



November 2008 – SUPPORT Summary of a systematic review

## Should magnesium sulphate be used for preventing preterm birth and its sequelae?

Preterm birth remains the principal cause of early neonatal death and long-term morbidity. The prevention of preterm birth therefore remains an important priority, particularly in under-resourced areas.

### Key messages

- Preterm birth remains the principal cause of early neonatal death.
- Magnesium sulphate is ineffective at delaying birth or preventing preterm birth and was associated with increase of fetal and paediatric deaths.
- Trials assessing serious morbidity and mortality, comparing different dose regimens, and providing long-term neurodevelopmental outcomes for the child are needed.



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### Who is this summary for?

People making decisions concerning maternal morbidity and mortality.

### ! This summary includes:

- **Key findings** from research based on a systematic review
- **Considerations about the relevance of this research** for low and middle-income countries

### X Not included:

- Recommendations
- Additional evidence not included in the systematic review
- Detailed descriptions of interventions or their implementation

### This summary is based on the following systematic review:

CA Crowther, JE Hiller, LW Doyle. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD001060. DOI: 10.1002/14651858.CD001060.

### What is a systematic review?

A summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise the relevant research, and to collect and analyse data from the included studies.

**SUPPORT** – an international collaboration funded by the EU 6th Framework Programme to support the use of policy relevant reviews and trials to inform decisions about maternal and child health in low and middle-income countries.

[www.support-collaboration.org](http://www.support-collaboration.org)

**Glossary of terms used in this report:**

[www.support-collaboration.org/summaries/explanations.htm](http://www.support-collaboration.org/summaries/explanations.htm)

**Background references on this topic:**

See back page.

# Background

Infants born preterm (before 37 weeks gestation) often suffer important and immediate morbidity and need lengthy stays in neonatal intensive care units. The more preterm the baby, the greater the risks, especially when birth occurs before 32 weeks. Moreover, there is a significant risk of long-term neurological morbidity in survivors. A variety of agents have been used to inhibit uterine activity in women in preterm labour and so attempt to prevent preterm birth. Agents used include betamimetics, prostaglandin inhibitors, calcium channel blockers, ethanol, oxytocin receptor antagonists and magnesium sulphate.

## How this summary was prepared

After searching widely for systematic reviews that can help inform decisions about health systems, we have selected ones that provide information that is relevant to low and middle-income countries. The methods used to assess the quality of the review and to make judgements about its relevance are described here: [www.support-collaboration.org/summaries/methods.htm](http://www.support-collaboration.org/summaries/methods.htm)

## Knowing what's not known is important

A good quality review might not find any studies from low and middle-income countries or might not find any well-designed studies. Although that is disappointing, it is important to know what is not known as well as what is known.

## About the systematic review underlying this summary

**Review objective:** To assess the effectiveness and safety of magnesium sulphate therapy given to women in threatened preterm labour with the primary aim of preventing preterm birth and its sequelae.

|                      | What the review authors searched for   | What the review authors found   |
|----------------------|--|---|
| <b>Interventions</b> | Magnesium sulphate (MgSO <sub>4</sub> ) as the only tocolytic, administered intravenously or orally, compared with either placebo, no placebo or an alternative tocolytic (AT) therapy.  | 2036 women were included into 23 trials. Trials used a 4 g initial IV dose of MgSO <sub>4</sub> , although it was also used 5 g (2 trials), 6 g (4 trials) and one trial did not state the dose used. Three trials did not use an AT drug, and the other 20 used a variety of AT drugs for the control group: betamimetics (10 trials), calcium channel blockers (4), prostaglandin synthetase inhibitors (2), nitroglycerin (1), alcohol (1), one trial had two control groups (a betamimetic and a dextrose infusion), and one trial used an 'unblinded obstetrician's choice of ritodrine, terbutaline, indomethacin or nifedipine'. |
| <b>Participants</b>  | Women thought to be in preterm labour  | Women in preterm labour   |
| <b>Settings</b>      | Not stated   | China (2 trials), Mexico (1 trial), Iran (1 trial) and USA (19 trials)  |
| <b>Outcomes</b>      | Primary: Birth less than 48 hs after trial entry, extremely preterm birth, serious infant outcome, serious maternal outcome. Secondary: measures of effectiveness and complications (for the child and the woman), satisfaction with care and health services use. | Birth in less than 48 hours from treatment (12 trials), preterm birth (6 trials); fetal and paediatric death (7 trials), gestational age at birth (4 trials), neonatal morbidity (6 trials), maternal side effects (7 trials) and stopped treatment due to side effects (10 trials); rate of caesarean (3 trials).  |

**Date of most recent search:** May 2002

**Limitations:** This is a good quality systematic review with minor limitations.

CA Crowther, JE Hiller, LW Doyle. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD001060. DOI: 10.1002/14651858.CD001060.

# Summary of findings

Twenty-three trials involving 2036 women were included. There was considerable variation between the trials including: the gestational age at trial entry, the initial IV dose (between 4-6 gr) and the maintenance dosage (between 1.5 to 6 g/hour) of magnesium sulphate. There was no evidence of any clinically important tocolytic effect for magnesium sulphate. No substantial effect on the proportion of women delivering within 48 hours, either overall, or in any subgroup analysis was found. Moreover, magnesium sulphate was associated with an increase in fetal and neonatal deaths.

## Magnesium sulphate vs placebo/no treatment or other tocolytic agent (all included trials).

- Although the trials are of low quality the evidence suggests that magnesium sulphate does not alter the proportion of women delivering within 48 hours.
- There is moderate quality of evidence that magnesium sulphate was associated with an increase in fetal and neonatal deaths.

### About quality of evidence (GRADE)

⊕⊕⊕⊕

**High:** Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕○

**Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕○○

**Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕○○○

**Very low:** We are very uncertain about the estimate.

For more information, see last page.

### Birth in less than 48 hours from treatment and total deaths

**Patient or population:** Patients with preterm labour.

**Settings:** China, Mexico, Iran and USA

**Intervention:** Magnesium sulphate

**Comparison:** Placebo/no treatment or other tocolytic agent (all included trials)

| Outcomes                                   | Illustrative comparative risks* (95% CI) |                             | Relative effect (95% CI) | N° of Participants (studies) | Quality of the evidence (GRADE) |
|--|--|-----------------------------|--------------------------|------------------------------|---------------------------------|
|  | Assumed risk                             | Corresponding risk (95% CI) |                          |                              |                                 |
|  | Without MgSO <sub>4</sub>                | With MgSO <sub>4</sub>      |                          |                              |                                 |
| Birth in less than 48 hours from treatment | 256 per 1000                             | 218 per 1000 (148 to 320)   | RR 0.85 (0.58 to 1.25)   | 881 (11)                     | ⊕⊕○○<br>low <sup>1,2</sup>      |
| Total deaths (fetal, neonatal and infant)  | 16 per 1000                              | 45 per 1000 (19 to 106)     | RR 2.82 (1.20 to 6.62)   | 727 (7)                      | ⊕⊕⊕○<br>moderate <sup>2</sup>   |

CI: Confidence interval RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

\*Illustrative comparative risks. The assumed risk **WITHOUT** the intervention is based on no treatment, placebo or alternative treatment. The corresponding risk **WITH** the intervention (and its 95% confidence interval) is based on the overall relative effect (and its 95% confidence interval).

<sup>1</sup> Allocation concealment unclear. <sup>2</sup> Confidence intervals wide.

# Relevance of the review for low and middle-income countries

→ Findings

▷ Interpretation\*

## APPLICABILITY

→ Given that magnesium sulphate has been widely used as a tocolytic for many years it was surprising that the evidence to support its use was scarce, and generally of poor quality. The ideal tocolytic agent should be easy to administer, inexpensive, without significant maternal, fetal or neonatal side effects, and effective at delaying preterm birth, at least long enough to permit the use of prenatal corticosteroids.

▷ *Other alternatives that allow a delay in the preterm birth enough to have time to administer steroids for lung maturation should be explored.*

## EQUITY

→ The included studies provided no data regarding differential effects of the interventions for disadvantaged populations.

▷ *Any addition of tocolytic agent to prevent preterm birth should ensure no increase inequalities.*

## ECONOMIC CONSIDERATIONS

→ There is no data on costs for either the health providers or the consumers.

▷ *Although no information regarding cost-effectiveness was provided, the evaluation of the effectiveness and safety of new tocolytic agents should also consider the costs, mainly in under-resourcing settings.*

## MONITORING & EVALUATION

→ Those wishing to evaluate magnesium sulphate should demonstrate it is beneficial and does not cause undue harm to either the mother or the fetus. If any further trials are done they should be of high quality and large enough to assess mortality and serious morbidity, and neurodevelopmental status of the child at follow up. Magnesium sulphate should be compared with placebo to assess its true effect.

▷ *The incorporation of tocolytic agents, other than magnesium sulfate, demand a careful evaluation of the safety for the mother and child.*

\*Judgements made by the authors of this summary, not necessarily those of the review authors, based on the findings of the review and consultation with researchers and policymakers in low and middle-income countries. For additional details about how these judgements were made see:

<http://www.support-collaboration.org/summaries/methods.htm>

# Additional information

## Related literature

- M Whitworth, S Quenby. Prophylactic oral betamimetics for preventing preterm labour in singleton pregnancies. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD006395. DOI: 10.1002/14651858.CD006395.pub2.
- JM Dodd, CA Crowther, MR Dare, P Middleton. Oral betamimetics for maintenance therapy after threatened preterm labour. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD003927. DOI: 10.1002/14651858.CD003927.pub2.
- J King, V Flenady, S Cole, S Thornton. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD001992. DOI: 10.1002/14651858.CD001992.pub2.
- D Papatsonis, V Flenady, S Cole, H Liley. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD004452. DOI: 10.1002/14651858.CD004452.pub2.
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- K Duckitt, S Thornton. Nitric oxide donors for the treatment of preterm labour. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No.: CD002860. DOI: 10.1002/14651858.CD002860.

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## Conflict of interest

None declared. For details, see: [www.support-collaboration.org/summaries/coi.htm](http://www.support-collaboration.org/summaries/coi.htm)

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## This summary should be cited as

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## About quality of evidence (GRADE)

The quality of the evidence is a judgement about the extent to which we can be confident that the estimates of effect are correct. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the type of study design (randomised trials versus observational studies), the risk of bias, the consistency of the results across studies, and the precision of the overall estimate across studies. For each outcome, the quality of the evidence is rated as high, moderate, low or very low using the definitions on page 3.

### For more information about GRADE:

[www.support-collaboration.org/summaries/grade.pdf](http://www.support-collaboration.org/summaries/grade.pdf)

## SUPPORT collaborators:

The **WHO Reproductive Health Library (RHL)** is an electronic review journal covering the field of sexual and reproductive health. It has been published annually since 1997 by the Department of Reproductive Health and Research at the World Health Organization. RHL takes the best available evidence on sexual and reproductive health from Cochrane systematic reviews and presents it as practical actions for clinicians to take to improve health outcomes, especially in developing countries. [www.who.int/rhl](http://www.who.int/rhl)

The **Cochrane Effective Practice and Organisation of Care Group (EPoC)** is a Collaborative Review Group of the Cochrane Collaboration: an international organisation that aims to help people make well informed decisions about health care by preparing, maintaining and ensuring the accessibility of systematic reviews of the effects of health care interventions. [www.epoc.cochrane.org](http://www.epoc.cochrane.org)

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