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Magnesium Sulphate for Neuroprotection of the fetus in women at risk of preterm birth

Originator: Labour ward Forum, maternity Services
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1.0 Introduction:

Cerebral Palsy (CP) is the most common cause of severe motor disability in childhood with a prevalence rate of approx. 2-3/1000 live births. At present there is no cure for CP which makes effective preventative interventions of paramount importance.

Meta-analyses of RCTs looking at the role of MgSO₄ for neuroprotection conclude that antenatal magnesium sulphate reduces cerebral palsy and motor deficits in preterm infants, irrespective of the reasons for preterm birth. There is strong evidence to suggest the giving MgSO₄ <24h prior to birth less than 32w reduces the risk of cerebral palsy and death without risk to mother or fetus.

The number of women needed to treat with MgSO₄ at <30 weeks gestation to prevent one child from having cerebral palsy is 37.

NICE guidelines recommend giving magnesium sulphate at less than 30 weeks gestation, with consideration being given to use up to 33+6 weeks gestation.

1.1 Abbreviations used within this guideline:

- CP - cerebral palsy
- PTL - preterm labour
- PPROM - preterm pre-labour Rupture of membranes
- NNT - number needed to treat
- IV - intravenous
- CI - confidence interval
- RR - relative risk

2.0 Purpose

To provide guidance to obstetric, midwifery, anaesthetic and neonatal staff on indications for and appropriate use of Magnesium Sulphate for neuroprotection of the fetus in women at risk of preterm birth.

3.0 Scope

This guideline applies to all obstetrics, midwifery and neonatal staff. It addresses the management of women who are at risk of delivering between 24+0 and 30+0 weeks gestation, whether as a result of spontaneous preterm labour or by iatrogenic delivery.

4.0 Indications for the use of Magnesium Sulphate for Neuroprotection of the Fetus

At **gestations between 24+0 to 30+0 weeks**, Magnesium Sulphate should be given to women in whom preterm delivery is likely.

Consider intravenous magnesium sulphate for neuroprotection of the baby for women between **30+0 and 33+6** weeks of pregnancy who are :

- In established preterm labour **OR**

- Having a planned preterm birth within 24 hours

5.0 Cautions

Women with **renal impairment** (serum Creatinine >90 µmol/L) should receive half the loading dose and half the maintenance dose (see Appendix 1). Check magnesium levels after 4 hours and re-check depending on the initial result. The therapeutic magnesium range is 2-4 mmol/L.

Severe cardiac disease – discuss with Obstetric Consultant before starting Magnesium Sulphate.

6.0 Regimen

The meta-analysis of this topic does not suggest a particular dosing regimen; the loading dose of Magnesium Sulphate used in the five trials ranged from 4 to 6g, followed by either no maintenance dose or between 1 and 3 g/hour. The most recent trial published by Rouse *et al* in 2008 included an empirical protocol for discontinuation of treatment if delivery was not imminent after 12 hours of treatment, with a further loading dose given if contractions recommenced more than 6 hours after treatment had been discontinued.

6.1 Magnesium Sulphate administration regimen.

Dosage-

Loading dose: **Pre-filled syringe** – 4g of MgSO₄ in 20ml of Normal Saline (0.2g in 1ml) given slowly over 5 minutes i.e set pump rate to 240ml/hr

Maintenance dose: **Pre-filled syringe** – 5g of MgSO₄ in 50ml of Normal Saline (0.1g in 1ml) to be administered via syringe pump, set pump rate to 10ml/hr

Monitoring on Magnesium Sulphate

- 4 hourly MEOWS should be recorded
- Oxygen saturation, respiratory rate, tendon reflexes 4 hourly.
- If Oxygen saturation <95%, respiratory rate < **12/minute**, loss of tendon reflexes a medical review is required and measurement of magnesium levels.
- In conditions where there is risk of oliguria (e.g. PET), monitor hourly urine output.
- Half the loading and maintenance dose if urine output is <25 mls/hr.

In the rare event of severe toxicity leading to cardiorespiratory arrest:

- Stop maintenance infusion; Dial 2222 'maternal cardiac arrest call'
- Institute CPR
- Administer 10 ml calcium gluconate IV, (kept on PET trolley)
- Intubate immediately and manage with assisted ventilation until resumption of spontaneous respirations.

6.2 See Appendix 1 for Magnesium Sulphate pharmacokinetics.

6.3 Preterm labour. The woman should be given the loading dose of Magnesium Sulphate and the maintenance infusion commenced immediately. The maintenance infusion should be continued until delivery but can be stopped immediately after delivery.

6.4 PPROM.

When delivery is indicated, the woman should be given the loading dose of Magnesium Sulphate and the maintenance infusion commenced immediately. The maintenance infusion should be continued until delivery but can be stopped immediately after delivery.

Rarely, a woman in apparent established preterm labour will not progress. In this situation, if delivery is not imminent after 12 hours of treatment, the magnesium infusion should be discontinued. If contractions recommence later, a further loading dose of magnesium may be given if more than 6 hours have elapsed since the treatment has been discontinued.

6.5 Elective preterm delivery:

When elective preterm delivery between 24+0 and 30+0 weeks' gestation is planned, the woman should be given only the loading dose of Magnesium Sulphate within 4 hours prior to delivery. Magnesium sulphate should also be considered for neuroprotection of the baby for women between 30+0 and 33+6 weeks of pregnancy who are having a planned preterm delivery within 24 hours.

7 Anaesthetic considerations for delivery of pre-term infant on magnesium

- Anaesthetist must be informed where magnesium has been given.
- Magnesium can cause significant hypotension in combination with regional anaesthetic so this must be prepared for.
- When giving a general anaesthetic magnesium can reduce or even eliminate fasciculations due to suxamethonium so this must be expected. However, the onset of action is still the same so intubation can be commenced 30-60 seconds after giving suxamethonium.
- Magnesium prolongs neuromuscular blockade so care should be taken with dosing non-depolarising neuromuscular blockers.
- Where there is fetal compromise the anaesthetic **MUST NOT** delay delivery. The above complications must be expected and dealt with appropriately.
- However, where there is no urgent need for delivery i.e. Cat 3 or 4 delivery it may be beneficial to have a time delay (30 minutes) between the bolus of magnesium and anaesthetic, to minimise the risk of hypotension.

Although birth should not be delayed in situations where urgent delivery is necessary because of actual or imminent maternal or fetal compromise (e.g. severe fetal distress or antepartum haemorrhage), all efforts should be made to administer the loading dose of Magnesium Sulphate from prefilled syringes.

8.0 Side effects and monitoring

8.1 Minor side effects include pain at the site of injection, nausea or vomiting, thirst, drowsiness and confusion. These symptoms resolve quickly when treatment is stopped.

8.2 Magnesium Sulphate toxicity may cause muscle weakness (due to neuromuscular blockade) which may lead to decreased deep tendon reflexes and respiratory suppression, so monitoring of respiratory rate and oxygen saturation is important.

9.0 Evidence

9.1

Several trials and two large systemic reviews suggest that Magnesium Sulphate given to the mother around the time of the delivery reduces the risk of CP in babies delivered preterm. All showed that the risk of death or CP is lower in children at 2 years if the mothers were allocated Magnesium Sulphate rather than placebo. The 2009 Cochrane review included five randomised control trials (involving 6145 babies) of antenatal Magnesium Sulphate in women at risk of preterm delivery (before 37 weeks gestation). This review concluded that Magnesium Sulphate substantially reduced the risk of CP (RR 0.68; 95%CI 0.54 to 0.87).

There was also a significant reduction in gross motor function deficit (RR 0.61; 95%CI 0.44 to 0.85). However, there was no effect on neonatal mortality (RR 1.04; 95% CI 0.92 to 1.17).

9.2

The most recent study (which prompted the Cochrane review) was published in 2008 and studied 2241 babies born in 20 centres in the USA between 1997 and 2004. All were born before 32 weeks gestation, 87% were associated with preterm pre-labour rupture of membrane (PPROM), and all were followed up for 24 months. The incidence of moderate or severe CP was lower in the Magnesium Sulphate group (1.9% vs 3.5%; RR 0.55, 95% CI: 0.32 to 0.95). However, the perinatal mortality rate was similar (9.5% vs 8.5%; RR 1.12 CI: 0.85 to 1.47).

The numbers needed to treat (ie the number of women who need to be given Magnesium Sulphate to prevent one case of cerebral palsy) for all gestations under 37 weeks is **63** (95% CI: 43 to 87); NNT for gestation less than 28 weeks is **29**.

The ACOG (American College of Obstetricians and Gynaecologists) and the Society for Maternal-Fetal Medicine published an opinion paper in which they recognize that the available evidence suggests that Magnesium Sulphate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants.

10.0 References

1. Confidential Enquiry into Maternal and Child Health (CEMACH) Perinatal Mortality 2007: United Kingdom. CEMACH: London, 2009.
2. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo controlled trial. *Lancet*. 2002; 359:1877-90.
3. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2002
4. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009;1:CD004661.
5. Mittendorf R, Dambrosia J, Pryde PG, et al. Association between the use of antenatal magnesium sulfate in preterm labour and adverse health outcomes in infants. *Am J Obstet Gynecol* 2002;186:1111-8.
6. Crowther CA, Hiller JE, Doyle LW, et al; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulphate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA* 2003;290:2669-76.
7. Magpie Trial Follow-Up Study Collaborative Group. The Magpie trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia: outcome for children at 18months. *BJOG* 2007;114:289-99.
8. Marret S, Marpeau L, Zupan-Simunek V, et al; PREMAG trial group. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*. *BJOG* 2007;114:310-8.
9. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulphate for the prevention of cerebral palsy. *N Engl J Med* 2008;359:895-905.
10. Conde-Agudelo A, Romero R. Antenatal magnesium sulphate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2009;200:595-609.
11. American College of Obstetricians and Gynaecologists Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Committee Opinion No. 455: Magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstetric Gynecol*. 2010;115:669-71.
12. Bain E, Middleton P, Crothers CA. Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD009302. DOI: 10.1002/14651858.CD009302.pub2.
13. Antenatal magnesium individual participant data international collaboration: assessing the benefits for babies using the best level of evidence (AMICABLE). *Systematic Reviews* 2012 1:21.
14. Taber EB, Tan L, Chao CR, Beal MH, Ross MG. Pharmacokinetics of ionized versus total magnesium in subjects with preterm labour and preeclampsia. *Am J Obstet Gynecol* 2002;186:1017-1021.

15. The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. Antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child: National clinical practice guidelines. Adelaide: The University of Adelaide, 2010.

www.adelaide.edu.au/arch

16. Pre Term Labour and Birth. NICE guidance November 2015

17. British Association of Perinatal Medicine

Appendix 1: Pharmacokinetics of Magnesium Sulphate

With intravenous administration, the onset of anticonvulsant action is immediate and lasts around 30 minutes. Peak magnesium levels are reached at around 20 minutes. Magnesium is excreted solely by the kidney at a rate proportional to the plasma concentration and glomerular filtration.

When used as an intravenous infusion in pregnant women, the elimination half-life of ionised magnesium (the active form) is 313 ± 29 minutes.

Directorate of Women & Child Health Checklist for Clinical Guidelines being Submitted for Approval by Quality & Safety Group

Title of Guideline:	MAGNESIUM SULPHATE FOR NEUROPROTECTION OF THE FETUS IN WOMEN AT RISK OF PRETERM BIRTH
Name(s) of Author:	<i>Labour Ward Forum</i>
Chair of Group or Committee supporting submission:	Labour Ward Forum
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Brief outline giving reasons for document being submitted for ratification	To provide guidance to obstetric, midwifery and neonatal staff on indications for and appropriate use of Magnesium Sulphate for neuroprotection of the fetus in women at risk of preterm birth.
Name of Pharmacist (mandatory if drugs involved):	n/a

Please list any policies/guidelines this document will supercede:	<i>Previous guideline</i>
Please indicate key words you wish to be linked to document	Magnesium, Sulphate, Neuroprotection, Fetus, Preterm
Date approved by Directorate Quality & Safety Group:	Nov 2021
File Name: Used to locate where file is stores on hard drive	pow_fs1\ABM_W&CH_mgt\Clinical Governance - Q&S\Policies & Procedures etc - Ratified\Maternity

Appendix 2

Flow chart for consideration of magnesium sulphate for neuroprotection in preterm infants

Eligible case identified – **ALL** deliveries anticipated within 24 hours (confirmed preterm labour or planned elective delivery) of babies 22+0– 30+0 weeks gestation, **offer** for babies up to 33+6 weeks

Include in care plan discussions with families, discuss expected side effects with patients and inform anaesthetist.

Perform baseline maternal observations to include P, BP, respiratory rate, oxygen saturations,

Loading dose: **Pre-filled syringe** – 4g of MgSO₄ in 20ml of Normal Saline (0.2g in 1ml) given slowly over 5 minutes i.e set pump rate to 240ml/hr

Maintenance dose: **Pre-filled syringe** – 5g of MgSO₄ in 50ml of Normal Saline (0.1g in 1ml) to be administered via syringe pump, set pump rate to 10ml/hr continue until delivery or upto 24hours (no evidence of progression of preterm labour by cervical dilatation after 12 hours then the infusion should be stopped and the clinical picture reviewed)

4 hourly observations recorded on MEOWS chart during maintenance infusion and 4 hourly tendon reflexes tested

Stop magnesium sulphate following delivery /no evidence of imminent delivery after 24 hours

Document any cases where eligible babies did not receive magnesium sulphate for neuroprotection