**SALBUTAMOL**

**Objectives:**
The objectives of this evidence summary are to advise a decision on the retention of salbutamol as a tocolytic in the Essential Drugs List, and to illustrate why its indication as a treatment for preterm birth needs to be removed. Salbutamol is considered as representative of other betamimetic drugs in this context.

**Background:**
Preterm birth affects 5-22% of pregnancies\(^{(1)}\) and is one of the main global causes of newborn deaths. It burdens healthcare systems, communities, and is distressing to families. Preterm babies are at higher risk of dying or suffering complications and sequelae. Care of preterm babies frequently demands hospitalisation in units staffed by highly skilled personnel and requiring technologically advanced equipment.

Tocolytics are used to treat women with threatened preterm birth under the premise that stopping uterine activity will reduce preterm birth and its associated complications, and will give more time for treatments aimed at maturing the baby’s lungs. WHO Model Formulary 2004 lists salbutamol as the betamimetic for use in preterm birth (p 379).

**Evidence summary:**

**IN PRETERM BIRTH**
Drugs used as tocolytics include betamimetics (β2 Agonists), calcium channel blockers, magnesium sulphate, oxytocin receptor antagonists, prostaglandin inhibitors and ethanol. An overview (search date September 2003) assessed the clinical effects of tocolytics in women with threatened preterm labor\(^{(3)}\) and identified one systematic review of 8 randomised controlled trials (RCTs)\(^{(3)}\). A subsequently published Cochrane Review (Search date May 2003) assessed the effects of betamimetics in preterm labor with a meta-analysis of 11 RCTs including 4 unpublished RCTs\(^{(3)}\). In comparing betamimetics with placebo, the overview and recent Cochrane review shared seven studies. Salbutamol was not evaluated in any of the RCTs comparing betamimetics with placebo. The overview and the Cochrane review concluded that compared with placebo, betamimetics do not significantly reduce preterm deliveries, perinatal mortality or neonatal morbidity despite prolonging pregnancy\(^{(1-3)}\). Betamimetics significantly increased maternal adverse effects in a high proportion of women\(^{(1-3)}\). Major outcomes are summarised in Table 1. **Prevention of respiratory distress syndrome:** Betamimetics should in theory reduce respiratory distress syndrome by prolonging exposure to lung maturing agents, but this has not been found in RCTs yet\(^{(1-3; 5)}\).

**OTHER INDICATIONS**

**External cephalic version:** A systemic review found that betamimetics are effective in facilitating external cephalic version, and reducing related cesarean sections\(^{(4)}\). Only one small RCT out of the six RCTs in the review evaluated salbutamol, and it found no significant reduction in failed cephalic version (15/30 with salbutamol v 16/30 with placebo; RR 0.94, 95%CI 0.57 - 1.53)\(^{(4)}\). The systematic review didn’t evaluate adverse effects.

**Impaired fetal growth:** Betamimetics have been used to reduce impaired fetal growth although the evidence collated in a systematic review was insufficient to demonstrate that they are safe and effective\(^{(6)}\).

**Placenta previa:** use of betamimetics in placenta previa is controversial and lacks supporting evidence\(^{(7)}\).

**Fetal distress:** There is no evidence to support the use of betamimetics for fetal distress in second stage of labor, and the only RCT identified in a systematic review found an unwanted increase of forceps deliveries\(^{(8)}\). A Cochrane review found three RCTs that evaluated betamimetics in intrapartum fetal distress. Two of these trials compared a betamimetic to placebo and one
compared to magnesium sulfate. There was no evidence for or against the use of betamimetics in terms of substantive outcomes. However, surrogate outcomes such as stopping the uterine contractions and reduced fetal heart rate abnormalities suggest that betamimetics may be useful for “buying time” to transfer patients to appropriate facilities and prepare them for cesarean section or operative delivery.\(^9\)

**Facilitating cesarean section**: A systematic review of the evidence on the effects of tocolysis for assisting delivery at cesarean section is under way\(^{10}\).

It must be noted that the regimen used for indications other than the treatment of preterm labor are typically single, slow injection with close monitoring of the heart rate as compared to more prolonged use in the treatment of preterm labor.

**Recommendation:**
- Retain betamimetics in the essential drug list because
  - There is evidence that they are useful in facilitating external cephalic version and reduce the need for related cesarean sections.
  - They may be useful for "buying time" for intrapartum fetal distress
- Remove its indication as a tocolytic in preterm birth.
- Recommendations and any other indications in pregnancy need to be revisited as new evidence on the safety and effectiveness of salbutamol and other betamimetics in pregnancy becomes available.

### Table 1. Effects of tocolysis with betamimetics for preterm labor, compared with placebo\(^{11; 13}\)

<table>
<thead>
<tr>
<th>Outcomes Overview</th>
<th>RCTs</th>
<th>AR [%]</th>
<th>AR [%]</th>
<th>OR</th>
<th>95% CI</th>
<th>Original Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal death</td>
<td>8(^2)</td>
<td>62/682 [9%]</td>
<td>48/604 [8%]</td>
<td>1.08</td>
<td>0.72 to 1.62</td>
<td>(11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22)</td>
</tr>
<tr>
<td>Perinatal death (7 days)</td>
<td>11(^3)</td>
<td>16/712 [2%]</td>
<td>20/620 [3%]</td>
<td>0.84</td>
<td>0.46 to 1.55</td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>6(^2)</td>
<td>117/639 [18%]</td>
<td>140/565 [25%]</td>
<td>0.76</td>
<td>0.57 to 1.01</td>
<td>(11; 12; 13; 14; 15; 16; 19; 20; 22)</td>
</tr>
<tr>
<td>Need to stop treatment</td>
<td>3(^2)</td>
<td>25/88 [28%]</td>
<td>0/86 [0%]</td>
<td>11.50</td>
<td>4.80 to 27.50</td>
<td>(11; 12; 15; 16; 18)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>3(^2)</td>
<td>200/420 [48%]</td>
<td>19/243 [4%]</td>
<td>10.15</td>
<td>7.42 to 13.87</td>
<td>(11; 14; 15; 16)</td>
</tr>
<tr>
<td>Dyspnea †</td>
<td>2(^2)</td>
<td>55/406 [14%]</td>
<td>4/408 [1%]</td>
<td>6.37</td>
<td>3.87 to 11.18</td>
<td>(11; 15)</td>
</tr>
<tr>
<td>Chest pains</td>
<td>2(^2)</td>
<td>39/406 [10%]</td>
<td>3/408 [1%]</td>
<td>6.17</td>
<td>3.31 to 11.51</td>
<td>(11; 15)</td>
</tr>
<tr>
<td>Headache</td>
<td>3(^2)</td>
<td>84/236 [33%]</td>
<td>22/371 [6%]</td>
<td>3.97</td>
<td>2.63 to 5.99</td>
<td>(11; 14; 16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1(^2)</td>
<td>72/352 [20%]</td>
<td>42/356 [12%]</td>
<td>1.90</td>
<td>1.27 to 2.83</td>
<td>(11)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2(^2)</td>
<td>48/366 [13%]</td>
<td>29/371 [8%]</td>
<td>1.79</td>
<td>1.11 to 2.87</td>
<td>(11; 14)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>3(^2)</td>
<td>107/516 [21%]</td>
<td>50/416 [12%]</td>
<td>1.76</td>
<td>1.29 to 2.42</td>
<td>(11; 14; 16)</td>
</tr>
</tbody>
</table>

AR = Absolute Risk; OR = Odds ratio; CI = Confidence interval. Percentages in brackets were not published in the original report.

\(^\circ\)RCT numbers in bold in the second column highlight perfect study matches; differences can be attributed to variation in statistics used.

\(^\dagger\)Citation in bold in the last column represent studies included in both systematic reviews.

\(^\ddagger\)Data suggests that one of the reviews had an error in data input and analysis that may explain the difference in magnitudes.
References


