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Medical Policy



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Title: Acute and Maintenance Tocolysis

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: • With preterm labor or threatened preterm labor	Interventions of interest are: • Acute tocolytic therapy	Comparators of interest are: • No tocolytic therapy	Relevant outcomes include: • Overall survival • Morbid events • Functional outcomes • Treatment-related morbidity
Individuals: • With successful acute tocolysis for preterm labor	Interventions of interest are: • Maintenance tocolytic therapy	Comparators of interest are: • No tocolytic therapy	Relevant outcomes include: • Overall survival • Morbid events • Functional outcomes • Treatment-related morbidity

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DESCRIPTION

Tocolysis refers to the suppression of preterm labor to delay delivery. A variety of medications are used as tocolytic agents, although none are currently approved by the U.S. Food and Drug Administration (FDA) for the purpose of suppressing labor. These medications have also been evaluated as maintenance therapy following successful tocolysis.

OBJECTIVE

The objectives of this policy are to determine whether (a) acute or (b) maintenance tocolytic therapy improves the net health outcome in individuals (a) who have or are at risk of preterm labor or (b) who have had successful tocolytic therapy.

BACKGROUND

Tocolysis

General indications for tocolysis, or the suppression of preterm labor, include continued regular uterine contractions associated with cervical changes in a pregnant woman at less than 37 weeks' gestation. Successful delay of preterm delivery allows further fetal development and precludes potential complications of preterm delivery, especially neonatal respiratory distress syndrome (RDS). Even short-term delay of delivery is thought to be beneficial in that it allows treatment of the patient with corticosteroids, which has proved beneficial in ameliorating the effects of neonatal RDS. In some cases, a short delay in delivery may also allow transport of the pregnant woman to a medical center better equipped to handle premature delivery and neonatal intensive care.

Treatment

Several agents have been used for tocolysis. The only tocolytic drug approved by the U.S. Food and Drug Administration (FDA) has been ritodrine, a beta-sympathomimetic. Ritodrine is no longer available in the United States, and thus only off-label medications are available. Terbutaline sulfate, FDA-approved for several nontocolytic indications, is also a beta-sympathomimetic. Terbutaline is available as an oral or intravenous medication and, more recently, has been administered by continuous subcutaneous infusion via a portable pump for maintenance tocolysis. Other tocolytic drugs include calcium channel blockers (eg, nifedipine), magnesium sulfate, oxytocin receptor antagonists (eg, atosiban), prostaglandin inhibitors (eg, indomethacin), and nitrates (eg, nitroglycerin).

Tocolytic agents have potential risks and benefits. The 2012 guidelines (reaffirmed 2014) issued by the American College of Obstetricians and Gynecologists summarized the potential adverse events of common classes of tocolytic agents¹:

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Calcium Channel Blockers

- Maternal side effects: dizziness, flushing, and hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate; and elevation of hepatic transaminases
- Fetal or newborn adverse events: no known adverse effects

Nonsteroidal Anti-inflammatory Drugs

- Maternal side effects: nausea, esophageal reflux, gastritis, and emesis; platelet dysfunction is rarely of clinical significance in patients without underlying bleeding disorder
- Fetal or newborn adverse events: in utero constriction of ductus arteriosus,* oligohydramnios,* necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn†

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

† Data are conflicting on this association.

Beta-Adrenergic Receptor Agonists

- Maternal side effects: tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia
- Fetal or newborn adverse events: fetal tachycardia

Magnesium Sulfate

- Maternal side effects: 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
- Fetal or newborn adverse events: neonatal depression (note: 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)

REGULATORY STATUS

FDA approved ritodrine for use as a tocolytic agent. Ritodrine was voluntarily withdrawn from the U.S. market in 1998.

Terbutaline has been approved by FDA for the prevention and treatment of bronchospasm in patients with asthma and reversible bronchospasm associated with bronchitis and emphysema. Like other tocolytic agents, its use for tocolysis is off-label. In response to a 2008 citizen petition, FDA reviewed safety data on terbutaline sulfate. FDA issued a safety announcement on February 2011.² Based on animal studies, FDA reclassified terbutaline from pregnancy risk category B to pregnancy risk category C. In

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addition, FDA required a boxed warning stating that injectable terbutaline should not be used for prevention or prolonged (beyond 2 to 3 days) treatment of preterm labor, and oral terbutaline should not be used for acute or maintenance tocolysis. The labeling change was based on a review of postmarketing safety reports submitted to the FDA's Adverse Event Reporting System of maternal death and serious maternal cardiovascular events associated with the use of terbutaline.

POLICY

- A. Acute tocolytic therapy with calcium channel blockers, magnesium sulfate, prostaglandin inhibitors, and parenteral terbutaline may be considered **medically necessary** for induction of tocolysis in patients with preterm (<37 weeks gestational age) labor.

- B. Maintenance (beyond 48-72 hours) tocolytic therapy with any medication is considered **experimental / investigational**.

Policy Guidelines

Patient selection criteria for induction of tocolysis include regular uterine contractions associated with cervical changes. Induction of tocolysis typically requires hospitalization to monitor for incipient delivery.

RATIONALE

The literature was reviewed through June 4, 2018. Following is a summary of the literature to date.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

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preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Acute Tocolysis

Clinical Context and Therapy Purpose

The purpose of acute tocolysis in patients who have preterm labor is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does acute tocolysis improve the net health outcome in women with or at risk of preterm labor?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women experiencing or at risk of preterm labor.

Interventions

The therapy being considered is acute tocolysis. Tocolytic medications include terbutaline sulfate, calcium channel blockers (eg, nifedipine), magnesium sulfate, oxytocin receptor antagonists (eg, atosiban), prostaglandin inhibitors (eg, indomethacin), and nitrates (eg, nitroglycerin)

Comparators

The following practice is currently being used to make decisions about reducing or mitigating the risk and harms of preterm labor: no tocolytic therapy.

Outcomes

The outcomes of interest are the gestational age at birth, morbidity and mortality of the infant, and adverse events of treatment on the mother.

Timing

The timing of therapy is the 24- to 72-hour period during which tocolysis occurs and the gestational age in weeks.

Setting

Therapy is administered in an inpatient care setting by a specialist (eg, obstetrician-gynecologist).

Systematic Reviews

Studies have focused on whether tocolytic agents prevent preterm delivery and thereby reduce associated maternal and neonatal risks. Numerous RCTs on acute tocolysis have been published and Haas et al (2009) conducted a comprehensive systematic review and meta-analysis of RCTs.⁴ They included 58 studies that directly compared different tocolytic medications or compared 1 medication with placebo or usual care. Studies were selected if they compared 2 drugs in the

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same class but excluded if they included 2 doses of the same medication. Participants were women diagnosed with preterm labor or threatened preterm labor. The analysis was limited to studies with fetuses of mean gestational ages between 28 weeks and 32 weeks of gestation. Multiple gestations was not an exclusion criterion—but if trials stratified on this variable, only data on singleton pregnancies were used. Data were extracted for each outcome and combined by drug class to calculate a weighted mean and standard error for proportions of successful events; proportions were weighted based on the number of participants in each study. Primary efficacy and safety outcomes are as follows in Tables 1 and 2.

Table 1. Effect of Tocolytics on Delaying Birth (Weighted Percentage of Women Experiencing Outcome)

Medication Class	48-Hour Delay		7-Day Delay		After 37 Weeks	
	No. of Studies	Percent (95% CI)	No. of Studies	Percent (95% CI)	No. of Studies	Percent (95% CI)
Placebo/control	9	53 (45 to 61)	8	39 (28 to 49)	3	36 (20 to 52)
Betamimetics	29	75 (65 to 85)	26	65 (59 to 71)	15	46 (36 to 56)
Calcium channel blockers	17	76 (57 to 95)	10	62 (56 to 69)	12	47 (32 to 62)
Magnesium sulfate	11	89 (85 to 93)	5	61 (39 to 84)	7	42 (31 to 53)
Oxytocin receptor antagonists	8	86 (80 to 91)	6	78 (68 to 88)		No data
Prostaglandin inhibitors	8	93 (90 to 95)	3	76 (67 to 85)	4	43 (6 to 79)

Adapted from Haas et al (2009).⁴

CI: confidence interval.

Table 2. Adverse Maternal and Neonatal Events Associated with Tocolytics (Weighted Percentage of Women/Neonates Experiencing Outcome)

Medication Class	Maternal Adverse Events ^a		Neonates With RDS		Neonatal Death	
	No. of Studies	Percent (95% CI)	No. of Studies	Percent (95% CI)	No. of Studies	Percent (95% CI)
Placebo/control	6	(0 to 2)	3	21 (17 to 26)	6	1 (0 to 2)
Betamimetics	32	14 (9 to 18)	17	13 (8 to 18)	32	14 (9 to 18)
Calcium channel blockers	16	1 (0 to 3)	11	19 (4 to 33)	16	1 (0 to 3)
Magnesium sulfate	16	3 (1 to 6)	9	16 (11 to 20)	16	3 (1 to 6)
Oxytocin receptor antagonists	6	2 (0 to 5)	5	14 (8 to 21)	6	2 (0 to 5)
Prostaglandin inhibitors	6	0 (0 to 2)	4	2 (0 to 4)	6	0 (0 to 2)

Adapted from Haas et al (2009).⁴

CI: confidence interval; RDS: respiratory distress syndrome.

^aMaternal adverse events are those that required discontinuation of the medication.

All tocolytic agents were significantly better than placebo/control at delaying delivery for 48 hours and for 7 days; none significantly improved delivery rates until after 37 weeks of gestation. The rate of discontinuation due to adverse events was significantly higher for betamimetics than placebo/control but not for any other categories of medication.

Reviewers also conducted a decision analysis to determine the optimal medication based on the balance of benefits and risks. The decision analysis model found that prostaglandin inhibitors might be the superior agent up to 32 weeks of gestation due to a high effectiveness at delaying delivery by at least 7 days and offering a low rate of adverse events. Calcium channel blockers were the superior agent for delaying delivery until 37 weeks. Compared with other tocolytics,

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calcium channel blockers reduced the incidence of birth within 7 days of treatment (relative risk [RR], 0.76; 95% confidence interval [CI], 0.60 to 0.97) and before 34 weeks of gestation (RR=0.83; 95% CI, 0.69 to 0.99).

In another review, Haas et al (2012) conducted a systematic review and network meta-analysis in which direct and indirect evidence on relative impacts of tocolytics on health outcomes were pooled simultaneously.⁵ Consequently, the analysis was not limited to comparisons in head-to-head trials that the research team had addressed in 2009. Reviewers identified 95 RCTs: 25 contained a placebo arm, 60 included betamimetics, 29 included magnesium sulfate, 29 included calcium channel blockers, 18 included prostaglandin inhibitors, 13 included oxytocin receptor blockers, 4 included nitrates, and 5 included "other" drugs. Reviewers assumed that all drugs in the same class had a similar effect.

Fifty-five studies were included in the network analysis for the primary efficacy outcome, delivery delayed by 48 hours. All active classes were found to be superior to placebo. The analysis also suggested that prostaglandin inhibitors had a greater beneficial effect than any other active class of medication, and calcium channel blockers and magnesium sulfate had a greater beneficial effect than oxytocin receptor blockers, nitrates, and betamimetics. Prostaglandin inhibitors had an 83% probability of being the "best" class of active medications. The probability of being ranked among the 3 most efficacious classes was 96% for prostaglandin inhibitors, 63% for magnesium sulfate, 57% for calcium channel blockers, 33% for betamimetics, 24% for nitrates, and 14% for oxytocin receptor blockers.

Forty trials were included in the network analysis for the outcome of neonatal mortality. There was no clear evidence for any class of medication being superior to placebo. Calcium channel blockers were found to be the "best" class, but the probability was only 41%, which reflects the considerable uncertainty in the estimate. Prostaglandin inhibitors had a 28% chance of being the "best" class, which was the second highest probability of any class. Similarly, calcium channel blockers were the "best" class for reducing neonatal respiratory distress syndrome (RDS), but the probability was only 47%.

Fifty-eight trials were included in the network analysis for the outcome all-cause maternal side effects. Other than placebo, prostaglandin inhibitors had a 79% chance of being the drug class with the fewest maternal side effects. This was followed by oxytocin receptor blockers, at 70% probability, and calcium channel blockers, at 15%.

Overall, prostaglandin inhibitors and calcium channel blockers had the highest probability of being the best classes of medication based on all 4 outcome measures: delivery delayed by 48 hours, neonatal mortality, neonatal RDS, and maternal side effects.

Several systematic reviews and meta-analyses have focused on a single tocolytic class or agent. A Cochrane review by Flenady et al (2014) identified 38 trials evaluating calcium channel blockers for tocolysis (total N=3550 women).⁶ The calcium channel blocker was nifedipine in 35 trials and nifedipine in the other 3. Thirty-five trials used other tocolytic agents as the comparator (19 used betamimetics), one compared doses of nifedipine, and the other two compared calcium

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channel blockers with placebo or no intervention. Only 1 trial was double-blinded. Reviewers evaluated several primary and secondary outcomes and conducted pooled analyses when sufficient data were available. Findings were mixed among primary outcomes, but several favored calcium channel blockers over betamimetics. There was a significantly lower rate of “very preterm birth” before 34 weeks of gestation with calcium channel blockers compared with betamimetics (6 trials; RR=0.78; 95% CI, 0.66 to 0.93) and a significantly lower rate of maternal adverse events (15 trials; RR=0.36; 95% CI, 0.24 to 0.53). The incidence of birth less than 48 hours after trial entry and the rate of perinatal mortality did not differ significantly between calcium channel blockers and other tocolytic agents. Among secondary outcome measures, there was a significantly lower rate of preterm birth before completion of 37 weeks of gestation with calcium channel blockers compared with betamimetics (13 trials; RR=0.89; 95% CI, 0.80 to 0.98), and there were too few studies to compare with other tocolytic agents. Reviewers noted that the quality of studies (eg, lack of blinding, limited placebo controls) limited the ability to draw firm conclusions about the efficacy of calcium channel blockers compared with other tocolytic agents.

An updated Cochrane review by Flenady et al (2014) identified 14 trials on oxytocin inhibitors (total N=2485 women).⁷ The control intervention was a placebo in 4 trials, betamimetics in 8 trials, and a calcium channel blocker in 2 studies. Pooled analyses did not demonstrate the superiority of oxytocin receptor antagonists over betamimetics or placebo in terms of reduction in preterm birth or adverse neonatal outcomes (note that oxytocin inhibitors are not approved by the Food and Drug Administration for use in the United States).

In another Cochrane review, Crowther et al (2014) identified 37 trials (total N=3571 women) evaluating the use of tocolysis.⁸ Comparison interventions included other tocolytic drugs, predominantly betamimetics, nitroglycerine, human chorionic gonadotropin, saline, and dextrose. No placebo-controlled trials were identified. Pooled analyses found no statistically significant differences between magnesium sulfate and comparator interventions for outcomes including birth less than 48 hours after trial entry, serious infant adverse events, and preterm birth before 37 weeks of gestation.

Conde-Agudelo et al (2011) reviewed trials on nifedipine.⁹ They identified 26 randomized trials (total N=2179 women) comparing nifedipine with placebo, no treatment, or a different tocolytic agent. Twenty-three trials evaluated acute tocolysis and 3 evaluated maintenance tocolysis (discussed later in the Rationale section). Findings were mixed. Pooled analyses of trials comparing nifedipine with beta-agonists found significantly lower rates of delivery within 7 days of treatment (10 trials; RR=0.82; 95% CI, 0.70 to 0.97) and preterm birth before 34 weeks of gestation (5 trials; RR=0.77; 95% CI, 0.66 to 0.91), but no significant differences in the rates of preterm delivery within 48 hours of treatment (13 trials; RR=0.84, 95% CI, 0.68 to 1.05) or preterm delivery before 37 weeks of gestation (9 trials; RR=0.97; 95% CI, 0.87 to 1.08). There were no significant differences in any of the preterm delivery variables when nifedipine was compared with magnesium sulfate, but the number of trials and total sample sizes were both small, making it difficult to draw conclusions about comparative efficacy.

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A Cochrane review by King et al (2005) included 13 trials on cyclooxygenase inhibitors (total N=713 women); indomethacin was used in 10 of the trials.¹⁰ Only 1 trial compared cyclooxygenase inhibitors with placebo. Pooled analysis of studies comparing cyclooxygenase inhibitors with other tocolytics found a significant reduction in the incidence of birth before 37 weeks of gestation (RR=0.53; 54 women). Reviewers noted that sample sizes were small, and thus estimates were imprecise and not definitive.

In addition to these reviews of single agents, Vogel et al (2014) published a Cochrane review on combinations of tocolytic agents for preventing preterm labor.¹¹ Reviewers searched for RCTs comparing any combination of tocolytic agents with any other treatment (including other combinations, single tocolytic agents, no intervention, or placebo). Eleven trials evaluating 7 different comparisons met reviewers' inclusion criteria; two of them did not report relevant outcome data. Thus, few studies with small combined sample sizes were available for analysis, and reviewers could not pool data or draw conclusions about the safety and efficacy of any combination of tocolytics vs any comparator intervention.

Section Summary: Acute Tocolysis

Multiple RCTs and systematic reviews have found tocolytics to be effective at decreasing rates of preterm birth in women with preterm labor (eg, delaying delivery for 7 days and/or decreasing rates of delivery before 34 or 37 weeks of gestation). The optimal first-line medication is uncertain. A 2012 network meta-analysis suggested that prostaglandin inhibitors and calcium channel blockers may have greater efficacy and fewer adverse events than other classes of medication. However, there was considerable uncertainty in the estimates of which class of medication was "best" for each outcome. Cochrane reviews of various tocolytic agents have not found any single agent to be superior to another.

Maintenance of Tocolysis

Clinical Context and Therapy Purpose

The purpose of maintenance of tocolysis in patients who have had preterm labor is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does maintenance with tocolytic agents improve the net health outcome in women who have had successful tocolytic therapy for preterm labor?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women treated successfully with tocolytic agents for preterm labor.

Interventions

The therapy being considered is maintenance tocolysis. Tocolytic medications include terbutaline sulfate, calcium channel blockers (eg, nifedipine), magnesium sulfate, oxytocin receptor

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antagonists (eg, atosiban), prostaglandin inhibitors (eg, indomethacin), and nitrates (eg, nitroglycerin).

Comparators

The following practice is currently being used to make decisions about use of maintenance tocolysis to prevent recurrence of preterm labor: no tocolytic therapy.

Outcomes

The outcomes of interest are the gestational age at birth, morbidity and mortality of the infant, and adverse effects of treatment on the mother.

Timing

The timing is up to 37 weeks gestation.

Setting

Therapy is administered in an inpatient care setting by a specialist (eg, obstetrician-gynecologist).

Systematic Reviews

A Cochrane review by Papatsonis et al (2013), evaluating maintenance therapy with oxytocin antagonists, identified only 1 trial.¹² This trial, by Valenzuela et al (2000), did not find that atosiban reduced the rate of preterm birth after threatened preterm birth compared with placebo.¹³

Another Cochrane review, conducted by Naik Gaunekar et al (2013), identified 6 RCTs on maintenance therapy with calcium channel blockers.¹⁴ Nifedipine was used in all trials, and a total of 794 women were included. The comparison intervention was placebo in 3 trials and no treatment in the other 3 trials. Pooled analyses did not find that calcium channel blockers significantly reduced the rate of preterm birth before 37 weeks (5 trials; RR=0.97; 95% CI, 0.87 to 1.09) or 34 weeks (3 trials; RR=1.07; 95% CI, 0.88 to 1.30). A pooled analysis of 2 trials did not find significant differences between calcium channel blockers and controls for the outcome birth within 48 hours of treatment. There were insufficient data to draw conclusions about other outcomes.

Dodd et al (2012) conducted a Cochrane review on oral betamimetics for maintenance tocolysis after threatened preterm labor.¹⁵ They identified 13 RCTs, some of which had more than 2 arms. There were 10 comparisons of a betamimetic and placebo or no treatment, 1 comparison of a betamimetic and indomethacin, 1 comparison between 2 different betamimetics, and 3 comparisons between a betamimetic and magnesium. Data could not be pooled in a number of outcomes due to insufficient data on a particular comparison. In a pooled analysis of 6 studies, there was no statistically significant difference in the rate of preterm birth before 37 weeks in patients receiving a maintenance betamimetic vs placebo or no treatment (RR=1.11; 95% CI, 0.91 to 1.35). In other pooled analyses of findings from studies comparing maintenance betamimetics with placebo or no treatment, there were no statistically significant differences between groups in birth weight (7 studies; mean difference, 4.13; 95% CI, -91.89 to 100.16),

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risk of perinatal mortality (6 studies; RR=2.41; 95% CI, 0.86 to 6.74), or risk of RDS in infants (6 studies; RR=1.10; 95% CI, 0.61 to 1.98).

A review by Han et al (2010) evaluated magnesium maintenance therapy and did not find a statistically significant effect of that maintenance therapy on prevention of preterm birth before 37 weeks of gestation.¹⁶ A meta-analysis of 2 studies (n=99 patients) that compared magnesium therapy with placebo or no treatment found a combined RR of 1.05 (99% CI, 0.80 to 1.40). Two studies (n=100 patients) were also available for a meta-analysis of studies comparing magnesium therapy with an alternative treatment. In that analysis, the combined RR was 0.99 (95% CI, 0.57 to 1.72).

The Conde-Agudelo systematic review and meta-analysis (2011), described earlier, included 3 studies evaluating a calcium channel blocker (nifedipine) for maintenance tocolysis.⁹ A pooled analysis of these 3 trials (n=215 patients) did not find a significant difference in the rate of preterm birth before 37 weeks of gestation with nifedipine or with placebo or no treatment (RR=0.87; 97% CI, 0.69 to 1.08). There were insufficient data to conduct pooled analyses on other pregnancy outcome variables.

A health technology assessment by Honest et al (2009) addressed a wider range of maintenance tocolytic agents.¹⁷ However, for the outcomes prevention of preterm birth before 34 or 37 weeks of gestation, there were only a sufficient number of trials to conduct pooled analyses for 2 comparisons. Neither analysis found a statistically significant benefit of tocolysis. In a pooled analysis comparing magnesium maintenance therapy with other tocolytic agents, the combined RR was 0.98 (95% CI, 0.56 to 1.72). In addition, a pooled analysis of 4 trials (n=384 patients) did not find a significant benefit of oral betamimetics compared with placebo or no treatment for preventing preterm birth before 37 weeks of gestation. The combined RR was 1.08 (95% CI, 0.88 to 1.22).

Nonrandomized Studies

Follow-up data from the APOSTEL II trial were reported by van Vliet et al (2016) on maintenance tocolysis using nifedipine.¹⁸ Two-year outcomes data from this RCT were available for 135 (52.5%) of 276 participants. Outcomes were mixed for infants of women in the nifedipine maintenance group compared with the placebo group. Those on nifedipine maintenance doses had a higher incidence of fine motor problems (22% vs 8%, odds ratio, 3.43; 95% CI, 1.29 to 9.14) and a lower incidence of poor problem-solving ability (22% vs 29%; odds ratio, 0.27; 95% CI, 0.08 to 0.95).

Section Summary: Maintenance of Tocolysis

There are fewer RCTs comparing maintenance tocolysis with acute tocolysis. RCTs and systematic reviews on maintenance tocolysis have not found that tocolytic agents significantly improve health outcomes. Moreover, there are insufficient data from placebo-controlled trials.

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SUMMARY OF EVIDENCE

For individuals who have preterm labor or threatened preterm labor who receive acute tocolytic therapy, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. Overall, the body of evidence has shown that the commonly used tocolytic agents presented herein are effective at inducing tocolysis in patients with preterm labor or threatened preterm labor. Data have suggested that oral terbutaline is associated with more adverse events than parenteral terbutaline for acute tocolysis. Each medication has a different risk-benefit profile, and there is no clear first-line tocolytic agent. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have successful acute tocolysis for preterm labor who receive maintenance tocolytic therapy, the evidence includes randomized controlled trials and systematic reviews. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. Studies have generally not found that maintenance tocolysis lowers the rate of preterm birth or perinatal mortality, or increases the birth weight. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN MEDICAL SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2012. There was consensus that acute tocolysis may be considered medically necessary for the induction of tocolysis in patients with preterm labor and near consensus that preterm should be defined as "<37 weeks" gestational age. There was mixed input on the investigational policy statement on maintenance tocolysis (beyond 48-72 hours).

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Obstetricians and Gynecologists

In 2016, the American College of Obstetricians and Gynecologists published a practice bulletin on the management of preterm labor, which replaced previous bulletins on this topic.¹⁹ The 2016 bulletin contained the following relevant recommendations based on "good and consistent" scientific evidence:

- "A single course of corticosteroids is recommended for pregnant women between 24 weeks of gestation and 34 weeks of gestation who are at risk of preterm 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

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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 [non-steroidal anti-inflammatory drugs] 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 pre-term labor and intact membranes.”

National Institute for Health and Care Excellence

A 2015 guidance from the National Institute for Health and Care Excellence on preterm labor and birth has stated the following recommendations relevant to tocolysis²⁰:

- 1.8.2 “Consider nifedipine for tocolysis for women between 24+0 and 25+6 weeks of pregnancy who have intact membranes and are in suspected preterm labour.
- 1.8.3 Offer nifedipine for tocolysis to women between 26+0 and 33+6 weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour.
- 1.8.4 If nifedipine is contraindicated, offer oxytocin receptor antagonists for tocolysis.
- 1.8.5 Do not offer betamimetics for tocolysis.”
- 1.9.1 “For women between 23+0 and 23+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM [preterm prelabour rupture of membranes] ... discuss with the woman (and her family members or carers as appropriate) the use of maternal corticosteroids in the context of her individual circumstances.
- 1.9.2 Consider maternal corticosteroids for women between 24+0 and 25+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM.
- 1.9.3 Offer maternal corticosteroids to women between 26+0 and 33+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM.
- 1.9.4 Consider maternal corticosteroids for women between 34+0 and 35+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM.”
- 1.10.1 “Offer intravenous magnesium sulfate for neuroprotection of the baby to women between 24+0 and 29+6 weeks of pregnancy who are:
 - in established preterm labour or
 - having a planned preterm birth within 24 hours.
- 1.10.2 Consider intravenous magnesium sulfate for neuroprotection of the baby for women between 30+0 and 33+6 weeks of pregnancy who are:
 - in established preterm labour or
 - having a planned preterm birth within 24 hours.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

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ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov in July 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
- 96374 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
- J3105 Injection, terbutaline sulfate, up to 1 mg
- J3475 Injection, magnesium sulfate, per 500 mg
- S9349 Home infusion therapy, tocolytic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 Diagnoses

- O47.02 False labor before 37 completed weeks of gestation, second trimester
- O47.03 False labor before 37 completed weeks of gestation, third trimester
- O47.1 False labor at or after 37 completed weeks of gestation
- O60.02 Preterm labor without delivery, second trimester
- O60.03 Preterm labor without delivery, third trimester

REVISIONS

9-10-2010	Policy added to the bcbsks.com web site. In Policy Section: <ul style="list-style-type: none"> ▪ Liberalized to current policy language from: "Maintenance tocolytic therapy with subcutaneous or intravenous terbutaline is considered medically necessary when all of the following conditions are met: 1. Uterine contractions suggestive of impending preterm labor 2. Oral tocolysis has failed to control uterine contractions that result in progressive cervical change 3. Patient is less than 34 weeks pregnant 4. Consultation and request from a perinatologist All other indications are considered not medically necessary."
01-09-2012	In the Policy section: <ul style="list-style-type: none"> • Item A, removed "betamimetics," to read "Acute tocolytic therapy with calcium channel blocker..."

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	<ul style="list-style-type: none"> In Item A, removed "and" in front of "prostaglandin inhibitors" and inserted ",and parenteral terbutaline" behind "prostaglandin inhibitors" to read "...magnesium sulfate, prostaglandin inhibitors, and parenteral terbutaline may be considered medically necessary..." In Item B, inserted "(beyond 48-72 hours)" to read "Maintenance (beyond 48-72 hours) subcutaneous or intravenous..."
	Updated Rationale
	Updated References
12-31-2013	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> Added ICD-10 Diagnosis (<i>Effective October 1, 2014</i>)
	Updated Reference section.
02-03-2016	Title revised from "Acute and Maintenance Subcutaneous and Intravenous Tocolysis"
	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> In Item A, added "37" and removed "34" to read, "Acute tocolytic therapy with calcium channel blockers, magnesium sulfate, prostaglandin inhibitors, and parenteral terbutaline may be considered medically necessary for induction of tocolysis in patients with preterm (<37 weeks gestational age) labor." In Item B, added "experimental/investigational" and removed "subcutaneous or intravenous" and "not medically necessary" to read, "Maintenance (beyond 48-72 hours) tocolytic therapy with any medication is considered experimental / investigational." Added Policy Guidelines.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> Added ICD-10 codes O47.02, O47.03, and O47.1.
	Updated References section.
09-28-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
11-07-2018	Policy Archived
	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> Removed ICD-9 codes.
	Updated References section.

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