We have invited select authorities to present background information on challenging clinical problems and practical information on diagnosis and treatment for use by practitioners.

The Management of Preterm Labor

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Preterm birth is the leading cause of neonatal mortality and a substantial portion of all birth-related short- and long-term morbidity. Spontaneous preterm labor is responsible for more than half of preterm births. Its management is the topic of this review. Although there are many maternal characteristics associated with preterm birth, the etiology in most cases is not clear, although, for the earliest cases, the role of intrauterine infection is assuming greater importance. Most efforts to prevent preterm labor have not proven to be effective, and equally frustrating, most efforts at arresting preterm labor once started have failed. The most important components of management, therefore, are aimed at preventing neonatal complications through the use of corticosteroids and antibiotics to prevent group B streptococcal neonatal sepsis, and avoiding traumatic deliveries. Delivery in a medical center with an experienced resuscitation team and the availability of a newborn intensive care unit will ensure the best possible neonatal outcomes. Obstetric practices for which there is little evidence of effectiveness in preventing or treating preterm labor include the following: bed rest, hydration, sedation, home uterine activity monitoring, oral terbutaline after successful intravenous tocolysis, and tocolysis without the concomitant use of corticosteroids. (Obstet Gynecol 2002;100: 1020–37. © 2002 by The American College of Obstetricians and Gynecologists.)

PREMATURITY

A preterm delivery, as defined by the World Health Organization, is one that occurs at less than 37 and more than 20 weeks' gestational age. In the United States, the preterm delivery rate is approximately 11%, whereas in Europe it varies between 5% and 7%. In spite of advances in obstetric care, the rate of prematurity has not decreased over the past 40 years. In fact, in most industrialized countries it has increased slightly (Figure 1). Prematurity remains a leading cause of neonatal morbidity and mortality in developed countries, accounting for 60–80% of deaths of infants without congenital anomalies. As the risk of neonatal morbidity and mortality near term is low, greater attention is now being focused on early preterm birth (<32 weeks' gestation). Although births in this gestational age group represent 1% to 2% of all deliveries, they account for nearly 50% of all long-term neurological morbidity and about 60% of perinatal mortality.

Neonatal mortality rates have declined in recent years largely because of improved neonatal intensive care and better access to these services. With appropriate medical care, neonatal survival dramatically improves as gestational age progresses, with over 50% of neonates surviving at 25 weeks' gestation, and over 90% surviving by 28 to 29 weeks' gestation (Table 1). In the United States, survival rates of 20–30% have been reported in neonates delivered at 22 to 23 weeks' gestation; however, these premature infants are often left with long-term neurological impairment.[1] Because of the rapid improvement in both survival and freedom from major handicap as delivery gestational age increases from 22 to 28 weeks, the major benefits from delaying delivery are seen in this time. Short-term morbidities associated with preterm delivery include respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and patent ductus arteriosus. Long-term morbid-

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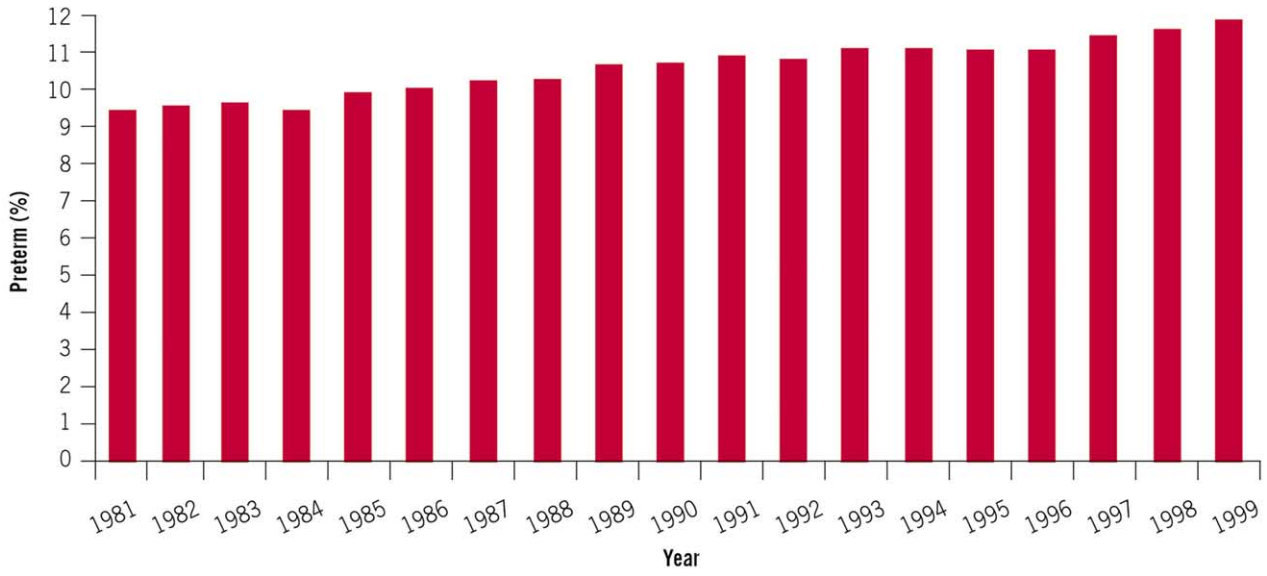

Figure 1. Incidence of preterm birth in the United States, 1981–1999. Source of data: National Center for Health Statistics.[97]

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ities include cerebral palsy, mental retardation, and retinopathy of prematurity. The risk for these morbidities is directly related to the gestational age and birth weight. For example, cerebral palsy, defined as a nonprogressive motor dysfunction with origin around the time of birth, complicates approximately two per 1000 of all live births. The relative risk for a preterm infant developing cerebral palsy is nearly 40 times that for term infants.

Table 1. Neonatal Survival by Gestational Age and Improvement in Survival by Week

Gestational age (wk)	Approximate survival (%)	Approximate improvement in survival per week (%)
21	0	–
22	Rare	–
23	25	25
24	50	25
25	70	20
26	80	10
27	86	6
28	91	5
29	94	3
30	95	1
31	96	1
32	97	1
33	98	1
34	99	1
35	99+	<1
36	99+	<1

Approximately 8–10% of surviving newborns weighing less than 1000 g at birth will develop cerebral palsy. These infants also have substantially higher rates of mental retardation and visual disabilities, as well as neurobehavioral dysfunction and poor school performance.[2]

PRETERM LABOR

Preterm labor is usually defined as regular contractions accompanied by cervical change occurring at less than 37 weeks' gestation. Spontaneous preterm labor accounts for 40–50% of all preterm deliveries, with the remainder resulting from preterm premature rupture of membranes (PROM) (25–40%) and obstetrically indicated preterm delivery (20–25%).[3] In this article I will deal only with the management of preterm labor.

The pathogenesis of preterm labor is not well understood, and it is often not clear whether preterm labor represents early idiopathic activation of the normal labor process or results from a pathologic mechanism. Several theories exist regarding the initiation of labor, including 1) progesterone withdrawal, 2) oxytocin initiation, and 3) premature decidual activation. The progesterone withdrawal theory stems from the large body of work previously done with sheep. As parturition nears, the fetal-adrenal axis becomes more sensitive to adrenocorticotropic hormone, increasing the secretion of cortisol. Fetal cortisol then stimulates trophoblast 17α-hydroxy-

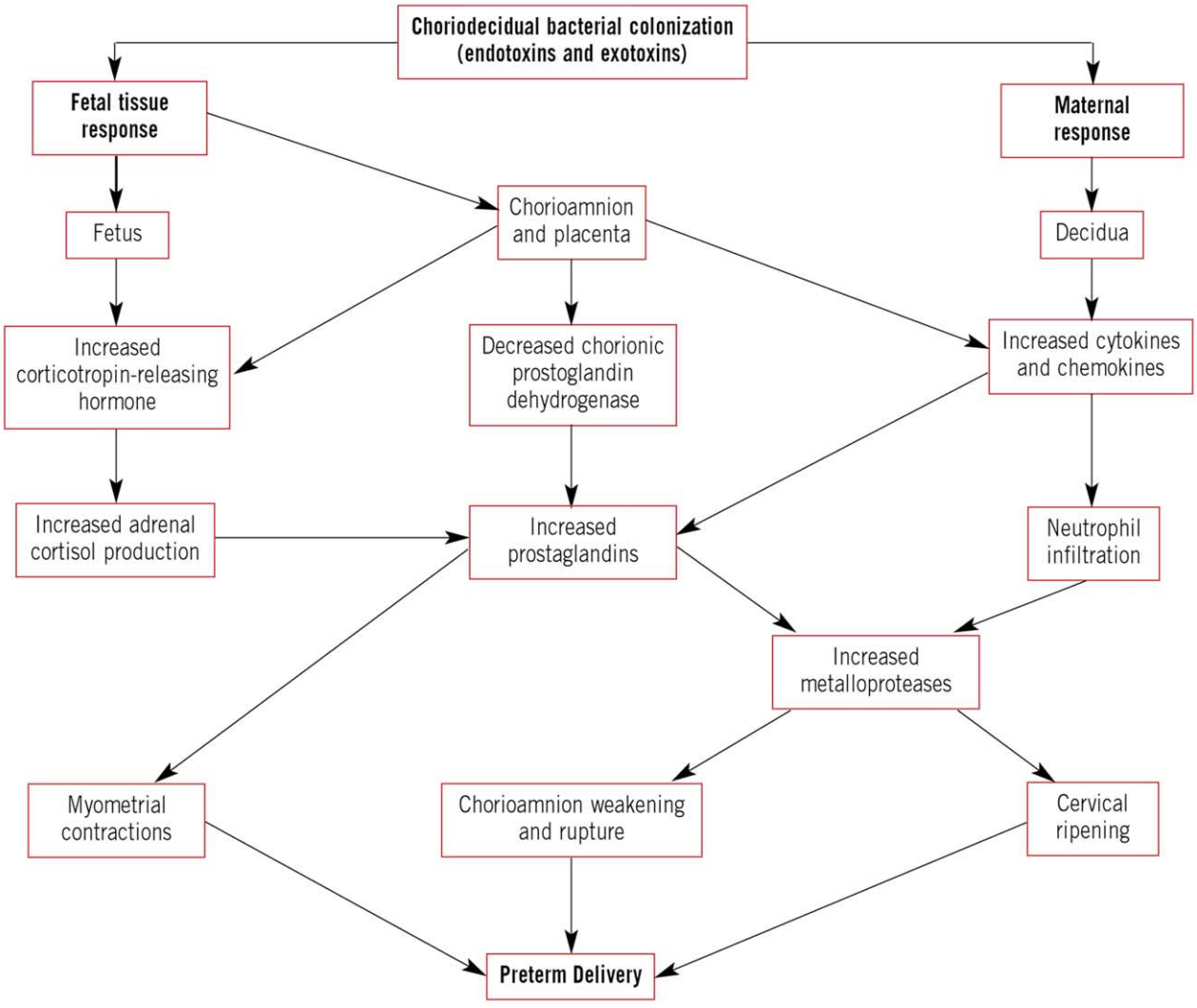

Figure 2. Pathways leading from choriodecidual bacterial colonization to preterm labor and delivery. (Reprinted with permission from Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm birth. N Engl J Med 2000;342:1500–7. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

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lase activity, which decreases progesterone secretion and leads to a subsequent increase in estrogen production. This reversal in the estrogen/progesterone ratio results in increased prostaglandin formation, initiating a cascade of events that culminate in labor and subsequent delivery. Although this mechanism is well established in sheep, its role in humans has not been confirmed.

The second parturition theory involves oxytocin as an initiator of labor. Because intravenously administered oxytocin increases the frequency and intensity of uterine contractions, it is natural to assume that oxytocin plays an important role in the initiation of labor. Accepting oxytocin as the initiating agent for the onset of labor, however, is difficult for two reasons: blood levels of oxytocin do not rise before labor, and the clearance of oxytocin remains constant during pregnancy. Thus, though oxytocin likely plays a role in the support of labor, its role in the initiation of labor, either at term or preterm, is not established. The most likely pathway to the initiation of preterm labor probably involves premature decidual activation. Although decidual activation may be mediated in part by the fetal-decidual paracrine system, and potentially by intrauterine bleeding, in many cases, especially those involving early preterm labor, it appears that this activation occurs in the context of an occult upper genital tract infection (Figure 2).

INFECTION AND PRETERM BIRTH

There is a growing body of evidence that infection of the decidua, fetal membranes, and amniotic fluid is associated with preterm delivery.[4] Clinical chorioamnionitis complicates 1–5% of term pregnancies, but nearly 25% of preterm deliveries. In a study by Guzick and Winn,[5] histological chorioamnionitis was more common in preterm deliveries than in term ones (32.8% versus 10%). Watts et al[6] investigated patients in preterm labor and demonstrated that positive amniotic fluid cultures were present in 19% of women with intact membranes with no clinical evidence of intrauterine infection. In women with spontaneous preterm labor, an inverse relationship exists between colonization of the chorioamnion and amniotic fluid and gestational age at delivery. In one study, chorioamnion colonization was associated with 83% of the very early spontaneous preterm births, but played a much less important role in the initiation of parturition at or near term.[4] Organisms that have been associated with histological chorioamnionitis include *Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis,* peptostreptococci, and *Bacteroides* species.[4]

RISK FACTORS

In the United States, race is a significant risk factor for preterm delivery. Black women have a prematurity rate of about 16–18%, compared to 7–9% for white women. Women younger than 17 and older than 35 carry a higher risk of preterm delivery. Less education and lower socioeconomic status are also risk factors, although they probably are not independent of one other. The relative contribution of various causes of preterm birth differs by ethnic group. For example, preterm labor more commonly leads to preterm birth in white women, whereas preterm PROM is more common in black women.[7] Various behavioral factors also increase the risk for preterm delivery. Both poor and excessive weight gain are associated with an increase in preterm birth, whereas women with a low body mass index (less than 19.8 kg/m^2) are at higher risk for preterm delivery.[8] Smoking plays a more significant role in fetal growth restriction than it does in preterm delivery. However, women who smoke still have about a 20–30% increase in preterm birth.[9] In the United States about 20% of pregnant women smoke, and 10–15% of all preterm births can be attributed to maternal smoking. A history of a preterm delivery is one of the most significant risk factors. The recurrence risk of preterm birth in women with a history of preterm delivery ranges from 17% to 40%, and appears to depend on the number of prior preterm deliveries. Mercer et al[10] recently reported that women who had a prior preterm delivery had a 2.5-fold increased risk of spontaneous preterm delivery with their next pregnancy. The earlier the gestational age of the prior preterm delivery, the greater the risk for a subsequent early spontaneous preterm delivery.

Multiple gestations carry one of the highest risks of preterm delivery. Approximately 50% of twin and nearly all higher multiple gestations end before 37 completed weeks. The average length of gestation is significantly shorter for twins (36 weeks), triplets (33 weeks), and quadruplets (31 weeks) than it is for singletons (39 weeks).[11] Vaginal bleeding caused by placenta previa or marginal placental separation is associated with almost as high a risk of preterm delivery as multiple gestation. Additionally, second-trimester bleeding not associated with either placenta previa or separation has also been significantly associated with preterm birth.

In addition to the risk factors discussed above, a variety of other factors have been associated with an increased risk for preterm labor. Extremes in the volume of amniotic fluid, such as hydramnios or oligohydramnios, have been associated with an increased risk for preterm labor. Maternal abdominal surgery in the late second and third trimesters can cause an increase in uterine activity that may culminate in preterm delivery. Maternal medical conditions, such as gestational or preexisting diabetes and hypertension (essential or pregnancy induced), are associated with a higher rate of preterm delivery; however, these preterm births are often indicated preterm deliveries due to maternal complications rather than the result of spontaneous preterm labor. Asymptomatic bacteriuria is associated with an increased rate of prematurity.[12] Systemic infections, such as bacterial pneumonia, pyelonephritis, and acute appendicitis, often lead to increased uterine activity, potentially leading to premature delivery.

Another potentially important clinical risk factor is the presence of uterine contractions. In a study involving approximately 2500 patients, in which multiple gestations, vaginal bleeding, preterm PROM, and hydramnios were excluded, Nageotte et al[13] evaluated uterine activity in patients with preterm, term, and postterm deliveries. The authors demonstrated an increase in uterine activity beginning 6 weeks before delivery, regardless of gestational age at birth. A surge in uterine activity occurred within 72 hours of delivery in all three groups. Unfortunately, these patients depended on tocodynamometry to determine this increase in frequency. When patients are instructed to self-detect an increase in uterine activity, they can identify only 15% of the contractions noted by tocodynamometry. Copper et al[14] evaluated the use of tocodynamometry and cervical examination at 28 weeks' gestation in 589 nulliparous women to determine whether patients at risk for preterm

delivery could be identified. The investigators noted that the best predictor of spontaneous preterm birth was the presence of a soft or medium consistency cervix. In this study, the risk for spontaneous preterm delivery increased from 4.2% for those women with no contractions detected to 18.2% for those patients having four or more contractions in 30 minutes. In a recent study from the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, Iams et al[15] again found an association between the presence of contractions and preterm delivery. However, because of the large overlap in contraction frequency between those who delivered at term and those who delivered preterm, monitoring contraction frequency was not found to be useful in defining a population at especially high risk for spontaneous preterm birth. For this, among other reasons, the use of home uterine activity monitoring has not generally resulted in a reduction of preterm births.

Biochemical and Ultrasound Predictors

As stated above, the biochemical processes leading to the initiation of either term or preterm labor have not been well established in humans. Recently, however, important insights into the pathophysiology of spontaneous preterm labor have helped to identify various biochemical markers that may predict preterm delivery. The most powerful biochemical marker identified to date is fetal fibronectin. Fetal fibronectin is a glycoprotein found in the extracellular matrix and, when found in the vagina or cervix, appears to be a marker of choriodecidual disruption. Typically, fetal fibronectin is absent from cervicovaginal secretions from around the 20th week of gestation until near term. In women undergoing routine screening during prenatal care or when tested with a diagnosis of potential preterm labor, detection of elevated cervicovaginal levels of fetal fibronectin has been shown to be strongly associated with an increased risk for preterm delivery.[16,17] For clinical care, the most important characteristic of the fetal fibronectin test is its negative predictive value. In women in questionable preterm labor, if the test is negative, less than 1% of women will deliver in the next week or two. If the test is positive, the risk of subsequent preterm delivery in the next week or two is higher–approximately 20%.

As labor approaches, the cervix tends to shorten, soften, rotate anteriorly, and then dilate. These changes tend to begin weeks before delivery, regardless of gestational age. Digital examination is the traditional method used to detect cervical maturation, but quantifying these changes is often difficult. For example, if the external portion of the cervix is closed, it is impossible to evaluate the internal os by digital examination. Vaginal ultrasonography allows a more objective approach to examination of the cervix. In asymptomatic women, cervical changes described by ultrasound, including shortening and funneling, appear to have high predictive value for subsequent preterm birth. Okitsu et al[18] noted that alterations in length begin to occur approximately 10 weeks before delivery. Digital examination changes, however, tend to occur only 3 to 4 weeks before delivery.

One of the most difficult decisions an obstetrician has to make is determining whether a woman presenting with symptoms of preterm labor, such as contractions and a small amount of cervical effacement or dilatation, is in preterm labor. Numerous studies confirm that between 50% and 75% of women who fit this description will, without treatment, go on to deliver at term. For this reason, traditionally, patients are observed for several hours or more to await additional cervical change before a decision is made to initiate tocolytic treatment, give corticosteroids, or discharge home. In many cases, a decision regarding true or false labor cannot be made with assurance even then. In recent years it has become apparent that, in some women, the presence of cervical or vaginal fetal fibronectin, and perhaps a short cervix as determined by ultrasound, can separate those women not in labor from those who carry a more significant risk of early delivery. Therefore, for women in whom the diagnosis of preterm labor is uncertain, obtaining one of these tests is a reasonable strategy. For those women whose fetal fibronectin is negative, and perhaps for those with a cervical length of greater than 30 mm, the likelihood of delivering in the next week is less than 1%. Thus most women with a negative test can safely be sent home without treatment.

PREVENTION

Conceptually, prevention of preterm labor may be divided into two major areas. The first involves a reduction in the presence of one or more of the specific risk factors described above or, in a more general approach, an improvement in quality of life including income and nutritional enhancement, and a reduction in physical and emotional stress. Although space does not permit a thorough review of these attempts, suffice it to say that in developed countries these approaches have not consistently been found to reduce the incidence of preterm labor. Other programs attempting to decrease the rate of preterm delivery have focused on screening for detection of preterm contractions or cervical change before the onset of true labor. These approaches include 1) patient education to recognize preterm contractions, 2) provider surveillance for cervical changes, and 3) home uterine activity monitoring. Educational programs generally train women to recognize symptoms of preterm labor

including contractions, pelvic pressure, and vaginal discharge. In addition, weekly vaginal examinations have been used in an attempt to detect early cervical changes before the onset of labor. Several explanations have been advanced as to why these interventions have generally failed to demonstrate significant reductions in the preterm birth rate. For example, the level of education and supervision may have been inadequate for the patient population under evaluation. One of the more important reasons, however, may be that early symptoms of premature labor are often subtle and varied, and women often do not perceive contractions until labor is relatively advanced. In a study by Newman et al,[19] women who had been trained in self-palpation of uterine activity identified only 15% of the contractions detected by a monitor, and as few as 11% could identify 50% of their contractions. Home uterine activity monitoring was proposed as a potential solution to this problem. Although some of the early, small trials with home uterine activity monitoring demonstrated a significant decrease in preterm births among enrolled subjects, subsequent larger studies have not.[20] Hence, it appears that home uterine activity monitoring is of little or no benefit in reducing the frequency of preterm birth. One potential reason for this failure is that the interventions available to treat early preterm labor once detected are, for the most part, not effective. Thus, overall, attempts at prevention and treatment of preterm labor through risk reduction and early detection, though conceptually appealing, have not generally led to reductions in preterm birth.

TREATMENT

The therapeutic interventions considered in the setting of preterm labor generally have the following goals: 1) to inhibit or reduce the strength and frequency of contractions, thus delaying the time to delivery, and 2) to optimize fetal status before preterm delivery. In this section, many of the contemporary obstetric therapeutic strategies proposed to achieve these goals are reviewed.

Bed Rest

Bed rest represents one of the most common interventions used for the prevention and/or treatment of threatened preterm labor. In fact, it is recommended for a wide range of pregnancy-related conditions. One survey[21] found that bed rest was prescribed for at least 1 week for 20% of pregnancies in the United States. Unfortunately, there are no prospective randomized studies that have independently evaluated the effectiveness of bed rest for the prevention of preterm labor or its treatment in singleton pregnancies. In four randomized trials of hospitalization and bed rest for the prevention and/or treatment of preterm delivery in twin pregnancies, two studies found no benefit, and two showed an increase in preterm birth. Therefore, although a reduction of physical activity may seem appropriate for some women at risk of preterm birth, there is no evidence that this intervention, especially when extended to full bed rest, will result in a reduction in preterm birth. In fact, in twins this intervention may be harmful. Therefore, no evidence exists that bed rest should be a standard component of prevention or treatment for preterm labor.

Hydration/Sedation

Another common practice used for the initial treatment of preterm labor is oral or intravenous hydration. Some physicians attempt to differentiate true preterm labor from false labor using this strategy. Several theories are offered as to why hydration may be effective in treating preterm labor. First, at least in animals, hydration inhibits the release of antidiuretic hormone through the Henry-Gauer reflex. Second, women in preterm labor may have plasma volumes below normal. Few studies have evaluated the use of hydration in a prospective manner. Pircon et al[22] conducted a prospective randomized study of 48 women with preterm contractions and found no benefit from hydration. Guinn et al,[23] in a prospective randomized study of 179 women with preterm contractions, reported similar findings. Patients in this investigation were randomized to observation alone, intravenous hydration, or a single dose of subcutaneous terbutaline. No significant differences were noted between the three groups in the mean days to delivery or the incidence of preterm delivery. Hence, intravenous hydration does not appear to reduce preterm birth, and the routine use of hydration to treat preterm labor or to differentiate true from false labor cannot be recommended.

Sedation is also a commonly used strategy to differentiate true preterm labor from preterm contractions. Similar to hydration, there are limited data documenting the efficacy of sedation in this clinical setting. Helfgott et al[24] performed a prospective comparative study of 119 women with preterm labor who were randomly assigned to treatment with hydration and sedation or to treatment with bed rest alone. Women randomized to the hydration and/or sedation group received 500 mL of lactated Ringer's solution intravenously over 30 minutes and 8–12 mg of intramuscular morphine sulfate. There was no significant difference between hydration and/or sedation and bed rest alone with regard to contraction cessation and rates of preterm delivery. Therefore, the literature does not support the use of hydration and/or sedation in the initial treatment of preterm labor. In many cases, initial hydration with intravenous infusion of fluid occurs before the start of intravenous infusion of

Table 2. Some Currently Used Tocolytics

Generic name	Brand name	Mechanism of action	Usual dosing	Major side effects	Comments
Magnesium sulfate	–	Calcium antagonist	4-g loading dose IV, then 1–3 g/h	Respiratory arrest; cardiac arrest	Monitor deep tendon reflexes and serum magnesium levels
Ritodrine	Utopar	β_2 activator	Start at 50 μg/min IV, increasing to a maximum of 350 μg/min	Cardiac arrhythmias; pulmonary edema; myocardial ischemia	Monitor cardiac rhythm and fluid and electrolyte status
Terbutaline	Brethine	β_2 activator	5–10 μg/min IV, increasing to a maximum of 80 μg/min	Cardiac arrhythmias; pulmonary edema; myocardial ischemia	Monitor cardiac rhythm and fluid and electrolyte status
Nifedipine	Procardia	Calcium channel blocker	20 mg orally followed by 10–20 mg orally every 6–8 h	Maternal hypotension	Monitor blood pressure
Indomethacin	Indocin	Prostaglandin synthetase inhibitor	50-mg loading dose PO, PV, or PR, followed by 25–50 mg every 6 h	Maternal gastrointestinal disturbance; oligohydraminios; ductal constriction	Not usually used after 32 wk; careful monitoring required >48 h

IV = intravenously; PO = orally; PV = per vagina; PR = per rectum.

a tocolytic agent. A large fluid bolus may increase the risk of fluid overload and subsequent development of pulmonary edema.

Progesterone

Based on the progesterone withdrawal hypothesis of labor initiation, over the years there has been interest in the use of progesterone and other progestins for the treatment and/or prevention of preterm labor. A meta-analysis of six randomized controlled trials of 17α-hydroxyprogesterone caproate used prophylactically to prevent preterm labor revealed a significant decrease in preterm birth (odds ratio 0.5; 95% confidence interval 0.3, 0.85).[25] However, the use of progestins, including large doses of intramuscular progesterone or 6α-methyl-17α-acetoxyprogesterone, has not successfully inhibited active preterm labor.[26,27]

Tocolytics

***β*-Sympathomimetic Agents.** There are three known types of β-adrenergic receptors in humans: β_1 receptors occur primarily in the heart, small intestine, and adipose tissue; β_2 receptors are found in the uterus, blood vessels, bronchioles, and liver; and β_3 receptors are found predominantly on white and brown adipocytes. β-sympathomimetic agents are structurally related to catecholamines and, when administered in vivo, stimulate all β-receptors throughout the body. Stimulation of the β_2 receptors results in uterine smooth muscle relaxation. Although some β-sympathomimetic agents have been proposed as β_2-selective agents, at the dosages used pharmacologically, stimulation of all receptor types often occurs. Such stimulation results in many of the side effects associated with the β-sympathomimetic agents. Of the β-sympathomimetic agents, the β_2-selective agents (eg, ritodrine, terbutaline) (Table 2) have been the primary drugs utilized for the treatment of preterm labor.

Ritodrine is the only medication approved by the United States Food and Drug Administration for the treatment of preterm labor. This approval resulted largely from studies done by Barden et al[28] and Merkatz et al[29] demonstrating efficacy similar to that of other tocolytic agents but with fewer side effects. The initial reports also suggested an increase in pregnancy duration with a reduction in neonatal morbidity and mortality. Subsequent reports have not been as positive. The Canadian Preterm Labor Investigators Group[30] conducted a large multicenter clinical trial comparing ritodrine with a placebo. They concluded that ritodrine treatment significantly delayed delivery for 24 hours, but that it did not significantly improve other perinatal outcomes. King et al[31] conducted a meta-analysis involving 16 clinical trials with a total of 890 women and demonstrated that women treated with ritodrine had significantly fewer deliveries within 24 and 48 hours of the start of therapy. However, no statistically significant decrease in the incidence of respiratory distress syndrome, birth weight less than 2500 g, or perinatal death was demonstrated. These studies were completed before the use of antenatal steroid therapy became widespread.

Although ritodrine can be administered either intravenously or orally, treatment usually begins with intrave-

nous infusion. The initial recommended infusion rate was 100 μg per minute. However, more recently, Caritis et al[32] suggested an initial infusion of 50 μg per minute with a maximal rate of 350 μg per minute. With cessation of uterine activity the infusion rate should be reduced. The patient should be closely monitored for fluid balance, cardiac status, and electrolytes, including potassium and glucose. Relative contraindications to any type of β-mimetic therapy include diabetes mellitus, underlying cardiac disease, use of digitalis, hyperthyroidism, severe anemia, and hypertension.

Many of the maternal side effects are due to stimulation of β-receptors throughout the body. Serious maternal cardiopulmonary side effects include pulmonary edema, myocardial ischemia, arrhythmia, and even maternal death. Pulmonary edema may occur in about 4% of patients receiving parenteral ritodrine. Predisposing factors associated with this complication include a multiple gestation, positive fluid balance, blood transfusion, anemia, infection, polyhydramnios, and underlying cardiac disease. The associated use of corticosteroids has also been implicated in the development of pulmonary edema. However, because the two most commonly used antepartum steroids, betamethasone and dexamethasone, have minimal mineralocorticoid activity, it is unlikely that these drugs contribute significantly to this complication. The maternal mortality that has been reported with intravenous ritodrine therapy is generally associated with pulmonary edema or cardiac arrhythmia. For those reasons pulse, blood pressure, and respiratory status should be closely monitored and discontinuation of therapy be strongly considered with any respiratory distress or a heart rate greater than 130 beats per minute. Metabolic effects of ritodrine include hypokalemia resulting from an increase in insulin and glucose concentrations, which drives potassium intracellularly. This condition generally resolves within 6–12 hours of discontinuing therapy.

A wide range of fetal cardiac complications has been described, including rhythm disturbances such as supraventricular tachycardia and atrial flutter. These usually resolve within a few days to 2 weeks after cessation of therapy. Fetal cardiac septal hypertrophy has been described with maternal ritodrine treatment. The degree of hypertrophy correlates with the duration of therapy and usually resolves within 3 months of age. Other, more serious fetal complications have included hydrops, pulmonary edema, and cardiac failure. Fetal and neonatal death, with histological evidence of myocardial ischemia, have also been reported. Neonatal hypoglycemia is another potential complication with β-sympathomimetics and usually develops when delivery occurs within 2 days of treatment. The hypoglycemia is transient and results in medication-induced hyperinsulinemia. Neonatal periventricular-intraventricular hemorrhage may be increased with β-sympathomimetic therapy. In a retrospective study of 2827 women delivering preterm, there was a two-fold increase in intraventricular hemorrhage in neonates whose mothers received β-mimetics, but this finding has not been consistently demonstrated in other studies.[33] Studies evaluating long-term exposure to β-sympathomimetics demonstrate no differences in Apgar scores, head circumference, or neurological status. Largely as a result of potential complications, as well as the limited evidence for improvements in important perinatal outcomes associated with its use, and perhaps because of its cost relative to magnesium sulfate, ritodrine has fallen out of favor as a tocolytic agent in the United States.

Terbutaline is now the most commonly used β_2-selective β-mimetic agent in pregnancy and can be administered via oral, subcutaneous, or intravenous routes. It was initially studied by Ingemarsson,[34] who randomly assigned 30 patients with preterm labor to intravenous terbutaline therapy and demonstrated an 80% success rate, in comparison with 20% for the placebo. Unfortunately, as with other tocolytic agents, subsequent studies have not reported similar success rates. Similar to ritodrine, terbutaline has been effective in temporarily arresting premature labor, but not reducing the rate of preterm birth. The initial infusion is 5–10 μg per minute, with the rate increased when necessary every 10–15 minutes to a maximum of 80 μg per minute. Terbutaline may be administered subcutaneously in 0.25-mg doses every 20–30 minutes (four to six doses) as the first-line tocolytic agent for preterm labor. Lam et al[35] compared the use of the terbutaline pump with oral terbutaline therapy, and Guinn et al[36] conducted a prospective double-blind randomized clinical trial comparing terbutaline pump maintenance therapy with a placebo. These investigators demonstrated no significant decreases in the preterm delivery rate or improvement in neonatal outcomes with use of the terbutaline pump. Orally administered terbutaline has mostly been used to prevent recurrence of already inhibited contractions. The usual oral dosages range from 2.5 to 5 mg every 4–6 hours, titrated by patient response and maternal pulse. Most studies of oral terbutaline have not shown a reduction in preterm birth. Maternal and neonatal side effects and complications are generally similar to those stated for ritodrine.

Magnesium Sulfate. The use of magnesium sulfate as a tocolytic agent was first described by Steer and Petrie in a randomized study of 71 women with preterm labor.[37] Patients were allocated to intravenous infusion of magnesium, ethanol, or dextrose in water. The magnesium

group received a 4-g bolus followed by a maintenance infusion of 2 g per hour. The success rate, defined by the absence of contractions for 24 hours, was 77% for the magnesium group, versus 45% for ethanol and 44% for the placebo. Miller et al[38] conducted a randomized comparison of magnesium and terbutaline and demonstrated that magnesium had efficacy similar to and fewer side effects than terbutaline. Orally administered magnesium has not been shown to be effective in reversing preterm labor or preventing its recurrence.[39–41]

Magnesium sulfate is usually administered intravenously as an initial bolus of 4–6 g over 30 minutes, followed by a maintenance infusion of 1–3 g per hour. Serum magnesium levels of 5–8 mg/dL are considered therapeutic for inhibiting myometrial activity. Once cessation of uterine activity is achieved, the patient is generally maintained at the lowest effective infusion rate for 12–24 hours and then weaned. Maternal side effects secondary to magnesium sulfate are typically dose related. Common side effects noted with the use of magnesium sulfate include flushing, nausea, headache, drowsiness, and blurry vision. Diminishment of deep tendon reflexes occurs when serum magnesium levels exceed 12 mg/dL (10 mEq/L). Significant respiratory depression can occur as serum levels reach 14–18 mg/dL (12–14 mEq/L), and cardiac arrest may occur with levels greater than 18 mg/dL (15 mEq/L). In general, respiratory depression does not occur before loss of deep tendon reflexes. The toxic effects of high magnesium levels can be rapidly reversed with the infusion of 1 g of calcium gluconate.

Absolute contraindications to the use of magnesium sulfate include myasthenia gravis and heart block. Relative contraindications include underlying renal disease and recent myocardial infarction. Concurrent use of calcium channel blockers and magnesium sulfate can theoretically result in profound hypotension and probably should be avoided, especially because there is no evidence of greater efficacy for combination treatment relative to either treatment used alone.[42] Pulmonary edema has been reported in approximately 1% of women treated with magnesium sulfate, and the risk is increased in patients with multifetal gestations and those receiving combined tocolytic therapy. Because of the potential risk of fluid overload and the subsequent development of pulmonary edema, periodic assessment of fluid intake and output is essential.

Magnesium readily crosses the placenta, achieving fetal steady-state levels within hours of the start of treatment. No significant alterations in neurological states or Apgar scores have been reported with umbilical cord concentrations of 4 mg/dL or less. At cord concentrations between 4 and 11 mg/dL, respiratory depression and motor depression have been seen. Serum calcium levels in the fetus and newborn are unchanged or minimally reduced. Several observational reports have suggested that antenatal magnesium sulfate treatment for preterm labor or preeclampsia is associated with a decreased risk for cerebral palsy in very low birth weight infants.[43] A large prospective multicenter trial is now ongoing to further explore the neonatal benefits of antenatal magnesium sulfate therapy.

In summary, although both maternal and neonatal side effects occur with magnesium use, they appear to be less common as well as generally less severe when compared with those seen with β-sympathomimetic therapy. If we are going to use tocolytic drugs, none of which work particularly well in reducing preterm birth or improving important neonatal outcomes, we ought to use the safest one available, and for now, this seems to be magnesium sulfate. It is for this reason that I and most other practitioners now use magnesium sulfate as the primary tocolytic agent.

Prostaglandin Synthetase Inhibitors. Prostaglandins are 20-carbon cyclopentane carboxylic acids derived from membrane phospholipids (primarily arachadonic acid) via the enzymatic action of phospholipase A and cyclooxygenase (prostaglandin synthetase). Therefore, this pathway represents a key target for pharmacological intervention. A number of drugs that inhibit the action of prostaglandin synthetase (eg, aspirin, ibuprofen, indomethacin, sulindac) are available. Of these drugs, indomethacin has been the most extensively studied.

Indomethacin was first used as a tocolytic agent by Zuckerman et al,[44] who administered it to 50 patients with preterm labor. Tocolysis was achieved in 40 of the 50 patients for at least 48 hours. The first prospective, randomized, double-blind, placebo control study was performed by Niebyl et al.[45] In this study of 30 women with preterm labor, only one of 15 women in the indomethacin group failed therapy after 24 hours, in comparison with nine of 15 women in the placebo group. Morales et al[46] compared indomethacin with ritodrine in a randomized trial and found similar efficacy in delaying deliveries 48 hours and 7 days. Maternal side effects causing discontinuation of treatment were much more common in the ritodrine group (24% versus 0%). Similar efficacy was noted by the same authors in a comparative trial of indomethacin and magnesium sulfate.[47]

Indomethacin is usually administered orally or rectally. A loading dose of 50–100 mg is followed by a total 24-hour dose not greater than 200 mg. Indomethacin blood concentrations usually peak 1 to 2 hours after oral administration, whereas rectal administration is associated with levels that peak slightly sooner. Most studies have limited the use of indomethacin to 24–48 hours'

duration because of concerns regarding the development of oligohydramnios and constriction of the ductus arteriosus. Major maternal side effects are infrequent. Gastrointestinal upset may occur but can usually be relieved by taking the medication with meals or using an antacid. Maternal contraindications to indomethacin use include peptic ulcer disease; allergies to indomethacin or related compounds; hematological, hepatic, or renal dysfunction; or drug-induced asthma. Fetal contraindications include preexisting oligohydramnios and congenital fetal heart disease in which the fetal circulation is dependent on the ductus arteriosus.

Indomethacin readily crosses the placenta, with fetal levels equilibrating with maternal concentrations about 5 hours after administration. Several fetal side effects have been reported with the use of indomethacin. Fetal urine output has been shown to decrease after administration of indomethacin. Long-term therapy may result in the development of oligohydramnios, although the timing of the onset is unpredictable. Therefore the amniotic fluid index should be followed while the patient is receiving long-term therapy, and if the amniotic fluid index falls below 5 cm, therapy is usually discontinued. Resolution of oligohydramnios usually occurs within 48 hours of discontinuation of treatment. However, persistent anuria, renal microcystic lesions, and neonatal death have been reported with prenatal indomethacin exposure. Most of these infants were exposed to doses greater than 200 mg per day for more than 48 hours without adequate amniotic fluid assessment. Another important potential complication related to indomethacin use is the development of ductal constriction or closure, which leads to the diversion of right ventricular blood flow into the pulmonary vasculature. With time, this causes pulmonary arterial hypertrophy. After birth, relative pulmonary hypertension can cause shunting of blood through the foramen ovale and away from the lungs, resulting in persistent fetal circulation. This complication has been described with long-term indomethacin therapy but not in fetuses exposed to the drug for less than 48 hours. For this reason, it has been recommended that, for longer term treatment, patency of the ductus arteriosus be monitored and, if the pulsatility index is less than 2 cm per second, discontinuation of therapy be considered. The effects on ductal constriction have been shown to increase with advancing gestational age. At 32 weeks' gestational age, it is estimated that 50% of fetuses will demonstrate ductal constriction. On the basis of these data, indomethacin therapy should be discontinued by 32 weeks at the latest.

Another reported complication in fetuses exposed to indomethacin prenatally and delivered at less than 30 weeks is an increased risk of necrotizing enterocolitis. Norton et al[48] performed a retrospective case-control study of 57 fetuses delivered at less than 30 weeks' gestation after recent exposure to indomethacin and compared them with 57 matched control fetuses. The incidence of necrotizing enterocolitis was 29% in the indomethacin group, versus 8% in the control group. Additionally, higher incidences of intraventricular hemorrhage and patent ductus arteriosus were noted in the indomethacin treatment group. The effect of the duration of treatment and the timing of the exposure in relation to delivery were not reported. Although these results are of concern, when used with appropriate caution (less than 48 hours of therapy, less than 30–32 weeks' gestation), indomethacin appears to be a relatively safe and effective tocolytic agent. I generally use indomethacin as a second-line tocolytic agent after failure of magnesium sulfate in early gestational age preterm labors.

Sulindac is another prostaglandin synthetase inhibitor, closely related to indomethacin in structure, which likely has similar efficacy in inhibiting preterm labor. Initially, suldinac was reported to have fewer side effects than indomethacin when used for tocolysis. However, Kramer et al (Kramer W, Saade G, Belfort M, Dorman K, Mayes M, Mose K. Randomized, double-blind study comparing sulindac to terbutaline: Fetal renal and amniotic fluid effects [abstract]. Am J Obstet Gynecol 1996; 174:326) conducted a randomized double-blind study to evaluate the comparative effects of sulindac and terbutaline on fetal urine production and amniotic fluid volume. Sulindac administration resulted in a significant decrease in fetal urine flow and amniotic fluid volume. Additionally, two fetuses developed severe ductal constriction. Thus, sulindac shares many of the fetal side effects associated with indomethacin, and its safety, relative to indomethacin, is unknown.

Calcium Channel Blockers. Calcium channel blockers are agents that reduce transmembrane calcium influx, thus controlling muscle contractility and pacemaker activity in cardiac, vascular, and uterine tissue. To date, the majority of clinical investigations evaluating the use of calcium channel blockers for the treatment of preterm labor have utilized nifedipine. Ulmsten et al[49] first reported the use of nifedipine for the treatment of preterm labor in a study involving 10 patients, with resultant cessation of uterine activity for 3 days in all patients undergoing treatment. In a subsequent randomized study, Read and Wellby[50] reported that the nifedipine group had a significantly longer time interval from presentation to delivery than either a ritodrine or placebo control group. Ferguson et al[51] demonstrated that nifedipine was as effective as ritodrine in prolonging pregnancy, but had far fewer side effects leading to discon-

tinuation of therapy. Several subsequent studies and meta-analyses also suggest that nifedipine has a better safety profile than ritodrine and is at least equally effective in delaying delivery.[52–54] Nifedipine is reported to be as equally effective in delaying delivery as magnesium sulfate.[55,56] In women with a diagnosis of sucessfully treated preterm labor, maintenance oral nifedipine did not prolong pregnancy relative to a no-treatment or control group.[57]

Nifedipine can be administered orally or in sublingual form. It is rapidly absorbed by the gastrointestinal tract, with detectable blood levels attained within 5 minutes of sublingual administration. Nifedipine readily crosses the placenta, and serum concentrations of the fetus and the mother are comparable. An initial loading dose of 20 mg orally is typically given, followed by 10–20 mg every 6–8 hours. The sublingual form is not recommended for treatment of preterm labor because it acts more rapidly than the oral form and can cause acute hypotension. Contraindications to the use of nifedipine, or any of the calcium channel blockers, include hypotension, congestive heart failure, and aortic stenosis. As stated previously, concurrent use of calcium channel blockers and magnesium sulfate can theoretically result in profound hypotension and should probably be avoided.[42] Maternal side effects of orally administered nifedipine result from the vasodilatory effects and include dizziness, lightheadedness, flushing, headache, and peripheral edema. The incidence of these side effects is approximately 17%, with severe effects resulting in the discontinuation of therapy in 2–5% of patients.

Studies evaluating the fetal effects of calcium channel blocker therapy have been limited to date. One concern is the potential adverse effect calcium channel blockers may have on uteroplacental blood flow, as has been reported in animal studies. However, several reports have examined uteroplacental blood flow in patients receiving nifedipine and have demonstrated no significant adverse effects on fetal or uteroplacental blood flow during treatment.[58] As with many of the other tocolytic agents, additional studies are needed to more completely evaluate the potential fetal effects of calcium channel blocker therapy and the overall role of calcium channel blockers as a tocolytic agent for the treatment of preterm labor. To date, the available literature provides little evidence that calcium channel blockers have better efficacy in treating preterm labor than magnesium sulfate.

Oxytocin Antagonists. Although oxytocin antagonists are not available for use in the United States, because they are available elsewhere, their use to inhibit preterm labor will be discussed. Oxytocin antagonists have been shown to effectively inhibit oxytocin-induced uterine contractions in both in vitro and in vivo animal models. The initial human studies were performed in the late 1980s. Akerlund et al[59] reported 13 patients who received a short-term infusion of an oxytocin antagonist that resulted in inhibition of premature labor in all patients; however, ten of these patients subsequently required treatment with β-agonists. Similarly, Andersen et al[60] reported 12 patients who were treated with an oxytocin receptor antagonist. Nine had arrest of contractions. The most studied oxytocin antagonist is atosiban, which is a nonapeptide oxytocin analogue that competitively binds with the oxytocin-vasopressin receptor and is capable of inhibiting oxytocin-induced uterine contractions. Atosiban is typically administered intravenously, beginning with a single bolus of 6.75 mg, followed by an infusion at 300 μg per minute for 3 hours, and then 100 μg per minute for up to 18 hours.

Several prospective randomized, blinded clinical trials have demonstrated that atosiban is effective in diminishing uterine contractions in women with threatened preterm birth without causing significant maternal fetal or neonatal adverse effects. Goodwin et al[61] demonstrated that a 2-hour infusion of atosiban significantly decreased contraction frequency relative to placebo. Romero et al,[62] in a prospective randomized, double-blind investigation of 501 women with preterm labor, demonstrated that atosiban is significantly more effective than a placebo in delaying delivery 24 hours, 48 hours, and 7 days. However, there was no improvement in perinatal outcomes. Moutquin et al[63] compared atosiban with ritodrine for the treatment of preterm labor. In this randomized controlled trial involving 212 women, the investigators demonstrated that atosiban's tocolytic efficacy was comparable to that of ritodrine therapy. However, atosiban use was associated with fewer adverse side effects. No differences were noted between the groups with respect to neonatal outcomes. In a recent international study of atosiban versus β-mimetic agents,[64] the efficacy of atosiban was similar to that of β-mimetic therapy, but the maternal cardiovascular side effects were considerably fewer in those women receiving atosiban. The potential use of atosiban for maintenance therapy in patients with arrested preterm labor has also recently been evaluated. Valenzuela et al[65] reported experience from a multicenter double-blind, placebo-controlled trial of 513 women with arrested preterm labor. Median time from start of maintenance therapy to first recurrence of labor was significantly longer for women treated with atosiban (32.6 days) than for the placebo-treated women (27.6 days). These data suggest that atosiban may be useful in delaying delivery 24–48 hours in the setting of preterm labor. However, this delay appears to have minimal impact on neonatal outcomes. Further studies are needed to more clearly eluci-

date the role of the oxytocin antagonists for the treatment of preterm labor.

Nitric Oxide Donors. Nitric oxide is a potent endogenous hormone that facilitates smooth muscle relaxation in the vasculature, the gut, and the uterus. The use of nitric oxide donors (eg, nitroglycerin, glycerol trinitrate) for tocolytic therapy has been investigated. Lees et al[66] compared transdermal glycerol trinitrate with ritodrine for tocolysis in 245 women with documented preterm labor between 24 and 36 weeks' gestation. There were no differences with respect to tocolytic effect and neonatal outcomes. Clavin et al (Clavin DK, Bayhi DA, Nolan TE, Rigby FB, Cork RC, Miller JM. Comparison of intravenous magnesium sulfate and nitroglycerin for preterm labor [abstract]. Am J Obstet Gynecol 1996;174: 307) randomized 34 women in preterm labor to either tocolysis with intravenous nitroglycerin or magnesium sulfate. No difference in the tocolytic efficacy was noted between the two treatments; However, three of the 15 women who received nitroglycerin experienced severe hypotension. Similarly, El-Sayed et al[67] compared intravenous nitroglycerin with magnesium sulfate in 31 women studied before 35 weeks' gestation. Tocolytic failures (tocolysis 12 hours or longer) were significantly more common in patients treated with nitroglycerin than in the women treated with magnesium sulfate. Importantly, 25% of the patients treated with nitroglycerin experienced significant hypotension that required discontinuation of treatment. Given the potential profound hemodynamic effects of these nitric oxide donors on the central and peripheral circulation, these agents should be used with caution in the pregnant patient. Clinical use of these agents for the treatment of preterm labor remains experimental.

Tocolytics–Summary. More than 20 years ago, in an editorial,[68] the *British Medical Journal* stated that, in women in preterm labor, the use of tocolytics was frequently unnecessary, often ineffective, and occasionally harmful. Not much is different today. In many women, tocolytics seem to stop contractions temporarily, but rarely prevent preterm birth. Most importantly, used alone, they appear to convey little or no benefit for any fetal or neonatal outcome. For example, a recent meta-analysis of tocolytic therapy[69] concluded that although tocolytics may prolong pregnancy, they have not been shown to improve perinatal outcomes, but do have adverse health effects on women. However, in some women they do appear to delay delivery long enough for successful administration of corticosteroids, one of the few interventions of clear benefit. Therefore, as a general rule, if tocolytics are given, they should be given concomitantly with corticosteroids. The gestational age range in which tocolytics should be used is open to debate, but because corticosteroids are not generally used at or after 34 weeks, and because the perinatal outcomes in later gestational age preterm infants are generally good, most authorities do not recommend use of tocolytics at or after 34 weeks' gestational age. There is no consensus on a lower gestational age limit for the use of tocolytic agents.

ANTIBIOTICS

Preterm labor, especially at less than 30 weeks' gestation, has been associated with occult upper genital tract infection (Figure 2). Many, if not all, of the bacterial species involved in this occult infection are capable of inciting an inflammatory response, which ultimately may culminate in preterm labor and delivery. Antibiotics therefore have the potential to prevent and/or treat spontaneous preterm labor. Elder et al[70] were among the first investigators to study the use of antibiotics to prevent preterm birth, and demonstrated that treatment of nonbacteriuric asymptomatic pregnant patients with daily tetracycline therapy resulted in fewer preterm births. However, although the data are mixed, many subsequent prospective trials of prenatal administration of antibiotics in women colonized with *Chlamydia trachomatis, Ureaplasma urealyticum,* and group B streptococcus have not shown a significant decrease in preterm birth. Recently, however, the association of bacterial vaginosis with preterm birth has prompted renewed interest in the use of antibiotics to prevent preterm birth in asymptomatic women. The results of the trials have been mixed as well. Similarly, the use of antibiotics for the *treatment* of documented preterm labor has also produced mixed results[71–87] (Table 3). A recent Cochrane meta-analysis[71] summarizing eight of the randomized controlled clinical trials comparing antibiotic therapy (mostly penicillin derivatives) with a placebo for the treatment of documented preterm labor demonstrated no difference between the placebo and antibiotic treatment in pregnancy prolongation, preterm delivery, respiratory distress syndrome, or neonatal sepsis. Antibiotics were, however, associated with a significantly decreased risk for maternal infection and neonatal necrotizing enterocolitis. Two randomized studies in women in early preterm labor, one performed in South Africa and one in Denmark, suggest that a combination of metronidazole and ampicillin, given to women with preterm labor for 6–8 days, may significantly delay delivery, increase birth weight, and improve neonatal outcomes such as sepsis and necrotizing enterocolitis.[81,85] As a profession, we adopt many clinical practices without such randomized trial evidence, and in specific cases, this intervention might be considered. Clearly, further studies are needed to evaluate various antibiotic

Table 3. Randomized Controlled Trials of Antibiotics in Women in Preterm Labor With Intact Membranes

Author	Year	Weeks' gestation	*n*	Antibiotics (type)	Outcomes		
					Delay in delivery	Decrease in preterm delivery	Decrease in perinatal mortality and morbidity
McGregor et al[74]	1986	<34	17	Erythromycin	Yes	No	No
Morales et al[75]	1988	21–34	150	Erythromycin, ampicillin	Yes	Yes	Not stated
Newton et al[76]	1989	24–34	95	Ampicillin, erythromycin	No	No	No
McGregor et al[77]	1991	≤34	103	Clindamycin	Yes	No	No
Newton et al[78]	1991	24–33	86	Ampicillin, sulbactam	No	No	No
McCaul et al[79]	1992	19–33	40	Ampicillin	No	No	No
Romero et al[80]	1993	24–34	277	Ampicillin, erythromycin, amoxicillin	No	No	No
Norman et al[81]	1994	26–34	81	Ampicillin, amoxicillin, metronidazole	Yes	No	Yes
Watts et al[82]	1994	<34	56	Mezlocillin, erythromycin	No	No	No
Gordon et al[83]	1995	24–35	95	Ceftizoxine			
Cox et al[84]	1996	24–34	78	Ampicillin, sulbactam, Augmentin	No	No	No
Svare et al[85]	1997	26–34	110	Ampicillin, metronidazole	Yes	Yes	No
Oyarzun et al[86]	1998	22–36	170	Amoxicillin, erythromycin	No	No	No
Kenyon et al[87]	2001	24–33	6295	Erythromycin, amoxicillin, clavulonic acid	No	No	No

regimens for the treatment of women with preterm labor with intact membranes. However, in the interim period, treatment of women in preterm labor with antibiotics *for the sole purpose of preventing preterm delivery* is not generally recommended.

GROUP B STREPTOCOCCUS

Group B streptococcus is an important cause of neonatal morbidity and death, especially in premature infants, but its role in the initiation of preterm labor is uncertain. Approximately 10–20% of US women are group B streptococcus positive during pregnancy. The risk of preterm birth appears to be greatest in women with group B streptococcus in the urine, perhaps indicating a greater degree of colonization; thus treatment of the urinary tract infection may result in a reduction in preterm birth. As an example, in a randomized trial of women who had a urine culture positive for group B streptococcus treated with antibiotics, Thomsen et al[88] reported that the treated group had a lower incidence of premature delivery than the nontreated group (37.5% versus 5.4%). These studies may be interpreted as showing that asymptomatic bacteriuria with group B streptococcus (or in fact with any organism) is a risk factor for preterm delivery and that eradication with antibiotics decreases the risk. From a labor management perspective, these and other data suggest that women in preterm labor should be evaluated for bacteriuria and, if positive, treated. However, whether this strategy applied to laboring patients will result in a significant reduction in preterm birth is unknown.

Group B streptococcus can cause significant neonatal morbidity and mortality. Usually acquired from the maternal genital tract after membrane rupture, the port of entry is generally the fetal lung. Sepsis often follows. In 1996, the Centers for Disease Control and Prevention in conjunction with The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics set forth recommendations regarding two different approaches to the prevention of early-onset neonatal group B streptococcus disease.[89] In the first strategy, intrapartum antibiotic prophylaxis is offered to women identified as being at high risk for having infants who develop early-onset group B streptococcus sepsis. Unless shown to be group B streptococcus negative, all women in preterm labor are in this category. In the second strategy, prenatal screening cultures are collected at 35–37 weeks' gestation, and women who are positive are considered high risk. For intrapartum chemoprophylaxis, intravenous penicillin G (5 mU initially and then 2.5 mU every 4 hours) until delivery is recommended. Intravenous ampicillin (2 g initially and then 1 g every 4 hours until delivery) is an acceptable alternative to penicillin G. Clindamycin or erythromycin may be used for women allergic to penicillin, although the efficacy of these drugs for group B streptococcus disease prevention has not been measured in controlled trials. It should be emphasized that the goal of this strategy is to prevent transmission of the group B streptococcus from the

mother to the fetus and subsequent neonatal sepsis, and not to prevent preterm birth. Therefore, unless proven to be group B streptococcus negative, all women in preterm labor should receive group B streptococcus prophylaxis.

CORTICOSTEROIDS

The use of antenatal corticosteroids for the prevention of neonatal respiratory distress syndrome stems from the animal work by Liggins and Howie in the late 1960s.[90] They observed that gravid sheep, which had received glucocorticoids to induce preterm labor, gave birth to lambs that had accelerated fetal lung maturity and decreased respiratory problems at birth. After this observation, these investigators conducted the first trial of antenatal glucocorticoid therapy in humans and found that 12 mg of betamethasone on two occasions 24 hours apart resulted in a significant decrease in the incidence of respiratory distress syndrome associated with a decrease in perinatal mortality in newborns born before 34 weeks. The beneficial effect was noted only if delivery occurred after more than 24 hours had elapsed from the first dose and before 7 days.

Since then, 15 additional prospective randomized controlled trials have been performed. Crowley conducted a meta-analysis of these trials[91] confirming that antenatal glucocorticoid therapy significantly decreased the incidence and severity of neonatal respiratory distress syndrome. Neonatal mortality was also significantly reduced, as was the incidence of intraventricular hemorrhage and necrotizing enterocolitis. These benefits appeared to be maximal if delivery occurred more than 24 hours after start of treatment but within 7 days.

Despite these data, antenatal corticosteroids remained underused throughout the 1980s and early 1990s. For this reason, the National Institutes of Health convened a Consensus Development Conference on Antenatal Steroids in 1994 to review the potential risks and benefits of antenatal corticosteroid therapy.[92] The panel concluded that antenatally administered corticosteroids (betamethasone or dexamethasone) significantly reduce the risk of respiratory distress syndrome, intraventricular hemorrhage, and neonatal death. The panel recommended that all women between 24 and 34 weeks' gestation at risk for preterm delivery should be considered candidates for antenatal corticosteroid treatment. Additionally, given that treatment for less than 24 hours was associated with a significantly decreased risk for respiratory distress syndrome, intraventricular hemorrhage, and mortality, the panel concluded that steroids should be administered unless delivery is imminent. For patients with preterm PROM, treatment was recommended for patients at less than 30–32 weeks because of the high risk of intraventricular hemorrhage. Recent studies suggesting worse outcomes in newborns whose mothers received multiple courses of corticosteroids, and one randomized trial showing no benefit, strongly suggest that the practice of giving repetitive weekly dose courses until 34 weeks be discontinued, unless data from ongoing randomized clinical trials demonstrate benefit for this practice. Long-term follow-up of infants exposed in utero to a single course of antenatal corticosteroid therapy has not demonstrated any adverse effect on growth, physical development, motor or cognitive skills, or school progress at 3 and 6 years. Hence, the use of a single course of corticosteroids appears to be an efficacious and safe treatment for improving neonatal outcomes in patients with preterm labor.

The commonly utilized steroids for the enhancement of fetal maturity are betamethasone (12 mg intramuscularly every 24 hours, two doses) and dexamethasone (6 mg intravenously every 6 hours, four doses). These two glucocorticoids have been identified as the most appropriate for antenatal use as they readily cross the placenta and have long half-lives and limited mineralocorticoid activity. One study,[93] however, suggests that betamethasone is more effective in reducing intraventricular hemorrhage and periventricular leukomalacia than dexamethasone. Therefore, in the absence of other data, betamethasone given as a single course appears to be the better choice.

DELIVERY

The remarkable reduction in neonatal mortality that has occurred in the last several decades is mostly due to the widespread use of newborn intensive care for preterm newborns. Birth in close proximity to a newborn intensive care unit with an experienced resuscitation team in attendance is one of the best predictors of neonatal survival. Obstetricians and other delivery attendants should do all in their power to insure that each preterm newborn can benefit from this technology.

Women in preterm labor are more likely to have fetuses in the breech presentation than those at term, and the earlier the preterm labor, the more likely the breech fetus is to have a nonfrank presentation. Fetuses in the breech position, especially those less than 32 weeks, when delivered vaginally are prone to cord prolapse, muscle trauma, and head entrapment. They appear less likely to have traumatic and asphyxial injuries when delivered by cesarean delivery. Vaginally delivered preterm breech fetuses near term appear to have outcomes nearly comparable to those of vertex infants of the same gestational age, but few randomized trials exist to guide

our choice of delivery method. Nevertheless, in most institutions virtually all preterm breech infants are delivered by cesarean delivery. Given the limited experience of most obstetricians in conducting breech deliveries and the reported increases in morbidity and mortality with vaginal delivery, this practice seems appropriate, and is consistent with the ACOG position on breech delivery at term.[94] There is little or no evidence that routinely delivering preterm vertex infants by cesarean delivery improves outcome. Therefore, in preterm vertex infants, cesarean delivery should generally be performed for the same indications as in term infants. How to select the earliest gestational age for which cesarean delivery should be offered is a complicated issue. However, factors considered should include the gestational age–specific survival and short- and long-term neonatal morbidity rates at the delivering institution. In specific cases, after appropriate counseling, the parents' wishes should be strongly considered as a guide to management. That said, it is the practice in many institutions with a good newborn intensive care unit to offer cesarean deliveries when indicated at about 24 weeks, and to strongly recommend them when indicated beginning at 26 weeks' gestational age.

Preterm infants, and especially very early preterm infants, are more vulnerable to trauma during delivery than fetuses at term. They are far more likely to suffer soft tissue damage, neurological injury, and traumatic intracranial hemorrhage than term infants. For this reason, special care should be taken not to traumatize these infants, especially during cesarean delivery or when using forceps. Vacuum extraction in preterm births may add extra risk and is considered to be contraindicated by some authorities. Although there are no randomized trials to confirm it, there appears to be less labor and delivery trauma when preterm labor is conducted with intact membranes. For this reason, especially for early preterm deliveries, artificial membrane rupture should be performed only for a clear indication. For the very early preterm breech fetus of borderline viability for which a cesarean delivery will not be performed, an in caul delivery appears to result in the least trauma.[95] The choice of anesthesia should be based on similar considerations for both term and preterm labors.

SUMMARY

The epidemiology, pathophysiology, and current therapeutic strategies utilized in the setting of preterm labor have been reviewed. Despite our best efforts, preterm delivery remains a significant clinical problem, accounting for a substantial component of all neonatal morbidity and mortality. Although we have gained important insights into the pathophysiology of preterm labor over the past several decades, effective therapeutic interventions to decrease spontaneous preterm delivery have not been discovered.[96] Therefore the successful management of preterm labor includes preventing neonatal disease when possible, including the use of corticosteroids and, when appropriate, group B streptococcus prophylaxis, and reducing trauma and asphyxia during delivery. Preterm newborns should be delivered at a site that can perform expert resuscitation and provide intensive care when necessary. Clearly, additional research is needed to further explore the pathophysiology of spontaneous preterm labor and potential therapeutic approaches to deal with this important clinical problem. In the meantime, it seems important to practice evidence-based medicine, doing the things that work, and to eliminate from our practices those things for which there is no evidence of efficacy. The latter practices include hydration, sedation, bed rest, home uterine activity monitoring, tocolysis without the concomitant use of corticosteriods, and oral terbutaline after successful intravenous tocolysis.

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