Preterm birth is defined as birth before the completion of 37 weeks of gestation. The frequency of preterm birth in the United States increased from 10.7% in 1992 to 12.3% in 2003. Preterm births can be categorized as those undertaken because of a specific indication or as spontaneous preterm births. Indicated preterm births occur when a health care provider delivers a baby because of medical or obstetrical complications that jeopardize the health of the mother or the fetus. Spontaneous preterm births occur as a consequence of spontaneous preterm labor or preterm rupture of fetal membranes before the onset of labor. This review focuses on therapeutic strategies for the prevention and treatment of spontaneous preterm labor and delivery.

Mechanisms of Preterm Labor

Preterm parturition is not necessarily the result of premature physiologic activation of processes that normally occur at term; rather, preterm labor commonly results from pathologic processes. Regardless of when parturition occurs in gestation, the process itself is generally heralded by synchronous changes in the myometrium and cervix that permit expulsion of the fetus. The molecular processes underlying parturition were recently comprehensively reviewed by Smith in the Journal.

Pathophysiology of Preterm Birth
Spontaneous preterm birth is a physiologically heterogeneous syndrome. The cascade of events that culminate in spontaneous preterm birth has several possible underlying pathways. Four of these pathways are supported by a considerable body of clinical and experimental evidence: excessive myometrial and fetal membrane overdistention, decidual hemorrhage, precocious fetal endocrine activation, and intrauterine infection or inflammation. These pathways may be initiated weeks to months before clinically apparent preterm labor. The processes leading to preterm parturition may originate from one or more of these pathways; for example, intrauterine infection or inflammation and placental abruption often coexist in preterm births. Decidual hemorrhage and intrauterine infection share several inflammatory molecular mechanisms that contribute to parturition. Our understanding of the nature of the molecular cross-talk among these pathways is in its infancy. The etiologic heterogeneity of preterm birth adds complexity to therapeutic approaches. Although the ultimate clinical presentation of women with preterm labor may appear to be homogeneous, the antecedent contributing factors probably differ considerably from woman to woman.

Certain clinical presentations and risk factors preferentially predispose the maternal–fetal unit to preterm birth in a pathway-specific fashion. For example, women with multifetal pregnancies are at particular risk for preterm birth, presumably owing to pathologic uterine overdistention. Women with preterm rupture of membranes or preterm labor at a very early gestational age (e.g., 24 to 28 weeks) are at increased risk for having underlying intrauterine infection; the precise nature of such predispositions is not known at this time.

Diagnosis of Acute Preterm Labor

For decades, the clinical diagnosis of preterm labor has been based on the presence of regular, painful uterine contractions accompanied by cervical dilatation or effacement. If framed as screening criteria for the outcome of “preterm birth,” such factors generally demonstrate poor sensitivity and specificity. The identification of women with preterm contractions who will actually deliver preterm is an inexact process. A systematic review showed that in approximately 30% of patients, preterm labor resolved spontaneously. In subsequent studies, 50% of patients who were hospitalized for preterm labor actually delivered at term. The inability to distinguish accurately between women in “true” preterm labor and those in “false” labor has greatly hampered the assessment of therapeutic interventions, since up to 50% of untreated (or placebo-treated) subjects do not actually deliver preterm.

Parturition is characterized by molecular changes in the myometrium, cervix, and other gestational tissues. These changes cannot routinely be detected clinically; thus, surrogate markers (e.g., either uterine contractions or cervical dilatation, softening, and shortening) are used as indicators of the biochemical events previously described. Unfortunately, these clinical
surrogates are imprecise markers of an activated process of parturition. For example, both uterine contractions and cervical changes are common, especially in parous women who do not deliver prematurely. Measurement of a biochemical marker, fetal fibronectin, obtained from vaginal fluid, and ultrasonography of the cervix used either alone or together to predict the risk of preterm delivery appear to hold promise for improving the diagnostic accuracy beyond clinical impression alone.

Treatment Strategies

Because the contracting uterus is the most frequently recognized antecedent of preterm birth, stopping contractions has been the focus of therapeutic approaches. This strategy is based on the naive assumption that clinically apparent contractions are commensurate with the initiation of the process of parturition; by logical extension, the successful inhibition of contractions should prevent delivery. The inhibition of myometrial contractions is called tocolysis, and a drug administered to that end is referred to as a tocolytic agent. The first and only agent approved for tocolysis by the Food and Drug Administration (FDA) was ritodrine. The approval of that drug in 1980 initiated a period of intense clinical exploration for other agents that might inhibit uterine contractions. The FDA has not approved any of the additional agents for the indication of tocolysis. Limited pharmacologic information about these drugs in pregnancy exists. Few placebo-controlled trials involving tocolytic agents have been conducted, and most agents were assessed by comparing them with ritodrine as the “gold standard.”

In the three decades since ritodrine was approved, none of these agents have lived up to the expectation that prematurity rates would be reduced by tocolysis. Although more than 80% of women with preterm labor who are treated with tocolytic agents have their pregnancies maintained for 24 to 48 hours, few data suggest that tocolysis maintains pregnancy for a longer period. Tocolysis probably has limited success because currently available tocolytic drugs do not alter the fundamental process leading to myometrial activation.

Although therapy that inhibits contractions does not prevent preterm birth, several goals may still be achieved. One critical goal is to delay delivery long enough to allow for the administration of corticosteroids, which reduces the risks of the neonatal respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and overall perinatal death. The initial benefit of corticosteroid therapy usually occurs approximately 18 hours after administration of the first dose; the maximal benefit occurs about 48 hours after the first dose. Thus, treatment of acute preterm labor may allow time for the administration and therapeutic effect of corticosteroids. Another major goal of treating acute preterm labor is to permit safe transport of the mother, if indicated, to a regional facility specializing in the care of premature neonates.
A variety of agents are used for the inhibition of acute preterm labor. Although these agents differ with respect to the mechanism of action, dose, route of administration, safety, and side-effect profile for mother and baby, the whole class of labor-inhibiting drugs is largely ineffective, because an attempt to paralyze the myometrium does not address the root stimulus of preterm labor in a cause-specific fashion. The labor-inhibiting agents used abrogate myometrial contractility by one of two major pathways: through generation or alteration of intracellular messengers or by inhibiting the synthesis or blocking the action of a known myometrial stimulant (Figure 1). Drugs affecting intracellular messengers include β-adrenergic-receptor agonists, agents that generate nitric oxide (nitric oxide donors), magnesium sulfate, and calcium-channel blockers. Drugs blocking the synthesis or action of known myometrial stimulants include prostaglandin-synthesis inhibitors and oxytocin antagonists. Figure 1 illustrates the mechanisms of action of these agents on the myometrial cell.

The ultimate goal in preventing preterm birth is to eliminate the risks of neonatal complications and death. However, individual trials of the efficacy of tocolytic agents have been too small to assess these outcomes. Surrogate or secondary outcomes that have been used in lieu of neonatal morbidity are the prolongation of pregnancy, frequency of preterm birth, and gestational age at birth. That being said, several types of agents are available.

**β-Adrenergic-Receptor Agonists**

The β-adrenergic-receptor agonists cause myometrial relaxation by binding to β₂-adrenergic receptors and subsequently increasing the levels of intracellular cyclic AMP. An increase in intracellular cyclic AMP activates protein kinase, which inactivates myosin light-chain kinase, thus diminishing myometrial contractility.²²,²³,²⁴ Available meta-analyses suggest that β-adrenergic-receptor agonists delay delivery and reduce the frequency of preterm birth and low birth weight, as compared with placebo.²⁵ For example, a meta-analysis by Anotayanonth et al.²⁵ considered 11 randomized, controlled trials involving 1320 women that compared β-adrenergic-
receptor agonists with placebo. Among the women with preterm labor who received β-adrenergic-receptor agonists, fewer gave birth within 48 hours (relative risk, 0.63; 95% confidence interval [CI], 0.53 to 0.75), but there was no decrease in the number of births within 7 days. This meta-analysis also showed no benefit of β-adrenergic-receptor agonists with respect to either the rate of perinatal death (relative risk, 0.84; 95% CI, 0.46 to 1.55) or, in five trials enrolling 1174 women, the rate of neonatal death (relative risk, 1.00; 95% CI, 0.48 to 2.09). Eight trials enrolling 1239 women did not show any significant effect of β-adrenergic-receptor agonists with respect to the neonatal respiratory distress syndrome (relative risk, 0.87; 95% CI, 0.71 to 1.08).

Thus, despite the prolongation of pregnancy and an apparent reduction in the immediate risk of preterm birth, a significant reduction in perinatal morbidity and mortality has not been demonstrated. The lack of evidence for a neonatal benefit may be an issue of sample size and may reflect the inclusion criteria for most studies of labor-inhibiting therapy. Indeed, although deliveries at gestational ages from 34 to 36 weeks are preterm, babies born at these later preterm gestational ages do not typically have high rates of complications. Because a poor neonatal outcome at later preterm gestational ages is unusual, it is difficult to detect an effect on morbidity in studies involving small numbers of subjects.

Nitric Oxide Donors

Nitric oxide, a vasodilator that is essential for the maintenance of normal smooth-muscle tone, is produced in a variety of cells. Nitric oxide is synthesized during the oxidation of L-arginine (an essential amino acid) to L-citrulline. This reaction is catalyzed by the enzyme nitric oxide synthase, which exists in several isoforms. Both inducible (type 2) and brain (type 1) nitric oxide synthases are expressed in myometrial cells and blood-vessel endothelial cells, whereas endothelial (type 3) nitric oxide synthase is expressed exclusively in blood-vessel endothelial cells. The interaction between nitric oxide and soluble guanylyl cyclase, which is present in nearby effector cells, represents a widespread signal-transduction mechanism that couples diverse extracellular stimuli of nitric oxide formation to the synthesis of cyclic guanosine monophosphate (cGMP) in target cells. The increase in cGMP content in smooth-muscle cells inactivates myosin light-chain kinases, leading to smooth-muscle relaxation. In a randomized comparison of intravenous nitroglycerin, which is a nitric oxide donor, and magnesium sulfate, the latter was more likely to delay delivery for at least 12 hours. However, transdermal nitroglycerin was superior to placebo in prolonging pregnancy for 48 hours in a randomized, controlled trial involving 33 women.

In the largest randomized, controlled study of tocolysis with a nitric oxide donor (involving 245 subjects), transdermal glyceryl trinitrate was similar to ritodrine with respect to delaying delivery...
for 48 hours and prolonging gestation to 37 weeks. Smith et al. randomly assigned 153 women who were in labor at 24 to 32 weeks of gestation to receive either transdermal nitroglycerin or placebo patches. The primary outcome was a composite of neonatal complications (chronic lung disease, intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis) and death. The composite outcome was significantly reduced in infants born to 74 women who received transdermal nitroglycerin, as compared with those born to 79 women who received placebo (relative risk, 0.29; 95% CI, 0.08 to 1.00; P<0.05).

Magnesium Sulfate

The basis for the clinical use of magnesium sulfate as a labor-inhibiting agent is the observation from the 1960s that the agent was associated with a reduction in human uterine contractility both in vivo and in vitro. At a pharmacologic concentration (5 mmol per liter), magnesium sulfate inhibits the contractile response and decreases the intracellular concentration of calcium in myometrial strips obtained from pregnant women in a pattern that is consistent with both extracellular and intracellular mechanisms of action. This agent hyperpolarizes the plasma membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium, which in turn reduces myometrial contractility.

However, the largest placebo-controlled, randomized trial of magnesium sulfate as a tocolytic agent did not show any benefit over placebo in the prolongation of pregnancy. A meta-analysis of 11 trials comparing the outcome in 881 women who received magnesium sulfate, placebo, or another active drug showed no significant difference in the risk of birth within 48 hours after administration of magnesium sulfate (relative risk, 0.85; 95% CI, 0.58 to 1.25). Magnesium sulfate appeared to confer no benefit with respect to the risk of preterm birth (at ≤37 weeks) or very preterm birth (at ≤34 weeks). In seven trials involving 727 infants, the risk of death (both fetal and pediatric) was increased for infants who had been exposed to magnesium sulfate (relative risk, 2.82; 95% CI, 1.20 to 6.62). Thus, the literature does not support the efficacy of magnesium sulfate, leading Grimes and Nanda to call for the discontinuation of its use as a tocolytic agent. We agree with this recommendation.

Calcium-Channel Blockers

Agents that block the calcium channel directly inhibit the influx of calcium ions through the cell membrane and the release of intracellular calcium from the sarcoplasmic reticulum. The ensuing decrease in intracellular free calcium leads to the inhibition of myosin light-chain kinase-mediated phosphorylation, which depends on calcium, and results in myometrial relaxation. Nifedipine is the agent in this class that has been used most commonly to inhibit labor, but no placebo-controlled trials have studied the efficacy and safety of the drug for this indication.
Consequently, assessment of the efficacy and safety of nifedipine for labor inhibition is based on comparative trials, with their inherent biases.

King et al. carried out a systematic review of 12 randomized, controlled trials involving 1029 women. In this meta-analysis, as compared with any other tocolytic agent (mainly beta mimetics), calcium-channel blockers reduced the number of women giving birth within 7 days after receiving treatment (relative risk, 0.76; 95% CI, 0.60 to 0.97) and before 34 weeks of gestation (relative risk, 0.83; 95% CI, 0.69 to 0.99). King et al. also noted that calcium-channel blockers appeared to reduce the frequency of the neonatal respiratory distress syndrome (relative risk, 0.63; 95% CI, 0.46 to 0.88), necrotizing enterocolitis (relative risk, 0.21; 95% CI, 0.05 to 0.96), intraventricular hemorrhage (relative risk, 0.59; 95% CI, 0.36 to 0.98), and neonatal jaundice (relative risk, 0.73; 95% CI, 0.57 to 0.93). However, the largest randomized trial of calcium-channel blockers and β-adrenergic–receptor agonist therapy (involving 185 subjects) showed the greatest improvement in outcomes with the use of calcium-channel blockers, and the inclusion of this trial might have driven the results of the meta-analysis.

Cyclooxygenase Inhibitors

Cyclooxygenase (COX, or prostaglandin synthase), which exists in two isoforms, COX-1 and COX-2, converts arachidonic acid to prostaglandin H₂, which serves as a substrate for tissue-specific enzymes; the products of these enzymes are critical in parturition. Prostaglandins enhance the formation of myometrial gap junctions and increase available intracellular calcium by raising transmembrane influx and sarcolemmal release of calcium. COX-1 is expressed constitutively in human decidua, myometrium, and fetal membranes, whereas COX-2, the inducible form, dramatically increases in the decidua and myometrium during term and preterm labor. COX inhibitors decrease prostaglandin production either by general inhibition of COX or by specific inhibition of COX-2, depending on the agent. Indomethacin, a nonspecific COX inhibitor, is the most commonly used tocolytic agent in this class.

In a recent meta-analysis of outcome data from placebo, COX inhibition (with indomethacin only) resulted in a reduction in births before 37 weeks of gestation in one trial involving 36 women (relative risk, 0.21) and an increase in gestational age (weighted mean difference, 3.53 weeks) and birth weight (weighted mean difference, 716 g) in two trials involving 67 women. As compared with the use of other active agents, the use of a COX inhibitor resulted in a reduction in births before 37 weeks of gestation in three trials involving 168 women (relative risk, 0.53).

COX-2 inhibitors have become available for clinical use more recently. Data from studies in animals suggest that COX-2 inhibitors reduce myometrial contractility and may delay preterm delivery. Other data show that COX-2 inhibitors reduce prostaglandin production in
human gestational tissues. The literature contains a case report of the use of the COX-2 inhibitor nimesulide for preterm labor, but there is insufficient evidence to recommend the use of COX-2 inhibitors for this indication.

Oxytocin-Receptor Antagonists

In normal parturition, oxytocin stimulates contractions by inducing the conversion of phosphatidylinositol triphosphate to inositol triphosphate, which binds to a protein in the sarcoplasmic reticulum, causing the release of calcium into the cytoplasm. Oxytocin-receptor antagonists compete with oxytocin for binding to receptors in the myometrium and decidua, thus preventing the increase in intracellular free calcium that occurs with receptor binding.

In a recent meta-analysis of six trials involving 1695 women, the oxytocin-receptor antagonist atosiban did not reduce the incidence of preterm birth or improve the neonatal outcome, as compared with placebo. Two of the placebo-controlled trials (involving 613 women) showed that atosiban was associated with lower birth weight (weighted mean reduction, 138 g; 95% CI, 28 to 249) and more maternal adverse drug reactions (relative risk, 4.02; 95% CI, 2.05 to 7.85) than was placebo. Two other trials included in this meta-analysis, which compared atosiban with β-adrenergic-receptor agonists in 575 infants, showed that atosiban was associated with an increase in the number of infants who weighed less than 1500 g at birth (relative risk, 1.96; 95% CI, 1.15 to 3.35). In a placebo-controlled trial by Romero et al. involving 531 subjects, atosiban was associated with an increase in deaths in the first year of life (relative risk, 6.15; 95% CI, 1.39 to 27.22). In this trial, significantly more women were randomly assigned to receive atosiban before 26 weeks of gestation than were assigned to receive placebo, a factor that could account for the excess in deaths among the babies of women who received atosiban. Given the excess fetal and infant deaths with the administration of atosiban before 28 weeks of gestation, the FDA has not approved the use of this drug for tocolysis.

Implications of Treatment

Each class of agents in the preceding discussion has a specific profile of side effects when used for the inhibition of acute preterm labor. Table 1 lists the side-effect profiles of each of these classes of drugs for both women and their fetuses or neonates. It is worthwhile to consider the safety of inhibition of preterm labor, in general. As previously noted, preterm labor, particularly at gestational ages before 32 weeks, is likely to result from intrauterine infection or bleeding. Expulsion of the fetus and placenta may limit the untoward consequences of ongoing maternal infection. It is entirely possible that inhibition of labor in this setting not only is likely to be unsuccessful at prolonging pregnancy but also may actually harm the mother by allowing blood loss to continue or infection to remain unchecked.
Current Clinical Tools and Management

Although basic and translational research have provided some understanding of the causal pathways underlying preterm birth, there are no adequate clinical tools to distinguish among the contributions of these pathways in any given patient. The treatment of acute preterm labor as a means of preventing preterm birth is analogous to the treatment of acute myocardial infarction as a means of preventing coronary artery disease. Both coronary artery disease and preterm birth are common yet complex conditions that have heterogeneous causes antedating clinically apparent disease by weeks, months, or even years. Certainly, application of an evidenced-based therapeutic approach to acute myocardial infarction has been a worthwhile effort. Yet no practitioner expects that the treatment of acute myocardial infarction will prevent coronary artery disease. Likewise, as previously noted, treatment of acute preterm labor also has some benefit with respect to the perinatal outcome but will probably do little to prevent preterm birth. However, as with cardiovascular disease, efforts to prevent prematurity should also focus on primary and secondary prevention.

Just as major efforts have been made to identify asymptomatic adults who are at risk for coronary artery disease by screening for risk factors (e.g., hyperlipidemia and hypertension), substantial work has been done to identify asymptomatic women early in pregnancy who are at high risk for preterm birth. Several clinical risk-scoring systems have been proposed, but unfortunately, such systems appear to be poor predictors of preterm birth. Screening for and treatment of asymptomatic bacteriuria can reduce the frequency of preterm birth or low birth weight by approximately 50%. Systemic biochemical markers, genital tract markers (e.g., fetal fibronectin), ultrasonographic measurement of the cervix, and identification of asymptomatic contractions with the use of a home uterine-activity monitor have all been examined as predictors of preterm birth.

The application of some or all of these screening strategies to the general obstetrical population has not been recommended for several reasons. First, any individual test has poor positive predictive value for subsequent preterm birth. Second, there are no effective, evidenced-based preventive strategies to offer women who have positive results on screening. The administration of broad-spectrum antibiotics has not prevented preterm birth among women who have bacterial vaginosis or positive results on a test for fetal fibronectin. Unfortunately, evidence-based preventive strategies along these lines are currently unavailable for women who have positive results on tests of markers that have been identified to date.

There are evidenced-based preventive strategies for women with a history of preterm birth. Although controversial, data suggest that among women who have had a previous preterm birth,
screening for and treating bacterial vaginosis reduce the risk of recurrence of preterm birth. Data from meta-analyses and a multicenter, randomized clinical trial suggest that weekly administration of 17 alpha-hydroxyprogesterone caproate in women with a previous preterm birth reduces the risk of recurrence by 33%. However, the majority of preterm births in the United States do not occur in women with a history of preterm birth. Petrini et al. projected that the administration of 17 alpha-hydroxyprogesterone caproate in eligible women in the United States might lower the overall frequency of preterm birth by a modest, though significant, percentage, as compared with an untreated population (12.1% vs. 11.8%, P<0.001). The effect of the use of 17 alpha-hydroxyprogesterone caproate, however, should not be underestimated. If the population of U.S. women with previous preterm birth were universally and successfully treated with 17 alpha-hydroxyprogesterone caproate, lifetime medical costs for their offspring might be reduced by more than $2 billion annually.

The use of progestational agents to prevent preterm birth among women with risk factors other than previous preterm birth is an area of active research interest. In this issue of the Journal, two studies report on the use of progestins to prevent preterm birth among high-risk women. Fonseca et al. report that daily administration of vaginal progesterone reduced by more than 40% the frequency of birth before 34 weeks of gestation among asymptomatic women with a short cervix as seen on ultrasonography. However, the study by Rouse et al. does not show a reduction in the frequency of preterm birth with the prophylactic administration of intramuscular 17 alpha-hydroxyprogesterone caproate in women pregnant with twins. These studies differ greatly with respect to the risk factor on which inclusion was based, the progestational agent used, the route of administration, and the gestational age.

Although the use of progestational agents to prevent preterm birth among high-risk women is promising, the results of these two trials highlight the gaps in our current knowledge of the biologic contribution of various risk factors to preterm birth. Unanswered questions regarding the possible mechanisms of action of the various progestins in preventing preterm birth have led to uncertainty with respect to choice of agent, route of administration, dose regimen, and clinical indication. Clearly, further research on progestational agents is needed, since the potential is immense for both clinical benefit and advancement of our understanding of the biology of preterm birth.

Therapy Decisions

The treatment of women who have acute preterm labor has been the focus for prevention of preterm birth. Although such a strategy has not reduced the frequency of preterm births in the United States, it is still important to use available evidence to guide the treatment of women with preterm labor. Accurate estimation of gestational age and clinical and laboratory evaluation of
pathologic causes of preterm labor are vital before embarking on a plan for tocolysis.

For the selection of a tocolytic agent, the literature describing the balance between safety and efficacy is fraught with design flaws but offers some guidance. In sum, as compared with β-adrenergic–receptor agonists, nifedipine would seem to be a reasonable choice for initial tocolysis, given the oral route of administration, low frequency of side effects, and efficacy in reducing neonatal complications. Nifedipine can be used at any gestational age when labor-inhibition therapy is being considered.

For pregnancies of less than 32 weeks’ gestation, a reasonable alternative to nifedipine is indomethacin or other COX inhibitors. These agents have been shown to be more effective than the β-adrenergic–receptor agonists in comparative studies. Indomethacin should be avoided in women with a platelet dysfunction or bleeding disorder, hepatic or renal dysfunction, gastrointestinal ulcerative disease, or asthma (in women with hypersensitivity to aspirin). We generally avoid the use of these agents in gestations of more than 32 weeks to avoid in utero closure or narrowing or neonatal patency of the ductus arteriosus.

The use of β-adrenergic–receptor agonists is an alternative to therapy with nifedipine and indomethacin. The side-effect profile of this class of drugs is less favorable than that of nifedipine, but their effectiveness in stopping contractions appears to be similar.

In Preterm Birth: Causes, Consequences, and Prevention, the Institute of Medicine cites critical gaps in our knowledge regarding the identification and treatment of women at high risk for preterm labor; it also targets this area for future research. To be responsive to this need, studies of new tocolytic drugs or drug classes and efforts to optimize the use of currently available drugs must be informed by a fuller understanding of the biology of preterm parturition.

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