Magnesium sulphate for women at term for neuroprotection of the fetus (Review)

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**Abstract**

**Background**

Magnesium sulphate is extensively used in obstetrics for the treatment and prevention of eclampsia. A recent meta-analysis has shown that magnesium sulphate is an effective fetal neuroprotective agent when given antenatally to women at risk of very preterm birth. Term infants account for more than half of all cases of cerebral palsy, and the incidence has remained fairly constant. It is important to assess if antenatal administration of magnesium sulphate to women at term protects the fetus from brain injury, and associated neurosensory disabilities including cerebral palsy.

**Objectives**

To assess the effectiveness of magnesium sulphate given to women at term as a neuroprotective agent for the fetus.

**Search methods**

We searched the Cochrane Pregnancy and Childbirth Group's Trial Register (31 July 2012) and the reference lists of other Cochrane reviews assessing magnesium sulphate in pregnancy.

**Selection criteria**

Randomised controlled trials comparing antenatally administered magnesium sulphate to women at term with placebo, no treatment or a different fetal neuroprotective agent. We also planned to include cluster-randomised trials, and exclude cross-over trials and quasi-randomised trials. We planned to exclude studies reported as abstracts only.

**Data collection and analysis**

Two review authors independently assessed trials for eligibility and for risk of bias. Two authors independently extracted data. Data were checked for accuracy.
Main results

We included one trial (involving 135 women with mild pre-eclampsia at term). An additional six studies are awaiting further assessment. The included trial compared magnesium sulphate with a placebo and was at a low risk of bias. The trial did not report any of this review’s prespecified primary outcomes. There was no significant difference between magnesium sulphate and placebo in Apgar score less than seven at five minutes (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.05 to 5.46; 135 infants), nor gestational age at birth (mean difference (MD) -0.20 weeks; 95% CI -0.62 to 0.22; 135 infants).

There were significantly more maternal side effects (feeling warm and flushed) in the magnesium sulphate group than in the placebo group (RR 3.81; 95% CI 2.22 to 6.53; 135 women). However, no significant difference in adverse effects severe enough to cease treatment was observed (RR 3.04; 95% CI 0.13 to 73.42; 135 women). There were no significant differences seen between groups in the rates of postpartum haemorrhage (RR 4.06; 95% CI 0.47 to 35.38; 135 women) and caesarean section (RR 0.80; 95% CI 0.39 to 1.63; 135 women).

Authors’ conclusions

There is currently insufficient evidence to assess the efficacy and safety of magnesium sulphate when administered to women for neuroprotection of the term fetus. As there has been recent evidence for the use of magnesium sulphate for neuroprotection of the preterm fetus, high-quality randomised controlled trials are needed to determine the safety profile and neurological outcomes for the term fetus. Strategies to reduce maternal side effects during treatment also require evaluation.

**PLAIN LANGUAGE SUMMARY**

**Magnesium sulphate for women at term for neuroprotection of the term fetus**

Babies born to mothers who experience complications during pregnancy such as preterm birth (early birth before 37 weeks of pregnancy) and intrauterine infection (infections in the uterus) have a higher risk of a movement disorder called cerebral palsy. Cerebral palsy is a broad term used to describe a non-progressive physical disorder of movement or posture that is acquired in early life, and that results from complications in brain development. It may also be associated with intellectual disabilities, behavioural disorders, sensory defects (blindness and deafness) and seizures.

Another Cochrane review found that magnesium sulphate given to mothers before preterm birth could protect the baby’s brain and improve long-term outcomes into childhood. This review aimed to assess whether magnesium sulphate given to mothers before term birth (birth at 37 weeks of pregnancy or later) could also protect the baby’s brain and improve long-term outcomes.

This review included one randomised controlled study involving 135 women with mild pre-eclampsia (high blood pressure and/or protein in the urine). There was not enough evidence from this study to determine the effects of magnesium sulphate on babies born at term. Women receiving magnesium sulphate were more likely to feel warm and flushed in this study than women who received a placebo, but they were not more likely to stop treatment due to side effects. The rates of haemorrhage after birth and rates of caesarean birth were similar for women who received magnesium sulphate and those who received a placebo.

More studies are needed to establish whether magnesium sulphate given to the mother at term is protective for the baby’s brain. The babies in these trials should be followed up over a long period so that we can monitor the effects of magnesium on child development.

We are awaiting further information from another six studies so that they can be assessed.

**BACKGROUND**

Cerebral palsy (CP) is a broad term encompassing a non-progressive physical disorder of movement or posture that is acquired in...
early life, and that results from complications in brain development (Australian Register 2009; Blair 2006). CP is the most frequent cause of childhood motor disability, affecting approximately two per 1000 live births in high-income countries (Australian Register 2009). Although rates are difficult to obtain in resource-poor areas (Gladstone 2010), rates of CP are reported to be five to 10 times higher in low- to middle-income countries (Cruz 2006), with population-based studies reporting rates from 31 up to 160 per 1000 children (Gladstone 2010). The motor forms of CP have a profound effect on children’s lives: 86% of children have spasticity causing pain and restricting movement and 28% of children are unable to walk (Australian Register 2009). In addition to physical disability, CP may be associated with intellectual disabilities, behavioural disorders, sensory defects and seizures (Stanley 2000), compounding the burden of disease and impairing rehabilitation. Term infants (of at least 37 weeks’ gestation) account for more than half of all cases of CP (Australian Register 2009). The incidence of CP has remained fairly constant, particularly in term births (Blair 2006). Any therapy that offered neuroprotection to the term fetus and reduced the incidence of CP would be of global public health importance. There are several known risk factors for CP, including multiple births, prematurity, intrauterine growth restriction, chorioamnionitis, perinatal asphyxia and pre-eclampsia. Increasing plurality is linked with an increased risk of CP for both preterm and term births. The Western Australia Cerebral Palsy Register reported a 3.8-fold increase in the rate of CP for term multiple births compared with term singletons (Blair 2006). Preterm birth (before 37 weeks’ gestation) is a major risk factor for the development of CP. In the Australian population, where approximately 7.9% of all births are preterm, 41.5% of children with CP were born preterm from 1993-2003 (Australian Register 2009). However, most children with CP are born at term (Australian Register 2009; Stanley 2000; Wu 2003). Deviating from the optimum birthweight for gestational age is associated with an increased risk and severity of CP (Jarvis 2006). Intrauterine growth restriction and being small-for-gestational age at birth are linked with the development of CP (Jacobsson 2008). Infants born severely growth restricted at term, have a five- to seven-fold increased risk of developing CP (Jacobsson 2008). Being large-for-gestational age is also associated with an increased risk of CP development (Jarvis 2006). Clinical chorioamnionitis is a recognised risk factor for children born at term (Blair 2006; Wu 2003). Chorioamnionitis is believed to be due to ascending bacteria from the lower genital and urinary tract and there is an association with prolonged rupture of the membranes (Bracci 2003; Menon 2009). There are several hypothesised mechanisms for chorioamnionitis leading to hypoxic-ischaemic brain injury and CP including direct ascending infection, elevated levels of fetal cytokines in response to maternal infection, and inflammation of the membranes (Wu 2003). The risk of perinatal asphyxia is variably reported as occurring in two to 30 per 1000 live births and has associated sequelae of death, CP, intellectual disability and epilepsy (Dilenge 2001). Perinatal asphyxia is clinically defined as progressive hypoxaemia and hypercapnia (excessive carbon dioxide in the blood) with profound metabolic acidosis (pH less than 7.00) and can be described by timing in relation to birth and as acute or chronic in nature (MacLennan 1999). Antepartum asphyxia accounts for 50% of perinatal asphyxia cases; intrapartum asphyxia for 40% and postpartum asphyxia for 10% of cases (Dilenge 2001). It has been suggested that most events leading to CP occur before the onset of labour or after birth and not during labour itself (MacLennan 1999). It is now believed that intrapartum asphyxia accounts for far fewer cases of CP than previously thought (Stanley 2000). Intrapartum signs of asphyxia can lead to obstetric intervention to relieve acute insults (MacLennan 1999). Finally, pre-eclampsia is associated with CP, with term infants born to mothers with pre-eclampsia having a 40% increased risk of CP (Stanley 2000). Conversely, pre-eclampsia in the very preterm fetus appears to be neuroprotective when compared with gestational age-matched infants born to mothers without pre-eclampsia (Stanley 2000; Wu 2009).

**Description of the intervention**

Antenatal magnesium sulphate is currently used extensively in obstetrics as a first line anticonvulsant in the treatment of eclampsia and in preventing the progression of pre-eclampsia to eclampsia. Magnesium sulphate used as an maternal neuroprotective agent for these indications is covered in the Cochrane review: ‘Magnesium sulphate and other anticonvulsants for women with pre-eclampsia’ (Duley 2010). Magnesium sulphate has also been used as a tocolytic for women in preterm labour; however, a meta-analysis of relevant trials has been unable to confirm its efficacy for this indication (Crowther 2002). When administered for its anticonvulsant or tocolytic properties, a case-control analysis from the California Cerebral Palsy Project found magnesium sulphate was associated with a decreased risk of CP and mortality in singletons born preterm with birthweight less than 1500 g (Nelson 1995). Two further observational studies supported these findings (Finesmith 1997; Schendel 1996) while others failed to show the neuroprotective benefit of magnesium sulphate (Canterino 1999; Grether 1998; Kimberlin 1998). Four randomised controlled trials studying the use of antenatal administration of magnesium sulphate to mothers at risk of preterm birth for fetal neuroprotection (Crowther 2003; Marret 2006; Mittendorf 2002; Rouse 2008) have been conducted, and one trial that used magnesium sulphate for women with pre-eclampsia has reported on neurodevelopmental follow-up of the children (Maggie 2002). Meta-analyses of these five randomised controlled trials have established antenatal magnesium sulphate therapy as neuroprotective for the preterm fetus (Conde-Agudelo 2009; Doyle 2009), and are covered in...
the Cochrane review 'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus' (Doyle 2009). Magnesium sulphate can be administered intravenously or intramuscularly. The intravenous dose given for maternal neuroprotection against eclampsia has been recommended to be 4 g magnesium sulphate with a maintenance dose of 1 g per hour (Duley 2010). For neuroprotection of the preterm fetus, the trials have variously used 4 g to 6 g magnesium sulphate as a loading dose followed by 1 g to 2 g per hour maintenance or no maintenance (Cowther 2003; Marret 2006; Mittendorf 2002; Rouse 2008). The intramuscular regimen recommended for prevention of eclampsia has been recommended as 5 g bilateral buttock injections (as loading) with maintenance of 5 g four-hourly (Duley 2010).

Due to its vasodilatory effects, intravenous administration of magnesium sulphate can cause flushing, sweating and hypotension. Other adverse effects include nausea, vomiting, slurred speech and muscle weakness (Cowther 2003; Duley 2010). Serious adverse effects are considered rare, but can include maternal respiratory and cardiac arrest and death. No women were reported as having any serious adverse effects in the previous reviews where antenatal magnesium sulphate has been assessed (Cowther 2002; Doyle 2009; Duley 2010). Adverse effects for the infant may include poor cry, hyporeflexia, flaccidity and rarely, respiratory depression requiring mechanical ventilation (Lipsitz 1971).

How the intervention might work

The exact mechanism by which magnesium sulphate provides neuroprotection for the fetus, is not currently known. Experimental evidence and animal studies have however, supported a number of possible neuroprotective roles for magnesium, highlighting in particular the antioxidant and anti-inflammatory properties of magnesium, along with the ability of magnesium to provide haemodynamic stability, and protect against excitotoxic brain injury (Costantine 2011; Marret 2007).

Magnesium can readily cross the placenta and exert antagonistic effects on N-methyl-D-aspartate (NMDA) and calcium receptors. Animal studies have shown that magnesium sulphate administration can protect the developing fetal brain from in-utero hypoxia by inhibiting the hypoxia-induced increase in neuronal nuclear calcium influx, and thus preventing modification of neuronal nuclear membrane function (Maulik 2005). In addition, magnesium sulphate may block the excess release of glutamate in the calcium channel, protecting the susceptible fetal and newborn brains from glutamate-induced damage.

This raises the possibility that magnesium sulphate may be neuroprotective for the fetus when given to women at term prior to birth. Benefits for use prior to very preterm birth have been established (Doyle 2009). Whether use for the term fetus shows similar benefits, without risks, and at what cost is unclear. Use of magnesium sulphate for women at term for neuroprotection of the fetus could potentially be assessed whenever the fetus may be considered at risk of perinatal brain injury. This could include when the fetus is growth restricted, in the presence of chorioamnionitis, after prelabour rupture of the membranes, during labour, in pre-eclampsia, or where there is fetal distress during the antenatal or intrapartum period.

Why it is important to do this review

As benefit of antenatally administered magnesium sulphate has been established for the preterm fetus, this review assesses whether antenatal magnesium sulphate therapy given to women at term is effective and safe for neuroprotection of the term fetus.

OBJECTIVES

To determine the potential effectiveness of magnesium sulphate given to women at term as a neuroprotective agent for the fetus.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials examining the effects of antenatally administered magnesium sulphate on various maternal and infant/child outcomes compared with controls (placebo, no treatment or a different fetal neuroprotective agent). We planned to include cluster-randomised trials, and exclude cross-over trials and quasi-randomised trials. We planned to exclude studies reported as abstracts only.

Types of participants

Women administered antenatal magnesium sulphate at a gestational age of 37 weeks or later. We planned to include trials regardless of the reason for administration of magnesium sulphate and we planned to categorise the trials according to the primary reason magnesium sulphate was used. This may have included, for example: neuroprotection of the fetus, growth restriction, chorioamnionitis, prelabour rupture of the membranes, antenatal fetal distress, intrapartum fetal distress, pre-eclampsia, labour and other.
Types of interventions
All randomised comparisons of intravenous or intramuscular magnesium sulphate given to women at term, with placebo, no treatment, or any other agent given with fetal neuroprotective intent. Where the alternative agent was not administered with fetal neuroprotective intent, we planned to exclude the trial.

Types of outcome measures

Primary outcomes
Outcome measures considered for this review encompass measures of effectiveness and safety for the women and their infants/children.

For the infant/child
- Death or cerebral palsy
- Death (defined as fetal, neonatal or later death) (at latest time reported)
- Cerebral palsy (abnormality of tone with motor dysfunction (as diagnosed at 18 months of age or later))

For the mother
- Serious adverse cardiovascular/respiratory outcomes (defined as maternal death, respiratory or cardiac arrest)

Secondary outcomes
The secondary outcomes encompass measures of effectiveness, safety and use of health services.

For the infant
- Gestational age at birth
- Apgar scores of less than seven at five minutes
- Endotracheal intubation for resuscitation at birth
- Use of respiratory support (mechanical ventilation or continuous positive airways pressure, or both)
- Proven neonatal sepsis (positive blood or sterile site culture)
- Neonatal encephalopathy (however defined by the trialists)
- Hypoxic ischaemic encephalopathy
- Intracranial haemorrhage (including severity, grade one to four)
- Abnormal neurological examination (however defined by the trialists, at a point earlier than 18 months of age)

For the mother
- Any adverse effects severe enough to stop treatment
- Postpartum haemorrhage (however reported by the trialists)
- Mode of birth (normal vaginal birth, operative vaginal birth, caesarean section)
- Chorioamnionitis
- Intrapartum fever treated with antibiotics
- Women's satisfaction with the therapy
- Side effects of therapy including: nausea, vomiting, burning or flushing sensations, hypotension, respiratory depression

Use of health services
- Length of postnatal hospitalisation for the mother
- Admission to intensive care unit for the mother
- Admission to the neonatal intensive care unit for the infant
- Length of neonatal hospitalisation
- Costs of care for the mother or baby, or both (however determined/defined by the trialists)

For the child
- Any neurological disabilities (defined as developmental delay or intellectual impairment, blindness (corrected visual acuity worse than 6/60 in the better eye), deafness (hearing loss requiring amplification or worse), cerebral palsy, motor dysfunction). The severity of the disability due to cerebral palsy will be graded into severe, moderate and mild. Severe disability will include children who are non-ambulant and are likely to remain so, moderate disability will comprise those children who have substantial limitation of movement, and mild disability will comprise those children walking with little limitation of movement. The neurosensory disabilities imposed by the various sensorineural impairments will be classified as severe, moderate, and mild, as follows: Severe disability will comprise any of severe cerebral palsy, an intelligence quotient (IQ) < minus three standard deviations (SD) below the mean, or blindness. Moderate disability will comprise moderate cerebral palsy, deafness, or an IQ from minus three SD to < minus two SD below the mean. Mild disability will comprise mild cerebral palsy or an IQ from minus two SD to < minus one SD below the mean.
- Gross motor dysfunction (defined using the Palisano criteria)
- Major neurological disability (defined as any of: legal blindness, neurosensory deafness requiring hearing aids, moderate or severe cerebral palsy, or moderate or severe developmental delay/intellectual impairment (defined as developmental quotient or IQ less than minus two SD below the mean))
- Combination of death with any neurological disability
- Combination of death with major neurological disability (this combined outcome recognises the potential for competing risks of death or survival with neurological problems)
• Educational achievements (however determined/defined by the trialists)

Search methods for identification of studies

Electronic searches
We searched the Cochrane Pregnancy and Childbirth Group’s Trials Register (31 July 2012). The Cochrane Pregnancy and Childbirth Group’s Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. monthly 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.
Trials 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.
We also searched through reference lists of other Cochrane reviews discussing magnesium sulphate in pregnancy, including Duley 2010.

Data collection and analysis

Selection of studies
Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, when required, we consulted a third review author.

Data extraction and management
We designed a form to extract data. For eligible studies, at least two review authors extracted the data using the agreed form. Whenever possible, we sought unpublished data from investigators. We resolved discrepancies through discussion or, when required, we consulted a third review author. We entered data into Review Manager software (RevMan 2011) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

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

(1) Random sequence generation (checking for possible selection bias)
We described for the 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 assessed 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 described for the included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed 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 described for the included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at a low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed 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 described for the included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed 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 described for the included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated 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 planned to re-included missing data in the analyses which we undertook.
We assessed methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- 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 described for the included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:
- low risk of bias (where it was clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review were reported);
- high risk of bias (where not all the study’s pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed 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 described for the included study any important concerns we had about other possible sources of bias.
We assessed whether the included 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 whether there is risk of other bias.

(7) Overall risk of bias
We have made an explicit judgement about whether the included study is at high risk of bias, according to the criteria given in the Cochrane Handbook (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to 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 have presented results as summary risk ratio with 95% confidence intervals.

Continuous data
For continuous data, if we had included more than one trial, we planned to use the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials
We planned to include cluster-randomised trials in the analyses along with individually-randomised trials. In future updates of this review, if we include cluster-randomised trials, we plan to adjust their standard errors using the methods described in the Cochrane Handbook (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 plan to 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 plan to synthesise the relevant information. We 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 plan to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Multiple pregnancy
In future updates of this review, where trials have included women with twin pregnancies, we plan to use cluster-trial methods if possible to account for non-independence of infants from multiple pregnancies.

Dealing with missing data
We noted levels of attrition for the included study. If we had included more than one trial, we planned to 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 carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed 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 was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity
As we included only one trial in this review, we were unable to conduct any meta-analyses. In future updates of this review, we plan to assess statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$ and $\chi^2$ statistics. We will regard heterogeneity as substantial if the $I^2$ is greater than 30% and either the $T^2$ 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 had been 10 or more studies in a meta-analysis we planned to investigate reporting biases (such as publication bias) using funnel plots. In future updates of this review, we plan to assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we plan to use the test proposed by Egger 1997, and for dichotomous outcomes we plan to use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we plan to perform exploratory analyses to investigate it.

Data synthesis
We carried out statistical analyses using the Review Manager software (RevMan 2011). As we included only one trial in this review, we were unable to conduct any meta-analyses. In future updates of this review we plan to use a 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 plan to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We plan to treat the random-effects summary 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.

In future updates of this review, if we use random-effects analyses, we plan to present the results as the average treatment effect with 95% confidence intervals, with the estimates of $T^2$ and $I^2$.

Subgroup analysis and investigation of heterogeneity
As we included only one randomised trial in this review, we were not able to conduct any of the pre-specific subgroup analyses, or investigate heterogeneity. In future updates of this review, if we identify substantial heterogeneity, we plan to investigate it using subgroup analyses and sensitivity analyses. We plan to consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

In future updates of this review, if possible, we plan to carry out the following subgroup analyses, stratifying for:
- the reasons the mother was considered for magnesium sulphate treatment (prolonged prelabour rupture of membrane, increased risk of chorioamnionitis, pre-eclampsia/eclampsia, increased risk of perinatal asphyxia, neuroprotection of the fetus, other);
- the numbers of babies in utero (singleton or multiple);
- the total dose of magnesium sulphate administered; (4 g or less: > 4 g to 6 g; > 6 g to 12 g; > 12 g to 24 g; > 24 g).
- the type of magnesium preparation administered; (50% solution; < 50% solution);
- the mode of administration (intramuscularly or intravenously);
- whether repeat treatment was permitted; (no repeat permitted; repeat permitted);
- the time treatment was given prior to birth; (< four hours; four to < eight hours; eight to < 12 hours; 12 to < 24 hours; 24 or more hours).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2011). We will report the results of subgroup analyses quoting the $\chi^2$ statistic and $P$ value, and the interaction test $P$ value. We will use only the primary outcomes in subgroup analyses.
Sensitivity analysis
As we included only one trial in this review, we were not able to carry out a sensitivity analysis. In future updates of this review, we plan to carry out sensitivity analysis to explore the effects of trial quality assessed by sequence generation and allocation concealment, by omitting studies rated as ‘high risk of bias’ for this components. Sensitivity analysis will be restricted to the primary outcomes.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification. See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification.

Results of the search
The search of the Pregnancy and Childbirth Group’s Trials Register identified three reports relating to one trial (Blackwell 2001) and our own search of the reference lists of other Cochrane reviews assessing magnesium sulphate in pregnancy, including Duley 2010, found an additional seven trials (Chen 1995; Coetzee 1998; Livingston 2003; Magann 1995; Magpie 2002; Moodley 1994; Witlin 1997).

We have included one trial (Witlin 1997) involving 135 women. Six trials are awaiting further assessment (Blackwell 2001; Chen 1995; Coetzee 1998; Livingston 2003; Magpie 2002; Moodley 1994), and one trial was excluded (Magann 1995).

The trials awaiting further assessment (Blackwell 2001; Chen 1995; Coetzee 1998; Livingston 2003; Magpie 2002; Moodley 1994) include magnesium sulphate administration at less than 37 weeks’ gestation in the reported data. We have contacted the trial authors regarding the provision of data relating only to those women administered antenatal magnesium sulphate at a gestational age of 37 weeks or later. See Characteristics of studies awaiting classification.

Included studies
The one included trial (Witlin 1997) was conducted in the United States and enrolled 135 women with mild pre-eclampsia at term from March 1995 to June 1996. The women were randomised to receive either intravenous magnesium sulphate (n = 67) or an identically appearing saline infusion (n = 68) during labour and for 12 hours postpartum. The magnesium sulphate loading dose was 6 g given over 15 to 20 minutes, followed by a 2 g per hour maintenance infusion continuing until 12 hours postpartum. The primary outcome was the length of labour. Secondary outcomes included the infant Apgar score and, for the mother, postpartum haemorrhage, caesarean delivery, maternal infection and maternal side effects. For further details, see Characteristics of included studies.

Excluded studies
One study was excluded (Magann 1995) as it compared magnesium sulphate to terbutaline. For further details, see Characteristics of excluded studies.

Risk of bias in included studies
The one included trial was judged to be at a low risk of bias overall. A summary of the risk of bias for the included study is provided in Figure 1.
Allocation
The one included study, Witlin 1997 used an adequate method for generating the random sequence (using a computer-generated table of random numbers). The method of allocation concealment was also judged as adequate with the use of sealed, sequentially numbered, opaque envelopes; trial treatments were prepared and dispensed by the hospital pharmacy, further concealing allocation.

Blinding
Blinding of participants, clinicians and outcome assessors was reported in the included study (Witlin 1997), and was considered adequate with the use of an identical-appearing placebo prepared in and dispensed by the hospital pharmacy.

Incomplete outcome data
There were no reports of any women lost to follow-up, withdrawals or exclusion after randomisation in the included study (Witlin 1997).

Selective reporting
We judged the included trial to be at an unclear risk of reporting bias, with no access to the trial’s protocol (Witlin 1997). The primary outcomes relevant to this review were not reported in this study.

Other potential sources of bias
The trial was judged to be at an unclear risk of other bias, at is was terminated early. The trial was stopped at 68% of the planned enrolment, following a single interim analysis that determined only 37 women in each group were needed to rule out that magnesium sulphate was associated with a 33% increase in the length of labour (Witlin 1997).

**Effects of interventions**

**Primary outcomes**

**For the infant/child**

Witlin 1997 did not report on any of the review's primary outcomes of death (all fetal, infant and later), cerebral palsy, or death or cerebral palsy for the infant/child.

**For the mother**

Witlin 1997 did not report on any serious adverse maternal outcomes (death, cardiac arrest or respiratory arrest).

**Secondary outcomes**

**For the infant/child**

Witlin 1997 reported no significant difference between magnesium sulphate and placebo in Apgar score less than seven at five minutes (risk ratio (RR) 0.51; 95% confidence interval (CI) 0.05 to 5.46; 135 infants; Analysis 1.1), and no significant difference was shown between groups for gestational age at birth (mean difference (MD) -0.20 weeks; 95% CI -0.62 to 0.22; 135 infants; Analysis 1.2).

Witlin 1997 did not report on any of the other secondary review outcomes for the infant/child.

**For the mother**

In regards to side effects, women in the magnesium sulphate group were significantly more likely to feel warm and flushed than women in the placebo group (RR 3.81; 95% CI 2.22 to 6.53; 135 women; Analysis 1.6) (Witlin 1997).

Considering cessation of treatment due to adverse effects, no significant difference was observed between the magnesium sulphate and placebo groups (RR 3.04; 95% CI 0.13 to 73.42; 135 women; Analysis 1.3). Witlin 1997 reported that “one woman had chest tightness and decreased oxygen saturation and required cessation of the magnesium sulfate infusion” in the magnesium sulphate group. “A second woman was inadvertently given twice the usual infused dose of magnesium sulfate (4 g/hour) and was found to be lethargic with slurred speech post partum” however, no cessation of treatment for this woman was documented (Witlin 1997). No women required cessation in the placebo group.

There were no significant differences seen between groups for postpartum haemorrhage (RR 4.06; 95% CI 0.47 to 35.38; 135 women; Analysis 1.4) or caesarean section (RR 0.80; 95% CI 0.39 to 1.63; 135 women; Analysis 1.5) in Witlin 1997.

Witlin 1997 did not report on any of the review's other secondary maternal outcomes.

**Use of health services**

No data regarding the use of health services were reported by Witlin 1997.

**DISCUSSION**

**Summary of main results**

Two recent meta-analyses have reported the neuroprotective benefit of magnesium sulphate for the preterm fetus (Conde-Agudelo 2009; Doyle 2009). Literature examining the neuroprotective effects of magnesium sulphate in the term fetus is, however, scant.

We included one randomised controlled trial (Witlin 1997, involving 135 women) that compared magnesium sulphate with a placebo for women with mild pre-eclampsia at term in this review. We are considering a further six trials for possible future inclusion in this review. As none of the pre-specified primary outcomes for this review were reported in the included trial (Witlin 1997), we cannot make any conclusions surrounding the role of magnesium sulphate in protecting against fetal mortality and providing neuroprotection for the term fetus. There was no clear evidence in this trial to support an association between magnesium sulphate and improved infant Apgar score, nor to support an association with gestational age at birth (Witlin 1997).

The included trial showed an increase in maternal side effects, specifically warmth and flushing, for women receiving magnesium sulphate as compared with a placebo (Witlin 1997). Whilst two women receiving magnesium sulphate experienced additional adverse effects (one experienced chest tightness and decreased oxygen saturation and required cessation of the infusion, and one was found to be lethargic with slurred speech after inadvertently being given twice the usual dose), no significant increase in serious maternal outcomes (death, cardiac arrest or respiratory arrest) or need for cessation of magnesium therapy was noted. No differences were observed between groups for the outcomes postpartum haemorrhage and caesarean section (Witlin 1997).
Overall completeness and applicability of evidence

This review is limited with the inclusion of only one trial of 135 women (Witlin 1997) that did not report on any of this review’s pre-specified primary outcomes, and was not powered to detect important differences in outcomes including death and neurosensory disability. For further completeness, we are awaiting the assessment of six other trials for possible inclusion, should data regarding solely women administered antenatal magnesium sulphate at a gestational age of 37 weeks or later (and their babies) become available from the study authors (Blackwell 2001; Chen 1995; Coetzee 1998; Livingston 2003; Magpie 2002; Moodley 1994).

Quality of the evidence

Witlin 1997 was judged to have adequate methods of random sequence generation, allocation concealment and blinding. There were no women lost to follow-up or exclusions, however, selective reporting was judged to be unclear in this trial. The trial was also judged to be at an unclear risk of other bias, due to its early termination.

Potential biases in the review process

The evidence for this review is derived from one study identified through a detailed search process. It is possible (but unlikely) that additional trials comparing the use of magnesium sulphate versus a placebo or no treatment, or an alternative fetal neuroprotective agent, including women at term (reporting on the pre-stated outcomes), have been published but not identified. It is also possible that other studies have been conducted but not published. Should such studies be identified, we will endeavour to include them in future updates of this review.

Agreements and disagreements with other studies or reviews

This review confirms that there is currently insufficient evidence to support magnesium sulphate as neuroprotective for the term fetus. There have not been other reviews on the use of magnesium sulphate at term for fetal neuroprotection. Another Cochrane review has shown that magnesium sulphate is neuroprotective for the fetus when given to women at risk of preterm birth (Doyle 2009). Magnesium sulphate is now recommended in clinical practice guidelines for neuroprotection of the preterm fetus (NHMRC 2010; SOGC 2011).

Previous Cochrane reviews comparing magnesium sulphate with a placebo, have similarly shown an increase risk of side effects for mothers receiving treatment (Doyle 2009; Duley 2010).

Authors’ conclusions

Implications for practice

There is currently insufficient evidence to assess the efficacy and safety of magnesium sulphate when administered to women at term for neuroprotection of their fetus.

Implications for research

The incidence of cerebral palsy remains constant despite advancements in the management of its maternal risk factors. Thus, any therapy that offers neuroprotection to the term fetus, leading to a reduction in the incidence of cerebral palsy, would be of global public health importance.

Magnesium sulphate has been shown to have a neuroprotective role for the preterm fetus when administered to women at risk of preterm birth. Whether there are similar benefits of this treatment for the term fetus, however, remains unknown. Randomised controlled trials are required to determine the safety profile and neurological outcomes of magnesium sulphate for the term fetus. Such studies should be of high quality and sufficient sample size, and should report long-term follow-up of the infants to allow assessment of cerebral palsy and neurodevelopment.

Strategies to reduce maternal side effects associated with magnesium sulphate, and to ensure the safety of administration, additionally require evaluation.

Acknowledgements

A warm thank you to Emer Heatley, Cochrane Fellow for the Australian Satellite of the Pregnancy and Childbirth Cochrane Review Group in 2011, The University of Adelaide, who kindly reviewed drafts of the protocol and provided guidance.

The Liverpool office and Lynn Hampson kindly provided their support and conducted the search for trials.

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.
References to studies included in this review

Witlin 1997  {published data only}

Magann 1995 {published data only}

References to studies excluded from this review

Magann 1995 {published data only}

References to studies awaiting assessment

Blackwell 2001 {published and unpublished data}


Chen 1995 {published and unpublished data}

Coetzee 1998 {published and unpublished data}

Livingston 2003 {published and unpublished data}

Magpie 2002 {published and unpublished data}

Moodley 1994 {published and unpublished data}

Additional references

Australian Register 2009

Blair 2006

Bracci 2003

Canterino 1999

Conde-Agudelo 2009

Costantine 2011

Crowther 2002

Crowther 2003

Cruz 2006

Dilenge 2001
**Magnesium sulphate for women at term for neuroprotection of the fetus (Review)**

**Doyle 2009**

**Duley 2010**

**Egger 1997**

**Finesmith 1997**

**Glodstone 2010**

**Grether 1998**

**Harbord 2006**

**Higgins 2011**

**Jacobsson 2008**

**Jarvis 2006**

**Kimberlin 1998**

**Lipsitz 1971**

**MacLennan 1999**

**Marret 2006**

**Marret 2007**

**Maulik 2005**

**Menon 2009**

**Mittendorf 2002**

**Nelson 1995**

**NHMRC 2010**

**RevMan 2011**
Rouse 2008

Schendel 1996

SOGC 2011

Wu 2003

Wu 2009

*Indicates the major publication for the study.
CHARACTERISTICS OF STUDIES

Characteristics of included studies  [ordered by study ID]

Witlin 1997

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>135 women were randomised.</td>
</tr>
<tr>
<td>Setting</td>
<td>Memphis, US.</td>
</tr>
<tr>
<td>Recruitment</td>
<td>March 1995 to June 1996.</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>women at least 37 weeks’ gestation with blood pressure ( \geq 140 ) mmHg systolic, ( \geq 90 ) mmHg diastolic and/or proteinuria (( \geq 300 ) mg per 24 hours)</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>severe pre-eclampsia, fetal malpresentation, congenital anomalies, non reassuring fetal testing, contraindications to the use of magnesium sulphate, contraindications to a trial of labour</td>
</tr>
<tr>
<td>Interventions</td>
<td>Magnesium sulphate (n = 67)</td>
</tr>
<tr>
<td></td>
<td>Women were given a loading infusion of 6 g magnesium sulphate over 15-20 minutes followed by a maintenance infusion of 2 g per hour continued until 12 hours postpartum</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 68)</td>
</tr>
<tr>
<td></td>
<td>Women were given an equal volume of a saline solution by infusion</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Maternal: length of labour, postpartum haemorrhage, caesarean delivery, maternal infection, maternal side effects, maternal side effects requiring treatment cessation</td>
</tr>
<tr>
<td></td>
<td>Infant: Apgar score ( \leq 6 ) at 1 and 5 minutes, gestational age at birth</td>
</tr>
<tr>
<td>Notes</td>
<td>Participant enrolment ceased at 68% of planned enrolment following a single interim analysis</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>“Randomisation was performed by use of computer-generated tables of random numbers.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>“The women and their care givers were blinded to the randomisation assignment through the use of sealed, sequentially numbered, opaque envelopes.”</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Low risk</td>
<td>Magnesium sulphate and placebo infusions were “… dispensed by the hospital pharmacy”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>All women and their caregivers were blind to group allocation; an identically appearing placebo infusion was used</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Low risk</td>
<td>As above.</td>
</tr>
</tbody>
</table>
Incomplete outcome data (attrition bias)

<table>
<thead>
<tr>
<th>All outcomes</th>
<th>Low risk</th>
<th>No losses to follow-up were reported. No drop outs or withdrawals were reported</th>
</tr>
</thead>
</table>

Selective reporting (reporting bias)

<table>
<thead>
<tr>
<th>Unclear risk</th>
<th>With no access to a trial protocol, it was not possible to determine if outcome data for all pre-specified outcomes were reported</th>
</tr>
</thead>
</table>

Other bias

<table>
<thead>
<tr>
<th>Unclear risk</th>
<th>Reason for early termination of study: enrolment of women into study was terminated at 68% of planned enrolment - following a single interim analysis determining that only 37 women in each group were needed to rule out a 33% increase in the length of labour resulting from magnesium sulphate</th>
</tr>
</thead>
</table>

**Characteristics of excluded studies**  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magann 1995</td>
<td>Study compared magnesium sulphate with terbutaline. Participants: 46 women. Intervention: 4 g IV magnesium sulphate. Comparison: 0.25 mg subcutaneous terbutaline. Outcomes: mean arterial pressure, arterial pressure before and after the induction of anaesthesia, maternal heart rate, maternal oxygen saturation, estimated blood loss, pre- and postoperative haematocrits. No fetal outcomes were reported</td>
</tr>
</tbody>
</table>

**Characteristics of studies awaiting assessment**  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Blackwell 2001</th>
<th>Randomised, placebo-controlled, double-blinded trial.</th>
</tr>
</thead>
</table>

**Inclusion criteria:** women with singleton gestations at at least 32 weeks with no clinical indications for magnesium sulphate therapy (pre-eclampsia or tocolysis) and either clinical chorioamnionitis or prolonged rupture of membranes

**Exclusion criteria:** any indication for magnesium sulphate therapy (seizure prophylaxis or tocolysis), known maternal hypersensitivity to magnesium sulphate, fetal structural defects, fetal growth restriction (birth weight < 10th percentile for gestational age), systemic maternal infection (e.g., pneumonia or pyelonephritis), advanced cervical dilation (8 cm), or imminent delivery and disorders such as any renal, cardiac, or pulmonary disease, pulmonary hypertension, or myasthenia gravis
### Blackwell 2001 (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th><strong>Magnesium sulphate (n = 11)</strong>&lt;br&gt;Women were given a 6 g magnesium sulphate loading dose followed by 2 g per hour until birth</th>
<th><strong>Placebo (n = 11)</strong>&lt;br&gt;Women were given a matched volume of lactated Ringer's solution until birth</th>
</tr>
</thead>
</table>

| Outcomes | Maternal: mode of delivery, histological chorioamnionitis. Infants: fetal blood for total magnesium, ionised magnesium, IL-1beta, IL-6, and TNF-alpha; birth weight; 5-minute Apgar score; fetal death; major intraventricular haemorrhage; necrotising enterocolitis, bronchopulmonary dysphasia |

| Notes | 3 publications (including 2 abstracts) were identified likely relating to the same trial. Women included were at “at least 32 weeks gestation”. Author has been contacted regarding the availability of relevant data |

### Chen 1995

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised trial - no further information provided.</th>
</tr>
</thead>
</table>

| Participants | 64 women were randomised. **Inclusion criteria:** women with blood pressure ≥ 150/100 fulfilling at least 1 of 11 features of severe pre-eclampsia that were listed **Exclusion criteria:** intrauterine death, chronic hypertension, eclampsia. |

| Interventions | **Magnesium sulphate (n = 34)**<br>Women were given a 4 g IV loading dose of magnesium sulphate over 10 minutes followed by a maintenance dose of 1 g per hour until 1 day after birth | **Comparison (n = 30)**<br>No treatment. |

| Outcomes | Maternal: mode of delivery (caesarean section, spontaneous), convulsions, abruption Infant: Apgar score ≤ 6 at 1 minute. |

| Notes | |

### Coetzee 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, placebo-controlled trial. Women were allocated using consecutively numbered cards placed inside sealed opaque envelopes instructing the use of solution A or B. Envelopes were distributed in mixed batches of 20 and always had equal numbers of A and B. The solutions were prepared by the pharmacy and the identity of the solutions marked A or B were changed periodically</th>
</tr>
</thead>
</table>

| Participants | 822 women were randomised (data presented for 645 women). **Setting:** South Africa. **Inclusion criteria:** women with severe pre-eclampsia (at least 2 of: of diastolic blood pressure ≥ 110 mmHg, significant proteinuria, symptoms of imminent eclampsia) requiring termination of pregnancy by induction of labour or caesarean section **Exclusion criteria:** women less than 16 years old; women already receiving anticonvulsant therapy |

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Magnesium sulphate for women at term for neuroprotection of the fetus (Review)  
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### Coetzee 1998

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Magnesium sulphate (n = 345)</th>
<th>Placebo (n = 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women were given a 4 g IV magnesium sulphate loading dose in 200 mL saline over 20 minutes, followed by 1 g per hour (200 mL over 4 hours) until 24 hours after birth.</td>
<td>Women were given 200 mL of a placebo solution over 20 minutes, followed by 200 mL over 4 hours until 24 hours after birth. Treatment was stopped if urine output was less than 30 mL per hour</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Maternal: convulsions, maternal death, adverse reaction, antihypertensive therapy, caesarean section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant: live births, stillbirths.</td>
<td></td>
</tr>
</tbody>
</table>

### Livingston 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, placebo-controlled trial. Allocation was by sealed, consecutively numbered opaque envelopes. All medication was mixed in the pharmacy and labelled 'study drug'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>222 women were randomised.</td>
</tr>
<tr>
<td>Setting: Memphis, US.</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: women with mild pre-eclampsia (blood pressure ( \geq 140/90 ) taken on 2 occasions in the presence of new onset proteinuria). Women who developed mild pre-eclampsia only during the postpartum period were also included</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: chronic hypertension, severe pre-eclampsia.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Magnesium sulphate (n = 109)</th>
<th>Placebo (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women were given a 6 g IV loading dose in 100 mL normal saline over 20 minutes, followed by a maintenance dose of 2 g per hour until 12 hours postpartum</td>
<td>Women were given an identical, indistinguishable IV saline solution</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Maternal: caesarean delivery, uterine atony, blood loss, chorioamnionitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant: Apgar score at 1 and 5 minutes, meconium.</td>
<td></td>
</tr>
</tbody>
</table>

### Magpie 2002

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial. Randomisation through central telephone randomisation service (computer-generated allocation sequence) based in Oxford or consecutively numbered local pack system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>10141 women were randomised.</td>
</tr>
<tr>
<td>Setting: 175 centres in 33 countries.</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: the woman was included if she had not given birth, or was ( \leq 24 ) hours postpartum; blood pressure ( \geq 140/90 ) on at least 2 occasions; proteinuria of at least 1+ (30 mg/dL); and there was clinical uncertainty about whether magnesium sulphate would be beneficial</td>
<td></td>
</tr>
</tbody>
</table>

**Notes** Only 51% of intended sample size enrolled. Group assignment was revealed for 33 women who developed severe pre-eclampsia and they were given magnesium sulphate.
**Exclusion criteria:** hypersensitivity to magnesium, hepatic coma with a risk of renal failure, or myasthenia gravis. Women with oliguria (urine output < 25 mL per hour) were eligible, but the volume of trial treatment was halved for each dose.

**Interventions**

**Magnesium sulphate (n = 5071)**

Women were given a 4 g IV magnesium sulphate loading dose then either a 1 g per hour IV infusion, or 10 g intramuscularly with the loading dose, followed by 5 g every 4 hours. Continued for 24 hours.

2 centres in Bangladesh used 5 g intramuscular loading dose then 2.5 g every 4 hours as maintenance.

**Placebo (n = 5070)**

Women received a placebo solution by an identical regimen. Dose halved if oliguria present. Clinical monitoring alone for all women.

**Outcomes**

**Notes**

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**Moodley 1994**

**Methods**

Randomised controlled trial. Consecutively numbered sealed opaque envelopes were used.

**Participants**

228 women were randomised.

**Inclusion criteria:** women with severe proteinuric hypertension (diastolic blood pressure ≥ 110 mmHg for 4-6 hours, proteinuria +) or imminent eclampsia requiring delivery.

**Exclusion criteria:** prior anticonvulsant (except single dose of phenobarbitone 200 mg IM) or antihypertensive therapy.

**Interventions**

**Magnesium sulphate (n = 112)**

Women were given the 'Pritchard regime' where a 4 g magnesium sulphate IV loading dose in 200 mL of normal saline was given over 20 minutes, followed by 5 g intramuscularly in each buttock, and 5 g intramuscularly 4 hourly as maintenance, with a maximum of 4 doses.

**Comparison (n = 116)**

No anticonvulsant.

**Outcomes**

Maternal: mode of delivery, convulsions, renal failure, pulmonary oedema.

Infant: death (stillbirth, early neonatal death).

**Notes**

---

IM: intramuscular

IV: intravenous

TNF: tumour necrosis factor
### DATA AND ANALYSES

**Comparison 1. Magnesium sulphate versus placebo or no treatment**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Apgar scores &lt; 7 at 5 minutes</td>
<td>1</td>
<td>135</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.51 [0.05, 5.46]</td>
</tr>
<tr>
<td>2 Gestational age at birth (weeks)</td>
<td>1</td>
<td>135</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.20 [-0.62, 0.22]</td>
</tr>
<tr>
<td>3 Maternal adverse effects requiring treatment cessation</td>
<td>1</td>
<td>135</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.04 [0.13, 73.42]</td>
</tr>
<tr>
<td>4 Postpartum haemorrhage</td>
<td>1</td>
<td>135</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>4.06 [0.47, 35.38]</td>
</tr>
<tr>
<td>5 Caesarean section</td>
<td>1</td>
<td>135</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.80 [0.39, 1.63]</td>
</tr>
<tr>
<td>6 Side effects (feeling warm and flushed)</td>
<td>1</td>
<td>135</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.81 [2.22, 6.53]</td>
</tr>
</tbody>
</table>

#### Analysis 1.1. Comparison 1 Magnesium sulphate versus placebo or no treatment, Outcome 1 Apgar scores < 7 at 5 minutes.

Review: Magnesium sulphate for women at term for neuroprotection of the fetus

Comparison: 1 Magnesium sulphate versus placebo or no treatment

Outcome: 1 Apgar scores < 7 at 5 minutes

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Magnesium sulphate n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witlin 1997</td>
<td>1/67</td>
<td>2/68</td>
<td>0.51 [0.05, 5.46]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

67 68 100.0% 0.51 [0.05, 5.46]

Total events: 1 (Magnesium sulphate), 2 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable
### Analysis 1.2. Comparison 1 Magnesium sulphate versus placebo or no treatment, Outcome 2 Gestational age at birth (weeks).

**Review:** Magnesium sulphate for women at term for neuroprotection of the fetus

**Comparison:** 1 Magnesium sulphate versus placebo or no treatment

**Outcome:** 2 Gestational age at birth (weeks)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Magnesium</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witlin 1997</td>
<td>67 (38.7 (1.1))</td>
<td>68 (38.9 (1.4))</td>
<td>IV,Fixed,95% CI: -0.20 [-0.62, 0.22]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 67 (38.7 (1.1)) 68 (38.9 (1.4)) IV,Fixed,95% CI: -0.20 [-0.62, 0.22]

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

### Analysis 1.3. Comparison 1 Magnesium sulphate versus placebo or no treatment, Outcome 3 Maternal adverse effects requiring treatment cessation.

**Review:** Magnesium sulphate for women at term for neuroprotection of the fetus

**Comparison:** 1 Magnesium sulphate versus placebo or no treatment

**Outcome:** 3 Maternal adverse effects requiring treatment cessation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Magnesium sulphate</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witlin 1997</td>
<td>1/67</td>
<td>0/68</td>
<td>M-H,Fixed,95% CI: 3.04 [0.13, 73.42]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 67 68 M-H,Fixed,95% CI: 3.04 [0.13, 73.42]

Total events: 1 (Magnesium sulphate), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable
Analysis 1.4. Comparison 1 Magnesium sulphate versus placebo or no treatment, Outcome 4 Postpartum haemorrhage.

Review: Magnesium sulphate for women at term for neuroprotection of the fetus

Comparison: 1 Magnesium sulphate versus placebo or no treatment

Outcome: 4 Postpartum haemorrhage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Magnesium sulphate n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witlin 1997</td>
<td>4/67</td>
<td>1/68</td>
<td>100.0 %</td>
<td>4.06 [ 0.47, 35.38 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>67</strong></td>
<td><strong>68</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>4.06 [ 0.47, 35.38 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (Magnesium sulphate), 1 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Magnesium sulphate versus placebo or no treatment, Outcome 5 Caesarean section.

Review: Magnesium sulphate for women at term for neuroprotection of the fetus

Comparison: 1 Magnesium sulphate versus placebo or no treatment

Outcome: 5 Caesarean section

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Magnesium sulphate n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witlin 1997</td>
<td>11/67</td>
<td>14/68</td>
<td>100.0 %</td>
<td>0.80 [ 0.39, 1.63 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>67</strong></td>
<td><strong>68</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.80 [ 0.39, 1.63 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 11 (Magnesium sulphate), 14 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable
Analysis 1.6. Comparison 1 Magnesium sulphate versus placebo or no treatment, Outcome 6 Side effects (feeling warm and flushed).

Review: Magnesium sulphate for women at term for neuroprotection of the fetus

Comparison: 1 Magnesium sulphate versus placebo or no treatment

Outcome: 6 Side effects (feeling warm and flushed)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Magnesium sulphate</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Witlin 1997</td>
<td>45/67</td>
<td>12/68</td>
<td>3.81 [ 2.22, 6.53 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>67</td>
<td>68</td>
<td>3.81 [ 2.22, 6.53 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 45 (Magnesium sulphate), 12 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 4.85 (P < 0.00001)
Test for subgroup differences: Not applicable

CONTRIBUTIONS OF AUTHORS
Thuy-My Nguyen and Caroline Crowther conceptualised the protocol. Thuy-My Nguyen and Dominic Wilkinson searched the literature. Thuy-My Nguyen, Caroline Crowther and Emily Bain extracted the data and all four review authors contributed to the draft text of the review and all subsequent drafts.

DECLARATIONS OF INTEREST
Thuy-My Nguyen: none known.
Emily Bain: none known.

Caroline A Crowther was the principal investigator in the Australasian Collaborative Trial of Magnesium Sulphate given as a neuroprotective prior to very preterm birth for the prevention of mortality and cerebral palsy in their babies (ACTOMgSO4 - Crowther 2003). This trial was funded by the Australian National Health and Medical Research Council. She is also the principal investigator on The Magenta Trial, assessing antenatal magnesium sulphate for women at risk of preterm birth between 30 and 34 weeks' gestation for neuroprotection of their babies. This trial is funded by the Australian National Health and Medical Research Council.

Dominic Wilkinson is a chief investigator on The Magenta Trial, assessing antenatal magnesium sulphate for women at risk of preterm birth between 30 and 34 weeks' gestation for neuroprotection of their babies. This trial is funded by the Australian National Health and Medical Research Council.
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External sources
- National Health and Medical Research Council, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There has been a change to the inclusion criteria for this review. We have chosen to exclude trials where the alternative agent being compared to magnesium sulphate was not aimed at providing neuroprotection of the fetus.

Small amendments have also been made to the primary and secondary outcomes for assessment. Regarding the primary outcomes for the infant, we classify cerebral palsy as abnormality of tone with motor dysfunction as diagnosed at 18 months of age or later. We have also included abnormal neurological examination (however defined by the trialists, at a point earlier than 18 months of age) as a secondary outcome for the infant.

INDEX TERMS

Medical Subject Headings (MeSH)
Brain Injuries [prevention & control]; Cerebral Palsy [*prevention & control]; Fetus [*drug effects]; Infant, Newborn; Magnesium Sulfate [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; Pre-Eclampsia [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words
Female; Humans; Pregnancy