INTERIM UPDATE

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INTERIM UPDATE: This Practice Bulletin is updated to reflect a limited, focused change in the gestational age at which to consider antenatal corticosteroids, including administration during the late preterm period and rescue course timing.

Management of Preterm Labor

Preterm birth is the leading cause of neonatal mortality and the most common reason for antenatal hospitalization (1–4). In the United States, approximately 12% of all live births occur before term, and preterm labor preceded approximately 50% of these preterm births (5, 6). Although the causes of preterm labor are not well understood, the burden of preterm births is clear—preterm births account for approximately 70% of neonatal deaths and 36% of infant deaths as well as 25–50% of cases of long-term neurologic impairment in children (7–9). A 2006 report from the Institute of Medicine estimated the annual cost of preterm birth in the United States to be $26.2 billion or more than $51,000 per premature infant (10). However, identifying women who will give birth preterm is an inexact process. The purpose of this document is to present the various methods proposed to manage preterm labor and to review the evidence for the roles of these methods in clinical practice. Identification and management of risk factors for preterm labor are not addressed in this document.

Background

Preterm birth is defined as birth between 20 0/7 weeks of gestation and 36 6/7 weeks of gestation. The diagnosis of preterm labor generally is based on clinical criteria of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both, or initial presentation with regular contractions and cervical dilation of at least 2 cm. Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation (11). It is important to recognize that preterm labor with intact membranes is not the only cause of preterm birth; numerous preterm births are preceded by either rupture of membranes or other medical problems necessitating delivery (2, 6, 12).

Historically, nonpharmacologic treatments to prevent preterm births in women with preterm labor have included bed rest, abstention from intercourse and orgasm, and hydration. Evidence for the effectiveness of these interventions is lacking, and adverse effects have been reported (13–16). Proposed pharmacologic interventions to prolong pregnancy have included the use of tocolytic drugs to inhibit uterine contractions as well as antibiotics to treat intrauterine bacterial infection. The therapeutic agents currently thought to be clearly associated with improved neonatal outcomes include antenatal corticosteroids for maturation of fetal lungs and other developing organ systems, and the targeted use of magnesium sulfate for fetal neuroprotection.

Clinical Considerations and Recommendations

▶ *Which tests can be used to stratify risk for preterm delivery in patients who present with preterm contractions?*

Because the presence of fetal fibronectin or a short cervix has been associated with preterm birth (17–19), the utility of fetal fibronectin testing and the cervical length measurement, alone or in combination, to improve upon

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the clinical ability to diagnose preterm labor and predict preterm birth in symptomatic women were examined. Although the results of observational studies have suggested that knowledge of fetal fibronectin status or cervical length may help health care providers reduce use of unnecessary resources (20, 21), these findings have not been confirmed by randomized trials (22–24). Further, the positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms (25).

▶ *Which patients with preterm labor are appropriate candidates for intervention?*

Identifying women with preterm labor who ultimately will give birth preterm is difficult. Approximately 30% of preterm labor spontaneously resolves (26) and 50% of patients hospitalized for preterm labor actually give birth at term (27–29). Interventions to reduce the likelihood of delivery should be reserved for women with preterm labor at a gestational age at which a delay in delivery will provide benefit to the newborn. Because tocolytic therapy generally is effective for up to 48 hours (30), only women with fetuses that would benefit from a 48-hour delay in delivery should receive tocolytic treatment.

In general, tocolytics are not indicated for use before neonatal viability. Regardless of interventions, perinatal morbidity and mortality at that time are too high to justify the maternal risks associated with tocolytic therapy. Similarly, no data exist regarding the efficacy of corticosteroid use before viability. However, there may be times when it is appropriate to administer tocolytics before viability. For example, inhibiting contractions in a patient after an event known to cause preterm labor, such as intra-abdominal surgery, may be reasonable even at previable gestational ages, although the efficacy of such an intervention remains unproved (31, 32). The upper limit for the use of tocolytic agents to prevent preterm birth generally has been 34 weeks of gestation. Because of the possible risks associated with tocolytic and steroid therapies, the use of these drugs should be limited to women with preterm labor at high risk of spontaneous preterm birth. Tocolysis is contraindicated when the maternal and fetal risks of prolonging pregnancy or the risks associated with these drugs are greater than the risks associated with preterm birth (see Box 1).

▶ *Should women with preterm contractions but without cervical change be treated?*

Regular preterm contractions are common; however, these contractions do not reliably predict which women will have subsequent progressive cervical change (33). In a study of 763 women who had unscheduled triage visits for symptoms of preterm labor, only 18% gave birth before 37 weeks of gestation and only 3% gave birth within 2 weeks of presenting with symptoms (17). No evidence exists to support the use of prophylactic tocolytic therapy (34), home uterine activity monitoring, cerclage, or narcotics to prevent preterm delivery in women with contractions but no cervical change. Therefore, women with preterm contractions without cervical change, especially those with a cervical dilation of less than 2 cm, generally should not be treated with tocolytics.

Box 1. Contraindications to Tocolysis ⇦

- Intrauterine fetal demise
- Lethal fetal anomaly
- Nonreassuring fetal status
- Severe preeclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorioamnionitis
- Preterm premature rupture of membranes*
- Maternal contraindications to tocolysis (agent specific)

*In the absence of maternal infection, tocolytics may be considered for the purposes of maternal transport, steroid administration, or both.

▶ *Does the administration of antenatal corticosteroids improve neonatal outcomes?*

The most beneficial intervention for improvement of neonatal outcomes among patients who give birth preterm is the administration of antenatal corticosteroids. A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation who are at risk of delivery within 7 days. For women with ruptured membranes or multiple gestations who are at risk of delivery within 7 days, a single course of corticosteroids is recommended between 24 weeks and 34 weeks of gestation. A single course of corticosteroids may be considered starting at 23 weeks of gestation for pregnant women who are at risk of preterm delivery within 7 days, irrespective of membrane status (35–37). Recent data indicate that betamethasone decreases newborn respiratory morbidity when given to women in the late preterm period between 34 0/7 weeks and 36 6/7 weeks who are at risk of preterm delivery within 7 days and who have not previously received corticosteroids (38).

Administration of corticosteroids for pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding resuscitation and should be considered in that context.

A Cochrane meta-analysis of corticosteroids therapy before 34 weeks of gestation reinforces the beneficial effect of this therapy regardless of membrane status and concludes that a single course of antenatal corticosteroids should be considered routine for all preterm deliveries (39). The administration of antenatal corticosteroids to the woman who is at risk of imminent preterm birth is strongly associated with decreased neonatal morbidity and mortality (39–41). Neonates whose mothers receive antenatal corticosteroids have significantly lower severity, frequency, or both of respiratory distress syndrome (relative risk [RR], 0.66; 95% confidence interval [CI], 0.59–0.73), intracranial hemorrhage (RR, 0.54; 95% CI, 0.43–0.69), necrotizing enterocolitis (RR, 0.46; 95% CI, 0.29–0.74), and death (RR, 0.69; 95% CI, 0.58–0.81), compared with neonates whose mothers did not receive antenatal corticosteroids (39).

One randomized trial demonstrated that additional neonatal benefit could be derived from a single rescue course of corticosteroids (42). The investigators reserved this intervention for patients with intact membranes, if the antecedent treatment had been given at least 2 weeks before the rescue course, the gestational age was less than 33 weeks, and the women were judged by the clinician to be likely to give birth within the next week. A single repeat course of antenatal corticosteroids should, therefore, be considered in women who are less than 34 weeks of gestation, who are at risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario (38, 43). In the study of betamethasone in the late preterm period, patients who had received corticosteroids earlier in pregnancy were excluded, and it is unclear whether there is benefit to a repeat course of betamethasone in those women (38). Whether to administer a repeat or rescue course of corticosteroids with preterm premature rupture of membranes is controversial, and there is insufficient evidence to make a recommendation for or against.

Betamethasone and dexamethasone are the most widely studied corticosteroids and have been the preferred antenatal treatments to accelerate fetal organ maturation. The administration of betamethasone or dexamethasone has been shown to decrease neonatal mortality (44, 45). Treatment, for either a primary or a rescue course, should consist of either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone every 12 hours administered intramuscularly (45). Because treatment with corticosteroids for less than 24 hours is still associated with significant reductions in neonatal morbidity and mortality, a first dose of antenatal corticosteroids should be administered even if the ability to give the second dose is unlikely, based on the clinical scenario (36). However, no additional benefit has been demonstrated for courses of antenatal steroids with dosage intervals shorter than those outlined previously, often referred to as accelerated dosing, even when delivery appears imminent.

▶ *What is the role for magnesium sulfate for fetal neuroprotection?*

Early observational studies suggested an association between prenatal exposure to magnesium sulfate and the less frequent occurrence of subsequent neurologic morbidities (46–48). Subsequently, several large clinical studies have evaluated the evidence regarding magnesium sulfate, neuroprotection, and preterm births (49–53). A 2009 meta-analysis synthesized the results of the clinical trials of magnesium sulfate for neuroprotection (54). Pooling the results of the available clinical trials of magnesium sulfate for neuroprotection suggests that predelivery administration of magnesium sulfate reduces the occurrence of cerebral palsy when given with neuroprotective intent (RR, 0.71; 95% CI, 0.55–0.91) (55). Two subsequent meta-analyses of similar design have confirmed these results (56, 57).

None of the trials demonstrated significant pregnancy prolongation when magnesium sulfate was given for neuroprotection. Although minor maternal complications were more common with magnesium sulfate in the three major trials, serious maternal complications (eg, cardiac arrest, respiratory failure, and death) were not seen more frequently in these studies or in the larger meta-analyses (51–54).

Although the goal of each of the three major randomized clinical trials was to evaluate the effect of magnesium sulfate treatment on neurodevelopmental outcomes and death, comparison between the trials is made difficult by differences in inclusion and exclusion criteria, populations studied, magnesium sulfate regimens, gestational age at treatment, and outcome variables evaluated. However, accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation. Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and

specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials (6, 51–53).

▶ *Does tocolytic therapy improve neonatal outcomes?*

Tocolytic therapy may provide short-term prolongation of pregnancy, enabling the administration of antenatal corticosteroids and magnesium sulfate for neuroprotection, as well as transport, if indicated, to a tertiary facility. However, no evidence exists that tocolytic therapy has any direct favorable effect on neonatal outcomes or that any prolongation of pregnancy afforded by tocolytics actually translates into statistically significant neonatal benefit.

Contractions are the most commonly recognized antecedent of preterm birth. For this reason, cessation of uterine contractions has been the primary focus of therapeutic intervention. Many agents have been used to inhibit myometrial contractions, including magnesium sulfate, calcium channel blockers, oxytocin antagonists, nonsteroidal antiinflammatory drugs (NSAIDs), and beta-adrenergic receptor agonists (Table 1). Overall, the evidence supports the use of first-line tocolytic treatment with beta-adrenergic receptor agonists, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids (see Table 1) (30, 58, 59). One randomized trial suggested the potential role of transdermal nitroglycerine in short-term pregnancy prolongation, particularly those pregnancies at less than

Table 1. Common Tocolytic Agents ⇦

Agent or Class	Maternal Side Effects	Fetal or Newborn Adverse Effects	Contraindications
Calcium channel blockers	Dizziness, flushing, and hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate; and elevation of hepatic transaminases	No known adverse effects	Hypotension and preload-dependent cardiac lesions, such as aortic insufficiency
Nonsteroidal anti-inflammatory drugs	Nausea, esophageal reflux, gastritis, and emesis; platelet dysfunction is rarely of clinical significance in patients without underlying bleeding disorder	In utero constriction of ductus arteriosus*, oligohydramnios*, necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn†	Platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin)
Beta-adrenergic receptor agonists	Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia	Fetal tachycardia	Tachycardia-sensitive maternal cardiac disease and poorly controlled diabetes mellitus
Magnesium sulfate	Causes flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, and cardiac arrest; suppresses heart rate, contractility and left ventricular systolic pressure when used with calcium channel blockers; and produces neuromuscular blockade when used with calcium-channel blockers	Neonatal depression‡	Myasthenia gravis

*Greatest risk associated with use for longer than 48 hours.

†Data are conflicting regarding this association.

‡The use of magnesium sulfate in doses and duration for fetal neuroprotection alone does not appear to be associated with an increased risk of neonatal depression when correlated with cord blood magnesium levels. (Johnson LH, Mapp DC, Rouse DJ, Spong CY, Mercer BM, Leveno KJ, et al. Association of cord blood magnesium concentration and neonatal resuscitation. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. J Pediatr 2011;DOI: 10.1016/j.jpeds.2011.09.016.). [PubMed]

Modified from Hearne AE, Nagey DA. Therapeutic agents in preterm labor: tocolytic agents. Clin Obstet Gynecol 2000;43:787–801. [PubMed]

28 weeks of gestation. However, its use was associated with significant maternal side effects (60). Recommendations for its use would require additional data that demonstrate its efficacy and safety.

The use of magnesium sulfate to inhibit acute preterm labor has similar limitations when used for pregnancy prolongation (34, 61). However, if magnesium sulfate is being used in the context of preterm labor for fetal neuroprotection and the patient still is experiencing preterm labor, a different agent could be considered for short-term tocolysis. However, because of potential serious maternal complications, beta-adrenergic receptor agonists and calcium-channel blockers should be used with caution in combination with magnesium sulfate for this indication. Before 32 weeks of gestation, indomethacin is a potential option for use in conjunction with magnesium sulfate. Several retrospective case–control studies and cohort studies evaluated neonatal outcomes, including necrotizing enterocolitis, after short-term antenatal indomethacin therapy (62–66). They have shown conflicting results regarding duration of therapy, gestational age at exposure, and the interval between exposure and delivery. As with all other tocolytics, indomethacin for short-term treatment of preterm labor should be used after carefully weighing the potential benefits and risks.

In 2011, the U.S. Food and Drug Administration (FDA) issued a warning regarding the use of terbutaline to treat preterm labor because of reports of serious maternal side effects (67). Another review reported possible deleterious behavioral effects in offspring after in utero exposure to beta-adrenergic receptor agonists (68). These data suggest that the use of terbutaline should be limited to short-term inpatient use as a tocolytic or for the acute antepartum therapy of uterine tachysystole.

▶ *Should tocolytics be used after acute therapy?*

Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose. A meta-analysis has not shown any differences between magnesium sulfate maintenance therapy and either placebo or beta-adrenergic receptor agonists in preventing preterm birth after an initial treated episode of threatened preterm labor (69). Likewise, maintenance beta-agonist therapy has not been demonstrated to prolong pregnancy or prevent preterm birth and should not be used for this purpose (70). The FDA posted warnings specifically cautioning against the use of maintenance oral terbutaline during pregnancy (67). Because of the lack of efficacy and potential maternal risk, the FDA states that oral terbutaline should not be used at all to treat preterm labor. Injectable terbutaline may be used only in an inpatient, monitored setting but should not be used for longer than 48–72 hours (67). When compared with placebo, maintenance tocolysis with nifedipine does not appear to confer a reduction in preterm birth or improvement in neonatal outcomes (71). Atosiban is the only tocolytic that has demonstrated superiority as maintenance therapy over placebo in prolonging pregnancy, but atosiban is not available in the United States (72).

▶ *Is there a role for antibiotics in preterm labor?*

Intrauterine bacterial infection is an important cause of preterm labor, particularly at gestational ages less than 32 weeks (73, 74). It has been theorized that infection or inflammation is associated with contractions. Based on this concept, the utility of antibiotics to prolong pregnancy and reduce neonatal morbidity in women with preterm labor and intact membranes has been evaluated in numerous randomized clinical trials. However, most have failed to demonstrate antibiotic benefit; a meta-analysis of eight randomized controlled trials that compared antibiotic treatment with placebo for patients with documented preterm labor found no difference between the antibiotic treatment and placebo for prolonging pregnancy or preventing preterm delivery, respiratory distress syndrome, or neonatal sepsis (58). In fact, antibiotic use may be associated with long-term harm (75). Thus, antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labor and intact membranes. This recommendation is distinct from recommendations for antibiotic use for preterm premature rupture of membranes (76) and group B streptococci carrier status (77, 78).

▶ *Is there a role for nonpharmacologic management of women with preterm contractions or preterm labor?*

The assessment of preterm delivery risk based on symptoms and physical examination alone is inaccurate (17, 79, 80). Previously, when symptoms of possible preterm labor were present, clinicians recommended reduced maternal activity and hydration with or without sedatives, with the aim of reducing uterine activity. Most experts advocated awaiting cervical dilation or effacement before administering tocolytic drugs. However, prophylactic therapy (tocolytic drugs, bed rest, hydration, and sedation) in asymptomatic women at increased risk of preterm delivery has not been demonstrated to be effective (41, 81). Although bed rest and hydration have been recommended to women with symptoms of preterm labor to prevent preterm delivery, these measures have not been shown to be effective for the prevention of preterm birth and should not be routinely recommended.

Furthermore, the potential harm, including venous thromboembolism, bone demineralization, and deconditioning, and the negative effects, such as loss of employment, should not be underestimated (13–16, 82, 83).

▶ *Is preterm labor managed differently in women with multiple gestations?*

The use of tocolytics to inhibit preterm labor in multiple gestations has been associated with a greater risk of maternal complications, such as pulmonary edema (84, 85). In addition, prophylactic tocolytics have not been shown to reduce the risk of preterm birth or improve neonatal outcomes in women with multiple gestations (86–89). Adequate data do not exist to specifically demonstrate benefit from the use of antenatal corticosteroids in multiple gestations. However, because of the clear benefit attributable to the use of antenatal corticosteroids in singleton gestations, most experts recommend their use in preterm multiple gestations. Similar extrapolation could also apply to the use of magnesium sulfate for fetal neuroprotection in multiple gestations.

Summary of Recommendations

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation who are at risk of delivery within 7 days.
- Accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation. Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.
- The evidence supports the use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.
- Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose.
- Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labor and intact membranes.

The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):

- For women with ruptured membranes or multiple gestations who are at risk of delivery within 7 days, a single course of corticosteroids is recommended between 24 weeks and 34 weeks of gestation.
- A single course of corticosteroids may be considered starting at 23 weeks of gestation for pregnant women who are at risk of preterm delivery within 7 days, irrespective of membrane status.
- A single repeat course of antenatal corticosteroids should, therefore, be considered in women who are less than 34 weeks of gestation, who are at risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario.
- Bed rest and hydration have not been shown to be effective for the prevention of preterm birth and should not be routinely recommended.
- The positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms.

Proposed Performance Measure

The proportion of women with preterm labor at less than 34 weeks of gestation who receive corticosteroid therapy

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990 and October 2008. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

The American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

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