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CLINICAL MANAGEMENT GUIDELINES FOR
OBSTETRICIAN–GYNECOLOGISTS

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This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of John M. Thorp Jr, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Reaffirmed 2008



Management of Preterm Labor

Preterm birth is the leading cause of neonatal mortality in the United States, and preterm labor precedes 40–50% of preterm births (1–3). Preterm birth accounts for 35% of all U.S. health care spending for infants and 10% of all such spending for children (4). Approximately 467,000 live births annually (11.5% of all live births) occur before term in the United States, and preterm births are responsible for three quarters of neonatal mortality and one half of long-term neurologic impairments in children (1, 5–7). The purpose of this document is to present the various methods proposed to manage preterm labor and the evidence for their roles in clinical practice. Despite the numerous management methods proposed, the incidence of preterm birth has changed little over the past 40 years (Fig. 1) (1, 8, 9). Uncertainty persists about the best strategies for managing preterm labor.

Background

Preterm labor generally can be defined as regular contractions that occur before 37 weeks of gestation and are associated with changes in the cervix. Although the causes of preterm labor are not well understood, the incidence and burden of preterm births are more clear. Preterm labor is the most common cause of antenatal hospitalization (10). It is important to recognize that preterm labor is not the only mechanism leading to preterm birth; numerous preterm births are preceded by either rupture of membranes or other medical problems (Fig. 2) (10, 11).

Historically, nonpharmacologic treatments to prevent preterm births in women who have symptoms of preterm labor have included bed rest, abstinence from intercourse and orgasm, and hydration, either orally or parenterally. The effectiveness of these interventions is uncertain.

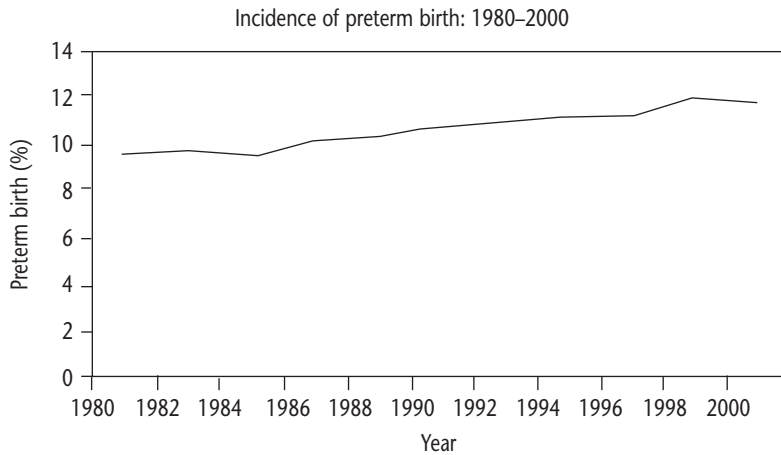


Figure 1. Incidence of preterm birth: 1980–2000. (Data from Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM, Sutton PD. Births: final data for 2001. Natl Vital Stat Rep 2002;51:1–104; Ventura SJ, Martin JA, Curtin SC, Mathews TJ. Report of final natality statistics, 1996. Monthly vital statistics report; vol. 46, no. 11, suppl. Hyattsville (MD): National Center for Health Statistics; 1998; and Ventura SJ, Martin JA, Taffel SM, Matthews ST, Clarke SC. Advance report of final natality statistics, 1992. Monthly vital statistics report; vol. 43, no. 5, suppl. Hyattsville (MD): National Center for Health Statistics; 1994.)

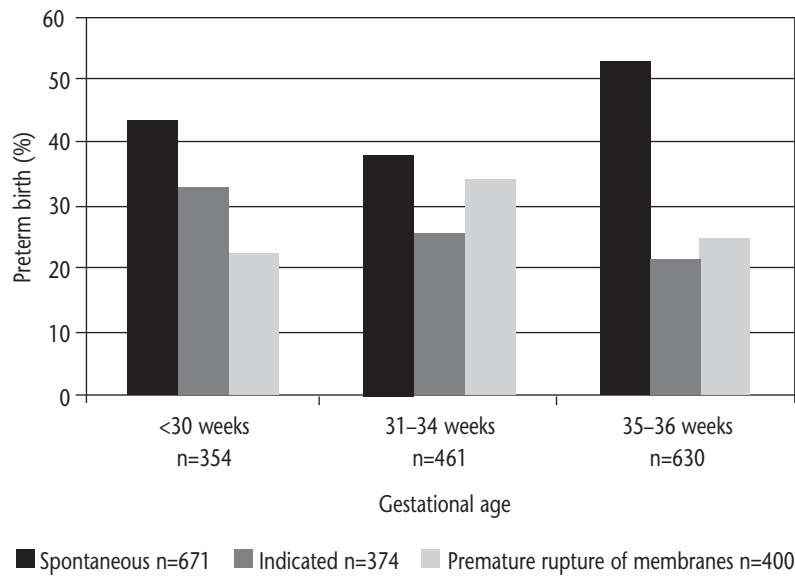


Figure 2. Gestational age distributions of spontaneous, indicated, and premature rupture of membranes preterm births. (Modified from Tucker JM, Goldenberg RL, Davis RO, Copper RL, Winkler CL, Hauth JC. Etiologies of preterm birth in an indigent population: is prevention a logical expectation? *Obstet Gynecol* 1991; 77:343–7.)

Tocolytic Drugs for Treatment of Preterm Labor

Tocolytic drugs inhibit myometrial contractions. Many agents have been used, including ethanol, magnesium sulfate, calcium channel blockers, oxytocin antagonists, nonsteroidal antiinflammatory drugs (NSAIDs), and beta-mimetic agonists. Tocolytics can be administered either parenterally or orally. Table 1 describes various tocolytic drugs, their mechanisms of action, and their side effects.

Antibiotics for Treatment of Preterm Labor

Women who present with symptoms of preterm labor may have infections of the upper genital tract (12, 13). It has been theorized that infections or inflammation are associated with contractions, and this theory provided the rationale for studies using antibiotics to decrease the risk of spontaneous preterm birth. Studies have shown mixed results, but most of the evidence has

Table 1. Tocolytics for Preterm Labor

Tocolytic Agent	Dosage and Administration	Contraindications	Maternal Side Effects	Fetal and Neonatal Side Effects
Beta-mimetic	Terbutaline, .25 mg subcutaneously every 20 min to 3 hr (hold for pulse >120 beats per minute)	Cardiac arrhythmias	Cardiac or cardiopulmonary arrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia	Fetal tachycardia, hyperinsulinemia, hyperglycemia, myocardial and septal hypertrophy, myocardial ischemia
	Ritodrine initial dose of 50–100 µg/min, increase 50 µg/min every 10 min until contractions cease or side effects develop	Poorly controlled thyroid disease	Metabolic hyperglycemia, hyperinsulinemia, hypokalemia, antidiuresis, altered thyroid function	Neonatal tachycardia, hypoglycemia, hypocalcemia, hyperbilirubinemia, hypotension, intraventricular hemorrhage
	Maximum dose = 350 µg/min	Poorly controlled diabetes mellitus	Physiologic tremor, palpitations, nervousness, nausea or vomiting, fever, hallucinations	—
Magnesium sulfate	4–6 g bolus for 20 min, then 2–3 g/hr	Myasthenia gravis	Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardiac arrest	Lethargy, hypotonia, respiratory depression, demineralization with prolonged use
Calcium channel blockers	30 mg loading dose, then 10–20 mg every 4–6 hr	Cardiac disease, use caution with renal disease, maternal hypotension (<90/50 mm Hg), avoid concomitant use with magnesium sulfate	Flushing, headache, dizziness, nausea, transient hypotension	None noted as yet
Prostaglandin synthetase inhibitors	Indomethacin loading dose of 50 mg rectally or 50–100 mg orally, then 25–50 mg orally every 6 hr × 48 hr	Significant renal or hepatic impairment	Nausea, heartburn	Constriction of ductus arteriosus, pulmonary hypertension, reversible decrease in renal function with oligohydramnios, intraventricular hemorrhage, hyperbilirubinemia, necrotizing enterocolitis
	Ketorolac loading dose of 60 mg intramuscularly, then 30 mg intramuscularly every 6 hr × 48 hr	Active peptic ulcer disease	—	—
	Sulindac, 200 mg orally every 12 hr × 48 hr	Coagulation disorders or thrombocytopenia, NSAID-sensitive asthma, other sensitivity to NSAIDs	—	—

Abbreviation: NSAIDs, nonsteroidal antiinflammatory drugs

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

failed to show a benefit from treatment with antibiotics (14–26).

Antenatal Corticosteroid Use

The most beneficial intervention for patients in true preterm labor is the administration of corticosteroids. A recent meta-analysis confirmed that antenatal corticosteroids significantly reduced the incidence and severity of neonatal respiratory distress syndrome (27). The incidence of intraventricular hemorrhage and necrotizing enterocolitis also are reduced by the use of antenatal corticosteroids. The administration of betamethasone has been shown to decrease neonatal mortality (28). All women who are at risk for preterm delivery between 24 weeks and 34 weeks of gestation are potential candidates for corticosteroid therapy. Treatment should consist of either two doses of betamethasone or four doses of dexamethasone, both administered intramuscularly.

Clinical Considerations and Recommendations

► *Who are appropriate candidates for intervention?*

In 80% of women with presumptive preterm labor, preterm delivery will not occur (29). Many factors influence the decision to intervene when women have symptoms of preterm labor, including the probability of progressive labor, gestational age, and the risks of treatment (30). Historically, the clinical criteria commonly suggested for determining when intervention is needed included regular uterine activity that does not diminish with bed rest or hydration, cervical change during an observation period, or a cervix that is dilated on presentation. However, all of these clinical conditions are inaccurate predictors of preterm delivery (31).

Gestational age is inversely proportional to the risk of neonatal morbidity and mortality. The upper limit of gestational age for the use of tocolytic drugs may be a function of the neonatal treatment capabilities in the hospital where a clinician practices. Examples of general contraindications for tocolysis may include severe preeclampsia, placental abruption, intrauterine infection, lethal congenital or chromosomal abnormalities, advanced cervical dilatation, and evidence of fetal compromise or placental insufficiency.

► *Are there tests that can help identify patients at risk for progressing to preterm birth?*

Many tests to identify women at risk of preterm birth have been proposed and evaluated; however, only ultra-

sonography and fetal fibronectin testing have been shown to have benefit (32–37). Ultrasonography to determine cervical length, fetal fibronectin testing, or a combination of both may be useful in determining which women are at high risk for preterm delivery. However, their clinical usefulness may rest primarily with their ability to identify women who are least likely to deliver (ie, their negative predictive value) given the lack of proven treatment options to prevent preterm birth. Fetal fibronectin testing may be useful in women with symptoms of preterm labor to identify those with negative values and a reduced risk of preterm birth, thereby avoiding unnecessary intervention (38).

► *Does tocolytic therapy improve neonatal outcome?*

Tocolytic drugs may prolong gestation for 2–7 days, which can provide time for administration of steroids and maternal transport to a facility with a neonatal intensive care unit (26). The benefits of prolonging pregnancy for 2–7 days are otherwise unclear (39–44).

► *Is there a clear “first-line” tocolytic drug?*

Comparison studies of the effectiveness of different tocolytic drugs show conflicting results between beta-mimetics, magnesium sulfate, calcium channel blockers, and NSAIDs (45–58). However, all have demonstrated only limited benefit. Hence, there is no clear first-line tocolytic drug. If tocolytic drugs are used, the choice of drug should be individualized and based on maternal condition, potential drug side effects, and gestational age (see Table 1). Prolonged use of any tocolytic drug may potentially increase the maternal–fetal risk without offering a clear benefit.

Serious adverse events are rare but potentially life-threatening. Beta-mimetics, magnesium sulfate, and calcium channel blockers are all associated with an increased risk of pulmonary edema. Beta-mimetics are potent cardiovascular stimulants and can cause serious complications, such as maternal myocardial ischemia, metabolic derangements (eg, hyperglycemia and hypokalemia), and fetal cardiac effects. Magnesium sulfate may cause maternal lethargy, drowsiness, double vision, nausea, and vomiting. The NSAIDs appear to have the fewest maternal risks, but fetal effects include oligohydramnios and premature closure of the ductus arteriosus. Calcium channel blockers used as a single agent appear to have a good maternal and fetal safety profile. However, concomitant use of calcium channel blockers and magnesium sulfate is potentially harmful and has resulted in cardiovascular collapse (59). Combining tocolytic drugs

potentially increases maternal morbidity and should be used with caution (60).

▶ ***Is there a role for adjunctive antibiotics?***

An array of antibiotics and bacteriostatic drugs have been evaluated in randomized, controlled trials to determine if they can prevent preterm birth in women with preterm labor, but these studies have reported mixed results. A recent meta-analysis assessed eight randomized controlled trials comparing antibiotic treatment with placebo for patients with documented preterm labor (26). No difference was noted between the antibiotic treatment and placebo for prolonging pregnancy or preventing preterm delivery respiratory distress syndrome or neonatal sepsis. Treating women in preterm labor with antibiotics for the sole purpose of preventing preterm delivery is not recommended (61). At present, it seems prudent to follow protocols for antibiotic prophylaxis against early-onset group B streptococcal sepsis, but there is little evidence that this approach also will prolong gestation (62).

▶ ***Is preventive treatment efficacious?***

Because of the large variations in symptoms of preterm labor and the inability of routine clinical tools to precisely determine a woman's risk, the assessment of preterm delivery risk is fraught with inaccuracy (29, 63, 64). Previously, when symptoms of preterm delivery were present, most clinicians handled this uncertainty by recommending reduced maternal activity and administering fluids with the aim of stopping the uterine activity. Most advocated awaiting clinical detection of cervical change before administering tocolytic drugs. Prophylactic therapy, including tocolytic drugs, bed rest, hydration, and sedation, in asymptomatic women at increased risk for preterm delivery has not been demonstrated to be effective (30, 61).

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

Regular preterm contractions are common. However, their presence does not reliably predict who will have subsequent progressive cervical change (65). In a study of 763 women who had unscheduled visits for symptoms of preterm labor, only 18% delivered before 37 weeks of gestation, and only 3% delivered within 2 weeks of presenting with symptoms (29). Although bed rest, pelvic rest, and hydration are commonly recommended to women with symptoms of preterm labor to prevent preterm delivery, the effectiveness of these measures is not known, and their potential harms (eg, thrombosis from stasis in the lower extremities) or negative impacts (eg, loss of employment) should not be underestimated

(66). No evidence exists to support the use of tocolytic therapy (67), home uterine activity monitoring, elective cerclage, or narcotics to prevent preterm delivery in women with contractions but no cervical change.

▶ ***Should women with multiple gestations be treated differently?***

Women with multiple gestations who have preterm contractions but no cervical change do not require tocolytic therapy. Although women with multiple gestations who are experiencing preterm labor may benefit from short-term tocolysis to allow for steroid administration, they have a greater risk of pulmonary edema when exposed to beta-mimetics or magnesium sulfate (68).

▶ ***Is there a role for maintenance treatment after completing acute treatment?***

Studies of maintenance tocolytic therapy in women who present with symptoms of preterm labor and receive tocolysis acutely show no differences in effectiveness between treatment and control groups (30). Meta-analysis likewise fails to demonstrate any benefit of maintenance tocolysis in terms of gestational age at birth, pregnancy prolongation, or birth weight (30). Prolonged oral, subcutaneous, or intravenous tocolytic treatment is not effective. Two prospective randomized trials showed the terbutaline pump was no more effective than saline (69, 70).

▶ ***Is tocolysis warranted for recurrent preterm labor?***

The role of repeated acute tocolytic therapy in women with recurring symptoms of preterm labor is unknown. Given the limited benefits of an initial course of treatment with a tocolytic drug and current recommendations that corticosteroids be administered only as a single course (71), the effectiveness of subsequent acute tocolysis is uncertain. Maternal transport is a potential rationale for a subsequent treatment course (72).

▶ ***Is there a role for amniocentesis?***

Amniocentesis to determine fetal lung maturity may have some benefit in guiding clinical decision making in women with symptoms of preterm labor. There is no evidence to suggest that routine amniocentesis to check for infection in these women can provide information that could be used to improve perinatal outcomes (30). In a multicenter study in women with preterm labor and intact membranes, the overall prevalence of microbial invasion of the amniotic cavity as documented by amniocentesis was 5.8% (17). Both amniotic fluid Gram stain and glu-

case levels have been used as rapid diagnostic tests of intraamniotic infection (73, 74). The results of amniotic fluid cultures, the best method for diagnosing intraamniotic infection, are unlikely to be available quickly enough to affect decision making.

Summary of Recommendations

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

- ▶ There are no clear “first-line” tocolytic drugs to manage preterm labor. Clinical circumstances and physician preferences should dictate treatment.
- ▶ Antibiotics do not appear to prolong gestation and should be reserved for group B streptococcal prophylaxis in patients in whom delivery is imminent.
- ▶ Neither maintenance treatment with tocolytic drugs nor repeated acute tocolysis improve perinatal outcome; neither should be undertaken as a general practice.
- ▶ Tocolytic drugs may prolong pregnancy for 2–7 days, which may allow for administration of steroids to improve fetal lung maturity and the consideration of maternal transport to a tertiary care facility.

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

- ▶ Cervical ultrasound examination and fetal fibronectin testing have good negative predictive value; thus, either approach or both combined may be helpful in determining which patients do not need tocolysis.
- ▶ Amniocentesis may be used in women in preterm labor to assess fetal lung maturity and intraamniotic infection.
- ▶ Bed rest, hydration, and pelvic rest do not appear to improve the rate of preterm birth and should not be routinely recommended.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and January 2003. 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.

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