Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Review)

Bain E, Middleton P, Crowther CA

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Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth

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A B S T R A C T

Background
The effectiveness of antenatal magnesium sulphate for neuroprotection of the fetus, infant, and child prior to very preterm birth, when given to women considered at risk of preterm birth, has been established. There is currently no consensus as to the regimen to use in terms of the dose, duration, the use of repeat dosing and timing.

Objectives
To assess the comparative effectiveness and adverse effects of different magnesium sulphate regimens for neuroprotection of the fetus in women considered at risk of preterm birth.

Search methods
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 December 2011).

Selection criteria
Randomised trials comparing different magnesium sulphate regimens when used for neuroprotection of the fetus in women considered at risk of preterm birth. We planned to include cluster trials. We planned to exclude quasi-randomised trials and those with a crossover design. We planned to include trials published as full-text papers, along with those published in abstract form only.

Data collection and analysis
We planned that at least two review authors would assess trial eligibility.

Main results
No eligible completed trials were identified.
**Authors’ conclusions**

Although strong evidence supports the use of antenatal magnesium sulphate for neuroprotection of the fetus prior to very preterm birth, no trials comparing different treatment regimens have been completed. Research should be directed towards comparisons of different dosages and other variations in regimens, evaluating both maternal and infant outcomes.

**Plain Language Summary**

Different magnesium sulphate regimens given to women at risk of preterm birth to help protect the baby’s brain and improve long-term outcomes

This review found that not enough research has been carried out to show what is the best dose of, and how best to provide, magnesium sulphate to mothers prior to very preterm birth to protect the baby's brain

Babies born early (preterm) are at an increased risk of dying, and those who survive are at risk of damage to the brain that may lead to cerebral palsy (a disorder that affects the ability to move normally), blindness, deafness or other disability. Magnesium is an important mineral essential for good health and normal body and brain function. High-quality evidence from a Cochrane review shows that giving magnesium sulphate therapy to the mother before birth can help protect the preterm baby’s brain and improve long-term outcomes for the infant as it grows.

Magnesium sulphate is given in different doses and in different ways. There are some adverse effects for the mother during therapy such as flushing, warmth, sweating, nausea and vomiting, which may vary by the dose and way the magnesium sulphate is given. Since there is no clear and agreed best way, hospitals may vary in how they give magnesium sulphate. We found no completed randomised trials comparing different magnesium sulphate regimens. Studies are needed to establish what is the best dose and best way to give the magnesium sulphate. The babies in these trials need to be followed up over a long period so that we can monitor the effects of magnesium on child development.

**Background**

**Preterm birth and neurologic outcome**

Infants born preterm (less than 37 weeks) have an increased risk of mortality during their first few weeks of life (Saigal 2008). Whilst survival rates for preterm infants have improved (Doyle 2004), those infants who survive may have a greater risk of neurodevelopmental impairments including cerebral palsy, cognitive dysfunction, and sensory impairments (blindness and deafness) (Doyle 2004; Drummond 2002; Lorenz 1998; Petrini 2009; Saigal 2008) and in turn a significant risk of substantial disability (Doyle 2001; Saigal 2008). Along with very low birthweight (VLBW), very preterm birth (less than 34 weeks) is a principal risk factor for cerebral palsy (Lorenz 1998); the prevalence of cerebral palsy increases significantly with decreasing gestational age (Drummond 2002; Hagberg 2001; Himpens 2008; Petrini 2009; Saigal 2008). Decreasing gestational age is associated with increased vulnerability of cerebral white matter, and is consequently predictive of an increasing risk of white matter damage such as periventricular leukomalacia (PVL), and of intraventricular haemorrhage (IVH) (Larroque 2003) - established risk factors for the development of cerebral palsy and other disabilities (Saliba 2001).

**Magnesium sulphate for women at risk of preterm birth**

An association between maternal administration of magnesium sulphate and a reduction in the risk of IVH was first described by Kuban and colleagues (Kuban 1992). A significantly lower risk of IVH was found among babies born to mothers who had received magnesium sulphate regardless of whether they had pre-eclampsia (Kuban 1992). Nelson and Grether later described an association between antenatal magnesium sulphate and a reduced risk of cerebral palsy in VLBW infants (less than 1500 g) (Nelson 1995). In their case-control study, in utero exposure to magnesium sulphate, whether given as a tocolytic to suppress preterm labour or for pre-eclampsia, was more frequent in controls than in children with cerebral palsy; the odds ratio (OR) (OR 0.14;
95% confidence interval (CI) 0.05 to 0.51) showed a significant association between antenatal magnesium sulphate exposure and a reduced risk of cerebral palsy (Nelson 1995). Additional observational studies have supported such findings. Antenatal magnesium sulphate has been reported to be associated with protective effects for PVL (FineSmith 1997), IVH (Perlman 1997), cerebral palsy (Hauth 1995; Matsuda 2000; Schendel 1996), and perinatal mortality (Grether 1998). Inconsistencies exist, however, with a number of observational studies not reporting beneficial effects for antenatal magnesium sulphate for the risk of PVL (Canterino 1999), IVH (Canterino 1999; Kimberlin 1999; Weintraub 2001), cerebral palsy (Boyle 2000; Costantine 2007; Grether 2000; O’Shea 1998; Paneth 1997; Wilson-Costello 1998), and perinatal mortality (Kimberlin 1999).

In order to establish more reliable evidence, a number of randomised controlled trials have been undertaken assessing the effects of in utero exposure to magnesium sulphate for preventing perinatal cerebral injuries, cerebral palsy, and perinatal mortality, when given to women at risk of preterm birth. The Doyle 2009 Cochrane systematic review ‘Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus’ included five randomised controlled trials (6145 infants) comparing antenatal magnesium sulphate with placebo or no treatment. The primary aim of five of the included studies, two from the United States (Mittendorf 2002; Rouse 2008), one from Australia and New Zealand (Crowther 2003), and one from France (Marret 2007a), was fetal neuroprotection, although one trial had a second tocolytic arm of the study (Mittendorf 2002). The primary aim of the fifth study (Maggie 2007), conducted worldwide, was the prevention of eclampsia; with long-term neurological outcomes reported for the infants.

In the Doyle 2009 review, magnesium sulphate administered to the mother specifically with neuroprotective intent was associated with a 15% relative reduction in the risk of death or cerebral palsy (risk ratio (RR) 0.85, 95% CI 0.74 to 0.98; four trials; 4446 infants). Overall, antenatal magnesium sulphate treatment was associated with a 32% relative reduction in the risk of cerebral palsy (RR 0.68, 95% CI 0.54 to 0.87; five trials; 6145 infants). This review established the neuroprotective role for antenatal magnesium sulphate, as compared with women not receiving magnesium sulphate. Importantly, significantly more women receiving magnesium sulphate ceased therapy because of adverse effects (RR 3.26, 95% CI 2.46 to 4.31) (Doyle 2009).

Maternal adverse effects of magnesium sulphate
Due to the widespread use of magnesium sulphate in obstetrics, the potential for adverse maternal effects following administration is well recognised, and has been noted in the Cochrane reviews assessing the various antenatal indications for use (Crowther 2002; Doyle 2009; Doyle 2010a; Doyle 2010b; Han 2010). Whilst life-threatening magnesium toxicity in obstetrics is extremely rare, and should not occur with correct administration (Lu 2000), consequences of severe hypermagnesaemia, including respiratory arrest, cardiac arrest and death have been detailed in case reports (Bohman 1990; McCubbin 1981; McDonnell 2009; Morisaki 2000; Richards 1985; Wax 1995). More frequently noted, however, are occurrences of well recognised minor adverse effects, including pain in the arm during intravenous infusion, and flushing, warmth, and sweating, due to the peripheral vasodilatory effects of magnesium. Further adverse effects associated with therapy include nausea, vomiting, headaches, muscle weakness, and blurred vision (Lu 2000).

In the randomised trials of antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, and in the meta-analysis in the Doyle 2009 review, serious maternal complications of therapy, such as death, cardiac arrest and respiratory arrest were not more frequent among women exposed to magnesium sulphate compared with women in the control groups. As expected, however, significantly higher rates of minor maternal adverse effects were observed among women exposed to magnesium sulphate compared with women in control groups; an approximate 50% increase of both hypotension and tachycardia were reported (hypotension: RR 1.51, 95% CI 1.09 to 2.09; tachycardia: RR 1.53, 95% CI 1.03 to 2.29). Additional adverse effects including flushing, nausea or vomiting, sweating, and problems at the injection site, were more frequent among women exposed to magnesium sulphate, as compared with women not receiving magnesium sulphate. Importantly, significantly more women receiving magnesium sulphate ceased therapy because of adverse effects (RR 3.26, 95% CI 2.46 to 4.31) (Doyle 2009).

As administration of antenatal magnesium sulphate prior to preterm birth for fetal neuroprotection is associated with a risk of different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Review)
adverse maternal effects and therapy cessation, it is important to determine the ideal treatment regimen, which maintains effectiveness whilst minimising adverse effects.

**Mode of action for magnesium sulphate**

The precise mechanism of action of magnesium sulphate for neuroprotection of the fetus is not known. Experimental evidence and animal studies have supported several possible neuroprotective effects of magnesium (Marret 2007b).

In humans, magnesium is essential for health, through key cellular processes including protein synthesis, lipid and nucleic acid metabolism, glycolysis, oxidative phosphorylation, and the maintenance of membrane integrity (McIntosh 1989). Magnesium is vital for normal functioning of CNS cells, activating ATP-ase, enhancing phosphorylation, and controlling calcium flow as the endogenous regulator of N-methyl-D-aspartate (NMDA) receptor calcium channel activity (Vink 2009).

Animal studies have revealed that magnesium is neuroprotective during perinatal brain injury (Hoffman 1994; Mami 2006; Marret 1995; McDonald 1990). The developing brain is regarded as particularly sensitive to glutamate-mediated damage, proposed to be associated with an up-regulation of NMDA receptors with enhanced function (Johnston 2002). It is thus plausible that magnesium can protect against hypoxic/ischaemic perinatal brain injury and neurological dysfunction through inhibiting glutamate-mediated NMDA receptor activation, consequently reducing calcium influx, and subsequent excitotoxic cell injury (Antonov 1999; Gathwala 2001; McIntosh 1989; Nowak 1984).

**Rationale for the review**

The effectiveness of antenatal magnesium sulphate for neuroprotection of the fetus, infant, and child prior to very preterm birth has been established (Doyle 2009). Implementation may be strengthened if recommendations for practice can be based on reliable evidence about the comparative effectiveness and adverse effect profiles of different magnesium sulphate regimens.

As administration of higher doses of magnesium sulphate may be associated with a greater risk of adverse effects, and the duration of therapy affects the requirement for supervision by trained staff, which is costly, it is important to assess the optimal regimen and minimum effective dose. No systematic review assessing studies making head-to-head comparisons of different regimens of magnesium sulphate for fetal neuroprotection has been identified. To assess the comparative effectiveness and adverse effects of different magnesium sulphate regimens for neuroprotection of the fetus in women considered at risk of preterm birth.

**METHODS**

**Objectives**

To assess the comparative effectiveness and adverse effects of different magnesium sulphate regimens for neuroprotection of the fetus in women considered at risk of preterm birth.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

We aimed to include all published, unpublished, and ongoing randomised trials with reported data that compared different magnesium sulphate regimens used for neuroprotection of the fetus in women at risk of preterm birth. The trials must have used some form of random allocation. We planned to include cluster trials. We planned to exclude quasi-randomised trials and those with a crossover design. We planned to include trials published as full-text papers, along with those published in abstract form only.

**Types of participants**

Women expected to give birth preterm (before 37 weeks), regardless of the reason, number of babies in utero, and parity.

**Types of interventions**

All randomised comparisons of different antenatal magnesium sulphate regimens for neuroprotection of the fetus given to women at risk of preterm birth. Comparisons could include different routes of administration, different loading or maintenance doses, different durations of therapy, timings of therapy, and whether re-treatment was permitted.

We intended to exclude trials where antenatal magnesium sulphate prior to preterm birth was compared with placebo or no treatment, as those trials are covered in a separate review 'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus' (Doyle 2009). We also planned to exclude trials where antenatal magnesium sulphate was given to women at term for neuroprotection of the fetus, as these trials will be covered in another Cochrane review, 'Magnesium sulphate for women at term for neuroprotection of the fetus' (Nguyen 2011).

**Types of outcome measures**

**Primary outcomes**

Primary outcomes were chosen to be those most representative of the clinically important measures of effectiveness and safety, including serious outcomes for women and their infants.
For the infant/child
- Death (fetal, neonatal, or later death up to the time of follow-up)
- Cerebral palsy (abnormality of tone with motor dysfunction, or as defined by trialists)
- Death or cerebral palsy (as they are competing outcomes this combined outcome is often considered the most clinically relevant for assessing neuroprotection)

For the woman
- Serious adverse cardiovascular or respiratory outcome related to therapy (respiratory arrest, cardiac arrest, death)
- Adverse effect(s) severe enough to stop treatment
- Need for calcium gluconate

Secondary outcomes
Secondary outcomes included other measures of effectiveness and safety.

For the infant
- Intraventricular haemorrhage (IVH)
- Grade 3 or 4 IVH
- Periventricular leukomalacia (PVL)
- Apgar score (less than seven at five minutes)
- Need for active resuscitation at birth (assisted ventilation via an endotracheal tube)
- Neonatal convulsions
- Neonatal hypotonia
- Use of respiratory support (mechanical ventilation or continuous positive airways pressure, or both)
- Chronic lung disease (need for continuous, supplemental oxygen at 28 days postnatal age or 36 weeks' postmenstrual age)
- Use of postnatal corticosteroids

For the child
- Major neurologic disability
  - Moderate or severe cerebral palsy (as defined by trialists)
  - Moderate or severe neurological impairment: developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than two SD below the mean)
    - Legal blindness
    - Sensorineural deafness requiring hearing aids
  - Death or any neurological impairment
  - Death or substantial gross motor dysfunction
  - Death or any major neurologic disability

For the woman
- Growth assessments at childhood follow-up (weight, head circumference, height)
- Educational achievements

For the infant/child
- Cerebral palsy (mild, moderate or severe, evaluated separately, as defined by trialists)
  - Other neurological impairments
    - Developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than one standard deviation (SD) below the mean)
    - Blindness (corrected visual acuity worse than 6/60 in the better eye)
    - Deafness (hearing loss requiring amplification or worse)
  - Substantial gross motor dysfunction (child was not walking at two years, or was unable to grasp and release a small block with both hands)

Use of health services
- Admission to intensive care unit for the mother
- Length of postnatal hospitalisation for the woman
- Admission to neonatal intensive care for the infant
- Length of stay in neonatal intensive care unit for the infant
- Length of neonatal hospitalisation for the infant

Search methods for identification of studies

Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth (Review)

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Electronic searches
We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group’s Trials Register (31 December 2011). The Cochrane Pregnancy and Childbirth Group’s Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the ‘Specialized Register’ section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Tries identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.

Data collection and analysis
See Appendix 1 Methods of data collection and analysis to be used in future updates of this review.

RESULTS

Description of studies
See: Characteristics of ongoing studies.
No completed studies that met the inclusion criteria of the review were found. One ongoing clinical trial was identified (Crowther 2011b); for more details, see Characteristics of ongoing studies.

Risk of bias in included studies
No randomised trials were found for inclusion in the review.

Effects of interventions
No randomised trials were found for inclusion in the review.

DISCUSSION
Cerebral palsy is a serious outcome after preterm birth, and thus the identification of primary preventive therapies is of crucial importance. Compelling evidence from recent clinical trials has shown that antenatal magnesium sulphate is a simple and effective primary preventative strategy for neuroprotection of the preterm fetus, infant and child, associated with minimal risks to the mother and fetus when administered appropriately (Doyle 2009). Whilst this beneficial therapy for preterm infants is now being recommended in clinical practice guidelines and protocols (ACOG 2010; NHMRC 2010; Reeves 2011; SOGC 2011), it is not currently clear what the optimal regimen is. It is possible that one regimen may be superior, in terms of achieving maximal effectiveness with minimal adverse effects for both the fetus and mother. Determining this is crucially important for pregnant women at risk of very preterm birth who are eligible for this beneficial therapy. Establishing the minimum effective dose is particularly important to ensure that the costs associated with the drug and monitoring required during therapy are minimised appropriately; and to ensure that the cessation of therapy associated with maternal adverse effects is minimised.

Three recent meta-analyses (Conde-Agudelo 2009; Costantine 2009; Doyle 2009) were not able to support a particular dosing regimen for antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus. We were unable to identify any completed trials to include in this review, and thus we are unable to reach a conclusion regarding the best regimen for administration. Recent clinical practice guideline documents (NHMRC 2010; SOGC 2011) and opinion papers (ACOG 2010; Mercer 2009; Reeves 2011) have provided recommendations for implementation, varying from advising clinicians to base their regimen on those used in the randomised trials (ACOG 2010; Mercer 2009), to specific regimen recommendations for administration of intravenous antenatal magnesium sulphate (NHMRC 2010; Reeves 2011; SOGC 2011), as shown in Table 2.

Future research is needed to establish what regimen, particularly in terms of the loading dose, the maintenance dose and duration, and repeat dosing, is most effective in reducing neonatal and infant mortality and morbidity, and this must include the assessment of later childhood outcomes. An individual patient data meta-analysis utilising data from the previous trials that assessed antenatal magnesium sulphate for neuroprotection of the fetus, infant and child may additionally provide further insight into the benefits and harms associated with different regimens, in order to guide the ideal antenatal magnesium sulphate regimen for fetal neuroprotection prior to preterm birth (Crowther 2011a).

AUTHORS’ CONCLUSIONS
Implications for practice

Due to the dearth of reliable evidence from randomised trials, we were not able to make any firm conclusions about the optimal magnesium sulphate regimen for fetal neuroprotection in women at risk of preterm birth. Clinicians are likely to choose a regimen that is recommended in local clinical practice guidelines, or expected to be guided by the regimens that were used in the randomised trials included in the Doyle 2009 Cochrane review that established the neuroprotective role for magnesium sulphate.

For neuroprotection of the fetus, the largest trials to date have been the ACTOMgSO4 Trial (Crowther 2003) and the BEAM Trial (Rouse 2008). These trials both used intravenous administration, however, their trial entry criteria and regimens differed notably (ACTOMgSO4: 4 g loading dose given over 20 minutes followed by infusion of 1 g per hour until birth or for up to 24 hours, with no repeat dosing permitted (Crowther 2003); BEAM: 6 g loading dose over 20 to 30 minutes followed by infusion of 2 g per hour stopped if delivery had not occurred within 12 hours, with repeat dosing permitted (Rouse 2008)). In the absence of a clear ‘optimal dose,’ the safest strategy may be to follow the lower dose regimens that have been employed (Crowther 2003; Marret 2007a), as has been recommended in the two recent clinical practice guideline documents (NHMRC 2010; SOGC 2011), until further research can answer this critical question.

Implications for research

A number of important questions remain about the optimal antenatal magnesium sulphate treatment regimen for neuroprotection of the fetus in women at risk of very preterm birth including: what is the minimum effective dose; is a single loading dose sufficient or is a maintenance dose required; what duration of maintenance is optimal; should repeat dosing be given, and when, in the event that birth does not occur and again appears imminent? Different strategies to reduce maternal adverse effects during therapy additionally require evaluation.

Further trials to address these questions are required, comparing different regimens when given to women at risk of very preterm birth. Such trials must be of a high quality, and of sufficient sample size to assess the comparative effects on fetus, infant and child mortality and morbidity including cerebral palsy, maternal outcomes including adverse effects, and the use of health services.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group’s Statistical Adviser.

REFERENCES

Boyle 2000

Canterino 1999

Conde-Agudelo 2009

Costantini 2007

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Costantine 2009

Crowther 2002

Crowther 2003

Crowther 2011a

Doyle 2001

Doyle 2004

Doyle 2009

Drummond 2002

Duley 2010a

Duley 2010b

Egger 1997

FineSmith 1997

Gathwala 2001

Grether 1998

Grether 2000

Hagberg 2001

Han 2010

Harbord 2006

Hauht 1995

Higgins 2011

Himpens 2008
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Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
NHMRC 2010

Nowak 1984

O'Shea 1998

Paneth 1997

Perlman 1997

Petrini 2009

Reeves 2011

RevMan 2011

Richards 1985

Rouse 2008

Saigal 2008

Saliba 2001
Saliba E, Marret S. Cerebral white matter damage in the preterm infant: pathophysiology and risk factors. Seminars in Neonatology 2001;6(2):121–33.

Schendel 1996

SOGC 2011

Vink 2009

Wax 1995

Weintraub 2001

Wilson-Costello 1998

* Indicates the major publication for the study
### Characteristics of ongoing studies (ordered by study ID)

**Crowther 2011b**

| Trial name or title | A randomised clinical trial of different infusion rates of magnesium sulphate given prenatally to women |
| Methods            | Randomised actively-controlled trial; computer-generated random number sequence; central telephone randomisation |
| Participants       | Women with a singleton or twin pregnancy, at a gestational age less than 30 weeks, where birth is planned or definitely expected within 24 hours. Excluding women with contraindications to magnesium sulphate, who are in the second stage of labour, and who have already received magnesium sulphate during this pregnancy |
| Interventions      | Women recruited will receive magnesium sulphate infusion until birth or for 24 hours (1 g/hour) and will be randomised to different rates of administration of the loading infusion (4 g over 20 minutes versus 4 g over 60 minutes) |
| Outcomes           | Maternal adverse effects during the infusion; cessation of therapy due to maternal adverse effects; total magnesium received prior to birth; cord blood magnesium concentration |
| Starting date      | Currently recruiting. |
| Contact information| Professor CA Crowther. ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia |
DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Different antenatal magnesium sulphate regimens for neuroprotection of the fetus in women considered at risk of preterm birth used in the randomised trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>Repeat dosing</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mittendorf 2002</td>
<td>4 g bolus.</td>
<td>No.</td>
<td>No.</td>
<td>Timing before birth not specified (women were in advanced preterm labour)</td>
</tr>
<tr>
<td>Crowther 2003</td>
<td>4 g over 20 minutes.</td>
<td>1 g per hour until birth or for up to 24 hours.</td>
<td>No.</td>
<td>When birth was planned or definitely expected within 24 hours. Median time: 3.7 hours (interquartile range (IQR) 1.4 to 13.8 hours)</td>
</tr>
<tr>
<td>Magpie 2007</td>
<td>4 g over 10 to 15 minutes.</td>
<td>1 g per hour for 24 hours.</td>
<td>No.</td>
<td>Timing before birth not specified (women were given magnesium sulphate for pre-eclampsia)</td>
</tr>
<tr>
<td>Marret 2007a</td>
<td>4 g over 30 minutes.</td>
<td>No.</td>
<td>No.</td>
<td>When birth was planned or definitely expected within 24 hours. Median time: 1.6 hours (IQR 0.08 to 25.08 hours)</td>
</tr>
<tr>
<td>Rouse 2008</td>
<td>6 g over 20 to 30 minutes.</td>
<td>2 g per hour until birth or for up to 12 hours.</td>
<td>If less than 6 hours had elapsed since cessation, maintenance was restarted. If at least 6 hours had elapsed, an additional loading dose was given before maintenance was restarted</td>
<td>87% of women were given magnesium sulphate for preterm prelabour rupture of membranes, with a 25 hour median time to birth (IQR 11 to 63 hours)</td>
</tr>
</tbody>
</table>

IQR: interquartile range
Table 2. Recommended regimens for antenatal magnesium sulphate prior to very preterm birth for neuroprotection of the fetus

<table>
<thead>
<tr>
<th>Recommended regimens</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>Repeat treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC 2010, SOGC 2011</td>
<td>4 g over 20 to 30 minutes.</td>
<td>1 g per hour continued until birth or for 24 hours.</td>
<td>No immediate repeat doses.</td>
</tr>
<tr>
<td>Reeves 2011</td>
<td>6 g over 20 to 30 minutes.</td>
<td>2 g per hour continued until birth of for 12 hours.</td>
<td>If less than 6 hours have elapsed since cessation, re-start maintenance. If at least 6 hours have elapsed, give an additional loading dose before re-starting maintenance.</td>
</tr>
</tbody>
</table>

APPENDICES

Appendix 1. Methods of data collection and analysis to be used in future updates of this review

Selection of studies
Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult the third author.

Data extraction and management
We designed a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third author. We will enter data into Review Manager software (RevMan 2011) and check for accuracy.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies
Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

1. Random sequence generation (checking for possible selection bias)
We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:
- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.
(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:
- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies were at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:
- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we will re-include missing data in the analyses which we undertook.

We will assess methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and unlikely to influence the outcome; missing data imputed using appropriate methods);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ‘as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:
- low risk of bias (where it is clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study’s pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.
(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)
We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:
• low risk of other bias;
• high risk of other bias;
• unclear risk of other bias.

(7) Overall risk of bias
We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data
For dichotomous data, we will present results as summary risk ratio (RR) with 95% confidence intervals (CIs).

Continuous data
For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials
We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Crossover trials
We consider crossover designs inappropriate for this research question.

Dealing with missing data
For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes were known to be missing.
Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$, and Chi$^2$ statistics. We will regard heterogeneity as substantial if $I^2$ is greater than 30% and either $T^2$ is greater than zero, or there is a low P value (less than 0.10) in the Chi$^2$ test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes, we will use the test proposed by Egger 1997, and for dichotomous outcomes, we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2011). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials’ populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with 95% CIs, and the estimates of $T^2$ and $I^2$.

Subgroup analysis and investigation of heterogeneity

We will perform separate comparisons for different types of regimens, i.e. different routes of administration, loading and maintenance doses, durations, timings, or whether repeat dosing was permitted.

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

Maternal characteristics are likely to affect health outcomes. We will carry out subgroup analyses, if sufficient data are available, based on:

- reason the woman was considered to be at risk of preterm birth (such as presence of ruptured membranes versus preterm labour versus pre-eclampsia versus antepartum haemorrhage);
- number of babies in utero: singleton versus multiple;
- gestational age at which treatment was given: before 28 weeks versus before 34 weeks versus before 37 weeks (at randomisation);
- use of prenatal corticosteroids: in more than 50% of those at risk versus in less than 50% of those at risk.

We will use primary outcomes in subgroup analyses.

For fixed-effect inverse variance meta-analyses, we will assess differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups’ CIs; non-overlapping CIs indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We will carry out sensitivity analysis to explore the effects of trial quality assessed by allocation concealment and other risk of bias components, by omitting studies rated as ‘high risk of bias’ for these components. We will restrict this to the primary outcomes.
HISTORY
Protocol first published: Issue 9, 2011
Review first published: Issue 2, 2012

CONTRIBUTIONS OF AUTHORS
Emily Bain wrote the first draft of the review. Caroline Crowther and Philippa Middleton made comments and contributed to subsequent drafts.

DECLARATIONS OF INTEREST
The three review authors (Emily Bain, Philippa Middleton, and Caroline Crowther) are investigators in the IRIS trial (A randomised clinical trial of different infusion rates of magnesium sulphate given prenatally to women), which may be included in a future update of the review (Crowther 2011b - see Characteristics of ongoing studies). Trial eligibility, data extraction and the risk of bias for this trial will therefore be carried out by two individuals independent to the trial. Caroline Crowther was the principal investigator for the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO4 - Crowther 2003).

Two review authors (Philippa Middleton and Caroline Crowther) were members of the Guideline Development Panel, for the Australian National Health and Medical Research Council approved Antenatal Magnesium Sulphate Prior to Preterm Birth for Neuroprotection of the Fetus, Infant and Child National Clinical Practice Guidelines (NHMRC 2010).

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- Australian Government, Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
In the background, we have replaced text with Table 1.

The secondary outcomes for the woman of death, cardiac arrest and respiratory arrest were added at the review stage. Hypotension, respiratory depression, tachycardia, postpartum haemorrhage, reduced or absent tendon reflexes, hypocalcaemia and pulmonary oedema have been listed separately rather than being grouped as in the protocol.

We have added antepartum haemorrhage as a possible reason the woman was considered to be at risk of preterm birth under subgroup analysis.
INDEX TERMS

Medical Subject Headings (MeSH)
*Premature Birth; Magnesium Sulfate [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; Risk

MeSH check words
Female; Humans; Pregnancy