Medial Policy

Title: Acute and Maintenance Tocolysis

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<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With preterm labor or</td>
<td>• Acute tocolytic therapy</td>
<td>are:</td>
<td>• Overall survival</td>
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<tr>
<td>threatened preterm labor</td>
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<td>• No tocolytic therapy</td>
<td>• Morbid events</td>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
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<td>• With successful acute</td>
<td>• Maintenance tocolytic therapy</td>
<td>are:</td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td>tocolysis for preterm labor</td>
<td></td>
<td>• No tocolytic therapy</td>
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**DESCRIPTION**

Tocolysis refers to the suppression of preterm labor to delay delivery. A variety of medications are proposed as tocolytic agents, and while none are currently approved by
the U.S. Food and Drug Administration (FDA) for the purpose of suppressing labor. The medications can be used 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 agents:

**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 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 22, 2017. Following is a summary of the literature to date.

Acute Tocolysis
Studies have focused on the ability of tocolytic agents to prevent preterm delivery and thereby to reduce associated maternal and neonatal risks. Numerous randomized controlled trials (RCTs) on acute tocolysis have been published and, in 2009, Haas et al conducted a comprehensive meta-analysis of RCTs.3 The investigators included 58 studies that directly compared different tocolytic medications or compared 1 medication with placebo or usual care. Studies were included if they compared 2 drugs in the 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 and 32 weeks of gestation. Multiple gestation 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)

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>48-Hour Delay</th>
<th>7-Day Delay</th>
<th>After 37 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Studies</td>
<td>% (95% CI)</td>
<td>No. of Studies</td>
</tr>
<tr>
<td>Placebo/control</td>
<td>9</td>
<td>53% (45 to 61)</td>
<td>8</td>
</tr>
<tr>
<td>Betamimetics</td>
<td>29</td>
<td>75% (65 to 85)</td>
<td>26</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>17</td>
<td>76% (57 to 95)</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>11</td>
<td>89% (85 to 93)</td>
<td>5</td>
</tr>
<tr>
<td>Oxytocin receptor antagonists</td>
<td>8</td>
<td>86% (80 to 91)</td>
<td>6</td>
</tr>
<tr>
<td>Prostaglandin inhibitors</td>
<td>8</td>
<td>93% (90 to 95)</td>
<td>3</td>
</tr>
</tbody>
</table>

CI=confidence interval

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

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Maternal Adverse Effects</th>
<th>Neonates With RDS</th>
<th>Neonatal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Studies</td>
<td>% (95% CI)</td>
<td>No. of Studies</td>
</tr>
<tr>
<td>Placebo/control</td>
<td>6 (0 to 2)</td>
<td>21% (17 to 26)</td>
<td>6 (0 to 2)</td>
</tr>
<tr>
<td>Betamimetics</td>
<td>32 (0 to 18)</td>
<td>13% (8 to 18)</td>
<td>32 (0 to 18)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>16 (0 to 3)</td>
<td>19% (4 to 33)</td>
<td>16 (0 to 3)</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>16 (0 to 3)</td>
<td>16% (11 to 20)</td>
<td>16 (0 to 3)</td>
</tr>
<tr>
<td>Oxytocin receptor antagonists</td>
<td>6 (0 to 5)</td>
<td>14% (8 to 21)</td>
<td>6 (0 to 5)</td>
</tr>
<tr>
<td>Prostaglandin inhibitors</td>
<td>6 (0 to 2)</td>
<td>2% (0 to 4)</td>
<td>6 (0 to 2)</td>
</tr>
</tbody>
</table>

*Maternal adverse effects are those that required discontinuation of the medication.

CI: confidence interval; RDS: respiratory distress syndrome

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

As part of their review, the investigators 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’ gestation due to a high effectiveness at delaying delivery by at least 7 days and a low rate of adverse effects. Calcium channel blockers were the superior agent for delaying delivery until 37 weeks. Compared to other tocolytics, calcium channel blockers reduced the incidence of birth within 7 days of treatment (relative risk [RR]: 0.76, 95% confidence interval [CI]: 0.60-0.97) and before 34 weeks’ gestation (RR: 0.83, 95% CI: 0.69-0.99).

In an additional study published in 2012, Haas and colleagues conducted a network meta-analysis in which direct and indirect evidence on relative impacts of tocolytics on health outcomes were pooled simultaneously. Consequently, the analysis was not limited to the comparisons in head-to-head trials that the research team had addressed in 2009. The investigators identified a total of 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. The authors 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 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 of this 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 was the “best” class for reducing neonatal respiratory distress syndrome (RD5), but the probability of being the best 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, which had a 70% probability of the class with the lowest rate of maternal side effects. Calcium channel blockers had a 15% chance of being included in the top 3 drug classes for the fewest maternal side effects. 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 respiratory distress syndrome and maternal side effects.

There are also meta-analyses on tocolysis focusing on a single tocolytic agent. In 2011, Conde-Agudelo and colleagues reviewed trials on nifedipine, a calcium channel blocker. The investigators identified 26 randomized trials with a total of 2,179 women comparing nifedipine to placebo, no treatment, or a different tocolytic agent. Twenty-three of the trials evaluated acute tocolysis and 3 evaluated maintenance tocolysis (maintenance tocolysis is discussed in a later section of the Rationale). Findings were mixed. Pooled analyses of trials comparing nifedipine and 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’ gestation (5 trials, RR: 77, 95% CI: 0.66 to 0.91) but no significant difference in the rate 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’ 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 small, making it difficult to draw conclusions about comparative efficacy.

Several Cochrane reviews on a single type of tocolytic agent are available and are described briefly next.

A 2014 review identified 38 trials evaluating calcium channel blockers for tocolysis (total N=3550 women). The calcium channel blocker was nifedipine in 35 trials and nicardipine in the other 3. Thirty-five trials used other tocolytic agents as the comparator (19 used betamimetics), 1 compared doses of nifedipine, and the other 2 compared calcium channel blockers with placebo or no intervention. Only 1 trial was double-blinded. The authors 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 effects (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. The authors noted that the quality of studies (e.g.,
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.

A 2014 updated Cochrane review identified 14 trials on oxytocin inhibitors (total N=2485
women). The control intervention was 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: Oxytocin inhibitors are not approved by the Food and Drug
Administration for use in the United States.)

Another 2014 Cochrane review identified 37 trials (total N=3571 women). 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.

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

In addition to these reviews of single agents, in 2014 Vogel et al published a Cochrane review on
combinations of tocolytic agents for preventing preterm labor. The investigators 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 the review's inclusion criteria; 2 of these did not report relevant
outcome data. Thus, few studies with small combined sample sizes were available for analysis,
and the authors were unable to pool data or draw conclusions about the safety and efficacy of
any combination of tocolytics versus any comparator intervention.

Section Summary: Acute Tocolysis
Multiple RCTs and meta-analyses have found tocolytics to be effective at decreasing rates of
preterm birth in women with preterm labor (e.g., 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-analyses suggests that prostaglandin inhibitors and calcium
channel blockers may have greater efficacy and fewer adverse effects 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 agent to be clearly superior to any other agent.

Maintenance of Tocolysis
Several meta-analyses of the published literature have been published. The 2011 Conde-Agudelo
et al. meta-analysis, described above, included 3 studies evaluating the calcium channel blocker
nifedipine for maintenance tocolysis. A pooled analysis of these 3 trials (total n=215) did not find
a significant difference in the rate of preterm birth before 37 weeks’ gestation with nifedipine
compared to 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.

In 2009, a Health Technology Assessment from the U.K. addressed a wider range of maintenance
tocolytic agents.\textsuperscript{11} However, for the outcomes prevention of preterm birth before 34 weeks’ or 37
weeks’ gestation, there were only a sufficient number of trials to conduct pooled analyses for 2
comparisons. Neither of the analyses found a statistically significant benefit of tocolysis. In a
pooled analysis of magnesium maintenance therapy to other tocolytic agents, the combined
relative risk was 0.98 (95% CI: 0.56 to 1.72). In addition, a pooled analysis of 4 trials (total
n=384) did not find a significant benefit of oral betamimetics compared to placebo or no
treatment for preventing pre-term birth before 37 weeks’ gestation. The combined relative risk
was 1.08 (95% CI: 0.88 to 1.22).

Several Cochrane reviews have addressed specific agents used for maintenance therapy and are
described briefly next.

A 2013 Cochrane review of maintenance therapy with oxytocin antagonists identified only 1
trial.\textsuperscript{12} This trial, published in 2000 by Valenzuela et al, did not find that atosiban reduced the
rate of preterm birth after threatened preterm birth compared with placebo.\textsuperscript{13}

Another 2013 Cochrane review identified 6 RCTs on maintenance therapy with calcium channel
blockers.\textsuperscript{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.

In 2016, follow-up data were published from an RCT evaluating maintenance tocolysis with
nifedipine.\textsuperscript{15} Two-year outcome data were available for 135 of 276 (52.5%) participants.
Outcomes were mixed for infants of women in the nifedipine maintenance group compared with
the placebo group. Those with nifedipine maintenance 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).

In 2012, Dodd et al published a Cochrane review on oral betamimetics for maintenance tocolysis
after threatened preterm labor.\textsuperscript{16} 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 for all outcomes
due to a shortage of studies 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 versus placebo or no treatment (RR=1.11; 95% CI, 0.91 to
1.35). In other pooled analysis of findings from studies comparing maintenance betamimetics
with placebo or no treatment, there were no statistically significant differences between groups in
birthweight (7 studies; mean difference, 4.13; 95% CI, -91.89 to 100.16), 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 2010 review by Han et al evaluated magnesium maintenance therapy and did not find a statistically significant effect of magnesium maintenance therapy on prevention of preterm birth before 37 weeks of gestation. A meta-analysis of 2 studies (total N=99 patients) that compared magnesium therapy with placebo or no treatment found a combined risk ratio of 1.05 (99% CI, 0.80 to 1.40). Two studies (total N=100 patients) were also available for a meta-analysis of studies comparing magnesium therapy with an alternative treatment. In this analysis, the combined RR was 0.99 (95% CI, 0.57 to 1.72).

Section Summary: Maintenance of Tocolysis
There are fewer RCTs on maintenance tocolysis compared with acute tocolysis. RCTs and meta-analyses on maintenance tocolysis have generally not found that tocolytic agents significantly improve health outcomes. Moreover, there are insufficient data from placebo-controlled trials.

Risks Associated with Terbutaline
An FDA-conducted search of its Adverse Event Reporting System (AERS) identified reports of 16 maternal deaths associated with terbutaline between 1976 and 2009. The FDA document stated that in 3 cases, it was specified that terbutaline was administered by a subcutaneous pump, and in 9 cases oral terbutaline was used instead of or in addition to injectable or subcutaneous terbutaline. (Presumably, in the remaining cases, the mode of administration was not reported.) Moreover, between 1998 and July 2009, 12 cases of serious maternal cardiovascular events associated with terbutaline were submitted to AERS; in 3 cases, use of subcutaneous terbutaline was specified and in 5 cases, it was reported that oral terbutaline was used alone or in addition to subcutaneous terbutaline.

A 2011 commentary examined the human and animal evidence on risks of autism spectrum disorders associated with terbutaline. The authors concluded that the literature does not support the hypothesis that β2-adrenergic agonists including terbutaline are associated with autism spectrum disorders in the offspring.

SUMMARY OF EVIDENCE
For individuals who have preterm labor or threatened preterm labor who receive acute tocolytic therapy, the evidence includes multiple randomized controlled trials and meta-analyses. 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 meta-analyses. 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 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.”

Royal College of Obstetricians and Gynecologists
The Royal College of Obstetricians and Gynecologists evidence-based guideline (updated February 2011, now archived) on use of tocolysis for women in preterm labor included the following conclusions relevant to this evidence review:

• “There is no clear evidence that tocolytic drugs improve outcome and therefore it is reasonable not to use them. However, tocolysis should be considered if the few days gained would be put to good use, such as completing a course of corticosteroids or in utero transfer.

• “Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days.

• “Compared with beta-agonists, nifedipine is associated with improvement in neonatal outcome, although there are no long-term data.

• “Beta-agonists have a high frequency of adverse effects. Nifedipine, atosiban and the COX inhibitors have fewer types of adverse effects, and they occur less frequently than for beta-agonists but how they compare with each other is unclear.

• “There is insufficient evidence for any firm conclusions about whether or not tocolysis leads to benefit in preterm labor in multiple pregnancy.

• “There is insufficient evidence for any firm conclusion about whether or not maintenance tocolytic therapy following threatened preterm labor is worthwhile. Thus, maintenance therapy is not recommended.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov in September 2015 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-9 Diagnoses
These diagnoses are otherwise subject to medical policy as stated above.
644.00  Threatened premature labor, unspecified as to episode of care
644.03  Threatened premature labor, antepartum

ICD-10 Diagnoses (Effective October 1, 2015)
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
<table>
<thead>
<tr>
<th>Date</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-10-2010</td>
<td>Policy added to the bcbsks.com web site.</td>
</tr>
<tr>
<td></td>
<td>In Policy Section:</td>
</tr>
<tr>
<td></td>
<td>• Liberalized to current policy language from:</td>
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<tr>
<td></td>
<td>&quot;Maintenance tocolytic therapy with subcutaneous or intravenous terbutaline is considered medically necessary when all of the following conditions are met:</td>
</tr>
<tr>
<td></td>
<td>1. Uterine contractions suggestive of impending preterm labor</td>
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<td></td>
<td>2. Oral tocolysis has failed to control uterine contractions that result in progressive cervical change</td>
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<td></td>
<td>3. Patient is less than 34 weeks pregnant</td>
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<td></td>
<td>4. Consultation and request from a perinatologist</td>
</tr>
<tr>
<td></td>
<td>All other indications are considered not medically necessary.</td>
</tr>
<tr>
<td>01-09-2012</td>
<td>In the Policy section:</td>
</tr>
<tr>
<td></td>
<td>• Item A, removed “betamimetics,” to read “Acute tocolytic therapy with calcium channel blocker...”</td>
</tr>
<tr>
<td></td>
<td>• 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&quot;</td>
</tr>
</tbody>
</table>
medically necessary...”

• In Item B, inserted “(beyond 48-72 hours)” to read “Maintenance (beyond 48-72 hours) subcutaneous or intravenous...”

<table>
<thead>
<tr>
<th>Updated Rationale</th>
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<tbody>
<tr>
<td>Updated References</td>
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</tbody>
</table>

12-31-2013

Updated Description section.
Updated Rationale section.

In Coding section:
- Added ICD-10 Diagnosis *(Effective October 1, 2014)*
Updated Reference section.

02-03-2016

Title revised from "Acute and Maintenance Subcutaneous and Intravenous Tocolysis"

Updated Description section.

In Policy section:
- 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:
- 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.

REFERENCES


Other References:
4. Blue Cross and Blue Shield of Kansas OB/GYN Liaison Committee CB, July 2010.