Magnesium sulphate for neuroprotection of the pre-term fetus

Target audience	Specialist/tertiary-level maternity and neonatal healthcare providers involved in the care of patients at risk of, or having a planned, pre-term birth below 30+0 weeks of gestation.
Patient group	Patients at risk of pre-term, or having a planned pre-term, birth below 30+0 weeks of gestation. The term 'women/birthing people' is used within this document to include women, girls, trans men, and non-binary and intersex people, who are pregnant or have recently been pregnant.

Summary

Randomised control trials and meta-analysis have shown that antenatal administration of magnesium sulphate to patients in established pre-term labour, or having a pre-term birth in the next 24 hours, reduces cerebral palsy (CP) rates and motor disturbance in the neonate.

The benefit is greatest before 30+0 weeks of gestation.

Magnesium sulphate should be offered to patients between 24+0 and 29+6 weeks of gestation in active pre-term labour (where the cervix is 4 or more centimetres dilated on digital vaginal examination) with or without pre-term, pre-labour rupture of membranes (PPROM) or in whom planned pre-term birth for maternal or fetal wellbeing is expected within the next 24 hours.

Magnesium sulphate may be considered for extremely pre-term fetuses between 23+0 and 23+6 weeks of gestation but this should be considered on an individualised, case-by-case basis.

A single 4g loading dose of intravenous (IV) magnesium sulphate should be administered over 15 minutes.

This should be followed by an infusion of magnesium sulphate at a rate of 1g per hour over the next 24 hours or until birth (whichever is earlier).

Ideally, 4 hours of magnesium sulphate should be administered prior to delivery but delivery should not be delayed to achieve this if concerns about fetal or maternal wellbeing exist.

Women/pregnant people receiving magnesium sulphate should be monitored for signs of magnesium toxicity, including respiratory rate and oxygen saturations, every 15 minutes. Tendon reflexes should be checked every 4 hours. Urinary output should be >100ml over 4 hours.

This document should be used in conjunction with the NHSL guideline entitled "Pre-term birth (intact membranes)" and "Extreme preterm birth (22+0 – 26+6 weeks of gestation)".

Contents

Rationale

The survival of infants born preterm have substantially improved with interventions such as antenatal corticosteroids and pulmonary surfactant, however this survival has been associated with a substantial risk of neurodevelopmental impairment. CP and cognitive dysfunction are the most frequently occurring neurological impairments associated with preterm birth.

CP is a non-progressive disorder of movement and posture related to injury to developing brain. The overall incidence of cerebral palsy is 1.6/1000 and the risk is highest at early gestational ages. There is a 40-60 fold increase in CP rates in extremely preterm babies (those born at less than 28 weeks of gestation). At present there is no cure for CP, which makes preventative interventions of paramount importance.

There is evidence from observational studies, randomised controlled trials and meta-analyses that there is significant reduction in rates of cerebral palsy and severe motor dysfunction with the use of magnesium sulphate without any difference in stillbirth or infant death rates. There were no significant differences in maternal outcomes such as death, cardiac or respiratory arrest with the use of magnesium sulphate for fetal neuroprotection.

Administration of magnesium sulphate has been found to reduce rates of cerebral palsy by up to 30% in infants born at less than 30 weeks of gestation.

Magnesium sulphate is essential for key cellular processes and has a neuroprotective effect in preventing post-hypoxic brain injury. It acts by blocking the cascade of calcium influx and neuronal cell death in damaged neurons.

Indications

Patients at high risk of imminent spontaneous preterm birth between 24+0 and 29+6 weeks of gestation should be administered magnesium sulphate for fetal neuroprotection.

Imminent preterm birth could be defined as active preterm labour with progressive cervical changes (with or without PPROM), or planned caesarean birth for maternal or fetal wellbeing within the next 24 hours.

Patients between 23+0 and 23+6 weeks of gestation at imminent risk of preterm birth should have the use of magnesium sulphate discussed with them and decision to use

based on individualised circumstances. A consultant obstetrician should be involved in this decision-making.

There is controversy about the upper gestational age limit for administration of this medication for fetal neuroprotection. The rates of CP were significantly reduced at all gestational ages. As CP rates are highest at earlier gestational ages, a consensus was reached that the upper gestational limit for administration of magnesium sulphate in NHS Lanarkshire is 29+6 weeks of gestation though the consultant obstetrician can use individual discretion in certain cases.

Magnesium sulphate should be considered in singleton and multiple birth pregnancies.

Timing

- Imminent spontaneous preterm birth – commence when cervical dilation is more than 4cm, with or without PPROM.
- Magnesium sulphate should be discontinued if delivery is no longer imminent or if a maximum of 24 hours of therapy has been administered. There is evidence of neurodevelopmental harm if the total dose exceeds 48g.
- Retreatment with antenatal magnesium sulphate is not recommended as there are insufficient data to support the benefit.
- Planned preterm birth, including caesarean burth – magnesium sulphate should be started ideally 4 hours before birth and maintenance dose administered until birth.
- Delivery should not be delayed for administration of magnesium sulphate for fetal neuroprotection if there are maternal and/or fetal indications for emergency birth.
- If induction of labour (IOL) is likely to take longer than 24 hours, it is reasonable to delay the start of the magnesium sulphate until cervical ripening is achieved.
- Magnesium sulphate should be discontinued after birth.
- Ensure that a full blood count, urea and electrolytes and liver function blood tests are normal prior to commencing the infusion.

Dosing and administration

- Use the same regime as for pre-eclampsia and eclampsia.
- Treatment should be given as a bolus in the first instance followed by an infusion:
    - **Bolus:**
        - 4g intravenous magnesium sulphate to be given over 15 minutes via an Agilia syringe pump.
        - Each vial of magnesium sulphate 50% contains 5g (20mmol) in 10ml.

- Draw up 10ml into a 50ml syringe and make the volume up to 50mls with 0.9% sodium chloride.
- Discard 10ml therefore leaving 40ml (containing 4g magnesium sulphate) in the syringe.
- Infuse this through an Agilia pump at a rate of 160ml/hour (15 minutes).

- **Infusion:**
  - IV infusion should be commenced at a rate of 1g/hour.
  - Dilute 10ml (5g) of magnesium sulphate 50% in 0.9% NaCl to a total of 50ml and infuse at a rate of 10ml/hour via an Agilia syringe pump (5 hours per syringe).
  - Continue this until birth or until the patient has received 24 hours of the infusion, whichever is earlier.

This dosage regimen resembles current clinical practice and hospital protocols for magnesium sulphate for eclampsia treatment/prophylaxis and minimises concerns about maternal safety.

Common side effects include flushing, sweating, headache, nausea and vomiting. Serious side effects are uncommon and include maternal hypotension and tachycardia.

Monitoring

Monitoring of women/pregnant people on magnesium sulphate is similar to those being administered magnesium for pre-eclampsia/eclampsia:

- Measure respiratory rate, oxygen saturations, pulse and blood pressure every 15 minutes.
- Maintain oxygen saturations above 94% and respiratory rate above 14 per minute.
- Urine output should be at least 100ml passed every 4 hours.
- Monitor reflexes every 4 hours. Loss of patellar reflexes is one of the first manifestations of hypermagnesemia.
- Routine monitoring of serum magnesium levels is not required but this should be done if there is a compromise of renal function or suspicion of toxicity.
- **If respiratory rate is less than 12 breaths per minute:**
  i. Stop the infusion.
  ii. Call the on-call obstetric anaesthetist.
- **If respiratory arrest occurs:**
  i. Call 2222 and declare “obstetric emergency”.
  ii. Stop the magnesium sulphate infusion.

iii. ventilate with an Ambu bag until intubation is possible by an experienced individual.
iv. Give calcium gluconate 1g intravenously over 5 minutes (10ml of 10% calcium gluconate).

- Continuous fetal surveillance should be provided throughout magnesium sulphate administration:
  - This should be by continuous electronic fetal monitoring after 26 weeks of gestation.
  - This should be by intermittent auscultation every 15 minutes in the first stage and every 5 minutes in the second stage at earlier gestations.
  - As magnesium sulphate crosses the placenta, there may be a slight decrease in the baseline heart rate and variability. This is not usually clinically significant.

Tocolysis/corticosteroids

- Tocolysis is not indicated in active labour (cervical dilatation of 4cm or greater).
- Magnesium sulphate is not a tocolytic agent and should not be used for this purpose.
- Tocolysis should be discontinued before commencing antenatal magnesium sulphate for fetal neuroprotection.
- Magnesium sulphate can be immediately commenced after stopping tocolytic medications.
- There is no known interaction between antenatal corticosteroids and magnesium sulphate.

Contraindications

Absolute contraindications:

- known hypersensitivity.
- patients with myasthenia gravis.
- hepatic coma.
- significant cardiac conduction defects and myocardial compromise.

Use with caution in:

- renal impairment – monitoring of serum magnesium levels is required.

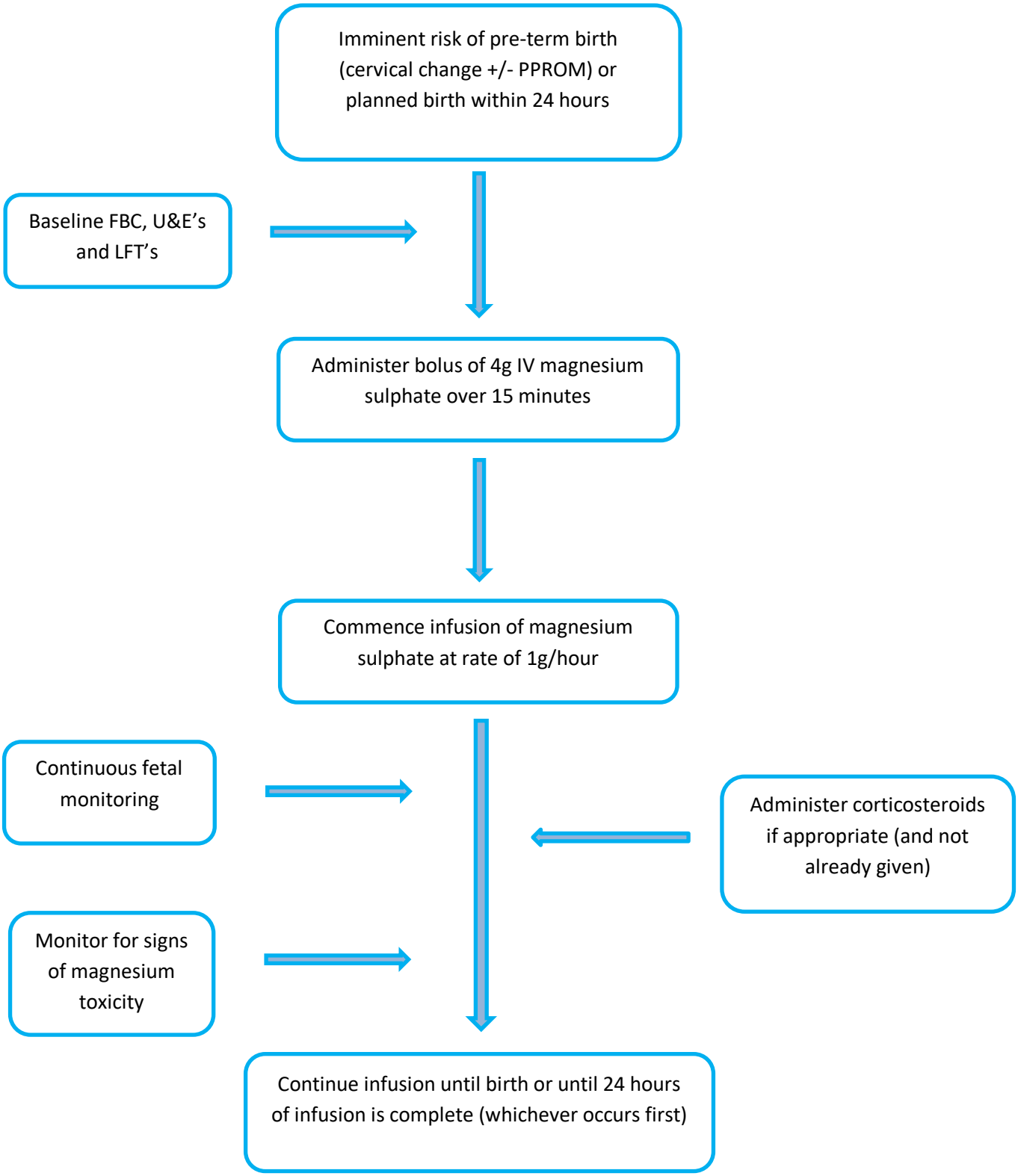
Other considerations

When maternal transport is being considered, magnesium administration should be decided upon in consultation with the receiving centre on a case-by-case basis.

The paediatric team attending birth should be made aware of antenatal magnesium sulphate exposure.

Neonates may present with potentially altered neuro-evaluation due to magnesium sulphate causing hypotonia or apnoea. Therefore, healthcare providers caring for the neonate should have an increased awareness of this effect.

Appendix 1 - flowchart



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Clinical governance

Lead author:	H Maclean
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Endorsing body:	Maternity Clinical Effectiveness Group (MCEG) 25.2.26 and Area Drug and Therapeutics Committee (ADTC) 18.3.26
Version number:	4
Approval date:	18.3.26
Review date:	18.3.29

Consultation/distribution record	
Contributing authors:	H Maclean (O&G trainee), S Maharaj (Cons O&G), N Cowan (O&G trainee)
Consultation process:	MCEG, ADTC
Distribution:	All in maternity

Change record			
Date	**Lead author**	**Change**	**Version**
Nov 2012	S Maharaj	Initial document	1
Nov 2017	S Maharaj	Update	2
Jul 2022	N Cowan	Update	3
18.3.26	H Maclean	New guideline format, change from 10 to 15 mins for duration of bolus therapy (NICE), change from 12 to 14/mm respiratory rate, improved wording on infusion preparation.	4