Pharmacologic Inhibition of Preterm Labor

ARUN JEYABALAN, MD and STEVE N. CARITIS, MD
University of Pittsburgh School of Medicine, Department of Obstetrics, Gynecology & Reproductive Sciences, Division of Maternal-Fetal Medicine, Magee-Womens Hospital, Pittsburgh, Pennsylvania

Introduction
Preterm birth is a significant public health and obstetric problem. While accounting for only 6–10% of all births, preterm delivery is responsible for 70–85% of neonatal morbidity and mortality. Approximately three fourths of these preterm births occur secondary to preterm labor or preterm rupture of membranes. Despite the advances in neonatal care and technology, these statistics have not changed dramatically over the last several decades. Obstetricians have approached this issue from preventative and therapeutic standpoints. Preventative measures and methods of identifying women at increased risk for preterm labor have met with limited success. These methods include risk scoring indices, home uterine activity monitoring, ultrasound evaluation of cervical length, serial digital cervical examinations, fetal fibronectin, and salivary estriol testing to name a few. Pharmacologic thera-
these clinical definitions seem straightforward, the underlying biochemical and hormonal mechanisms of parturition are quite complex and intricate. Parturition begins long before clinically detectable labor. The process is heralded by an increase in myometrial gap junctions, oxytocin receptors, enhanced myometrial contractile efficiency and changes in cervical collagens and matrix. This complex cascade results in contractions, effacement of the cervix, and ultimately expulsion of the fetus. Whether this complex process can be delayed and/or reversed remains the fundamental question. The present pharmacologic measures are aimed specifically at stopping uterine contractions at the level of the myocyte, a late step in the parturitional cascade.

**Goals of Preterm Labor Inhibition**

The goals of preterm labor inhibition have changed with the advent of antenatal glucocorticoids, improved neonatal intensive care, and surfactant to prevent neonatal respiratory distress syndrome. The traditional approach to stop labor until term gestation has given way to balancing the risks of prematurity against the maternal and fetal risks of prolonging gestation. Given the significant benefit of antenatal corticosteroids in decreasing the incidence of respiratory distress syndrome, necrotizing enterocolitis, and severe intraventricular hemorrhage, one of the short-term goals of labor inhibition therapy is to achieve a 24- to 48-hour delay to administer glucocorticoids. Another short-term goal may be to transfer the antepartum patient to a tertiary care facility for a higher level of neonatal intensive care. There are numerous long-term goals of labor inhibition therapy, but it is unclear if these goals can be achieved. One goal is to maintain labor suppression for a sufficient time to enable the fetus to mature in utero and, thus, to reduce the risk of mortality and morbidity. Another long-term goal of prolonged labor suppression is to reduce the duration of hospital stay as well as the number of hospital admissions for recurrent preterm labor.

**Criteria for Labor Inhibition**

Prior to initiating a discussion of labor inhibiting agents, the prerequisites for labor inhibition must be reviewed. These criteria include:

1. A diagnosis of preterm labor.
2. A gestational age greater than 15 weeks and less than 34 weeks (or the gestational age when perinatal morbidity is too low to justify labor inhibition).
3. An absence of medical or obstetrical contraindications to labor inhibition (Table 1.).
4. An absence of contraindications to specific labor inhibiting agents (This will be discussed in later sections while addressing the specific tocolytic classes.)

The accuracy in diagnosing preterm labor is poor. Since the biochemical changes in the myometrium and cervix that characterize the onset of the parturitional process cannot be ascertained directly, the diagnosis of preterm labor is based on the surrogates of contractions and cervical dilation and effacement. Consequently, the diagnosis is often incorrect. As many as 50–70% of subjects with the clinical diagnosis of preterm labor who are treated with placebo deliver at term. False-negative diagnoses are not infrequent with an 18% rate of preterm birth in women who were discharged without treatment after evaluation for possible preterm labor. Reasonable criteria for the diagnosis of preterm labor include documented uterine contractions (four in 20 minutes for 1 to 2

<table>
<thead>
<tr>
<th>Contraindications to Preterm Labor Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine fetal demise</td>
</tr>
<tr>
<td>Fetal anomaly incompatible with life</td>
</tr>
<tr>
<td>Fetal distress</td>
</tr>
<tr>
<td>Severe intrauterine growth restriction</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Severe maternal hemorrhage</td>
</tr>
<tr>
<td>Eclampsia or severe preeclampsia</td>
</tr>
</tbody>
</table>
hours) and intact membranes with documented cervical change, cervical effacement of 80%, or cervical dilation of greater than 2 cm. However, the symptoms of preterm labor are nonspecific and not necessarily those of labor at term. Patients may report symptoms of pelvic pressure, increased vaginal discharge, backache, and mild cramping that may also occur in normal pregnancy. The difficulty in accurately and consistently diagnosing preterm labor is a major limitation in evaluating and comparing the efficacy of various tocolytic agents. Therefore, any assessment of therapeutic efficacy can only be accurately judged by comparison with placebo.

The gestational age range at which labor inhibition should be instituted is also ill-defined. Theoretically, tocolysis could be undertaken as early as 15 weeks gestation when the risk of chromosomal abnormality decreases to less than 5%. However, many clinicians use 20 weeks as the earliest gestational age at which pharmacologic therapy is given. The upper gestational age cutoff is best determined by the risk of neonatal death or morbidity. Although less than a 37-week gestation is considered preterm, the current risks of neonatal morbidity and mortality at 32- and 34-week gestation approach those of term infants. Thus, the inclusion criteria for gestational age is another confounding factor when comparing studies that evaluate tocolytic efficacy.

**Mechanisms of Myometrial Contractility**

An understanding of the mechanism of uterine contractions is fundamental to the discussion of currently used tocolytic agents. The two major determinants of myometrial contractility are the intracellular calcium concentration and the activity of the calcium-dependent enzyme, myosin light chain kinase (MLCK). Figure 1 shows the mechanism by which these two determinants are regulated.

Increased intracellular calcium binds with calmodulin. This complex activates MLCK, which then phosphorylates myosin. Phosphorylated myosin then interacts with actin resulting in muscle contraction.

There are two major sites at which cytoplasmic-free calcium is regulated: (1) the plasma membrane and (2) the intracellular storage sites. The sarcoplasmic reticulum is the main intracellular site of calcium sequestration.

The various classes of tocolytic agents act directly on the myocyte by reducing intracellular calcium, activating cyclic adenosine monophosphate, inhibiting production of prostaglandins, or blocking the oxytocin receptor. The ultimate result is to prevent myosin-actin interaction rendering the myometrium unresponsive to stimulation.

**Efficacy of Tocolytic Agents**

If an evidence-based approach is used to evaluate the efficacy of tocolytic agents, one must consider the significant variation in the diagnosis of preterm labor, use of glucocorticoids and antibiotics, and inclusion of patients with ruptured membranes, infection, and bleeding. The placebo-controlled trial is the gold standard by which to judge a labor inhibiting agent because all the potential biases noted above are minimized. Randomized trials, that compare two labor-inhibiting agents commonly suffer from inclusion of women who are not at risk for preterm delivery and from small sample size. The risk of a type II error is high in such cases (ie, treatment is thought to be of no benefit when it actually is). Observational human studies, animal studies, and in vitro studies are of limited value in evaluating the efficacy of specific tocolytic agents, but may provide useful information about side effects, physiologic, and pharmacologic responses. In this discussion, the authors focus on the highest quality clinical studies available (ie, the placebo-controlled trial) to assess the efficacy of each class of tocolytic agent.

Beta-adrenergic receptor agonists, pros-
Taglandin inhibitors, and oxytocin antagonists are the only tocolytic classes that have been shown to be efficacious in randomized placebo-controlled trials. Ritodrine, a beta-agonist, has been shown to be superior to placebo in delaying delivery 24 and 48 hours. Meta-analysis of randomized controlled trials of beta-mimetic agents confirms not only short-term delay in delivery, but also suggests that treatment may reduce the frequency of preterm birth and low-birth weight. Prostaglandin synthetase inhibitors, specifically, indomethacin has been shown in two randomized, controlled trials to be superior to placebo in delaying delivery.

The oxytocin receptor antagonist, atosiban, has also been demonstrated in a randomized trial to delay delivery longer than placebo. Magnesium sulfate, the tocolytic agent most widely used in the United States, has also been studied in a randomized placebo-controlled fashion. Interestingly, it has been demonstrated to be clinically ineffective in delaying delivery. There have been no randomized placebo-controlled studies using the calcium channel blockers for tocolysis. However, several comparison randomized, controlled trials suggest the delay to delivery comparable to that of intravenous ritodrine. Recent meta-analysis of studies comparing nifedipine and beta-adrenergic agonists suggests that nifedipine is more effective in delaying delivery for more than 48 hours and overall time to delivery, reducing neonatal morbidity with fewer neonatal intensive care unit admissions, and lowering the incidence of

**FIG. 1.** Mechanisms of myometrial contractility. See text for details. AC-adenylate cyclase, CaM-calmodulin, Ca-calcium, cAMP-cyclic adenosine monophosphate, cGMP-cyclic guanosine monophosphate, GC-guanylate cyclase, Gs-guanylyl nucleotide regulatory protein, MLCK-myosin light chain kinase, NO-nitric oxide, PI-phosphatidylinositol, IP3-inositol triphosphate.
respiratory distress. However, these benefits are lost when the trial with the largest number of subjects is eliminated.

Transdermal nitroglycerin, a nitric oxide donor, was superior to placebo in delaying delivery for more than 48 hours in a small pilot study. More recent studies with a larger sample size compared nitric oxide donors with other tocolytic agents. Randomized comparison of intravenous nitroglycerin and magnesium sulfate revealed more tocolytic failures with nitroglycerin. In the largest multicenter randomized, controlled study of nitric oxide donors, transdermal glyceryl trinitrate was comparable to ritodrine in delaying delivery for 48 hours, but there was no significant difference between these agents in the primary outcome measure, percentage prolongation of gestation to 37 weeks.

**Labor Inhibiting Agents**

**BETA-ADRENERGIC RECEPTOR AGONISTS**

Like the endogenous catecholamines epinephrine and norepinephrine, this class of drugs stimulate beta-adrenergic receptors in the uterus and other organs. There are two types of beta-adrenergic receptors in humans. Beta-1 adrenergic receptors predominate in the heart, small intestine, and adipose tissue. Beta-2 adrenergic receptors are found in smooth muscle of the uterus, blood vessels, diaphragm, and bronchioles. Ritodrine, terbutaline, salbutamol, fenoterol, and hexoprenaline are more selective for the beta-2 adrenergic receptor. Ritodrine and terbutaline will be discussed in detail as these agents have been studied most extensively.

**Mechanism of Action**

The myometrial plasma membrane contains primarily beta-2 type receptors. The beta-agonist binds to its membrane receptor and this complex acts via the guanylyl nucleotide regulatory protein to activate adenylate cyclase. The resultant increase in cytoplasmic cyclic adenosine monophosphate decreases intracellular free calcium and directly inhibits MLCK. Decreased activity of MLCK decreases phosphorylation of myosin and results in decreased myocyte contractility (Fig. 1). Continued exposure to beta-adrenergic receptor to the beta-agonist leads to a decrease in organ response, termed tachyphylaxis. This may be secondary to the desensitization and down-regulation of membrane receptors. The rapidity and magnitude of these receptor changes and reduced response may be dose-related.

**Maternal Side Effects**

While the beta-adrenergic receptor agonists used for labor inhibition are beta-2 selective, they can stimulate beta-1 receptors and produce side effects that are often dose-related and consequently most apparent during intravenous administration. Stimulation of beta-1 receptors increases heart rate and stroke volume and causes lipolysis and intestinal smooth muscle relaxation. Stimulation of the beta-2 adrenergic receptor leads to uterine relaxation, muscle glycogenolysis, vasodilation, and bronchodilation. Beta-1 adrenergic receptor mediated cardiovascular and metabolic effects decrease with prolonged therapy, but not necessarily in the same time frame as the beta-2 adrenergic receptor mediated effects. Thus, myometrial tachyphylaxis may not mirror cardiovascular or metabolic tachyphylaxis.

Maternal cardiovascular side effects seen with beta-adrenergic agents include hypotension, tachycardia, and cardiac arrhythmias. The activation of beta-2 adrenergic receptors leads to vasodilation resulting in diastolic hypotension. This results in a reflex compensatory increase in heart rate, stroke volume, cardiac output, and increased systolic blood pressure. There are also some direct beta-1 adrenergic receptor mediated inotropic and chronotropic effects. Although the overall incidence of cardiac arrhythmias is low, supraventricular tachycardia without hemodynamic compromise is the most commonly seen arrhythmia.
Electrocardiographic changes suggestive of ischemia such as ST depression, T-wave flattening or inversion, and prolonged QT interval have been noted. Myocardial ischemia has been suspected with beta-agonist use. However, these electrocardiographic changes are likely associated with beta-agonist-induced tachycardia and hypokalemia and are not associated with elevations in cardiac isoenzymes and usually resolve when therapy is stopped.

Other maternal symptoms include chest pain, shortness of breath, palpitations, tremor, nausea and vomiting, headaches, nervousness, and anxiety. These symptoms are greatest when the infusion rate is increasing or at its maximum.

In the past, the incidence of pulmonary edema has been reported to be up to 5% with parenteral beta-agonist therapy. The pathophysiology of this serious complication has not been well-defined. The etiology may be multifactorial, including tachycardia, elevated cardiac output, excessive volume expansion, decreased plasma oncotic pressure, and increased vascular permeability secondary to infection. Cardiogenic dysfunction does not appear to be responsible. The incidence of pulmonary edema appears to be extremely low when fluid intake, drug dose, and duration of beta-mimetic therapy are kept to a minimum.

Metabolic effects of beta-adrenergic receptor agonists include alterations in glucose, insulin, potassium, and lactic acid. Parenteral administration of beta-agonists results in an acute rise in plasma glucose concentrations. This is likely mediated by direct beta-adrenergic stimulation of the maternal pancreas to secrete glucagon, which in turn results in gluconeogenesis and glycogenolysis. The serum potassium decreases during the first few hours of parenteral infusion but then normalizes to preinfusion levels with prolonged therapy. Replacement is rarely needed. It is recommended that glucose and serum potassium levels be monitored during infusion.

**Fetal/Neonatal Effects**

Beta-agonists cross the placenta and may cause physiologic changes in the fetus and neonate similar to those seen in the mother. Fetal heart rate elevation above preinfusion levels during maternal beta-mimetic therapy is not uncommon. The beta-2-specific agonists do not significantly alter uteroplacental blood flow, fetal blood gases, fetal acid/base status, or neonatal Apgar scores. Hyperinsulinemia with hypoglycemia can be seen in the neonate, but there are no apparent long-term neurologic, behavioral, or psychologic sequelae.

**Contraindications**

Based on the above outlined pharmacologic effects, beta-agonists should be avoided or used with extreme caution in women with cardiac disease, untreated hyperthyroidism, and uncontrolled diabetes mellitus. Women with controlled diabetes may require serial evaluations of glucose, potassium, and urine ketones. Parenteral insulin infusion may be warranted.

**Representative Agent: Pharmacology/ Dosage and Administration**

**Ritodrine**

Ritodrine is the only drug approved by the Food and Drug Administration for the inhibition of preterm labor, but it is no longer available because the manufacturer chose to withdraw it from the market. It can be administered intravenously, intramuscularly, or orally. The pharmacokinetics of ritodrine have been extensively studied and described. Since the other beta-adrenergic receptor agonists have not been studied as extensively in pregnant women, a review of the pharmacologic behavior of ritodrine is useful as a representative of the beta-adrenergic receptor agonist class. Ritodrine is metabolized in the liver and excreted in the urine. There is an initial half-life of 6 to 9 minutes followed by a second half-life of 2 to 3 hours and elimination time of 2.5 hours. It is recommended that ritodrine be administered intravenously for acute tocolysis to allow maximal bioavailability.
ever, when administered intramuscularly at a dose of 5 to 10 mg every 2 to 4 hours few side effects are seen (unpublished data). The authors have recommended that for intravenous administration, the infusion begin at 50 µg/min and increase every 20 minutes until uterine quiescence is achieved, unacceptable side effects occur, or a maximum infusion rate of 350 µg/min is reached. Once labor is inhibited, the labor inhibiting infusion rate is maintained for 60 minutes and then decreased by 50 µg/min every 30 minutes until the lowest effective rate is achieved (but not less than 50 µg/min). The lowest effective infusion rate is then arbitrarily maintained for 12 hours.33 If labor recurs within this 12-hour period, the process is repeated. Pharmacokinetic studies in pregnant women have demonstrated large differences in hepatic metabolism of ritodrine among subjects, so plasma concentrations vary widely with any given dosage. The regimen described minimizes the impact of these differences and should reduce side effects. The pharmacologic principles above also apply to other beta-adrenergic receptor agonists.

Terbutaline
Terbutaline is available in intravenous, subcutaneous, and oral formulations. It is not approved by the Food and Drug Administration for specific use in preterm labor, but there exists significant evidence for its safety and efficacy. The infusion regimen philosophy for terbutaline is similar to ritodrine at the authors’ institution. The intravenous infusion rate of terbutaline is generally started at 2.5 to 5 µg/min and increased every 20 minutes by increments of 5 µg/min to a maximum of 25 µg/min. Once labor is inhibited, the labor inhibiting rate is sustained for 60 minutes and thereafter reduced by 2.5 µg/min every 30 minutes until the lowest effective dose is established. This rate is maintained for 12 hours. Higher rates have been used by others. Subcutaneous administration is also used in acute tocolysis with a typical dose of 0.25 mg subcutaneously every 1 to 6 hours with repeated dosing titrated to uterine activity and maternal side effects. Oral dosing is empiric for the prevention of recurrent preterm labor. Generally, a dose of 5 mg every 4 hours is given and has been shown to be superior to oral ritodrine in preventing recurrent preterm labor and prolonging pregnancy.26

MAGNESIUM SULFATE

Mechanism of Action
The precise mechanism by which magnesium sulfate inhibits contractility is not well understood. It appears to function via the competitive inhibition of calcium at the voltage operated calcium channels at the plasma membrane leading to hyperpolarization of the membrane. Magnesium may directly compete with intracellular calcium by decreasing the calcium-calmodulin binding affinity to MLCK,34–36 thereby inhibiting myometrial contractility (Fig. 1).

Maternal Side Effects
Symptoms commonly experienced with magnesium sulfate infusion include flushing, perception of warmth, nausea, emesis, dizziness, blurry vision, nystagmus, and lethargy. These symptoms are maximal during the magnesium sulfate bolus infusion, but may persist for the duration of therapy. Pulmonary edema has been described in up to 1% of patients receiving magnesium sulfate tocolysis.37 Serious toxic maternal side effects may occur at serum levels just slightly greater than therapeutic levels. Loss of patellar reflexes occurs at serum levels of 7 to 10 mEq/L and respiratory depression occurs at levels of 10 to 12 mEq/L. Therefore, patients must be monitored closely with frequent vital signs, urine output, reflexes, and pulmonary status. Calcium gluconate (1-g intravenously) can be used as an antidote and ventilatory support may be necessary in severe cases.

Fetal/Neonatal Effects
The transplacental transfer of magnesium sulfate may result in a nonreactive heart rate or decreased fetal breathing movements.38
At delivery, neonatal concentrations are 10% lower than maternal concentrations. Neonates may show evidence of hypotonia and lethargy secondary to hypermagnesemia. This problem is more pronounced in the premature neonate because of decreased renal clearance. Prolonged magnesium sulfate infusion to the mother may be associated with demineralization of bones. Some epidemiologic data have suggested a possible fetal neuroprotective effect and decreased incidence of cerebral palsy with antenatal magnesium sulfate exposure. A concern has been raised for increasing perinatal mortality associated with high doses of magnesium sulfate, but this concern has not been supported. Currently, there is an ongoing study by the Maternal-Fetal Medicine Network to further evaluate fetal and neonatal effects of magnesium sulfate.

**Contraindications**

Due to the risk of cardiorespiratory depression, magnesium sulfate infusion should be avoided in patients with myasthenia gravis, heart block, and myocardial damage. Patients with renal insufficiency should be monitored closely for evidence of toxicity.

**Pharmacology/Dosage and Administration**

Magnesium sulfate can be administered via the intravenous, intramuscular, and oral routes, and it is excreted primarily by the kidneys. The recommended dosing consists of an initial loading dose of 6 g intravenously over 20 minutes followed by continuous infusion of 3 to 4 g/h. Maternal toxicity can be assessed by clinical means (eg, absence of deep tendon reflexes) or by evaluation of serum magnesium concentrations. Fluid restriction and close monitoring of fluid status is recommended. Oral magnesium gluconate or oxide are available, however, the efficacy of these preparations is questionable. Serum levels with oral therapy tend to be subtherapeutic and side effects such as diarrhea are significant. Oral preparations should not be used for acute tocolysis.

**PROSTAGLANDIN SYNTHETASE INHIBITORS**

**Mechanism of Action**

Prostaglandins have been shown to have a significant role in the labor process. Prostaglandins stimulate myometrial gap junction formation and raise intracellular calcium levels by increasing calcium flux across the cell membrane and stimulating calcium release from the sarcoplastic reticulum. Prostaglandins are formed by the conversion of arachidonic acid by the cyclooxygenase enzyme. Prostaglandin synthesis inhibitors, like indomethacin, are reversible competitive inhibitors of cyclooxygenase, thereby reducing the levels of prostaglandins and diminishing myometrial contractility (Fig. 1).

**Maternal Side Effects**

The maternal side effects seen with indomethacin are minimal. Nausea, dyspepsia, and vomiting are seen in approximately 4% of treated women. Hemodynamic alterations are minimal. Maternal contraindications include coagulation disorders, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma in aspirin-sensitive patients.

**Fetal/Neonatal Effects**

The primary concern with indomethacin has been constriction of the fetal ductus arteriosus and oligohydramnios. Premature narrowing or closure of the ductus arteriosus can lead to pulmonary hypertension, tricuspid regurgitation, and persistent fetal circulation. There were no cases of premature closure of the ductus or persistent fetal circulation in reports of neonatal outcome in more than 500 infants exposed to short-term indomethacin treatment in utero previous to 34-week gestation. However, these complications have been reported when exposure to indomethacin exceeds 48 hours. Ductal constriction appears to be gestational...
age dependent; therefore, indomethacin is not recommended after 32-week gestation. Fetal echocardiographic evaluation should be considered if the duration of therapy exceeds 48 hours.

Prostaglandin inhibitors may result in oligohydramnios by decreasing urinary output, an effect mediated by antidiuretic hormone. Oligohydramnios is reversible when the dose is decreased or discontinued.

Some reports have suggested that in utero exposure to indomethacin is a risk factor for necrotizing enterocolitis and intraventricular hemorrhage, grades III to IV. However, other studies reveal no significant increase in necrotizing enterocolitis and intraventricular hemorrhage with indomethacin tocolysis, suggesting a possible confounder based on the indication for indomethacin tocolysis.

Pharmacology/Dosage and Administration

Indomethacin can be administered orally or rectally with a 50- to 100-mg loading dose, followed by 25 mg every 4 to 6 hours. Indomethacin is metabolized extensively by the liver, and 10% is excreted unchanged in the urine. The maternal half-life is approximately 4.5 hours, but fetal blood concentrations are 50% of maternal values and the half-life in the neonate is substantially slower (14.7 hours). Frequent evaluations of amniotic fluid index and fetal cardiac function may be warranted if indomethacin is continued for longer than 48 hours.

CALCIUM CHANNEL ANTAGONISTS

Mechanism of Action

Nifedipine is the most common calcium channel blocker used for tocolysis. Calcium channel antagonists block the voltage-dependent calcium channels in the plasma membrane. They may also inhibit release of intracellular calcium from sarcoplasmic stores and increase calcium efflux from the cell. The resultant decrease in intracellular-free calcium leads to inhibition of calcium-dependent MLCK phosphorylation and results in myometrial relaxation (Fig. 1).

Maternal Side Effects

Nifedipine is a peripheral vasodilator and can result in symptoms of nausea, flushing, headache, dizziness, and palpitations. Nifedipine is also associated with a decrease in mean arterial pressure because of arteriolar smooth muscle relaxation and a reflex increase in heart rate. These changes are usually mild and less severe than seen after ritodrine treatment.

Fetal/Neonatal Effects

The primary concern with nifedipine has been its potential adverse effect on uterine and umbilical blood flow. Animal studies have been particularly concerning. In several species, nifedipine causes a decrease in uterine blood flow and fetal oxygen saturation. Fortunately, this has not been confirmed in humans. Doppler studies of fetal umbilical and uteroplacental blood flow in humans have been reassuring. Apgar scores and fetal acid-base state in the umbilical cord at delivery reveal no clear evidence of fetal hypoxia or acidosis.

Pharmacology/Dosage and Administration

Nifedipine is administered orally and is nearly completely absorbed from the gastrointestinal tract after ingestion. Maximum plasma concentrations occur within 15 to 90 minutes after oral administration. The half-life of nifedipine is 81 minutes and the duration of action is up to 6 hours. Nifedipine is almost completely metabolized in the liver and 70–80% is excreted by the kidneys. An appropriate dosing regimen of nifedipine for the treatment of preterm labor has not been demonstrated. One recommended regimen is to administer 10 mg orally every 20 minutes for up to four doses followed by 20 mg orally every 4 to 8 hours.
OXYSOCTIN RECEPTOR ANTAGONISTS

Mechanism of Action
Atosiban is a selective oxytocin-vasopressin receptor antagonist capable of inhibiting oxytocin induced myometrial contractions. The mechanism appears to be competitive inhibition of oxytocin receptors in the myometrium and decidua. Oxytocin stimulates contractions by stimulating the conversion of phosphatidylinositol to inositol triphosphate. This binds to a protein in the sarcoplasmic reticulum leading to calcium release into the cytoplasm. Thus, oxytocin antagonists result in a decrease in intracellular-free calcium that results in decreased myometrial contractility (Fig. 1).

Maternal Side Effects
Atosiban has the advantage of being highly organ-specific for the myometrium and fetal membranes, thus minimizing side effects. In placebo-controlled studies, side effects were similar in the atosiban and placebo groups with the exception of a higher proportion of injection-site reactions in women receiving atosiban.11

Fetal/Neonatal Effects
Atosiban crosses the placenta with a mean maternal-fetal ratio of 12. In one trial there was a suggestion of a higher rate of fetal-infant death in the atosiban group. While the adverse effect caused by atosiban cannot be excluded, it should be noted that these fetal-infant deaths were associated with infection and extreme prematurity. Despite randomization, most of the preterm infants (less than 28 weeks) were assigned to the atosiban group.11

Contraindications
There are no absolute maternal contraindications described. It has been suggested to limit use to greater than 28-week gestation.

Pharmacology/Dosage and Administration
Atosiban has not been approved by the Food and Drug Administration and is presently not available for use in the United States. This agent is used in Europe. Atosiban is a nonapeptide that is administered intravenously for acute tocolysis. Initial and terminal half-lives are 13 and 102 minutes, respectively. The regimen used in the largest randomized studies begins with an intravenous bolus of 6.75 mg followed immediately by a 300 µg/min intravenous infusion for 3 hours, and then 100 µg/min for up to 45 hours.11

NITRIC OXIDE DONORS

Mechanism of Action
Nitroglycerin is frequently used in pregnancy for rapid uterine relaxation during breech extraction, uterine inversion, retained placenta, and version. Nitric oxide donors, like nitroglycerin, activate the cyclic guanosine monophosphate pathway involved in smooth muscle relaxation. The activation of cyclic guanosine monophosphate results in decreased intracellular-free calcium that leads to decreased activation of MLCK and decreased myometrial contractility (Fig. 1).

Maternal Side Effects
The primary side effect is maternal hypotension related to smooth muscle relaxation of blood vessels. Symptoms included headache, light-headedness, nausea, and vomiting. Preexisting maternal hypotension is suggested as an exclusion criterion in studies.

Fetal/Neonatal Effects
There are no clear data indicating that nitric oxide donor therapy adversely affects the infant. There are no significant differences in neonatal hemodynamics, Apgar scores, or umbilical cord gases in cases of nitroglycerin exposure at elective cesarean delivery compared with controls.62

Pharmacology/Dosage and Administration
Nitric oxide donors have been administered intravenously and by transdermal patch. The
dosing and administration have varied in studies, but are primarily titrated to cessation of contractions while maintaining adequate blood pressure. The transdermal regimen used in the largest multicenter study was an initial 10-mg transdermal glyceryl trinitrate patch applied to the skin of the abdomen. If, after 1 hour, there was no reduction in contraction frequency or strength, an additional patch was applied. No more than two patches were administered simultaneously and these were left in place for 24 hours after which they were removed and patient reassessed.21

**Combination Tocolytic Therapy**

Few studies have assessed the concomitant use of two labor inhibiting agents. Two randomized trials address combination versus single agent therapy with ritodrine and magnesium. While there was a suggestion of improved efficacy with the combined ritodrine and magnesium regimen,63 this has not been supported by other trials.64 Side effects with this combined regimen were found to be significantly increased. Neuromuscular blockade has been reported with magnesium and nifedipine combined tocolytic therapy.65 Given the limited and conflicting data on efficacy and safety, the authors do not recommend the use of combined therapy for labor inhibition.

**Maintenance Tocolytic Therapy**

Maintenance tocolytic therapy refers to the continued use of a tocolytic agent after successful inhibition of an acute episode of preterm labor has been achieved. Commonly used agents are terbutaline, magnesium oxide or gluconate, and nifedipine. Oral magnesium is seldom used secondary to the side effect of diarrhea. In placebo-controlled trials none of the agents evaluated reduced perinatal mortality. However, the sample size in all studies was too small to detect any benefit in this uncommon outcome. Several placebo-controlled trials have demonstrated a benefit of beta-agonists and one trial documented a benefit of atosiban in prolonging pregnancy and reducing the recurrence of preterm labor.66–68 More recent studies with beta-adrenergic receptor agonists and one trial with nifedipine did not find any benefit in pregnancy prolongation.69–74 These more recent studies are seriously impacted by the fact that the mean gestational age at delivery in the women receiving placebo was 36 weeks. This suggests that women recruited to these studies were not at risk for preterm birth and that the studies can not be relied upon to judge the efficacy of any treatment.

**Practical Approach to Pharmacologic Inhibition of Preterm Labor**

Based on placebo-controlled studies, the beta-adrenergic receptor agonists (ritodrine and terbutaline), indomethacin, and atosiban appear to be effective labor inhibiting agents. However, neither ritodrine nor atosiban is available for use in the United States. Terbutaline is available, but not recommended by the manufacturer for use as a labor inhibiting agent. Terbutaline, like all beta-adrenergic receptor agonists, is associated with potentially serious side effects and requires close supervision of the patient and the infusion rate. Indomethacin is effective, but is limited by its impact on the fetus. Thus, of the available options for labor inhibition, none is optimal. It is because of these limitations that magnesium sulfate and nifedipine have become the most commonly used agents for labor inhibition therapy. The choice of these labor inhibiting agents is based on data indicating a superiority over beta-adrenergic receptor agonists in terms of side effects, toxicity profile and importantly, ease of use. Magnesium sulfate is the most commonly used agent for treating preterm labor despite the fact that the largest placebo
controlled trial and meta-analyses indicate the drug is no more effective at stopping preterm labor than placebo. However, nifedipine has not been compared with placebo but has been compared with beta-agonists and indomethacin. Meta-analysis suggests comparable efficacy to ritodrine. These studies do show a better safety profile with nifedipine than the beta-agonists and it is clearly easier to use. Nifedipine, unlike magnesium sulfate, is effective in suppressing contractions induced by oxytocin and prostaglandins or occurring spontaneously both in vitro and in animal models.\textsuperscript{75–77}

Thus, of those agents available to the clinician, it is the authors’ view that because of their proven efficacy, terbutaline (or another beta-adrenergic receptor agonist) or indomethacin should be the first line agent used for labor inhibition. Nifedipine or magnesium sulfate are viewed as second line agents because there is no proof they are more effective than placebo. These agents can be used if the first line agents fail, are not tolerated, or if there is a specific contraindication to their use. Nifedipine is preferred over magnesium sulfate because of abundant data in animal studies demonstrating in vivo effectiveness in suppressing myometrial contractility. Nitric oxide donors should be viewed as potentially useful agents, but further study is required before a general recommendation for their use can be made.

Conclusion
The morbidity and mortality related to premature labor and delivery remains a significant problem. Our present understanding of the varied etiologies of preterm labor and the intricacies of the parturitional cascade are limited. This is reflected in the use of pharmacologic agents aimed at paralyzing the uterus at the level of the myocyte, rather than inhibiting or reversing the fundamental problem that led to the preterm labor. The advantages and limitations of each tocolytic class must be recognized. Candidates for labor inhibition must be evaluated and chosen carefully with the goals of labor inhibition clearly defined in each situation. The choice of pharmacologic agent must be tailored to the individual patient with particular attention to side effects and contraindications to these potent medications. Maternal and fetal status should be closely monitored with frequent reassessment during therapy to identify the evolution of contraindications to labor inhibition, such as infection, and specific side effects and toxicities. Labor inhibition therapy should be stopped if the risks outweigh the benefits of continuing therapy.

The future direction of labor inhibition includes elucidating the mechanisms of the preterm labor process, identifying the patient at risk for preterm labor and prevention, targeting pharmacologic therapy to an earlier point in this cascade to achieve better maternal and fetal outcomes, and well-designed controlled trials to assess the efficacy of labor inhibiting agents.

References


