WHO recommendation on the use of magnesium sulfate for fetal protection from neurological complications

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Recommendation

The use of magnesium sulfate is recommended for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy in the infant and child.

(Strong recommendation based on moderate-quality evidence).

Publication history

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Assessed as up-to-date: November 2015

Remarks

- Evidence suggests that the protective effects of magnesium sulfate on neurological complications (neuroprotection) are likely to be increased at earlier gestational ages. The GDG is aware of an ongoing trial on the neuroprotective effects of magnesium sulfate at gestational ages below 34 weeks.
- Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours. The median time from 35 magnesium sulfate administration to birth was reported in only two of the trials that generated the evidence (1 hour 38 minutes and 3.7 hours). However, the GDG felt that administering magnesium sulfate at any time from immediately prior to birth, up to 24 hours prior to anticipated birth is appropriate.
- Three dosing regimens (IV 4 g over 20 minutes, then 1 g/hour until delivery or for 24 hours, whichever came first; IV 4 g over 30 minutes or IV bolus of 4 g given as single dose; and IV 6 g over 20–30 minutes, followed by IV maintenance of 2 g/hour) have been tested in the available studies, which – on meta-analysis – show effect on cerebral palsy, and death or cerebral palsy. There was insufficient evidence to recommend one specific dosing regimen over others. The GDG is aware that an individual patient data analysis of these studies is underway, which may affect this guidance in the future.
- This recommendation applies to women carrying either singleton or multiple pregnancies.
- In women at imminent risk of preterm birth, magnesium sulfate should be considered as the preferred
option whenever there is a valid obstetric indication (e.g. pre-eclampsia) and where it is considered safe and effective.

- There is a need for further research to establish whether repeated treatment with magnesium sulfate for neuroprotection is appropriate (i.e. in the event that delivery does not occur).

**Background**

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. (1) Globally, it is the leading cause of perinatal and neonatal mortality and morbidity. (2) Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection. (3-5) With the increasing contribution of neonatal deaths to overall child mortality, it is critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in child mortality. (6-8)

Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the mother before or during pregnancy, and to the preterm infant after birth. (9) Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programme) or aimed at minimizing the risk in women with known risk factors (e.g. progestational agents, cervical cerclage). (10) However, the most beneficial set of maternal interventions are those that are aimed at improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids, magnesium sulfate and antibiotic prophylaxis). (9) Special care of the preterm newborn to prevent and treat complications of prematurity is also critical to newborn survival. In high-income countries, reductions in mortality rates in infants that were born preterm have been driven largely by improved care and, more importantly, by appropriate policy changes.

**Methods**

The recommendations were developed using standard operating procedures in accordance with the process described in the WHO handbook for guideline development (11). Briefly, these included (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The scientific evidence underpinning the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (12). Up-to-date systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a Technical Consultation in May 2014 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the evidence profiles.

In November 2014, an online consultation of the GDG was conducted to review and revise the recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in low-resource countries.

Further information on procedures for developing this recommendation are available [here](#).
Recommendation question

For this recommendation, we aimed to answer the following question:

- Among pregnant women at risk of imminent preterm birth (P), is magnesium sulfate therapy (I), compared with no magnesium sulfate therapy (C), effective in protecting the fetus from neurological complications (i.e. fetal neuroprotection) (O)? If so:
  - Which population of pregnant women should be offered antenatal magnesium sulfate for fetal neuroprotection? (considering gestational age at presentation; interval between presentation and anticipated birth; single and multiple birth)
  - Which regimen of antenatal magnesium sulfate should be used for fetal neuroprotection in eligible women?

Evidence summary

Evidence on the use of magnesium sulfate for neuroprotection in preterm infants was extracted from a Cochrane systematic review (five studies including 6145 infants) investigating whether the administration of magnesium sulfate to women at risk of preterm labour conferred neuroprotective advantage to the fetus (13).

One trial was conducted in Australia and New Zealand, one in France, two in the USA, and the fifth was a multicentre study conducted in countries across the world. The final “Magpie” study was designed to prevent eclampsia by magnesium sulfate administration, but data relevant to the effect on preterm infants were included in the analysis. All studies were placebo controlled. The gestational age at recruitment to these trials ranged from below 30 weeks up to 37 weeks. Corticosteroids were given to more than 50% of women in three of the trials.

Magnesium sulfate versus no active treatment (all women and babies)

Maternal outcomes

*Maternal morbidity or death:* There were no significant differences between women receiving magnesium sulfate versus placebo or no active treatment in terms of maternal mortality or serious maternal morbidity in four studies with a total of more than 5000 women. Risks of maternal death, cardiac arrest, respiratory depression or arrest, and admission to intensive care were not significantly different between groups. The cases of maternal deaths and serious morbidity that were recorded were largely confined to the study that recruited women with severe pre-eclampsia rather than those studies that randomized women with preterm labour. There were no significant differences between the groups for rates of postpartum haemorrhage, caesarean births or length of maternal hospital stay.

*Maternal adverse effects:* Cessation of therapy as a result of maternal adverse effects was increased in the magnesium sulfate group compared with the placebo group (RR 3.26, 95% CI 2.46–4.31; 3 studies, 4847 women). Maternal hypotension (RR 1.51, 95% CI 1.09–2.09; 2 studies, 1626 women) and maternal tachycardia (RR 1.53, 95% CI 1.03–2.29; 1 study, 1062 women) were also more frequent in women who had received magnesium sulfate.

Infant outcomes

*Fetal and infant death:* For overall infant mortality (including fetal mortality), there was no significant difference between women who had received magnesium sulfate and controls (RR 1.02, 95% CI 0.90–1.15; 5 studies, 6039 infants). Rates for other measures of fetal and infant mortality were also comparable in both
groups (i.e. fetal death, infant death during hospitalization, infant death), to the latest age of follow up.

**Severe neonatal morbidity and long-term morbidity:** There were also no significant differences between groups for a range of composite outcomes (i.e. death or cerebral palsy, death or neurological impairment, death or serious motor dysfunction, and death or major neurological disability). There were no significant differences between women who received magnesium sulfate and those in the control group with regard to infant IVH, periventricular leukomalacia, major or any neurological impairment, blindness or deafness, or developmental delay or intellectual impairment. There were no significant differences between groups for neonatal convulsions, neonatal hypotonia or requirement for ongoing respiratory support, although there was a trend towards reduced risk in the magnesium sulfate group for the latter outcome (RR 0.94, 95% CI 0.89–1.00; 3 studies, 4387 infants). There was no clear difference in length of infant hospital stay, nor in the incidence of chronic lung disease requiring oxygen at 28 days and at 3 months. Infants exposed to magnesium sulfate were at reduced risk (39%) of substantial gross motor dysfunction compared to controls (RR 0.61, 95% CI 0.44–0.85; 4 studies, 5980 infants). The risk of cerebral palsy was also significantly reduced (by 30%) in the magnesium sulfate group (RR 0.70, 95% CI 0.55–0.89; 5 studies, 6039 infants).

**Magnesium sulfate versus placebo or no treatment (single versus multiple pregnancy)**

For all comparisons, the sample size and event rate for multiple pregnancies compared with those for singleton pregnancies were smaller (2 studies, 527 women). There were no clear differences between singleton and multiple pregnancies for most of the critical outcomes reported. The positive effects of magnesium sulfate on risk of cerebral palsy in singleton pregnancies was not observed in multiple pregnancies (RR 0.52, 95% CI 0.21–1.25; 2 studies, 527 babies), although the point estimate favoured benefit. The effects of magnesium sulfate on overall death rates, on composite outcomes (i.e. death or serious impairment) and on major neurological impairment were comparable for singleton and multiple pregnancies.

**Magnesium sulfate versus placebo or no treatment (gestational age at administration)**

Subgroup analysis was performed according to gestational age at administration (<30 weeks versus < 34 weeks at randomization). The evidence on the use of magnesium sulfate at < 30 weeks of gestation as opposed to < 34 weeks was not clear. Although statistical significance was more likely to be demonstrated for outcomes in the trials recruiting women up to 34 weeks of gestation, this was partly due to increased sample size and statistical power. Overall, the subgroup analysis findings largely reflected the findings in the main analysis. However, cerebral palsy was reduced in women randomized to magnesium sulfate versus placebo or no treatment at < 34 weeks of gestation (RR 0.69, 0.54–0.88; 4 studies, 5192 women) but not in women randomized at < 30 weeks (RR 0.86, 0.56–1.31; 2 studies, 1537 women), although the point estimate favoured a reduction in cerebral palsy with the use of magnesium sulfate in this population.

**Magnesium sulfate versus placebo or no treatment (with the intention to prevent preterm birth-related neurologic complications)**

When the Magpie study (where magnesium sulfate was aimed at preventing eclampsia in women with severe pre-eclampsia) was excluded from the analysis, the findings of the meta-analysis remained consistent for most critical outcomes. When confined to studies where the intention of the treatment was explicitly for neuroprotection, there were no significant differences between groups for overall paediatric mortality, fetal death or infant death. The composite outcome of death or cerebral palsy was significantly reduced in the treated group (RR 0.85, 95% CI 0.74–0.98; 4 studies, 4446 infants). Similarly, the reduction in risk of moderate/severe cerebral palsy in the treated group remained consistent (RR 0.64, 95% CI 0.44–0.92; 3
studies, 4837 infants). For another composite outcome – death or gross motor dysfunction – there was a trend towards reduction in the group receiving magnesium sulfate (RR 0.84, 95% CI 0.71–1.00; 3 studies, 4387 infants).

**Regimens of magnesium sulfate for fetal neuroprotection**

The route of administration and dose of magnesium sulfate varied in these trials:

1. IV 4 g over 20 minutes, then 1 g/hour until delivery or for 24 hours, whichever came first;
2. IV 4 g over 10–15 minutes, followed by either IV 1 g/hour for 24 hours, or by IM 5 g every 4 hours for 24 hours;
3. single dose of IV 4 g over 30 minutes;
4. single IV bolus of 4 g; and
5. IV 6 g over 20–30 minutes, followed by maintenance infusion of 2 g/hour for 12 hours, with retreatment permitted whenever birth was imminent.

All trials with neuroprotective intent used the intravenous route of administration. There were no clear differences between the various regimens for most of the critical outcomes reported. However, the reduction in cerebral palsy only reached statistical significance for the following subgroups: 4–6 g loading dose plus any maintenance; and 6 g loading dose and higher-dose (2 g/hour) maintenance. In the subgroup analysis according to whether retreatment was allowed or not after completing a course of therapy, the only trial that used high loading and maintenance doses showed a statistically significant reduction in the incidence of cerebral palsy (RR 0.59, 95% CI 0.40–0.85). This study was responsible for the overall point estimate related to cerebral palsy in the review. For the composite outcome of death or cerebral palsy, the results were consistent across the two subgroups: retreatment allowed (RR 0.90, 95% CI 0.73–1.10) and retreatment not allowed (RR 0.91, 95% CI 0.74–1.13). Maternal adverse effects related to magnesium sulfate appear to be dose dependent. However, the available evidence also points to better neuroprotection with higher dosing. Importantly, there is evidence to suggest that a maintenance dose is essential in order to observe an effect. It is unclear whether the effects on cerebral palsy of higher loading and higher maintenance dosing with a repeat treatment are due to the dosage regimen or a reflection of the size of the trial. However, as this protective effect was not demonstrated in terms of incidence of death or cerebral palsy, the relationship to dose is unlikely to be strong.

Further information and considerations related to this recommendation can be found in the WHO guidelines, available at:

[http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1)

[http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1)

**Implementation considerations**

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations, and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.

In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

Research implications

The GDG identified that further research on the following high-priority questions is needed:

- Are repeated doses of magnesium sulfate safe for fetal neuroprotection in the event that birth does not occur after completing the first dose?
- What is the minimum effective dose of magnesium sulfate for fetal neuroprotection?
- What is the comparative effectiveness of alternative regimens of magnesium sulfate when used for fetal neuroprotection (including effectiveness of intramuscular regimen)?
- What are the effects of task shifting in the context of magnesium sulfate administration (e.g. using the first dose in the community followed by referral to a health-care facility)?
- What are the effects of magnesium sulfate on the newborn in the immediate postpartum period (particularly on resuscitation)?

Related links

WHO recommendations on interventions to improve preterm birth outcomes (2015) –[full document](https://www.who.int/publications/i/item/9789241549147) and [evidence tables](https://www.who.int/publications/i/item/9789241549147)

Supporting systematic reviews:

- Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Other links of interest

- Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors
- Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice
- WHO Programmes: Sexual and Reproductive health
- Maternal Health
- Infant, Newborn Health

References

2. Kinney MV, Lawn JE, Howson CP, Belizan J. 15 million preterm births annually: what has changed


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