the cervix and uterine contraction. Although all agents used for labor induction carry the risk of uterine hyperstimulation, prostaglandins are more likely to cause hyperstimulation in women with favorable cervices. Furthermore, the current formulations of prostaglandins do not allow for tight control of blood levels and rapid clearance of medication if hyperstimulation occurs. Methyl ergonovine is an α-agonist that causes direct smooth muscle contraction. Carboprost tromethamine is a methylated analogue of prostaglandin $F_{2\alpha}$. It is highly potent in causing prolonged uterine contraction. Both medications are used for the control of uterine bleeding after delivery by causing tetanic uterine contractions. These medications are contraindicated for labor induction in women with live fetuses. Both medications can be used in facilitating medical abortions.

2. **C.** Carboprost tromethamine is methylated at the 15 position. This methylation causes the analogue to be 10 to 15 times more potent then the natural prostaglandin. Smooth muscles that are especially sensitive to prostaglandin $F_{2\alpha}$ are uterine, gastrointestinal, and bronchial. The uterine sensitivity allows for the therapeutic efficacy. The gastrointestinal sensitivity causes the diarrhea and nausea. Prostaglandins are involved in the pyretic response, and thus a side effect of their use may be fever. Oxytocin has antidiuretic hormone qualities, and with prolonged use may cause water intoxication.

3. **B.** Clinical evidence has shown that the use of this agent has saved many women from surgery by controlling postpartum hemorrhage. It can also induce labor but is not the drug of choice. It will induce rather than inhibit premature labor. A prostaglandin antagonist would be useful to produce closure of the fetal ductus arteriosus.

4. **E.** Magnesium has no known effect on prostaglandins. The mechanism of action by which magnesium sulfate causes smooth muscle contraction is complex and poorly understood. Magnesium sulfate uncouples excitation–contraction in myometrial cells through inhibition of cellular action potentials. Furthermore, magnesium sulfate decreases calcium uptake by competing for binding sites, activating adenylate cyclase (reducing intracellular calcium), and stimulating calcium-dependent ATPase, which promotes calcium uptake by sarcoplasmic reticulum.

5. **D.** Indomethacin is a potent prostaglandin synthesis inhibitor. Patency of the ductus arteriosis depends on the formation of prostaglandins. Closure of the ductus arteriosis can lead to fetal heart failure and death. Also, fetal closure can lead to neonatal pulmonary hypertension. Neonatologists use indomethacin for the treatment of neonatal patent ductus arteriosis, thus often obviating neonatal heart surgery. Prostaglandin synthesis inhibitors are associated with bleeding. Although bleeding is well documented in children and adults, the use of indomethacin has not been shown to cause hematuria or gastrointestinal bleeding in the fetus. There is some evidence, however, that maternal use of indomethacin may increase the risk of neonatal intraventricular hemorrhage. Neither muscular paralysis nor cardiac arrest has been demonstrated in the fetus with maternal use of indomethacin.

SUPPLEMENTAL READING

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CASE Study Is Labor Induction Justified?

A 25-year-old woman is 2 weeks beyond her estimated date of delivery. She reports no pain, no labor contractions, no vaginal bleeding, no leaking fluid from her vagina, and no vaginal discharge. She reports that her fetus is moving. On further history, you find that the patient reports no other complaints, and her medical, surgical, social, and family histories are all negative. The physical examination you perform produces normal findings. Notably, her uterine fundal size measurement is 40 cm. Her pelvic examination reveals that her cervix is 3 cm dilated, 50% effaced, soft in consistency, and midposition in the vagina. The fetal station is presenting at 0. You find no evidence of ruptured membranes. Uterine monitoring shows no contractions. You and the patient decide that labor induction would be safe and appropriate. What would be a good course of action?

ANSWER: In this case, the decision to induce labor is appropriate. In caring for patients, physicians must decide who are appropriate patients for labor induction. The median length of human pregnancy is 40 weeks (when using the woman's menstrual period to date the pregnancy). Pregnancy is considered to be full-term from the 37 0/7 weeks to 41 6/7 weeks.

Patients who are pregnant 2 or more weeks beyond their due date are classified as having postterm or postdate pregnancy. These prolonged pregnancies carry the increased risk of fetal death (2 to 6 times as high as for women who are at 40 weeks' gestation). Women who are postterm have a higher risk of cesarean section, trauma from delivery, prolonged bleeding after delivery, and prolonged hospitalization. Newborns who are born postterm have an increased risk of being pathologically large (macrosomia), birth trauma, intolerance to labor, meconium staining, meconium aspiration, and possible subsequent hypoxia or anoxia brain injury. With all these concerns, labor induction may be safer than continuing the pregnancy.

Oxytocin is the drug of choice for inducing labor. In appropriate patients, it nearly always leads to safe vaginal delivery. Patients whose cervix is favorable for labor are good candidates for oxytocin. Obstetricians traditionally use a scoring system to rate the cervix (Bishop EH. Pelvic Scoring for Elective Induction. Obstet Gynecol 1964;24: 266–268). The following table defines the scoring system. Scores of ≥6 are considered favorable. Our patient has a score of 8.

Score	Dilation (cm)	Effacement (%)	Station	Cervical Consistency	Cervical Position
0	Closed	0–30	−3	Firm	Posterior
1	1–2	40–50	−2	Medium	Midposition
2	3–4	60–70	−1,0	Soft	Anterior
3	≥5	≥80	≥+1	−	−