Acute and Maintenance Tocolysis

Description

Tocolysis refers to the suppression of preterm labor to delay delivery. A variety of medications are proposed as tocolytic agents; none of the currently available options are approved by the U.S. Food and Drug Administration (FDA) for this indication. The same medications can also be used as maintenance therapy following successful tocolysis.

General indications for tocolysis, or the suppression of preterm labor, include continued regular uterine contractions associated with cervical changes in a pregnant woman less than 37 weeks’ gestation. Successful delay of preterm delivery allows further fetal development and precludes the complications of preterm delivery, especially neonatal respiratory distress syndrome. 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 respiratory distress syndrome. 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. If successful acute tocolysis is achieved, patients may continue to receive pharmacologic therapy for maintenance.

A variety of agents have been used for tocolysis. The only FDA-approved tocolytic drug is ritodrine, a beta-sympathomimetic. Ritodrine is no longer available in the United States and thus only off-label medications are available. Terbutaline, also a beta-sympathomimetic, is an alternative to ritodrine, for acute and maintenance tocolysis. Terbutaline is available as an oral or intravenous medication and, more recently, terbutaline has been administered by continuous subcutaneous infusion via a portable pump for maintenance tocolysis. Other tocolytic drugs include calcium channel blockers (e.g., nifedipine), magnesium sulfate, oxytocin receptor antagonists (e.g., atosiban), prostaglandin inhibitors (e.g., indomethacin), and nitrates (e.g., nitroglycerin).

American College of Obstetricians and Gynecologists (ACOG) stated in a 2003 guideline (reaffirmed in 2008) that no optimal first-line agent for tocolysis has been identified. (1,2) Both
the potential benefits and harms of tocolytic agents need to be considered. According to the ACOG guideline, potential side effects of specific tocolytic agents include:

- **Terbutaline:**
  - Maternal side effects: cardiac or cardiopulmonary arrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia;
  - Fetal and neonatal side effects: fetal tachycardia, hyperinsulinemia, hyperglycemia, myocardial and septal hypertrophy, myocardial ischemia

- **Magnesium Sulfate:**
  - Maternal side effects: flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardiac arrest;
  - Fetal and neonatal side effects: lethargy, hypotonia, respiratory depression, demineralization with prolonged use.

- **Calcium Channel Blockers:**
  - Maternal side effects: flushing, headache, dizziness, nausea, transient hypotension;
  - Fetal and neonatal side effects: none noted as yet.

- **Indomethacin:**
  - Maternal side effects: nausea, heartburn;
  - Fetal and neonatal side effects: constriction of ductus arteriosus, pulmonary hypertension, reversible decrease in renal function with oligohydramnios, intraventricular hemorrhage, hyperbilirubinemia, necrotizing enterocolitis.

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

Terbutaline sulfate is FDA-approved 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 in tocolysis is off-label. In response to a citizen petition in June, 2008, the FDA reviewed safety data on terbutaline sulfate. They issued a safety announcement on February 17, 2011. (3) Based on animal studies, the FDA reclassified terbutaline sulfate from pregnancy risk category B to pregnancy risk category C. In addition, the FDA required a boxed warning stating that injectable terbutaline should not be used for prevention or prolonged (beyond 2-3 days) treatment of preterm labor and oral terbutaline should not be used for acute or maintenance tocolysis. The labeling change is based on a review of post-marketing safety reports submitted to the FDA’s Adverse Event Reporting System (AERS) of maternal death and serious maternal cardiovascular events associated with use of terbutaline.
Acute tocolytic therapy with calcium channel blockers, magnesium sulfate, prostaglandin inhibitors, and parenteral terbutaline may be considered **medically necessary** for the induction of tocolysis in patients with preterm (<37 weeks’ gestational age) labor.

Maintenance (beyond 48-72 hours) tocolytic therapy with any medication is considered **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**

An initial literature search was performed in 1997. The policy was updated regularly with a literature review using MEDLINE. Most recently, the literature was searched from February 2011 through July 2012. 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 reduce associated maternal and neonatal risks. A comprehensive meta-analysis of randomized controlled trials (RCTs) on acute tocolysis was published by Haas et al. in 2009. (3) Haas and colleagues included 58 studies that compared different tocolytic medications or compared 1 medication to 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 who were diagnosed with preterm labor or had threatened preterm labor. The analysis was limited to studies with fetuses of mean gestational ages between 28 and 32 weeks’ 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:

**Effect of tocolytics on delaying birth (weighted % of women experiencing outcome)**

<table>
<thead>
<tr>
<th></th>
<th>48 hours delay No. Studies</th>
<th>% (95% CI)</th>
<th>7 day delay No. Studies</th>
<th>% (95% CI)</th>
<th>After 37 weeks No. Studies</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/control</td>
<td>9</td>
<td>53 (45-61)</td>
<td>8</td>
<td>39 (28-49)</td>
<td>3</td>
<td>36 (20-52)</td>
</tr>
<tr>
<td>Betamimetics</td>
<td>29</td>
<td>75 (65-85)</td>
<td>26</td>
<td>65 (59-71)</td>
<td>15</td>
<td>46 (36-56)</td>
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<tr>
<td>Calcium channel blockers</td>
<td>17</td>
<td>76 (57-95)</td>
<td>10</td>
<td>62 (56-69)</td>
<td>12</td>
<td>47 (32-62)</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>11</td>
<td>89 (85-93)</td>
<td>5</td>
<td>61 (39-84)</td>
<td>7</td>
<td>42 (31-53)</td>
</tr>
</tbody>
</table>
**Table:**

<table>
<thead>
<tr>
<th>Tocolytic Agent</th>
<th>Maternal Adverse Effects</th>
<th>No. of Studies</th>
<th>% (95% CI)</th>
<th>Neonates with RDS</th>
<th>No. of Studies</th>
<th>% (95% CI)</th>
<th>Neonatal Death</th>
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<th>% (95% CI)</th>
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<tr>
<td>Placebo/control</td>
<td>6</td>
<td>(0-2)</td>
<td>3</td>
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<td>6</td>
<td>1 (0-2)</td>
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<tr>
<td>Betamimetics</td>
<td>32</td>
<td>14 (9-18)</td>
<td>17</td>
<td>13 (8-18)</td>
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<td>14 (9-18)</td>
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<tr>
<td>Calcium channel blockers</td>
<td>16</td>
<td>1 (0-3)</td>
<td>11</td>
<td>19 (4-33)</td>
<td>16</td>
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<tr>
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<td>3 (1-6)</td>
<td>9</td>
<td>16 (11-20)</td>
<td>16</td>
<td>3 (1-6)</td>
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</tr>
<tr>
<td>Oxytocin receptor antag.</td>
<td>6</td>
<td>2 (0-5)</td>
<td>5</td>
<td>14 (8-21)</td>
<td>6</td>
<td>2 (0-5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>6</td>
<td>0 (0-2)</td>
<td>4</td>
<td>2 (0-4)</td>
<td>6</td>
<td>0 (0-2)</td>
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**Note:**

CI = confidence interval

**Adverse maternal and neonatal effects associated with tocolytic agents (weighted % of women/neonates experiencing outcome)**

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**RDS = respiratory distress syndrome**

Maternal adverse effects are those they required discontinuation of the medication.

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.

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). The authors concluded that calcium channel blockers are preferred over other tocolytic agents.

A 2012 RCT by Klauser and colleagues compared neonatal outcomes after acute tocolysis with 1 of 3 medications: magnesium sulfate (n=95), nifedipine (n=119), or indomethacin (n=103). (4) The authors did not find significant differences between the 3 groups in outcomes, including gestational age at delivery, birthweight, and the neonatal mortality rate. For example, mean gestational age at delivery was 31.2 weeks with magnesium sulfate, 31.8 weeks with nifedipine.
and 31.8 weeks with indomethacin (p=0.55). In addition, neonatal morbidity rates, including respiratory distress syndrome (RDS), patent ductus arteriosus, sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia, did not differ significantly among groups. Rates of the most frequently occurring adverse event, RDS, were 39 (41%) with magnesium sulfate, 34 (28%) with nifedipine, and 42 (41%) with indomethacin (p=0.09).

There are also meta-analyses on tocolysis focusing on a single tocolytic agent. Most recently, in 2011, Conde-Agudelo and colleagues reviewed trials on nifedipine, a calcium channel blocker. (5) 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 have addressed the effectiveness of individual tocolytic agents. A 2003 review identified 12 trials evaluating calcium channel blockers for tocolysis, with a total of 1,029 women. (6) Compared to any other tocolytic agents, calcium channel blockers significantly reduced the incidence of birth within 7 days of treatment (RR: 0.76, 95% CI: 0.60-0.97) and before 34 weeks’ gestation (RR: 0.83, 95% CI: 0.69-0.99), and significantly reduced the likelihood that women would discontinue medication due to adverse effects (RR: 0.14, 95% CI: 0.05-0.36). The authors concluded that calcium channel blockers are preferred over other tocolytic agents. The review did not include studies that compared calcium channel blockers to placebo for tocolysis. A 2005 review by King and colleagues included 13 trials on cyclooxygenase (COX) inhibitors, with a total of 713 women; indomethacin was used in 10 of the trials. (7) Only one trial compared COX inhibitors to placebo. Pooled analysis of studies comparing COX inhibitors to other tocolytics found a significant reduction in the incidence of birth before 37 weeks’ gestation (RR: 0.53, 54 women). The authors noted that numbers were small, and thus estimates were imprecise and not definitive. A third Cochrane review, also published in 2005, identified 6 trials on oxytocin inhibitors, with a total of 1,695 women. (8) Pooled analyses did not demonstrate the superiority of oxytocin receptor antagonists over betamimetics or placebo in terms of reduction in preterm birth or neonatal outcomes. (Note: Oxytocin inhibitors are not approved by the FDA for use in the United States.)

Recent review articles published in 2010 or 2011 have discussed which tocolytic agent should be considered first-line. Nasser and colleagues reviewed calcium channel blockers for management of preterm birth and stated that no agent has been identified as the clear first-line tocolytic. (9) The authors state that nifedipine may be a preferred option for acute tocolysis due to its good safety profile compared to other tocolytic agents and that studies are needed on the optimal formulation and dose regimen of nifedipine. A review by de Haus and colleagues discussed the pros and cons of atosiban, an oxytocin inhibitor (available outside of the U.S.) or the calcium channel and did not conclude that either is clearly a preferred agent. (10) They noted that use of beta-agonists as first-line agents have decreased due to maternal adverse effects, that there are concerns about fetal adverse effects with COX inhibitors, and that there

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FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of
are fewer data that magnesium sulfate is an effective tocolytic. In a 2011 update on tocolysis, Hubinont and Debieve stated that atosiban is the authors’ first choice drug for safety, followed by prostaglandin inhibitors and nifedipine. (11)

Conclusions: Multiple RCTs and meta-analyses have found tocolytics to be effective at decreasing rates of preterm birth, e.g., delaying delivery for 7 days and/or decreasing rates of delivery before 34 or 37 weeks’ gestation. The optimal first-line medication is not known.

Maintenance of Tocolysis

There are fewer controlled studies on the efficacy of maintenance therapy after successful acute tocolysis; however, several meta-analyses of the published literature have been published. The Conde-Agudelo et al. meta-analysis, described above, (5) 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. One of the trials included in the Conde-Agudelo et al. meta-analysis was a 2008 study by Lyell and colleagues. (12) The investigators randomly assigned 71 women who had undergone successful tocolysis to 20 mg oral nifedipine or placebo until 37 weeks’ gestation. The study included women between 24 and 34 weeks’ gestation with singleton or twin pregnancies. There was no significant difference in the primary outcome, attainment of 37 weeks (39% nifedipine compared with 37% placebo, p>0.91). Other pregnancy outcomes and neonatal outcomes reported in the trial also did not differ significantly between groups.

A 2010 Cochrane review addressed magnesium maintenance therapy. (13) Their pooled analyses did not find a significant benefit of magnesium maintenance therapy for preventing preterm birth before 37 weeks’ gestation compared to either placebo/no treatment or an alternative treatment (ritodrine or terbutaline). A meta-analysis of 2 studies (total n=99) that compared magnesium therapy to placebo or no treatment found a combined risk ratio of 1.05 (99% CI: 0.80 to 1.40). Two studies (total n=100) were also available for a meta-analysis of studies comparing magnesium therapy to an alternative treatment. In this analysis, the combined risk ratio was 0.99 (95% CI: 0.57 to 1.72).

In 2009, a Health Technology Assessment from the U.K. addressed a wider range of maintenance tocolytic agents. (14) 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. One was the same comparison in the Cochrane analysis, magnesium maintenance therapy versus other tocolytic agents, and the findings were similar (there were minor differences due to the statistical techniques used). 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).

Conclusions: There are fewer RCTs on maintenance tocolysis compared to acute tocolysis. RCTs and meta-analyses on maintenance tocolysis have not consistently found that tocolytic agents reduce rates of preterm birth.

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. (2) 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. (15) The authors concluded that the literature does not support the hypothesis that beta-2-adrenergic agonists including terbutaline are associated with autism spectrum disorders in the offspring.

Clinical Input Received through Physician Medical Societies and Academic Medical Centers

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. 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. 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 2 investigational policy statements for maintenance tocolysis (beyond 48-72 hours) and tocolysis as a prophylactic measure to prevent preterm birth in women experiencing preterm premature rupture of membranes.

Summary

There is sufficient evidence that the commonly used tocolytic agents presented here are effective at inducing tocolysis in patients with preterm labor or threatened preterm labor. Thus, these agents are considered medically necessary for the acute prevention of preterm delivery. There are data suggesting 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. There are fewer studies on medications to maintain tocolysis. The available evidence does not suggest that maintenance tocolysis improves health outcomes, and therefore maintenance tocolysis is considered investigational.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists (ACOG), Management of preterm labor practice bulletin guideline (issued in 2003 and reaffirmed in 2008) (1)

The guideline states:

“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 to 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."

Royal College of Obstetricians and Gynecologists, UK guideline (updated in February 2011) (16)

This evidence-based guideline on use of tocolysis for women in preterm labor included the following conclusions relevant to this policy:

- 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.

Medicare National Coverage

No national coverage determination.

References:

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Several Cochrane reviews have addressed the effectiveness of individual tocolytic agents. A 2003 review identified 12 trials evaluating calcium channel blockers for tocolysis, with a total of 1,029 women. (6) Compared to any other tocolytic agents, calcium channel blockers significantly reduced the incidence of birth within 7 days of treatment (RR: 0.76, 95% CI: 0.60-0.97) and before 34 weeks’ gestation (RR: 0.83, 95% CI: 0.69-0.99), and significantly reduced the likelihood that women would discontinue medication due to adverse effects (RR: 0.14, 95% CI: 0.05-0.36). The authors concluded that calcium channel blockers are preferred over other tocolytic agents. The review did not include studies that compared calcium channel blockers to placebo for tocolysis. A 2005 review by King and colleagues included 13 trials on cyclo-oxygenase (COX) inhibitors, with a total of 713 women; indomethacin was used in 10 of the trials. (7) Only one trial compared COX inhibitors to placebo. Pooled analysis of studies comparing COX inhibitors to other tocolytics found a significant reduction in the incidence of birth before 37 weeks’ gestation (RR: 0.53, 54 women). The authors noted that numbers were small, and thus estimates were imprecise and not definitive. A third Cochrane review, also published in 2005, identified 6 trials on oxytocin inhibitors, with a total of 1,695 women. (8) Pooled analyses did not demonstrate the superiority of oxytocin receptor antagonists over beta-agonists or placebo in terms of reduction in preterm birth or neonatal outcomes. (Note: Oxytocin inhibitors are not approved by the FDA for use in the United States.)

Recent review articles published in 2010 or 2011 have discussed which tocolytic agent should be considered first-line. Nasser and colleagues reviewed calcium channel blockers for...
management of preterm birth and stated that no agent has been identified as the clear first-line tocolytic. (9) The authors state that nifedipine may be a preferred option for acute tocolysis due to its good safety profile compared to other tocolytic agents and that studies are needed on the optimal formulation and dose regimen of nifedipine. A review by de Haus and colleagues discussed the pros and cons of atosiban, an oxytocin inhibitor (available outside of the U.S.) or the calcium channel and did not conclude that either is clearly a preferred agent. (10) They noted that use of beta-agonists as first-line agents have decreased due to maternal adverse effects, that there are concerns about fetal adverse effects with COX inhibitors, and that there are fewer data that magnesium sulfate is an effective tocolytic. In a 2011 update on tocolysis, Hubinont and Debieve stated that atosiban is the authors’ first choice drug for safety, followed by prostaglandin inhibitors and nifedipine. (11)

Conclusions: Multiple RCTs and meta-analyses have found tocolytics to be effective at decreasing rates of preterm birth, e.g., delaying delivery for 7 days and/or decreasing rates of delivery before 34 or 37 weeks’ gestation. The optimal first-line medication is not known.

Maintenance of Tocolysis

There are fewer controlled studies on the efficacy of maintenance therapy after successful acute tocolysis; however, several meta-analyses of the published literature have been published. The Conde-Agudelo et al. meta-analysis, described above, (5) 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.

One of the trials included in the Conde-Agudelo et al. meta-analysis was a 2008 study by Lyell and colleagues. (12) The investigators randomly assigned 71 women who had undergone successful tocolysis to 20 mg oral nifedipine or placebo until 37 weeks’ gestation. The study included women between 24 and 34 weeks’ gestation with singleton or twin pregnancies. There was no significant difference in the primary outcome, attainment of 37 weeks (39% nifedipine compared with 37% placebo, p>0.91). Other pregnancy outcomes and neonatal outcomes reported in the trial also did not differ significantly between groups.

A 2010 Cochrane review addressed magnesium maintenance therapy. (13) Their pooled analyses did not find a significant benefit of magnesium maintenance therapy for preventing preterm birth before 37 weeks’ gestation compared to either placebo/no treatment or an alternative treatment (ritodrine or terbutaline). A meta-analysis of 2 studies (total n=99) that compared magnesium therapy to placebo or no treatment found a combined risk ratio of 1.05 (99% CI: 0.80 to 1.40). Two studies (total n=100) were also available for a meta-analysis of studies comparing magnesium therapy to an alternative treatment. In this analysis, the combined risk ratio was 0.99 (95% CI: 0.57 to 1.72).

In 2009, a Health Technology Assessment from the U.K. addressed a wider range of maintenance tocolytic agents. (14) 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. One was the same comparison in the Cochrane analysis, magnesium maintenance therapy versus other tocolytic agents, and the findings were similar (there were minor differences due to the statistical techniques used). 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).

Conclusions: There are fewer RCTs on maintenance tocolysis compared to acute tocolysis. RCTs and meta-analyses on maintenance tocolysis have not consistently found that tocolytic agents reduce rates of preterm birth.

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. (2) 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. (15) The authors concluded that the literature does not support the hypothesis that beta-2-adrenergic agonists including terbutaline are associated with autism spectrum disorders in the offspring.

Clinical Input Received through Physician Medical Societies and Academic Medical Centers

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. 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. 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 2 investigational policy statements for maintenance tocolysis (beyond 48-72 hours) and tocolysis as a prophylactic measure to prevent preterm birth in women experiencing preterm premature rupture of membranes.

Summary

There is sufficient evidence that the commonly used tocolytic agents presented here are effective at inducing tocolysis in patients with preterm labor or threatened preterm labor. Thus, these agents are considered medically necessary for the acute prevention of preterm delivery. There are data suggesting 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. There are fewer studies on medications to maintain tocolysis. The available evidence does not suggest that maintenance tocolysis improves health outcomes, and therefore maintenance tocolysis is considered investigational.

Practice Guidelines and Position Statements

The guideline states:

“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 to 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."

Royal College of Obstetricians and Gynecologists, UK guideline (updated in February 2011) (16)

This evidence-based guideline on use of tocolysis for women in preterm labor included the following conclusions relevant to this policy:

- 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.

Medicare National Coverage

No national coverage determination.

References:

2. FDA drug safety communication: New warnings against use of terbutaline to treat preterm labor.; February 17, 2011.


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<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<td>Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
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<td>96374</td>
<td>Intravenous push, single or initial substance/drug</td>
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