PROTOCOL

MAGENTA

MAGNESIUM SULPHATE AT 30 TO 34 WEEKS' GESTATIONAL AGE: NEUROPROTECTION TRIAL

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TITLE: MAGNESIUM SULPHATE AT 30 TO 34 WEEKS' GESTATIONAL AGE: NEUROPROTECTION TRIAL (MAGENTA)

PURPOSE OF THE TRIAL

The aim of this randomised controlled trial is to assess whether giving magnesium sulphate compared with placebo to women immediately prior to preterm birth between 30 and 34 weeks' gestation reduces the risk of death or cerebral palsy in their children at 2 years' corrected age.

TRIAL HYPOTHESES

The Primary hypothesis is that antenatal magnesium sulphate compared with placebo given to women at risk of preterm birth between 30 and 34 weeks' gestation when birth is imminent (defined as planned or definitely expected in the next 24 hours) reduces the risk of death or cerebral palsy in their children at two years' corrected age.

The Secondary hypotheses are that the above has **benefits** relating to:-

The infant/child: including individual components of the primary outcome (mortality and cerebral palsy), neonatal morbidity (including intraventricular haemorrhage [IVH]) and other neurosensory disabilities at two years' corrected age (blindness, deafness or developmental delay).

And for the mother: no clinically important effect on mode of birth or maternal morbidity as measured by risk of serious adverse cardiovascular effects of the infusion, side effects of the infusion and postpartum haemorrhage.

BACKGROUND

Preterm birth and cerebral palsy: the burden of disease

Babies born preterm have a higher chance of dying in the first few weeks of life (ANZNN 2009). Babies who survive have a greater risk of neurologic impairments, such as cerebral palsy, blindness, deafness, or cognitive dysfunction, and a greater risk of substantial disability as a result of these neurologic impairments (Doyle et al. 2004; Saigal & Doyle 2008; Petrini et al. 2009). The social and economic long-term costs are considerable (Mangham et al. 2009).

Cerebral palsy is a term which includes a number of different diseases or conditions that can arise at any time during brain development that involves a disorder of movement or posture, or both, and a disorder of motor function which is permanent but may change over time (Oxford Register of Early Childhood Impairment 2001). The cerebral palsies remain the most frequent cause of severe motor disability in childhood with a background prevalence of two per thousand live births (Oxford Register of Early Childhood Impairment 2001). The life expectancy shows 92% of affected children surviving to 20 years, contributing substantially to the burden of illness into adulthood (Hutton et al. 1994).

Very preterm birth (less than 34 weeks) is the principal risk factor for cerebral palsy (Drummond & Colver 2002; Winter et al. 2002), responsible for 17% to 32% of all cases of cerebral palsy. The latest Australian Cerebral Palsy Register Report (2009) shows that approximately 45% of all cases of cerebral palsy are associated with preterm birth (ACPR

Group 2009). Whilst the highest risks are for extremely preterm infants (Doyle et al. 2004), babies born between 30 and 33 completed weeks' gestation still have significant risks (Marret et al. 2007) with the risk of cerebral palsy being up to eight times more likely than babies born at term (Petrini et al. 2009). Moderate prematurity is responsible for as many cases of cerebral palsy as extreme prematurity (ACPR Group 2009).

At present there is no cure for cerebral palsy, which makes effective preventative interventions of paramount importance. Prevention of cerebral palsy has been identified by consumers, clinicians and researchers as a top priority for research by the Cerebral Palsy Institute (McIntyre et al. 2010). **To reduce the impact of cerebral palsy from preterm birth, efforts must be focused on primary prevention.**

Observational studies on the effect of antenatal magnesium sulphate on neurodevelopment

A landmark case-control study 15 years ago described the association of exposure to antenatal magnesium sulphate with a dramatic reduction in the risk of cerebral palsy (odds ratio 0.14; 95% confidence interval 0.05 to 0.51) (Nelson & Grether 1995). Other observational studies support a reduction in cerebral palsy in preterm babies after antenatal magnesium sulphate (Hauth et al. 1995; Schendel, et al. 1996; Wiswell et al. 1996) and some a reduction in the risk of IVH (Wiswell et al. 1996; FineSmith et al. 1997) and perinatal mortality (Grether et al. 1998). However, not all studies report benefit for antenatal magnesium sulphate on the risk of IVH (Paneth et al. 1997; Kimberlin et al. 1998; Weintraub et al. 2001), cerebral palsy (Paneth et al. 1997; O'Shea et al. 1998; Grether et al. 2000) or perinatal mortality (Kimberlin et al. 1998).

Biological plausibility for use of magnesium sulphate for fetal and infant neuroprotection

In humans, magnesium is essential for key cellular processes, including glycolysis, oxidative phosphorylation, protein synthesis, DNA and RNA aggregation and maintenance of plasma membrane integrity (Mildvan 1987; McIntosh et al. 1989). Magnesium favourably affects mechanisms implicated in cell death by decreasing proinflammatory cytokines or free radicals produced during hypoxic-ischaemic reperfusion and inflammatory diseases of pregnancy (Hoffman et al. 1994; Shogi et al. 2003). Magnesium prevents excitotoxic calcium-induced injury (Nowak et al. 1984), by a non-competitive voltage-dependent inhibition of the N-methyl-D-aspartate receptor to glutamate reducing calcium entry into the cell (Ovbiagele et al. 2003). The fetal and neonatal brain seems more susceptible to glutamate damage. Consequently blocking glutamate receptors through agents such as magnesium sulphate may reduce the risk of injury in the perinatal period. Magnesium has some beneficial haemodynamic effects including stabilising blood pressure during the first two days of life in preterm neonates (Rantonen et al. 2002), and may increase cerebral blood flow by reducing constriction of the cerebral arteries (Macdonald et al. 2004). Transplacental transfer of magnesium is rapid with magnesium concentrations increased in fetal serum within one hour of maternal intravenous administration (Hallak & Cotton 1993).

Maternal and neonatal adverse effects and side effects of magnesium sulphate

The best available evidence about potential maternal harms from antenatal magnesium sulphate administration comes from the four Cochrane reviews that compare magnesium sulphate with placebo or no treatment (Crowther et al. 1998; Crowther et al. 2002; Duley et al. 2003; Doyle et al. 2009). Magnesium sulphate, by its peripheral vasodilator effects when infused intravenously, produces a sensation of warmth and flushing. Reported maternal side-effects, relate to dosage and speed of infusion, include nausea, vomiting,

headache and palpitations. Hypotension and respiratory depression are more severe recognised risks. Magnesium sulphate acts as a neuromuscular blocking agent that causes abolition of tendon reflexes (Baraka & Yazigi 1987). Magnesium could aggravate the cardiovascular or neuromuscular side-effects of other drugs such as betamimetics, calcium-channel blockers and gentamicin (Snyder & Cardwell 1989; Ben-Ami et al. 1994). Infusion to concentrations above the recommended therapeutic range can have life threatening consequences for the women that include respiratory arrest and cardiac arrest leading to death (McDonnell 2009). For the neonate, hypermagnesaemia can lead to hyporeflexia, poor sucking, and, rarely, respiratory depression needing assisted ventilation (Lipsitz 1971; Levene et al. 1995).

How antenatal magnesium sulphate can reduce the burden of being born preterm

Systematic review of randomised trials of magnesium sulphate for neonatal neuroprotection

The updated Cochrane systematic review to assess the use of antenatal magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Doyle et al. 2009) included four trials (4446 babies), two from the US; the MagNet Trial (Mittendorf et al. 2002) and the Beam Trial (Rouse et al. 2008), one from Australia and New Zealand; the ACTOMgSO_4 Trial (Crowther et al. 2003), one from France; the PreMag Trial (Marret et al. 2008). There was diversity in the inclusion and exclusion criteria for the four included trials with wide variation in the gestational age women were eligible, reasons women were at risk of preterm birth and time of treatment prior to expected preterm birth (Doyle et al. 2009). All trials used intravenous magnesium sulphate although the dose used, whether a maintenance infusion was given and whether treatment could be repeated varied between trials.

Table 1: Magnesium sulphate vs placebo/no treatment: primary outcomes (Doyle 2009)

Primary outcomes	RR, 95% CI	Number of trials; participants
Death or cerebral palsy	**0.85, 0.74 to 0.98***	four trials; 4446 infants
Death (fetal and later)	0.95, 0.80 to 1.12	four trials; 4446 infants
Cerebral palsy	**0.71, 0.55 to 0.91***	four trials; 4446 infants
Any neurological impairment	1.03, 0.87 to 1.21	one trial; 1255 infants
Death or substantial gross motor dysfunction	0.84, 0.71 to 1.00	three trials; 4387 infants

significantly in favour of magnesium sulphate

Results of the meta-analysis of the Cochrane systematic review
The combined outcome of death or cerebral palsy or cerebral palsy alone showed significant reductions where women who were at risk of preterm birth were given magnesium sulphate antenatally with the intent of providing neuroprotection (Table 1). The review showed that 63 babies (95% confidence interval 44 to 155) need to be treated with magnesium sulphate for one baby to avoid cerebral palsy. The corresponding number needed to treat to benefit (NNTB) for combined death or cerebral palsy was 42 babies, 95% confidence interval 24 to 346.

Is there clinical evidence for the role of antenatal magnesium sulphate for neuroprotection of the fetus, infant and child prior to preterm birth at 30 to 34 weeks gestation?
The recently released National Clinical Practice Guidelines on the use of antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child summarise the evidence available from the four individual neuroprotective intent trials within the Doyle 2009 Cochrane Review (Doyle et al. 2009) that consider gestational age at trial entry and effect of antenatal magnesium sulphate. All women in the four included trials were given magnesium sulphate before 34 weeks' gestation. In Rouse 2008, all women were less than 32 weeks at trial entry with the majority (68% of trial participants) less than 30 weeks gestation (Rouse et al. 2008). Subgroup analyses for women at different gestational ages were possible for women with a gestational age of less than 34 weeks, less than 33 weeks, less than 32 weeks and less than 30 weeks. However there was only one trial within each subgroup available for analysis and the results are inconclusive due to small sample sizes (Table 2).

Table 2: Results of primary outcomes by gestational age subgroup (Doyle 2009)

Trial	N	Eligible (GA wks)	DEATH or CP	CP	DEATH
			RR, 95% CI	RR, 95% CI	RR, 95% CI
MagNet‡	59	>24 to <34	4.83, 0.60 to 38.90	6.77, 0.37 to 125.65	1.93, 0.19 to 20.18
Marret	688	viable to <33	0.80, 0.58 to 1.10	0.70, 0.41 to 1.19	0.85, 0.55 to 1.32
Rouse	2444	24 to <32	0.90, 0.73 to 1.10	0.59, 0.40 to 0.85*	1.13, 0.87 to 1.48
Crowther	1255	<30	0.82, 0.66 to 1.02	0.85, 0.55 to 1.31	0.81, 0.62 to 1.05
Overall	4446	viable to <34	0.85, 0.75 to 0.98*	0.71, 0.55 to 0.91*	0.95, 0.80 to 1.12

‡ ***neuroprotective arm; CP cerebral palsy; GA gestational age; * statistically significant.***

Summary of CPG evidence statement judgements for gestational age subgroup

The subgroup analyses are from trials with low risk of bias, with results between trials fairly consistent. While the evidence is applicable to the Australian and New Zealand context, generalisability was reduced as the majority of the women (87%) in the largest trial (Rouse et al. 2008) had PPROM and so represent a limited subset of women at risk of preterm birth. Overall clinical impact was judged to be very large (Table 2) but any differences in death and cerebral palsy by gestational age are unclear at present. To minimise the number of women exposed, the clinical practice guideline panel felt it would be prudent to restrict magnesium sulphate administration to the subgroup containing the lowest gestational age (less than 30 weeks).

Recommendations made by the National CPG panel for use of antenatal magnesium sulphate

The main clinical recommendation is *to use magnesium sulphate for neuroprotection of the fetus, infant and child "in women at risk of early preterm (gestational age is less than 30 weeks), imminent birth (when early preterm birth is planned or definitely expected within 24 hours)"* (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010).

In recognition of the need for further research, the guideline panel specifically recommended that further randomised trials were needed, comparing antenatal magnesium sulphate with placebo when given to women at risk of preterm birth at 30 weeks' gestation or more, that assess mortality, cerebral palsy and combined death and cerebral palsy (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010).

Preventative strategies that may reduce the risk of cerebral palsy need appropriate evaluation prior to introduction into clinical practice. Given the magnitude of the protective effect in the systematic review, the ongoing uncertainty about benefits at later gestational ages, the serious health and cost consequences of this condition for the child, family and society *a trial of magnesium sulphate for women at risk of preterm birth between 30 to 34 weeks' gestation is both justifiable and needed.*

IN SUMMARY

- Preterm birth remains the major cause of neonatal mortality and morbidity and long term disability. Over 4,294 pregnant women each year in Australia give birth preterm between 30 to 34 weeks' gestation and this rate is increasing (Laws et al. 2010).
- Based on high quality evidence of benefit, the National Clinical Practice Guidelines endorsed by NHMRC recommend the use of magnesium sulphate for neuroprotection of the preterm infant for women at risk of preterm birth at less than 30 weeks' gestation (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010).
- However there remains uncertainty as to whether these benefits apply at higher gestational ages (Cahill & Caughey 2009; ACOG 2010; Cahill et al. 2010; The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). The National Guidelines recommend further evaluation of magnesium sulphate for neuroprotection in women at risk of preterm birth at gestational ages over 30 weeks' gestation (Constantine et al. 2009; Doyle et al. 2009; The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010) by appropriate randomised trials that should include long-term outcomes.

- There is a need for unbiased information about the benefits and risks of magnesium sulphate prior to preterm birth between 30 to 34 weeks' gestation to enable pregnant women and their caregivers to make informed health-care choices.

RESEARCH PLAN

Study Design
Double-blind, multicentre, randomised, controlled trial.

Entry Criteria
Women are eligible for the trial if they are at risk of preterm birth between 30 to 34 weeks' gestation where birth is planned or definitely expected within 24 hours, have a singleton or twin pregnancy, no contraindications to the use of antenatal magnesium sulphate (respiratory depression, hypotension, absent patellar reflexes, renal failure, myasthenia gravis) and give informed, written consent. Women are not eligible if they have a higher-order multiple pregnancy, have received antenatal magnesium sulphate in the current pregnancy or if magnesium sulphate therapy is considered essential for the treatment of pre-eclampsia (Duley et al. 2003).

Trial Entry
Eligible women are given the trial information sheet, counselled by a member of the research team and encouraged to discuss the study with family before consent is sought.

The *Trial Entry Form* is completed and the woman is randomised by contacting the central telephone randomisation service at The University of Adelaide. During the short telephone call, information is given to check eligibility, describe the characteristics of the woman and enable stratification at randomisation for collaborating centre, gestational age (30 to 31 completed weeks; 32-33 completed weeks' gestation), and number of fetuses (1 or 2). The randomisation schedule uses balanced variable blocks, and will be prepared by an investigator not involved with recruitment or clinical care. Assignment is to either the **'magnesium sulphate group'** or the **'placebo group'.** A unique *Study Number* and *Trial Treatment Pack Number* are allocated to the woman.

Treatment Schedule
Each treatment pack looks identical and contains a 100ml infusion bag containing either 8g magnesium sulphate heptahydrate [16 mmol magnesium ions] or isotonic sodium chloride solution (0.9%). A volume of **50ml ONLY** [equivalent to 4g magnesium sulphate heptahydrate or 0.9% sodium chloride] of the infusion pack is to be given to the women through a dedicated intravenous infusion line over **30 minutes.** The woman's pulse, blood pressure, respiratory rate and patellar reflexes are assessed and recorded before the infusion is commenced, fifteen minutes after the infusion has started and at the end of the infusion. Any other monitoring as per the individual obstetric unit protocols for intravenous administration of magnesium sulphate is followed. Magnesium toxicity is unlikely with the regimen recommended in this protocol and serum magnesium concentrations do not need to be routinely measured. There is a potential theoretical interaction between magnesium sulphate and nifedipine of hypotension and neuromuscular blockade effects, although this is seldom reported in clinical practice (Snyder & Cardwell 1989; Ben-Ami et al. 1994).

The trial treatment infusion should be stopped if the respiratory rate decreases more than 4 breaths per minute below baseline, or is less than 12 breaths per minute; or diastolic blood pressure decreases more than 15 mm Hg below baseline level (The Antenatal

Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). The infusion may be continued when the respiratory rate or the blood pressure return to the baseline levels. Should hypotension or respiratory depression occur, prompt medical review is recommended. If there is clinical concern over respiratory depression calcium gluconate (1 g [10 ml of 10% solution] can be given slowly via the intravenous route over 10 minutes). Resuscitation and ventilatory support should be immediately available, if needed, during administration of the trial medication. At the end of the trial treatment infusion, the section on maternal side effects should be completed on the *Treatment form.*

Care During Labour and the Postnatal Stay

This will be managed by the obstetric team caring for the woman. Care of the neonate is the responsibility of the attending neonatologist.

Following Birth

The pregnancy and labour data are extracted from case notes by the masked research assistant at the collaborating hospitals. The postnatal and neonatal data are collected similarly after discharge of the mother and baby from hospital.

Schedule for Follow up after Primary Hospitalisation

Women enrolled in the trial give consent for follow-up of their children from birth until two years' corrected age at the time of the initial, prenatal recruitment. Mothers of all babies discharged home alive will be asked to fill out a brief developmental questionnaire (Ages & Stages 12 Month Questionnaire, Squires et al 2009) when their baby is 12 months of age, corrected for prematurity; this will take approximately 15 minutes to complete. Mothers of all babies discharged home alive will be contacted at 6, 12 and 18 months by a member of the trial research team at the coordinating centre to confirm their current residential address and document any changes of contact details for themselves and the contact people they provide at trial entry. Using a similar tracking approach, we have achieved very high two year follow up rates in our previous NHMRC funded preterm birth trials (98% in the ACTO$MgSO_4$ trial (Crowther et al. 2003) and 95% in the ACTORDS trial) (Crowther et al. 2007).

Two Years' Assessments

All surviving children will be formally assessed at two years of age, corrected for prematurity, by a developmental paediatrician and psychologist or other assessor trained to administer the Bayley Scales. All assessors will remain blinded to treatment group assignment. Assessments will be made of health, neurodevelopment, behaviour, growth and blood pressure. This format of assessment has been used in our previous trials (Crowther et al. 2003; Crowther et al. 2007). Although cerebral palsy may not remain a stable diagnosis before 5 years of age (Stanley & Watson 1992), a diagnosis of severe cerebral palsy (defined below) at 2 years of age is unlikely to change after that time (Paneth 2008). Moreover, 5 years is a long time to wait after recruiting the last patient to determine the most important endpoint for this study. If our hypothesis, that the rate of death and cerebral palsy is lower at 2 years of age with maternal magnesium therapy, is proven, then we will seek further funding to assess this trial cohort again after 5 years of age.

Gross Motor Function

The paediatric assessment will include a neurological examination to diagnose cerebral palsy (abnormality of tone with motor dysfunction) and other disability outcomes according to previously reported criteria (Doyle et al. 2004). Gross Motor Function will be assessed using the Gross Motor Function Classification System (GMFCS) level 0 to 5 (Palisano et al. 1997).

Psychological Assessments

The psychological assessment will include the cognitive, motor and language scales of the Third Edition of the Bayley Scales of Infant and Toddler Development (BSID-III) (Bayley 2006). This is well-standardised with demonstrated validity and reliability. Psychological test scores will be recorded as standardised scores [derived from raw test scores - mean/standard deviation (SD)]. Children with severe developmental delay who are unable to complete the psychological assessment will be given a standardised score of 4 SD below the mean.

Behaviour

The child's caregiver will be asked to complete the Child Behaviour Checklist (Achenbach 1992).

General Health, Health Resource Utilisation, Blood Pressure, Body Size and Quality Of Life

A general history and physical examination will determine the presence of any significant chronic illness, and data regarding hospital readmissions will be confirmed, where necessary, from the admitting hospital or doctor. Children whose vision has not previously been assessed will be referred to an ophthalmologist if they are considered to have abnormal vision. Children will be considered blind if visual acuity in both eyes is worse than 6/60. Hearing should have been assessed earlier in childhood. Those who have not been seen will be referred for audiological assessment if they are considered to have language delay or deafness is suspected. Children will be considered deaf if their hearing loss is sufficient to require hearing aids, or worse. Blood pressure will be measured and converted to Z-scores relative to American data for blood pressure for age, height and gender in childhood (Rosner et al. 1993). Questionnaires will be completed by the child's caregiver about any respiratory morbidity, history of illness or injury, use of health services since primary hospitalisation (Parent/Caregiver Questionnaire) and developmental progress (Ages & Stages 24 Month Questionnaire, Squires et al 2009). The child's height, weight, and head circumference will be measured, and values for the relevant centile, percent of median, and standard deviation scores (Z scores) specific for age and gender will be computed from the British Growth References (Freeman et al. 1995).

Categorisation of Neurosensory Disability

Children will be considered to have a neurosensory impairment if they have cerebral palsy, GMFCS level 1 to 5, blindness, deafness or a standardised score more than 1SD below the mean (< -1SD). The neurosensory disabilities imposed by the various neurosensory impairments will be classified as severe, moderate or mild (Doyle 2004), as follows:

Severe Disability comprises severe cerebral palsy (child non-ambulant and likely to remain so; GMFCS level 4 or 5), severe developmental delay (standardised score < -3SD) or blindness.

Moderate Disability comprises moderate cerebral palsy (child non-ambulant at 2 years of age but who is likely to ambulate subsequently; GMFCS level 2 or 3), or deafness, or moderate developmental delay (standardised score from -3SD to < -2SD).

Mild Disability comprises mild cerebral palsy (child walking at 2 years of age with only minimal limitation of movement (GMFCS level 1) or suspect development (standardised score from -2SD to < -1SD).

No Neurosensory Disability comprises children without any neurosensory impairment.

Primary Study Endpoint measured in the children at 2 years' corrected age:
Death and cerebral palsy are competing outcomes and the combined outcome of death or cerebral palsy is commonly considered the most clinically relevant outcome for assessing neuroprotection.

The incidence of death or cerebral palsy defined as stillbirth, death of live born infant before hospital discharge, or death after hospital discharge before 2 years' corrected age; or any cerebral palsy [abnormality of tone with motor dysfunction].

Secondary Study Endpoints
For the infant:
Health outcomes considered to be important measures of mortality and morbidity prior to primary hospital discharge; (defined as stillbirth and death of liveborn infant before hospital discharge; intraventricular haemorrhage (IVH), severe IVH, cystic periventricular leukomalacia (PVL), neonatal encephalopathy, neonatal convulsions, proven necrotising enterocolitis, retinopathy of prematurity needing treatment, patent ductus arteriosus needing treatment, respiratory distress syndrome, severity of any neonatal lung disease, chronic lung disease (oxygen dependent at 36 weeks post-menstrual age), use of respiratory support, airleak requiring drainage, confirmed infection within the first 48 hours, infection after the first 48 hours, body size at birth (weight, length, head circumference) and at discharge home).

Composite serious health outcome (defined as stillbirth and death of liveborn infant before hospital discharge severe respiratory disease, severe intraventricular haemorrhage (grade 3 & 4); chronic lung disease (oxygen dependent at 36 weeks post-menstrual age); proven necrotising enterocolitis; severe retinopathy of prematurity (Stage 3 or worse in the better eye); cystic periventricular leukomalacia).

For the child:
Key health outcomes assessed at 2 years' corrected age:

Individual components of the primary outcome including severity of cerebral palsy (defined as death; cerebral palsy).

Death or any neurosensory disability (***death*** defined as stillbirth, death of live born infant before hospital discharge or death after hospital discharge; and ***any neurosensory disabilities*** that includes the neurosensory impairments of ***cerebral palsy,*** [GMFCS level 1 to 5], ***blindness*** [corrected visual acuity worse than 6/60 in the better eye], ***deafness*** [hearing loss requiring amplification or worse], and any ***developmental delay*** defined as standardised score more than 1 SD below the mean (< -1SD).

Death or major neurosensory disability Major neurosensory disability includes ***severe and moderate disability*** (defined as any of: legal blindness, sensorineural deafness requiring hearing aids; moderate or severe cerebral palsy [GMFCS level 2 to 5] or developmental delay/intellectual impairment [standardised score more than two SD below the mean].

General health of the child (including use of health services since primary hospitalisation), *childhood respiratory morbidity, blood pressure* (Z scores and proportions in hypertensive ranges), and *behaviour* as assessed by the Child Behaviour Checklist (Achenbach 1992) and **Body size.**

For the mother:

Serious adverse cardiovascular and/or respiratory outcome of the infusion (defined as maternal death, cardiac arrest, respiratory arrest).

Maternal side effects of the infusion (including nausea; vomiting; flushing, infusion arm discomfort; mouth dryness; sweating; dizziness; blurred vision; respiratory rate decreased >4 breaths per minute below baseline or <12 breaths per minute; blood pressure decreased >15 mm Hg below baseline level; whether the infusion is discontinued because of side effects).

Incidence of postpartum haemorrhage, estimated blood loss at birth 500 mL or more; **and major postpartum haemorrhage,** estimated blood loss 1500 mL or more; **mode of birth.**

Sample Size

The rate of our primary outcome of death or cerebral palsy at 2 years' corrected age in an Australian/New Zealand population between 30 to 34 weeks' gestation is estimated to be 9.6%, using a predicted mortality rate up to 2 years of age of 4.4% (excluding lethal anomalies) (Laws et al. 2010) and a predicted rate of cerebral palsy in survivors of 5.2% (Crowther et al. 2007; Marret et al. 2008).

A trial of 1676 children (838 per group), allowing for a design effect of 1.2 for clustering of babies within mothers and a 5% loss to follow up, with an absolute risk difference of 4.2% (Crowther et al. 2003; Crowther et al. 2007; Marret et al. 2008) will have 80% power to detect a statistically significant difference at an alpha level of 0.05 (two-tailed) of a decrease in the combined outcome of death or cerebral palsy from 9.6% to 5.4% with magnesium sulphate compared with placebo.

Data Analyses

Data will be analysed by a statistician independent of the CIs and AIs. Analysis will be by intention to treat by researchers not involved in the clinical management. Potential confounding variables will comprise socio-demographic variables, such as ethnicity, language spoken at home, family structure, mother's marital status, social class, and mother's and father's education, as well as gender of the baby. Comparisons will be made between treatment groups for death and cerebral palsy, adjusting for the inter-correlation of observations on multiple births. Subsequent analyses will make adjustments for important baseline predictors including gestational age at birth, and reasons for risk of preterm birth. Survival analyses will be used to examine survival free of cerebral palsy. Logistic regression and multiple linear regressions will be used to examine dichotomous and continuous outcomes, with adjustment for any confounding variables. Regression analysis will account for the non-independence of observations on multiples from the same pregnancy with appropriate adjustment of standard errors. *P*-values <0.05 will be considered statistically significant.

Ethical Considerations & Confidentiality

Each woman eligible for recruitment is counselled about the trial by a member of the research team and given a written information sheet to assist her in making an informed decision about the study. Informed, signed consent is obtained for each participant. The woman is free to withdraw herself or her child(ren) from the study at any stage, without prejudice to her future care.

Information about women and their babies recruited to the trial will be stored securely (locked filing cabinets and password protected computer files). Identifying details will be separated from other information and no identifying information will be published.

OUTCOMES AND SIGNIFICANCE

The MAGENTA randomised trial assessing the use of antenatal magnesium sulphate to women at risk of preterm birth between 30 to 34 weeks' gestation for neuroprotection of their infants is important and relevant for clinical practice in Australia and internationally.

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