Closing Research Gaps for Cerebral Palsy Prevention and Magnesium Sulphate Neuroprotection

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CONTENTS

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LIST OF TABLES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

LIST OF FIGURES

Chapter 2

Chapter 3

Chapter 5

ABBREVIATIONS

ACOG: American College of Obstetricians and Gynecologists
ACPR: Australian Cerebral Palsy Register
ACTOMgSO_4: Australasian Collaborative Trial of Magnesium Sulphate
BEAM: Beneficial Effects of Antenatal Magnesium Sulfate
CDC: Centers for Disease Control and Prevention
CFCS: Communication Function Classification System
CI: confidence interval
CP: cerebral palsy
EDACS: Eating and Drinking Ability Classification System
GMFCS: Gross Motor Function Classification System
GMFM: Gross Motor Function Measure
GMH: germinal matrix haemorrhage
GMs: General Movements
HINE: Hammersmith Infant Neurological Examination
IVH: intraventricular haemorrhage
KCE: Belgian Health Care Knowledge Centre
MACS: Manual Ability Classification System
MAGENTA: Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial
MAGPIE: Magnesium Sulphate for Prevention of Eclampsia
MAG-CP: MAGnesium sulphate for fetal neuroprotection to prevent Cerebral Palsy
MagNET: Magnesium and Neurologic Endpoints Trial
MRI: magnetic resonance imaging
NCC-WCH: National Collaborating Centre for Women's and Children's Health
OR: odds ratio
PReCEPT: PREventing Cerebral palsy in Pre Term labour
PREMAG: Prevention of Cerebral Palsy by Magnesium Sulphate
PVL: periventricular leukomalacia
RCPI: Royal College of Physicians of Ireland
RCT: randomised controlled trial
RR: risk ratio
SCPE: Surveillance of Cerebral Palsy in Europe
SD: standard deviation
SMFM: Society for Maternal-Fetal Medicine
WHO: World Health Organization
WISH: Working to Improve Survival and Health for babies born very preterm

ABSTRACT

Background
Cerebral palsy (CP) is the leading cause of physical disability in childhood. Despite emerging evidence that the prevalence of CP has begun to decline, approximately one in 500 babies continue to be affected worldwide. While causes and risk factors for CP are well established, potential preventive interventions are under-researched.

Aims
1. To summarise and interpret the evidence regarding antenatal and intrapartum interventions for preventing CP.
2. To summarise and interpret the evidence regarding neonatal interventions for preventing CP.
3. To link data from a maternal perinatal randomised controlled trial (RCT) with a nationwide CP register to identify children with CP.
4. To assess whether antenatal magnesium sulphate is associated with perinatal death or other adverse neonatal outcomes.

Methods
To achieve the above aims, the following methodologies were employed:
1. An overview of Cochrane reviews regarding antenatal and intrapartum interventions for CP prevention.
2. An overview of Cochrane reviews regarding neonatal interventions for CP prevention.
3. A de-identified linkage of Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO_4) and Australian Cerebral Palsy Register (ACPR) data.
4. A systematic review of RCTs and non-randomised studies assessing antenatal magnesium sulphate, perinatal death and other adverse neonatal outcomes.

Results
1. The overview of antenatal and intrapartum interventions included 15 Cochrane reviews, with CP data from 27 RCTs (32,490 children). Magnesium sulphate for women at risk of very preterm birth for fetal neuroprotection reduced CP risk (high-quality evidence). CP risk was probably increased (moderate-quality evidence, 2 reviews), probably not changed (moderate-quality evidence, 1 review), or unclear (low- to very low-quality evidence, 11 reviews) with other interventions assessed.
2. The overview of neonatal interventions included 43 Cochrane reviews, with CP data from 96 RCTs (15,885 children). Therapeutic hypothermia in late preterm or term neonates with hypoxic-ischaemic encephalopathy reduced CP risk (high-quality evidence), and prophylactic methylxanthines for endotracheal extubation in preterm neonates probably reduced CP risk (moderate-quality evidence). CP risk was probably increased (moderate-quality evidence, 2 reviews), probably not changed (moderate-quality evidence, 5 reviews), or unclear (low- to very low-quality evidence, 26 reviews) with other interventions assessed.
3. Linkage of data from 913 ACTOMgSO_4 children (born 1996-2000) and the ACPR was achieved. Differences in ACTOMgSO_4 (at 2 years) and ACPR (up to 5 years) CP diagnoses were identified; attributed to limitations in CP diagnostic methods, and register under-ascertainment in this era.
4. The systematic review of adverse neonatal outcomes included 40 RCTs (19,265 women and their babies), 138 non-randomised studies, and 19 case reports. Perinatal death was not increased with antenatal magnesium sulphate in RCTs. RCTs showed no clear increased risks of other adverse neonatal outcomes; non-randomised studies identified a limited number of outcomes necessitating further evaluation.

Conclusions
Antenatal magnesium sulphate for fetal neuroprotection in women at risk of very preterm birth, and therapeutic hypothermia in late preterm or term neonates with hypoxic-ischaemic encephalopathy reduce the risk of CP. There is an urgent need for further research regarding the effects of other identified interventions on CP, and on strategies to assess CP following maternal perinatal RCTs.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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CHAPTER 1: LITERATURE REVIEW

Cerebral palsy: a vision of prevention

Definition and diagnosis

'Cerebral palsy' (CP) was originally defined by clinical description, at a time when there was little knowledge of aetiology or pathology (Korzeniewski et al. 2018). Discussion regarding definition and classification was first recorded in English, French and German medical literature in the nineteenth century; for over 150 years, exactly what the term CP describes was debated (Morris 2007). Definitions adopted by CP registries internationally have commonly included those proposed by Bax in the 1960s (Bax 1964), Mutch and colleagues in the 1990s (Mutch et al. 1992) and more recently, by Rosenbaum and colleagues (a revised version of Bax 1964) (Rosenbaum et al. 2007); "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy and by secondary musculoskeletal problems" (Rosenbaum et al. 2007).

Today, CP is still a clinical description, but many registries and surveillance programs, including in Australia, highlight the key elements that reflect the core features provided in definitions to date (and proposed by the Surveillance of Cerebral Palsy in Europe (SCPE 2000)): it is an 'umbrella term'; it is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non-progressive interference, lesion or abnormality; the interference, lesion or abnormality arose in the developing or immature brain (ACPR Group 2018; Smithers-Sheedy et al. 2014).

CP can be described by its motor type and body parts distribution (topography). Primary and secondary motor types include spasticity, dyskinesia, ataxia and hypotonia, and these are determined by a combination of structured neurological and motor assessments with observations corroborated by imaging findings in some cases (Stanley, Blair & Alberman 2000). In regards to topography of spasticity (the predominant primary motor type), hemiplegia (unilateral involvement), diplegia (bilateral involvement with the lower limbs more affected than the upper limbs), and quadriplegia (bilateral involvement with the upper limbs more or equally involved) are frequently used terms, with monoplegia and triplegia occasionally reported as separate entities or grouped with hemiplegia and quadriplegia, respectively (Stanley, Blair & Alberman 2000).

In response to the need for a standardised system to classify the severity of movement disability among individuals with CP, the Gross Motor Function Classification System (GMFCS) was developed (Palisano et al. 1997), and has since become the principal way to classify gross motor dysfunction, with uptake into research and clinical practice internationally (Gray, Ng & Bartlett 2010; Morris & Bartlett 2004). The GMFCS describes the gross movement ability of children in one of five ordinal levels (and provides descriptions for each level across five age bands: less than two years; two to four years; four to six years; six to 12 years; 12 to 18 years). Children in level I can perform activities similarly to their age-matched peers, with some difficulty with speed, balance and coordination (general heading: 'Walks without limitations'), while children in level V have difficulty controlling their head and trunk posture in most positions and achieving any voluntary control of movement (general heading: 'Transported in a manual wheelchair') (Palisano et al. 1997). Unlike classifications based on topography and motor type, the GMFCS has been shown to be a valid, reliable, stable and clinically relevant method for classification and, in conjunction with the Gross Motor Function Measure (GMFM), prediction of motor function in CP (Gray, Ng & Bartlett 2010; Morris & Bartlett 2004).

Since the development of the GMFCS, further progress has been made in classifying children's motor abilities, with the Manual Ability Classification System (MACS) providing a method analogous to the GMFCS to assess the ability of children with CP to handle objects (Eliasson et al.

2006). Additionally, the Communication Function Classification System (CFCS) provides a method to evaluate communication capacity within 'real-life' situations (Hidecker et al. 2011), and the Eating and Drinking Ability Classification System (EDACS) provides a method to assess the eating and drinking performance of children with CP (Sellers et al. 2014). Use of these standardised, reliable and complementary systems together draws a comprehensive picture of the functional performance in daily life of individuals with CP, to inform both research and clinical practice (Compagnone et al. 2014; Hidecker et al. 2012; Paulson & Vargus-Adams 2017).

Historically, a 'wait and see' approach to CP diagnosis was common, up to and beyond the perceived 'latent' period of 12 to 24 months, where it was believed that CP could not be identified accurately (te Velde et al. 2019). This provided time to "to rule out other diagnoses, delay the delivery of bad news or provide time for the child to grow out of it" (McIntyre et al. 2011). As CP is an umbrella term covering different clinical manifestations and aetiologies, the possibility for diagnosis reversal has been well recognised: "motor abnormalities detected in early childhood may subsequently lessen in degree, change in kind, or disappear altogether" (Nelson & Ellenberg 1982). Reports of children 'outgrowing' or 'losing' early CP diagnoses in later childhood began decades ago (Nelson & Ellenberg 1982), and continue today (Chen et al. 2019).

Recently, in recognition of the importance of early CP diagnosis in facilitating prompt referral for diagnostic-specific interventions (Byrne et al. 2019; Novak & Morgan 2019; te Velde et al. 2019), a comprehensive systematic review was conducted (Novak et al. 2017). This systematic review summarised the evidence base for the development of 2017 international clinical practice guidelines, which support early, accurate diagnosis and intervention in CP (Novak et al. 2017). Where appropriate, a diagnosis is now possible under the age of six months. As there is no one diagnostic tool, a combination of clinical history, neuroimaging (magnetic resonance imaging (MRI), 86-89% sensitivity), standardised neurological assessments (such as the Hammersmith Infant Neurological Examination (HINE), 90% sensitivity), and standardised motor assessments (particularly Prechtl's Qualitative Assessment of General Movements (GMs) before five months' corrected age, 98% sensitivity) are suggested, to enable the most accurate, earliest, diagnosis to be made (Novak et al. 2017; Spittle et al. 2018).

Prevalence

Despite variation in definitions and classifications of CP, there is wide agreement that it is the most common physical disability in childhood. In a meta-analysis, including 19 studies, the global pooled birth prevalence was 2.11 per 1,000 live births (95% confidence interval (CI) 1.98 to 2.25); a cumulative meta-analysis demonstrated stability in the prevalence over 10 years (Oskoui et al. 2013). Similar trends and relative stability of rates over time have been shown in geographical regions which have used consistent methods of ascertainment for 20 years or more (in countries such as Australia, Sweden and England), with most published estimates of total population birth prevalence in the region of 2 per 1,000 (Stavsky et al. 2017). In low and middle-income countries, birth prevalence estimates of CP have tended to be similar or higher compared with high-income countries (Kakooza-Mwesige et al. 2017; Khandaker et al. 2019), however, it is difficult to meaningfully compare rates, with very few such countries using registries or surveillance programs. Within individual countries, prevalence rates vary among different population groups. For example, in Australia, the birth prevalence of CP among the Aboriginal and/or Torres Strait Islander (Indigenous) population is significant higher compared with the non-Indigenous population (Blair et al. 2016). There is now emerging evidence, including from Australia (Galea et al. 2019), Europe (Hollung et al. 2018; Sellier et al. 2016), Canada (Robertson et al. 2017), and Japan (Touyama et al. 2016) that the birth prevalence and severity of CP have begun to decline for the first time.

In line with knowledge regarding risk factors for CP (discussed below), variations in prevalence rates are observed, such as when stratifying by gestational age or birthweight. In the aforementioned meta-analysis, the birth prevalence was highest for children weighing 1,000 to 1,499 grams at birth (59.18 per 1,000 live births) and born before 28 weeks' gestation (111.80 per 1,000 live births) (Oskoui et al. 2013).

Causes and risk factors

For approximately 6% of individuals with CP, their brain injury is believed to have occurred during a recognised event more than 28 days after birth and before the age of two to five; commonly, a cerebrovascular accident, spontaneous, associated with surgery or with complications of cardiac defects (ACPR Group 2018). For the remaining 94% of individuals with CP, their brain injury is believed to have occurred during the antenatal or the neonatal period of development, that is, during pregnancy, or within the first 28 days of life (ACPR Group 2018).

The pathogenesis of such brain injury is known to be complex and multifactorial, with interrelated pathways contributing to cellular dysfunction and death, including accumulation of reactive oxygen species, the release of excitatory amino acids, energy depletion and apoptosis (Inder & Volpe 2000; Vexler & Ferriero 2001). There are multiple causes of brain injury, including hypoxia-ischaemia (characterised by reduced oxygen in the blood combined with reduced blood flow to the brain), haemorrhage, infection, maldevelopment and metabolic derangement (Volpe 2001). Brain hypoxia (deficiency of oxygen) and ischaemia (insufficient blood supply) may lead to different neuropathology in babies born preterm and at term – with cerebral white matter injury predominating in preterm babies, and neuronal cell injury in term babies (Volpe 2001). Injury to the developing brain is known to be associated with long-term sequelae, including CP, as well as other hearing, sight, speech and behavioural disorders, seizures, and intellectual disabilities (Vexler & Ferriero 2001).

Preterm birth (before 37 weeks' gestation) is one of the principal risk factors for CP and associated neurodevelopmental disabilities (Himpens et al. 2008; Oskoui et al. 2013; van Lieshout et al. 2017). The degree of prematurity is associated with vulnerability of cerebral white matter, and is predictive of an increasing risk of white matter injury such as periventricular leukomalacia (PVL), and of intraventricular haemorrhage (IVH) (Larroque et al. 2003) – established risk factors for the development of CP (Gotardo et al. 2019; Saliba & Marret 2001). Although preterm birth is acknowledged as a major risk factor for CP, with over 40% of individuals with CP born preterm (compared with approximately 10% of the general population), most individuals with CP (50% to 60%) are born at term (ACPR Group 2018).

Studies on possible antenatal, intrapartum and neonatal risk factors for CP for preterm and term born individuals are abundant (with some risk factors reported more consistently than others). While a great number of potential risk factors for CP have been identified, their commonality is that separately, or in combination, they influence potentially preventable pathways to brain injury. Risk factors, in additional to preterm birth, often reported in the literature include: factors prior to conception, such as: low and advanced maternal age, high parity, nulliparity, a short or long inter-pregnancy interval, a history of stillbirth, multiple miscarriages, neonatal death or preterm birth, family history of CP and other genetic predispositions, low socioeconomic status, and pre-existing maternal conditions (e.g. intellectual disability and epilepsy); factors in early pregnancy, such as: male gender, multiple gestation, congenital malformations or birth defects, and infections (e.g. toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus); factors during pregnancy, such as: maternal disease (e.g. thyroid disorders), pregnancy complications (e.g. high blood pressure, pre-eclampsia, placenta praevia, placental abruption, and other placental abnormalities), intrauterine infection/inflammation and chorioamnionitis, intrauterine growth restriction, and other precursors to preterm birth; and factors around the time of birth and neonatal period, such as: acute intrapartum hypoxic events and neonatal encephalopathy, neonatal brain injury (e.g. IVH, PVL and hydrocephalus), strokes or seizures, cardiovascular disorders (e.g. patent ductus arteriosus and hypotension), vascular abnormalities (e.g. arteriovenous malformation), respiratory disorders and associated prolonged ventilation (e.g. for respiratory distress syndrome or bronchopulmonary dysplasia), infection (e.g. sepsis and necrotising enterocolitis), metabolic or endocrine disorders (e.g. hypoglycaemia and hypothyroidism), neonatal jaundice, and exposure to interventions (e.g. high dose dexamethasone), along with inborn errors of metabolism, particular syndromes or chromosomal abnormalities (Jacobsson & Hagberg 2004; Korzeniewski et al. 2018; McIntyre et al. 2013; Michael-Asalu et al. 2019; Nelson 2008; Stavsky et al. 2017; van Lieshout et al. 2017).

Common risk factors in the post-neonatal period (some of which also contribute in the neonatal period) include: infection (e.g. meningitis/encephalitis, or severe infection and subsequent dehydration), head injury (e.g. from traffic accidents, other traumatic injury, or non-accidental injury), vascular episodes (e.g. post-cardiac or brain surgery), and other events (e.g. near drowning or near sudden infant death) (Cans et al. 2004; Germany et al. 2013).

Research has shown that contrary to earlier beliefs, birth asphyxia is a relatively rare cause of CP (Blair & Stanley 1988; Ellenberg & Nelson 2013). A growing body of evidence now suggests that genetic abnormalities contribute to the development of CP in some cases (MacLennan, Thompson & Gecz 2015; Moreno-De-Luca, Ledbetter & Martin 2012; O'Callaghan et al. 2009; Oskoui et al. 2015; van Eyk et al. 2019). While previously, only 1% to 2% of CP cases were linked to a causative genetic mutation, recent studies have shown that between 14% and 31% of cases have possible causative single gene mutations or clinically relevant copy number variants respectively (MacLennan, Thompson & Gecz 2015). Possible genetic mutations and variants associated with CP are likely to be heterogeneous (van Eyk et al. 2019). However, they can similarly trigger pathways (either directly, or in the case of genetic susceptibility, when certain risk factors are present), leading to non-progressive neuropathology associated with motor dysfunction, and CP (MacLennan, Thompson & Gecz 2015).

In low- and middle-income countries, the risk factors and causes of CP are known to differ from those in high-income countries. With few survivors following very preterm birth in low- and middle-income countries, birth asphyxia, maternal Rhesus alloimmunisation or inherited disorders and subsequent bilirubin encephalopathy are more common risk factors for CP (Donald et al. 2015; Lagunju & Fatunde 2009; Monokwane et al. 2017). Additionally, in low- and middle-income countries, there are higher proportions of children with postnatally acquired CP, compared with in high-income countries, particularly associated with post-infectious brain damage (following meningitis, septicaemia and other conditions such as malaria) (Donald et al. 2015; Lagunju & Fatunde 2009; Monokwane et al. 2017).

Though there is currently no known cure for CP, with increasing knowledge of risk factors and causal pathways, there is now heightened hope for the development and implementation of primary preventive strategies: “we are on the move… the vision of prevention and cure no longer seems an unattainable goal” (Badawi & Keogh 2013).

Consequences

CP is the leading cause of physical disability in children. Though traditionally regarded as a paediatric condition, it is now recognised that CP is a condition with life-long impact – a ‘lifespan condition’ – and thus the outcomes of individuals with CP across the life course need to be considered, for example, when planning and directing interventions in childhood (Colver 2016; Colver, Fairhurst & Pharoah 2014; Makris, Dorstyn & Crettenden 2019).

Regarding life expectancy, most individuals with CP will survive to adulthood, with some studies suggesting life expectancy can be broadly similar to that of the general population (Colver 2016; Strauss et al. 2008). Higher mortality has, however, been shown for individuals with CP and co-existing morbidities (including severe intellectual impairment, difficulties swallowing and scoliosis) (Colver 2016; Strauss et al. 2008). Survival is poorest in those with the most severe motor dysfunction (GMFCS level V) (Hutton & Pharoah 2006). Findings related to quality of life in individuals with CP have been variable. In a recent systematic review and meta-analysis of 11 observational studies (10 cross-sectional studies and one longitudinal study), physical quality of life was shown to be significantly impaired for individuals with CP (Makris, Dorstyn & Crettenden 2019). The effects of CP on psychological and social quality of life however, were inconsistent. The review also demonstrated a tendency for parents’ assessments of quality of life for children with CP to be lower than children’s own assessments (Makris, Dorstyn & Crettenden 2019).

Frequently used definitions for CP importantly acknowledge common concomitant impairments, diseases and functional limitations, including hearing, sight and speech disorders, intellectual

disability and epilepsy (Colver 2016; Rosenbaum et al. 2007). A systematic review and meta-analysis of 30 observational studies (predominately retrospective cohort studies based on data from population-based CP registries) reported, for example, that among children with CP "3 in 4 were in pain; 1 in 2 had an intellectual disability; 1 in 3 could not walk; 1 in 3 had a hip displacement; 1 in 4 could not talk; 1 in 4 had epilepsy; 1 in 4 had a behavior disorder; 1 in 4 had bladder control problems; 1 in 5 had a sleep disorder; 1 in 5 dribbled; 1 in 10 were blind; 1 in 15 were tube-fed; and 1 in 25 were deaf" (Novak et al. 2012).

Economic studies have estimated lifetime costs of CP, including health care costs (such as primary health care, hospital care and pharmaceuticals), social care costs (such as specialised education and housing) and productivity costs (the cost for society when individuals never enter, or leave the labour market) as €860,000 for men and €800,000 for women in Denmark (in 2000) (Kruse et al. 2009), and US$921,000 for individuals in the United States (in 2003) (CDC 2004). In Australia, the annual financial cost of CP at a national level was estimated as A$1.47 billion (in 2007); the value of lost wellbeing (disability and premature death) was a further A$2.4 billion (Access Economics 2008). A recent systematic review, including 22 studies (all original articles, reporting costs, cost estimates, cost burden and/or expenditure related to CP), highlighted the significant costs incurred by families and the welfare system, to facilitate participation of individuals with CP (e.g. school and community engagement), along with a strong positive relationship between CP severity and expenditure (Tonmukayakul et al. 2018).

The impact of CP is considerable – not only for individuals, but for families, carers, communities and societies. Accordingly, the identification of primary preventive measures continues to be recognised as a top priority, by individuals with CP and their families, clinicians and researchers (McIntyre, Novak & Cusick 2010).

Antenatal, intrapartum and neonatal prevention

Research efforts focused on 'moving towards a future without CP' have increasingly focused on understanding the causes of CP. As it is now widely recognised that causes may differ, for example, by gestational age (i.e. for preterm and term born children), and also by clinical subtype of CP (Nelson & Chang 2008), it is reasonable to consider that successful preventive interventions may therefore also vary according to different aetiologies or risk factors. For example, spastic diplegia is the most common subtype of CP in preterm born children, most often caused by white matter injury initiated by cerebral ischaemia and/or maternal intrauterine infection and fetal systemic inflammation; quadriplegic CP, especially with dyskinesia, is a subtype of CP sometimes related to acute asphyxia around the time of birth (Nelson & Chang 2008).

Primary preventive interventions may include strategies close to the cause of brain damage (e.g. antenatal magnesium sulphate prior to preterm birth for fetal neuroprotection), strategies directed at preventing distal components on a causal pathway to CP (e.g. melatonin during pregnancy for intrauterine growth restriction), or public health strategies for the general population (e.g. periconceptional folate supplementation to reduce birth defects) (IMPACT for CP 2015). There are a broad range of antenatal, intrapartum and neonatal health care interventions (with varying primary aims or indications) that could influence CP risk (the examples, assessed in Cochrane systematic reviews, presented in Table 1, are not an exhaustive list).

Table 1: Antenatal, intrapartum and neonatal interventions assessed in Cochrane reviews that may mediate CP risk

Intervention category	Example interventions
Nutrition interventions in pregnancy	Periconceptional folate (De-Regil et al. 2015); omega-3 fatty acids (Middleton et al. 2018); vitamins C and E (Rumbold et al. 2015a; Rumbold et al. 2015b); vitamin D (De-Regil et al. 2016); zinc (Ota et al. 2015)
Behaviour/advice interventions in pregnancy	Advice for reducing alcohol or drug consumption (Stade et al. 2009); for supporting smoking cessation (Chamberlain et al. 2017)
Interventions for predicting or preventing preterm birth	Fetal fibronectin testing (Berghella & Saccone 2019b); cervical assessment by ultrasound (Berghella & Saccone 2019a); cervical cerclage (Alfirevic, Stampalija & Medley 2017); antenatal administration of progesterone (Dodd et al. 2013); acute tocolytic therapy and/or maintenance therapy (i.e. magnesium sulphate (Crowther et al. 2014); calcium channel blockers (nifedipine) (Flenady et al. 2014b); oxytocin receptor antagonists (atosiban) (Flenady et al. 2014a); betamimetics (terbutaline) (Neilson, West & Dowswell 2014); cyclo-oxygenase inhibitors (indomethacin) (Reinebrant et al. 2015))
Interventions prior to preterm or term birth for fetal neuroprotection	Antenatal corticosteroids (Roberts et al. 2017); magnesium sulphate (Doyle et al. 2009); creatine (Dickinson et al. 2014); melatonin (Wilkinson, Shepherd & Wallace 2016); allopurinol (Martinello et al. 2017)
Interventions for screening and managing fetal growth and well-being in pregnancy	Symphysial fundal height measurement for detecting abnormal fetal growth (Robert Peter et al. 2015); ultrasound for fetal assessment in early pregnancy (Whitworth, Bricker & Mullan 2015); routine ultrasound in late pregnancy (Bricker, Medley & Pratt 2015); antenatal cardiotocography for fetal assessment (Grivell et al. 2015); fetal and umbilical Doppler ultrasound (Alfirevic, Stampalija & Medley 2015)
Interventions for diagnosing or preventing fetal compromise in labour	Intermittent auscultation of fetal heart rate (Martis et al. 2017); continuous cardiotocography for electric fetal heart rate monitoring (Alfirevic et al. 2017); fetal electrocardiogram (Neilson 2015); fetal pulse oximetry (East et al. 2014)
Interventions for infection during pregnancy	Prevention of congenital infections (i.e. toxoplasmosis (Di Mario et al. 2013)); interventions for urinary tract infections (Schneeberger et al. 2015; Smaill & Vazquez 2019; Vazquez & Abalos 2011); interventions for lower genital tract infections (Brocklehurst et al. 2013; Sangkomkamhang et al. 2015)
Interventions for preterm or term prelabour rupture of membranes	Planned early birth (vs. expectant management) (Bond et al. 2017; Middleton et al. 2017); antibiotics (Kenyon, Boulvain & Neilson 2013; Wojcieszek, Stock & Flenady 2014); tocolytics (Mackeen et al. 2014)
Other specific interventions for medical problems in pregnancy	Screening and subsequent management for thyroid dysfunction (Spencer et al. 2015); anti-D administration for preventing Rhesus alloimmunisation in Rh-negative women (McBain, Crowther & Middleton 2015); interventions for the treatment of mild to moderate (Abalos et al. 2018), or severe hypertension (Duley, Meher & Jones 2013), and for the prevention (i.e. antioxidants (Rumbold et al. 2008); antiplatelet agents (Duley et al. 2019)) and treatment of pre-eclampsia or eclampsia (i.e. magnesium sulphate (Duley et al. 2010a); diazepam (Duley et al. 2010b); phenytoin (Duley, Henderson-Smart & Chou 2010)),

	interventions for placental praevia (Neilson 2003a), or abruption (Neilson 2003b)
Interventions for neonates following birth asphyxia or with evidence of hypoxic ischaemic encephalopathy	Cooling (Jacobs et al. 2013); anticonvulsants (Young, Berg & Soll 2016); allopurinol (Chaudhari & McGuire 2012)
Interventions for preventing or treating neonatal seizures	Anticonvulsants (Booth & Evans 2004)
Interventions for preventing or treating neonatal respiratory distress syndrome, and for respiratory function	Exogenous surfactant (Rojas-Reyes, Morley & Soll 2012); early or late postnatal corticosteroids (Doyle et al. 2017; Doyle, Ehrenkranz & Halliday 2014); targeting higher (vs. lower) arterial oxygen saturations (Askie et al. 2017); caffeine (Henderson-Smart & De Paoli 2010a, 2010b)
Interventions for preventing or treating hypoglycaemia	Oral dextrose gel (Weston et al. 2016)
Interventions for preventing or treating jaundice	Phototherapy (Okwundu, Okoromah & Shah 2012)
Interventions for preventing or treating neonatal infection	Prophylactic (vs. selective) antibiotics (such as for term born babies of mothers with risk factors (Ungerer et al. 2004); or neonates with catheters (Jardine, Inglis & Davies 2008)); antibiotics for bacterial meningitis (Shah, Ohlsson & Shah 2012); antibiotics for suspected late-onset sepsis (Gordon & Jeffery 2005); intravenous immunoglobulin (Ohlsson & Lacy 2015)
Other specific interventions in the neonatal period particularly for preterm born babies	Kangaroo mother care (Conde-Agudelo & Diaz-Rossello 2016); early developmental interventions post-discharge (Spittle et al. 2015)

How antenatal, intrapartum and neonatal prevention might work

Advances in research into several factors that modify the risk of CP suggest many opportunities for prevention. Some of the main strategies focus on preventing preterm birth, or protecting the developing fetal or neonatal brain through the antenatal, intrapartum or neonatal administration of neuroprotective agents (Favrais et al. 2014; Jameson & Bernstein 2019).

For example, because preterm birth and neurodevelopmental outcomes are so strongly associated, it is possible that interventions to prolong gestation or reduce the risk of preterm birth will also reduce the risk of CP (Chang 2015; Iams et al. 2008; O'Shea 2008). Specific approaches, with clear evidence of benefit to prevent preterm birth in specific populations of pregnant women include: midwife-led continuity models of care for pregnant women (Sandall et al. 2016); zinc supplementation for pregnant women without systemic illness (Ota et al. 2015); screening for lower genital tract infections for pregnant women less than 37 weeks' gestation, without signs of labour, bleeding or infection (Sangkomkamhang et al. 2015); and cervical cerlage for women with singleton pregnancies at high risk of preterm birth (Alfirevic, Stampalija & Medley 2017) (Medley et al. 2018). Possible benefits for the prevention of preterm birth have also been shown, for example, with group antenatal care for pregnant women (Catling et al. 2015); antibiotics for pregnant women with asymptomatic bacteriuria (Smaill & Vazquez 2019); and vitamin D supplements for pregnant women without pre-existing conditions such as diabetes (De-Regil et al. 2016) (Medley et al. 2018).

For women with an immediate risk of preterm birth, it is possible that antenatal interventions aimed at protecting the fetal brain from injury will also reduce CP risk. For example, antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth have been shown to be neuroprotective (Roberts et al. 2017). Beyond antenatal corticosteroids and magnesium sulphate (Doyle et al. 2009) a range of other potential antenatally administered agents, such as allopurinol (Martinello et al. 2017), melatonin (Wilkinson, Shepherd & Wallace 2016) and creatine

(Dickinson et al. 2014), may enhance the ability of the preterm or term developing fetal brain to withstand brain damage and in doing so, reduce CP risk (Ellery et al. 2018; Jameson & Bernstein 2019; Robertson et al. 2012).

There are numerous other antenatal and intrapartum interventions with potential to contribute to CP prevention, which may work through modifying known risk factors; for example: identification and subsequent management of maternal thyroid dysfunction (both hypo- and hyper-thyroidism) in pregnancy (Spencer et al. 2015); prevention, identification and treatment of hypertension and pre-eclampsia in pregnancy (Abalos et al. 2018; Duley et al. 2010a; Duley, Henderson-Smart & Chou 2010; Duley et al. 2010b; Duley et al. 2019; Duley, Meher & Jones 2013); and fetal monitoring (intermittent auscultation, cardiotocography, electrocardiogram, fetal pulse oximetry) in labour for early recognition or prevention of birth asphyxia (Alfirevic et al. 2017; East et al. 2014; Martis et al. 2017; Neilson 2015).

For many individuals born at or near term who develop CP, their neonatal course was seemingly unremarkable, with the exception of those following perinatal asphyxia and with neonatal encephalopathy (brain injury due to cerebral hypoxia and ischemia prior to birth) (O'Shea 2008). For these neonates, therapeutic hypothermia, applied selectively to the head (as a 'cooling cap') or to the whole body, is one such intervention with the potential to influence CP risk (Jacobs et al. 2013). Beyond cooling, there are a range of other interventions, such as melatonin and erythropoietin (including to be used as adjuvant therapy with cooling) which may contribute to CP prevention, either through protecting against secondary cell death and brain damage following hypoxic-ischaemic insult, or through treating the underlying cause(s) of encephalopathy (such as infection) (Robertson et al. 2012).

For preterm and very low birthweight neonates, or other groups of neonates (such as those with hypoglycaemia) who are at increased risk of brain injury, there are many pharmacological and non-pharmacological interventions in the neonatal period that may mediate CP risk (O'Shea 2008). These interventions differ in their primary aims (such as maintaining adequate ventilation (e.g. through the treatment of apnoea of prematurity with caffeine (Henderson-Smart & De Paoli 2010a, 2010b)); maintaining normal metabolic status (e.g. through the treatment of neonatal hypoglycaemia with dextrose gel (Weston et al. 2016)); or controlling neonatal seizures (e.g. through use of anticonvulsants (Booth & Evans 2004))). However, each may contribute to CP prevention through reducing the likelihood or severity of brain injury, and thus of long-term neurodevelopmental sequelae.

Research question: What is the current evidence regarding antenatal, intrapartum and neonatal preventive interventions for cerebral palsy?

Recognising that risk factors and causes of CP differ, there is a need to systematically consider all potentially relevant interventions for their ability to contribute to prevention. With increasing numbers of randomised controlled trials (RCTs) and the explosion of systematic reviews, 'wading through' available evidence can be challenging and overwhelming (Hartling, Vandermeer & Fernandes 2014; Hunt et al. 2018; Lunny et al. 2017). Overviews or 'umbrella reviews' of interventions for CP prevention could provide a higher level synthesis of the plethora of potential preventive interventions. To our knowledge, no 'overviews' have brought together the evidence around interventions for CP prevention from Cochrane reviews together into coherent documents to be used by researchers, funding bodies, policy makers, clinicians and consumers to aid decision making and evidence implementation.

Challenges of assessing preventive strategies for cerebral palsy

Despite the recognised potential for a range of antenatal, intrapartum and neonatal interventions to alter CP risk, there is evidence that only a minority of RCTs assessing these interventions are able to report on long-term neurodevelopmental health outcomes, including CP (Murray, Stock & Norman 2017). For example, although various strategies for preterm birth prevention exist (such as

progesterone, cervical cerclage or pessaries, tocolytics and antibiotics), there is little evidence reporting on the long-term outcomes of these strategies. Very few RCTs of preterm birth prevention report long-term follow up to two years of age, and even fewer beyond that time point (Murray, Stock & Norman 2017).

In a systematic review of 249 maternal and perinatal intervention RCTs that were designed to improve neonatal outcomes, 209 (84%) did not perform long-term follow up beyond the initial hospital discharge (Teune et al. 2013). When longer-term follow up was conducted (40 RCTs, 16%), an adequate power calculation for longer-term child outcomes was rarely reported (six RCTs, 15%), and commonly, not all eligible children were approached or included for follow up (rates varied from 11% to 100%) (Teune et al. 2013). Methods used for follow up also differed across RCTs; although 28 of the 40 RCTs assessed childhood neurodevelopment, some used questionnaire(s) only, others assessment(s) only, and some a combination. In a further review of 22 Cochrane systematic reviews of interventions in babies at risk of CP, 'neurodevelopmental outcomes' (e.g. CP, blindness, deafness, intellectual impairment) were reported to be the second most frequent review outcomes of interest (Hines et al. 2015). However, only a minority of the 203 included RCTs (22, 11%) were able to report these data (Hines et al. 2015). This review concluded that "[RCTs] did not routinely collect the long-term data required to provide information on CP as an outcome. This has resulted in lost opportunities for gathering more definitive answers from studies of the highest level of evidence about treatment effectiveness" (Hines et al. 2015).

While follow up rates of maternal perinatal RCTs have been low and relatively stable (Teune et al. 2013), there has been increasing acknowledgement of the importance of assessing longer-term outcomes, including CP (Doyle & Saigal 2009; van 't Hooft et al. 2016). In a systematic review (conducted almost two decades ago) assessing choice of primary outcomes for interventions for preterm birth prevention, none of the 103 included RCTs or 33 included systematic reviews reported long-term neurodevelopmental morbidity (including CP), as a primary outcome (Zhang & Schmidt 2001). However, in a recent core outcome set for studies evaluating preterm birth prevention, developed with international multidisciplinary involvement, 'late neurodevelopmental morbidity' was one of 13 maternal and neonatal core outcomes specified (van 't Hooft et al. 2016).

The challenges of long-term follow up are numerous and well recognised. The actual costs of conducting follow up assessments of children are high, and increase with the ages of the children (Doyle et al. 2015). These costs are much higher than researchers commonly request or are awarded. For example, while approximately A$400-500 per participant may be budgeted for two year paediatric and psychological assessments in a follow up study, the average staff costs alone have been estimated at in excess of A$700 (Doyle et al. 2015). When funded, there are further hurdles to follow up, including families declining to participate or non-attendance following consent (Teune et al. 2013). Failure to attend follow up appointments is common, leading to further costs associated with employing staff where assessments do not occur and re-booking appointments. Travel to other locations, such as children's homes or schools for assessments, to improve follow up rates, adds further expense (Doyle et al. 2015). However, children most difficult to follow up are those with, on average, poorer neurodevelopmental outcomes (Callanan et al. 2001; Doyle et al. 2018), and thus high follow up rates are crucial. When follow up is conducted, methods of examination, ages at assessments, and outcome definitions vary within and between RCTs (Hines et al. 2015; Teune et al. 2013). This creates further hurdles in the meaningful evaluation of preventive strategies for adverse neurodevelopmental outcomes, including CP.

Cerebral palsy registries for preventive research

With increasing obstacles of long-term outcome assessment, there is growing interest in the use of alternative strategies to follow up children from maternal perinatal intervention RCTs. One potential approach is linkage of RCT data to routine/administrative datasets or disease-specific registries (McCord et al. 2018), such as CP registries. While use of such data may present hurdles, including practical (regulatory and ethical), and methodological (dataset) barriers, there are great potential benefits, particularly surrounding feasibility – reducing time, resources and thus costs (McCord et al. 2018). A recent scoping review of long-term follow up by linkage to routinely collected data,

with literature searches spanning 1945 to 2016, identified only 133 RCTs utilising this approach (Fitzpatrick et al. 2018). Five (4%) of the 133 original RCTs assessed interventions in pregnant women or neonates; none reported on child neurodevelopment, including CP. The review concluded that "Against a background of more than 20 000 randomized trials registered each year… a small number of reports of trials that had been extended by linkage to registry and administrative data to evaluate long-term outcomes of trial interventions [were identified]…Trial extension by linkage to routinely collected data is a versatile, underused approach that may add critical insights beyond those of the original trial. Some beneficial and harmful outcomes of interventions are captured only in the extension phase of randomized trials" (Fitzpatrick et al. 2018).

In an international survey of 27 CP registries or surveillance systems from 11 countries across three geographical regions (Australia, Europe and North America), all reported the key aim of being a 'resource for CP research', including "identifying CP as a long term outcome" (Goldsmith et al. 2016). Of current research themes being investigated by the registers/surveillance systems, 'the evaluation of interventions' was reported by 40% (Goldsmith et al. 2016).

The Australian CP Register (ACPR) is an electronic database, established in 2008, and securely uploaded from each state and territory CP registry (ACPR Group 2018). This includes data from long-standing CP registries in Western Australia (established in 1979), Victoria (1987) and South Australia (1998), and newer (as recently as 2006) registries in New South Wales/Australian Capital Territory, Queensland, Tasmania, and the Northern Territory. To be included on the ACPR, a child's motor impairment must fulfil criteria contained in the definitional elements for CP (Rosenbaum et al. 2007; SCPE 2000). Children's CP is 'confirmed' when they reach five years of age. Where new information becomes available, cases may be updated leading to inclusion or exclusion. Along with monitoring the incidence and prevalence of CP, one of the ACPR's stated aims is to facilitate the evaluation of preventive strategies (ACPR Group 2018).

Research question: Can a nationwide cerebral palsy registry be used for long-term randomised trial follow up?

There are lost opportunities to determine the effects of maternal and perinatal interventions on CP, and a need to explore other strategies to facilitate RCT follow up. To date, data linkage of a large RCT with the ACPR for childhood CP follow up has not been conducted. The Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO_4) was a multi-centred RCT assessing magnesium sulphate prior to very preterm birth, for preventing paediatric mortality and CP (as is discussed further below).

The antenatal magnesium sulphate for fetal neuroprotection research cycle: closing the research gaps

Early signs of promise: observational studies

Two landmark observational studies published in the 1990s provided the first descriptions of an association between in utero exposure to magnesium sulphate and a reduced risk of perinatal brain injury and CP (Kuban et al. 1992; Nelson & Grether 1995). Kuban and colleagues conducted a prospective cohort study (449 babies born less than 1,501 grams), to test the hypothesis that babies born to mothers with pre-eclampsia were at a reduced risk of IVH (Kuban et al. 1992). In an unexpected finding, antenatal magnesium sulphate was associated with a reduced risk of germinal matrix haemorrhage (GMH)-IVH: 18.9% (68/359) of babies born to mothers who had not received magnesium sulphate developed GMH-IVH, compared with only 4.4% (4/90) of babies born to mothers who had received magnesium sulphate (Kuban et al. 1992). In a later retrospective case-control study (881 babies born less than 1,500 grams), Nelson and Grether assessed whether antenatal exposure to magnesium sulphate (indicated for pre-eclampsia or tocolysis) was associated with a reduced risk of CP (Nelson & Grether 1995). The 'control' children (without a CP diagnosis) were significantly more likely to have been exposed to antenatal magnesium sulphate than the

'cases' (children with CP) (36.0% vs. 7.1%); the odds ratio (OR 0.14; 95% CI 0.05 to 0.51) suggested a substantial protective effect (Nelson & Grether 1995).

Many subsequent observational studies have supported the potential neuroprotective effects of antenatal magnesium sulphate, demonstrating reductions in the risk of PVL (FineSmith et al. 1997; Wiswell et al. 1996), IVH (Wiswell et al. 1996), CP (Boyle et al. 2000; Grether et al. 1996; Hauth et al. 1995; Matsuda et al. 2000; Schendel et al. 1996) and perinatal mortality (Grether et al. 1998). Inconsistencies have however existed, with a number of studies not reporting benefits for IVH (Canterino et al. 1999; Kimberlin et al. 1998; Leviton et al. 1997; Paneth et al. 1997; Weintraub et al. 2001), CP (Boyle et al. 2000; Grether et al. 2000; O'Shea, Klinepeter & Dillard 1998; Paneth et al. 1997; Wilson-Costello et al. 1998), or mortality (Kimberlin et al. 1998). Encouragingly, in a systematic review and meta-analysis of 11 observational studies (five retrospective cohort studies and six case-control studies), reduced risks of mortality (risk ratio (RR) 0.73, 95% CI 0.61 to 0.89; five studies, 2,796 children) and CP (OR 0.64, 95% CI 0.47 to 0.89; four studies, 913 children) for children following antenatal magnesium sulphate were shown (Wolf et al. 2012).

Five randomised controlled trials and a Cochrane review

Due to the limitations and discrepancies of findings from previous observational studies, a need to establish reliable evidence, through the conduct of RCTs, was realised. From 1995 to 2004, five placebo-controlled RCTs including a total of 6,145 babies were conducted, testing the hypothesis that antenatal magnesium sulphate reduces the risk of perinatal brain injury, CP, and mortality in preterm born children (Crowther et al. 2003; Magpie Trial Follow-Up Study Collaborative Group 2007; Marret et al. 2008; Mittendorf et al. 2002; Rouse et al. 2008). The primary aim of four RCTs, (ACTOMgSO_4 (led by researchers at The University of Adelaide and The University of Melbourne) (Crowther et al. 2003); Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) (Rouse et al. 2008); Magnesium and Neurologic Endpoints Trial (MagNET) (Mittendorf et al. 2002); Prevention of Cerebral Palsy by Magnesium Sulphate (PREMAG) (Marret et al. 2008; Marret et al. 2007)) was fetal neuroprotection, although one RCT (MagNET (Mittendorf et al. 2002)) had a second tocolytic arm. The primary aim of the fifth RCT (Magnesium Sulphate for Prevention of Eclampsia (MAGPIE) (Altman et al. 2002)) was the prevention of eclampsia, however long-term outcomes were reported in the follow up study (Magpie Trial Follow-Up Study Collaborative Group 2007). There was diversity in the inclusion criteria for the RCTs, and in the antenatal magnesium sulphate regimens assessed (summarised in Table 2).

Table 2: Characteristics of RCTs assessing antenatal magnesium sulphate for fetal neuroprotection

RCT	Participants	Magnesium sulphate regimen(s)
MagNET (Mittendorf et al. 2002) 1995-1997 USA (single centre)	149 women randomised 25-33 weeks' GA; singleton or twins; in PTL; cervical dilatation > 4 cm (NP arm); cervical dilatation ≤ 4 cm (T arm)	4 g IV 'bolus' LD; no MD; no repeat dosing (NP arm); 4 g IV 'bolus' LD; 2-3 g/hour IV MD; no repeat dosing (T arm)
ACTOMgSO$_4$ (Crowther et al. 2003) 1996-2000 Australia and New Zealand (16 centres)	1,062 women randomised < 30 weeks' GA; singleton or higher order pregnancies; delivery expected within 24 hours	4 g IV LD (20 minutes); 1 g/hour IV MD until birth or 24 hours whichever came first; no retreatment
PREMAG (Marret et al. 2008; Marret et al. 2007) 1997-2003 France (13 centres)	573 women randomised < 33 weeks' GA; singleton, twins, or triplets; delivery planned or expected within 24 hours	4 g IV LD (30 minutes); no MD; no retreatment
BEAM (Rouse et al. 2008) 1997-2004 USA (20 centres)	2,241 women randomised 24 to < 32 weeks' GA; singleton or twins; high risk for spontaneous delivery: PPROM, PTL (dilatation 4-8 cm) or indicated preterm delivery within 2-24 hours	6 g IV LD (20-30 minutes); 2 g/hour IV MD until birth or 12 hours whichever came first; retreatment: if < 6 hours had transpired MD resumed; if ≥ 6 hours had transpired additional LD given
MAGPIE (Altman et al. 2002; Magpie Trial Follow-Up Study Collaborative Group 2007) 1998-2001 International (33 countries, 175 centres)	1,544 women randomised (subset randomised < 37 weeks' GA) Undelivered; singleton or higher order pregnancies; pre-eclampsia; uncertainty whether to use magnesium sulphate	4 g IV LD (10-15 minutes); MD of either 1 g/hour IV for 24 hours or 5 g/4 hours IM for 24 hours; no retreatment

Abbreviations: ACTOMgSO$_4$: Australasian Collaborative Trial of Magnesium Sulphate; BEAM: Beneficial Effects of Antenatal Magnesium Sulfate; g: gram; GA: gestational age; IM: intramuscular; IV: intravenous; LD: loading dose; MagNET: Magnesium and Neurologic Endpoints Trial; MAGPIE: Magnesium Sulphate for Prevention of Eclampsia; MD: maintenance dose; NP: neuroprotective; PREMAG: Prenatal Magnesium Sulfate for Neuroprotection in Preterm Infants; PPROM: preterm premature rupture of the membranes; PTL: preterm labour; RCT: randomised controlled trial; T: tocolytic; USA: United States of America

The primary and secondary outcomes of the five RCTs included death, and varying manifestations of neurologic injury, including CP. Considering the outcomes of death, CP, or a composite measure of death or CP, a number of the RCTs reported a possible reduction in the risk of CP (Crowther et al. 2003; Magpie Trial Follow-Up Study Collaborative Group 2007; Marret et al. 2008), and death or CP (Crowther et al. 2003; Marret et al. 2008; Rouse et al. 2008), for preterm born children exposed to magnesium sulphate. BEAM was the only RCT to individually show a statistically significant reduction in the risk of CP (RR 0.59, 95% CI 0.40 to 0.85) (Rouse et al. 2008).

In the meta-analysis of the RCTs in the 2009 Cochrane systematic review, 'Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus,' magnesium sulphate administered specifically with a neuroprotective intent, was shown to substantially decrease the risk of death or CP for preterm children (RR 0.85, 95% CI 0.74 to 0.98; four RCTs, 4,446 children) (Doyle et al. 2009). Overall magnesium sulphate significantly reduced the risk of CP; a 32% relative risk reduction (RR 0.68, 95% CI 0.54 to 0.87; five RCTs, 6,145 children). This review revealed convincingly the neuroprotective role for magnesium sulphate given to women at risk of preterm birth, reporting that 63 babies (95% CI 44 to 155) would need to be exposed to antenatal magnesium sulphate to benefit one baby by avoiding CP; the corresponding number needed to treat to prevent one preterm baby dying or developing CP was 42 (Doyle et al. 2009). Crucial reassurance was provided, with no increased risk of perinatal mortality observed, opposing earlier concern from the MagNET RCT (Mittendorf et al. 1997).

Subsequent systematic reviews and meta-analyses evaluating antenatal magnesium sulphate for fetal neuroprotection have reached similar conclusions (Conde-Agudelo & Romero 2009; Costantine & Weiner 2009; Zeng et al. 2016). Most recently, in an individual participant data meta-analysis of the aforementioned five RCTs, the benefits of antenatal magnesium sulphate were seen regardless of the reason for preterm birth, with minimal variation in effect across different gestational ages, and treatment regimens (Crowther et al. 2017). Despite this conclusive benefit demonstrated in numerous systematic reviews and meta-analyses, a Trial Sequential Analysis – a statistical method proposed for the purpose of managing the probability of type I (false positive) and type II (false negative) errors primarily arising when meta-analyses are updated (Wetterslev, Jakobsen & Gluud 2017) – suggested that additional data would be valuable to improve precision of results (Huusom et al. 2011). Thus, another RCT of antenatal magnesium sulphate for CP prevention at 24 to 32 weeks' gestation was undertaken; results are awaited following its completion in August 2019 (Huusom et al. 2012; Wolf et al. 2015). Given the uncertainty as to whether the benefits of antenatal magnesium sulphate apply at higher gestational ages, the MAGENTA RCT (Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial, led by The University of Adelaide and The University of Auckland), was also conducted, with completion expected in 2020 (Crowther et al. 2013b).

In a cost-effectiveness analysis, using multiple decision tree models and probabilistic sensitivity analyses, administration of magnesium sulphate for fetal neuroprotection to women at imminent risk of very preterm birth (at less than 32 weeks' gestation) was shown to be a cost-effective strategy from a societal perspective, and likely from a health system perspective (Bickford et al. 2013). Health system and societal savings for each quality-adjusted life year gained were estimated to be C$2,242 and C$112,602 respectively, while estimated savings for each case of CP averted were C$30,942 and C$1,554,198 respectively (in 2011) (Bickford et al. 2013). A recent systematic review of economic studies of interventions for CP confirmed "The economic case for administration of magnesium sulfate for imminent preterm birth is compelling, achieving both health gain and cost savings" (Shih et al. 2018).

As there is evidence to suggest that early childhood assessments do not always detect CP, and that later assessments may facilitate diagnoses, to date, two of the five RCTs have reported on longer-term follow up of children to school age. At a mean age of 11 years (range 7 to 14), 431 (73%) children eligible for follow up from PREMAG were assessed using a parent-completed neuropsychomotor developmental questionnaire (Chollat et al. 2014). Though no clear differences were observed between groups, rates of a number of outcomes including motor dysfunction or death, behavioural disorders, cognitive difficulties, school grade repetition and education services were lower in children born to mothers who received magnesium sulphate (Chollat et al. 2014). The childhood follow up of ACTOMgSO_4 assessed outcomes at school age (mean 8.4 years (standard deviation (SD): 1.0; range 6 to 11)) and involved a series of blinded paediatric, motor, and psychological assessments, and parent and teacher questionnaires (Doyle et al. 2014). Likewise, no clear differences in neurological, cognitive, behavioural, growth or functional outcomes were observed between groups; a similar rate of CP was shown (Doyle et al. 2014). It was however, only possible to assess 63% of children (due to sites not participating in the follow up study, families being lost to follow up, or declining to participate in the follow up assessments) (Doyle et al. 2014).

While an absence of clear longer-term benefits (or harms) was observed in these two RCTs, both had sub-optimal follow up rates. Ideally, further RCTs will report longer-term follow up allowing pooling of school-age data.

Guidelines and implementation studies

Following the compelling evidence from RCTs and systematic reviews showing that antenatal magnesium sulphate is an effective neuroprotective agent for the preterm fetus, in many countries, including Australia and New Zealand (led by researchers at The University of Adelaide) (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010), Canada (Magee et al. 2011; Magee et al. 2019) the United States (ACOG Committee on Obstetric Practice & SMFM 2010, 2016), Ireland (RCPI & Directorate of Strategy and Clinical Care Health Service Executive 2013), Belgium (KCE et al. 2014), the United Kingdom (NCC-WCH 2015) and France (Sentilhes et al. 2017) clinical practice guidelines and/or opinion papers have provided recommendations for the use of this therapy. In its 2015 recommendations on interventions to improve preterm birth outcomes, the World Health Organization (WHO) provided a strong recommendation supporting the use of magnesium sulphate for women at risk of imminent very preterm birth for prevention of CP (WHO 2015). A recent systematic review and critical appraisal of guidelines for antenatal magnesium sulphate for fetal neuroprotection clearly showed that all seven identified guidelines supported the use of this therapy for CP prevention (Jayaram et al. 2019).

As systematic reviews and meta-analyses have not supported a particular upper gestational age or dosing regimen (Crowther et al. 2017; Doyle et al. 2009), guidance has varied. In the absence of a clear 'optimal dose,' the lower dose regimens that were employed in RCTs (Crowther et al. 2003; Marret et al. 2007), have been commonly recommended. Table 3 summarises protocols for the administration of antenatal magnesium sulphate according to clinical practice guidelines (adapted from (Chollat & Marret 2018) and (Jayaram et al. 2019)).

Table 3: Summary of guideline recommendations for antenatal magnesium sulphate for fetal neuroprotection

Guideline	Released	GA	Magnesium sulphate regimen
Australia and New Zealand (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010)	2010	< 30 weeks	4 g LD; 1 g/hour MD for 24 hours or until birth; retreatment possible
USA (ACOG Committee on Obstetric Practice & SMFM 2010, 2016)	2010 (updated in 2016)	< 32 weeks	"Physicians… should develop specific guidelines regarding… treatment regimens… in accordance with one of the larger trials"
Canada (Magee et al. 2011; Magee et al. 2019)	2011 (updated in 2019)	< 34 weeks	4 g LD; with or without 1 g/hour MD for 24 hours or until birth; insufficient evidence to recommend retreatment
Ireland (RCPI & Directorate of Strategy and Clinical Care Health Service Executive 2013)	2013	< 32 weeks	4 g LD; 1 g/hour MD for 24 hours or until birth; retreatment possible
Belgium (KCE et al. 2014)	2014	< 32 weeks	IV for 24 hours maximum (LD and MD not specified); retreatment recommendation not specified
United Kingdom (NCC-WCH 2015)	2015 (updated in 2019)	< 30 weeks (consider < 34 weeks)	4 g LD; 1 g/hour MD for 24 hours or until birth; retreatment recommendation not specified
WHO (WHO 2015)	2015	< 32 weeks	Insufficient evidence to recommend regimen
France (Sentilhes et al. 2017)	2017	< 32 weeks	4 g LD; 1 g/hour MD for 12 hours or until birth; retreatment recommendation not specified

Abbreviations: ACOG: American College of Obstetrician and Gynecologists; g: gram; GA: gestational age; IV: intravenous; KCE: Belgian Health Care Knowledge Centre; LD: loading dose; MD: maintenance dose; NCC-WCH: National Collaborating Centre for Women's and Children's Health; RCPI: Royal College of Physicians of Ireland; SMFM: Society for Maternal-Fetal Medicine; USA: United States of America; WHO: World Health Organization

It is recognised that "the transfer of valid and relevant research findings into routine practice is unpredictable and tends to be slow and haphazard" (Penney & Foy 2007). Thus, to support the implementation of clinical practice guidelines, in a number of countries, including Australia (WISH: Working to Improve Survival and Health for babies born very preterm, led by researchers at The University of Adelaide) (Crowther et al. 2013a), Canada (MAG-CP: MAGnesium sulphate for fetal neuroprotection to prevent Cerebral Palsy) (Teela et al. 2015), and the United Kingdom (PReCEPT: PREventing Cerebral palsy in Pre Term labour) (Burhouse et al. 2017), knowledge translation projects have been undertaken.

In the last decade, since publication of clinical practice guidelines, and with support of knowledge translation projects, widespread implementation of antenatal magnesium sulphate for fetal neuroproection and CP prevention has been observed. Variable uptake, however, continues to be demonstrated in retrospective and prospective audit and cohort studies, including from centres in Australia (Bain et al. 2013a; Ow et al. 2012; Parker, Sethna & Kent 2017; Siwicki et al. 2015) and New Zealand (Pang 2017; Tan & Groom 2015), the United States (Gibbins et al. 2013), Canada (De Silva et al. 2018), France (Bouet et al. 2015), and throughout Europe (Wolf et al. 2017); and in

surveys of health professionals/centres, including from Australia and New Zealand (Bain et al. 2013b; Bousleiman et al. 2015; De Silva et al. 2015; Gatman, May & Crowther 2019; Middleton et al. 2013), the United States (Bousleiman et al. 2015) and Canada (De Silva et al. 2015).

Maternal adverse effects of antenatal magnesium sulphate: a systematic review

Given the extensive use of antenatal magnesium sulphate in obstetrics, to prevent or treat pre-eclampsia (beneficial) (Duley et al. 2010a), for tocolysis for women in and following threatened preterm labour (not beneficial) (Crowther et al. 2014), and most recently, for fetal neuroprotection and CP prevention (beneficial) (Doyle et al. 2009), the potential adverse effects for women are well known.

High-quality evidence regarding maternal adverse effects of antenatal magnesium sulphate can be drawn from a systematic review, including 143 publications (21 RCTs, 14 non-randomised comparative studies, 32 case series, and 74 reports of individual cases) (Bain, Middleton & Crowther 2013). Reassuringly, the review showed that antenatal magnesium sulphate was not associated with increased risks of maternal death, cardiac arrest or respiratory arrest; individual case reports, did, however support an association between iatrogenic overdose of magnesium sulphate and life-threatening consequences (Bain, Middleton & Crowther 2013). Appropriate administration was shown to increase the risk of 'any adverse maternal effects' (minor) (RR 4.62, 95% CI 2.42 to 8.83; four RCTs, 13,322 women), and treatment cessation due to adverse effects (minor) (RR 2.77, 95% CI 2.32 to 3.30; five RCTs, 13,666 women) (Bain, Middleton & Crowther 2013). This review concluded that for each antenatal indication for use, further RCTs designed to determine optimal regimens (aimed at achieving maximal effectiveness with minimal adverse effects) may be beneficial, and called for vigilance in the use of this therapy, in order to ensure women's safety (Bain, Middleton & Crowther 2013).

A further integrative review, including 24 studies (14 RCTs, nine prospective cohort studies, and one case-control study), assessed maternal adverse effects of magnesium sulphate, however specifically focused on treatment for pre-eclampsia or eclampsia in low- and middle-income countries (Smith et al. 2013). This review similarly revealed reassuring findings regarding safety, demonstrating infrequent occurrences of the most severe adverse effects (Smith et al. 2013). A more recent systematic review, focused on safety reporting in 60 RCTs in women with pre-eclampsia (23 assessing magnesium sulphate), demonstrated the regular omission of adverse effect data (Duffy et al. 2018). Only one of the 20 RCTs reporting serious adverse reactions to magnesium sulphate, and none of the 15 RCTs reporting mild adverse reactions to magnesium sulphate, were judged to have adequately presented these data (Duffy et al. 2018).

Potential neonatal adverse effects of antenatal magnesium sulphate

With the increased, widespread use of antenatal magnesium sulphate for fetal neuroprotection, concern has been raised about potential unintended adverse neonatal outcomes. In an evaluation of barriers and enablers to implementing antenatal magnesium sulphate in Australia and New Zealand (as part of the aforementioned WISH Project), the uncertainty surrounding adverse effects for neonates was specifically raised by health professionals, particularly neonatologists, as a potential barrier to increased use (Bain et al. 2015). In an assessment of health professionals' attitudes towards high-risk obstetric medications in the United States, the fear of adverse effects with antenatal magnesium sulphate was also noted as a barrier to administration (Bousleiman et al. 2015).

Magnesium has fundamental roles in many cellular process (such as gating of calcium channels; muscle contraction; neuronal activity; control of vasomotor tone; cardiac excitability; and neurotransmitter release) (Fawcett, Haxby & Male 1999), and thus above normal magnesium concentrations (associated with magnesium sulphate therapy), could plausibly be associated with fetal or neonatal adverse effects. Magnesium is known to cross the placenta readily, with fetal and neonatal serum concentrations correlated with maternal serum magnesium concentrations (Sherwin et al. 2014), and/or total maternal dose of magnesium sulphate received (Borja-Del-Rosario et al. 2014; Garcia Alonso et al. 2018).

In the Cochrane systematic reviews assessing magnesium sulphate for pre-eclampsia (Duley et al. 2010a), fetal neuroprotection (Doyle et al. 2009), and preterm labour tocolysis (Crowther et al. 2014), no clear increased risks of adverse neonatal outcomes with antenatal magnesium sulphate were shown, however a possible increase in death (fetal, neonatal or infant) with prolonged use for tocolysis was observed (RR 4.56, 95% CI 1.00 to 20.86; two RCTs, 257 babies) (Crowther et al. 2014). These reviews were, however, restricted to assessing RCT evidence, and a limited number of pre-specified outcomes.

Increasingly observational studies have reported risks of adverse neonatal outcomes with antenatal magnesium sulphate, necessitating further evaluation. For example, a retrospective cohort study (of 6,654 women and their babies) observed increasing maternal serum magnesium concentrations (given for pre-eclampsia) to be associated with lower one and five-minute Apgar scores, and higher risks of intubation in the delivery room, admission to special care nursery and neonatal hypotonia (Abbassi-Ghanavati et al. 2012). Two retrospective cohort studies (of 160 neonates born at less than 28 weeks gestation; and 954 neonates born 500 to 1,000 grams), suggested antenatal magnesium sulphate exposure (given for pre-eclampsia or for tocolysis) was associated with an increased risk of neonatal patent ductus arteriosus (del Moral et al. 2007; Katayama et al. 2011). Further, a retrospective cohort study (of 155 neonates born less than 1,000 grams) demonstrated an association between magnesium sulphate (given for fetal neuroprotection) and spontaneous intestinal perforation (Rattray et al. 2014). A number of studies (including retrospective cohort studies and case reports) have shown an association between prolonged magnesium sulphate exposure (given for tocolysis) and abnormal neonatal bone metabolism (Yokoyama et al. 2010), and rarely, bone fracture at birth (Wedig et al. 2006).

Recently, a systematic review (including two RCTs and 16 observational studies) summarised the effects of antenatal magnesium sulphate for treating pre-eclampsia, fetal neuroprotection, or preterm labour tocolysis specifically on fetal heart rate (Nensi et al. 2014). This review suggested a small negative effect on fetal heart rate, variability and accelerative pattern, “not sufficient clinically to warrant medical intervention” (Nensi et al. 2014).

Research question: Is antenatal magnesium sulphate associated with adverse neonatal outcomes?

There is current uncertainty surrounding the potential for unintended neonatal adverse effects following antenatal magnesium sulphate treatment, warranting further evaluation. To date, a systematic review of all available evidence surrounding antenatal magnesium sulphate and adverse neonatal outcomes has not been conducted. Implementation of magnesium sulphate for CP prevention can be strengthened, and safety improved, if clinical practice guidelines and their recommendations are based on such knowledge.

Summary of literature review and identified research questions

CP is the most common physical disability in childhood, affecting approximately one in 500 babies worldwide, with devastating long-term consequences. For 94% of individuals with CP, their brain injury occurred during pregnancy, labour, or the first 28 days of life; and there are diverse risk factors and aetiologies. Magnesium sulphate is one of the first interventions shown in RCTs and systematic reviews to prevent CP when given to women prior to very preterm birth.

This literature review has identified the following research gaps that need to be addressed:

1. What is the current evidence regarding antenatal, intrapartum and neonatal preventive interventions for CP?

It is important to bring together existing evidence surrounding all potential antenatal, intrapartum and neonatal preventive interventions for CP, to assist researchers and funding bodies, policy makers, clinicians and families in their decision making.

2. Can a nationwide CP registry be used for long-term RCT follow up?

It is imperative to explore alternative strategies by which to assess the impact of maternal perinatal interventions on CP, such as through linkage of RCT and CP registry data.

3. Is antenatal magnesium sulphate associated with adverse neonatal outcomes?

It is essential to address a research gap surrounding antenatal magnesium sulphate for CP prevention, to aid ongoing research translation efforts. Specifically, a systematic evaluation of whether antenatal magnesium sulphate exposure is associated with unintended adverse outcomes for neonates is required.

Thesis aims

To address these identified research gaps, the specific aims of this thesis are:

1. To summarise and interpret the evidence from Cochrane systematic reviews regarding the effects of antenatal and intrapartum interventions for preventing CP (Chapter 2).

2. To summarise and interpret the evidence from Cochrane systematic reviews regarding effects of neonatal interventions for preventing CP (Chapter 3).

3. To link data from a large maternal perinatal RCT (ACTOMgSO_4) with a nationwide CP registry (ACPR) to identify children with CP (Chapter 4).

4. To conduct a comprehensive systematic review to assess whether antenatal magnesium sulphate is associated with perinatal death and other adverse neonatal outcomes (Chapter 5).

CHAPTER 2: ANTENATAL AND INTRAPARTUM INTERVENTIONS FOR PREVENTING CEREBRAL PALSY: AN OVERVIEW OF COCHRANE SYSTEMATIC REVIEWS

Statement of authorship

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Principal author

Principal author (candidate)	Emily Shepherd		
Contribution to the paper	Conception and design of the overview, including first draft of protocol, and revisions. Conduct of the overview, including conducting searches, assessing review eligibility, data extraction, quality assessment, data entry, analysis and interpretation. First draft of overview manuscript and ongoing revisions of manuscript.		
Overall percentage (%)	75%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	10/10/2019

Co-author contributions

By signing the 'Statement of authorship', each author certified that:
The candidate's stated contribution to the publication is accurate (as detailed above);
Permission is granted for the candidate to include the publication in the thesis;
The sum of all co-authors is equal to 100% less the candidate's stated contribution.

Name of co-author	Rehana A Salam		
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Contribution to the paper	Input into conception and design of the overview, including critical revision of the protocol. Input into interpretation of the overview, including critical revision of the overview manuscript.		
Signature		Date	10/10/2019

Cochrane Database of Systematic Reviews

Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews (Review)

Shepherd E, Salam RA, Middleton P, Makrides M, McIntyre S, Badawi N, Crowther CA

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TABLE OF CONTENTS

[Overview of Reviews]

Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews

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ABSTRACT

Background

Cerebral palsy is an umbrella term encompassing disorders of movement and posture, attributed to non-progressive disturbances occurring in the developing fetal or infant brain. As there are diverse risk factors and causes, no one strategy will prevent all cerebral palsy. Therefore, there is a need to systematically consider all potentially relevant interventions for their contribution to prevention.

Objectives

To summarise the evidence from Cochrane reviews regarding the effects of antenatal and intrapartum interventions for preventing cerebral palsy.

Methods

We searched the *Cochrane Database of Systematic Reviews* on 7 August 2016, for reviews of antenatal or intrapartum interventions reporting on cerebral palsy. Two authors assessed reviews for inclusion, extracted data, assessed review quality, using AMSTAR and ROBIS, and quality of the evidence, using the GRADE approach. We organised reviews by topic, and summarised findings in text and tables. We categorised interventions as effective (high-quality evidence of effectiveness); possibly effective (moderate-quality evidence of effectiveness); ineffective (high-quality evidence of harm or of lack of effectiveness); probably ineffective (moderate-quality evidence of harm or of lack of effectiveness); and no conclusions possible (low- to very low-quality evidence).

Main results

We included 15 Cochrane reviews. A further 62 reviews pre-specified the outcome cerebral palsy in their methods, but none of the included randomised controlled trials (RCTs) reported this outcome. The included reviews were high quality and at low risk of bias. They included 279 RCTs; data for cerebral palsy were available from 27 (10%) RCTs, involving 32,490 children. They considered interventions for: treating mild to moderate hypertension (two) and pre-eclampsia (two); diagnosing and preventing fetal compromise

in labour (one); preventing preterm birth (four); preterm fetal maturation or neuroprotection (five); and managing preterm fetal compromise (one). Quality of evidence ranged from very low to high.

Effective interventions: high-quality evidence of effectiveness

There was a reduction in cerebral palsy in children born to women at risk of preterm birth who received magnesium sulphate for neuroprotection of the fetus compared with placebo (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.54 to 0.87; five RCTs; 6145 children).

Probably ineffective interventions: moderate-quality evidence of harm

There was an increase in cerebral palsy in children born to mothers in preterm labour with intact membranes who received any prophylactic antibiotics versus no antibiotics (RR 1.82, 95% CI 0.99 to 3.34; one RCT; 3173 children). There was an increase in cerebral palsy in children, who as preterm babies with suspected fetal compromise, were born immediately compared with those for whom birth was deferred (RR 5.88, 95% CI 1.33 to 26.02; one RCT; 507 children).

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness

There was no clear difference in the presence of cerebral palsy in children born to women at risk of preterm birth who received repeat doses of corticosteroids compared with a single course (RR 1.03, 95% CI 0.71 to 1.50; four RCTs; 3800 children).

No conclusions possible: low- to very low-quality evidence

Low-quality evidence found there was a possible reduction in cerebral palsy for children born to women at risk of preterm birth who received antenatal corticosteroids for accelerating fetal lung maturation compared with placebo (RR 0.60, 95% CI 0.34 to 1.03; five RCTs; 904 children). There was no clear difference in the presence of cerebral palsy with interventionist care for severe pre-eclampsia versus expectant care (RR 6.01, 95% CI 0.75 to 48.14; one RCT; 262 children); magnesium sulphate for pre-eclampsia versus placebo (RR 0.34, 95% CI 0.09 to 1.26; one RCT; 2895 children); continuous cardiotocography for fetal assessment during labour versus intermittent auscultation (average RR 1.75, 95% CI 0.84 to 3.63; two RCTs; 13,252 children); prenatal progesterone for prevention of preterm birth versus placebo (RR 0.14, 95% CI 0.01 to 3.48; one RCT; 274 children); and betamimetics for inhibiting preterm labour versus placebo (RR 0.19, 95% CI 0.02 to 1.63; one RCT; 246 children).

Very low-quality found no clear difference for the presence of cerebral palsy with any antihypertensive drug (oral beta-blockers) for treatment of mild to moderate hypertension versus placebo (RR 0.33, 95% CI 0.01 to 8.01; one RCT; 110 children); magnesium sulphate for prevention of preterm birth versus other tocolytic agents (RR 0.13, 95% CI 0.01 to 2.51; one RCT; 106 children); and vitamin K and phenobarbital prior to preterm birth for prevention of neonatal periventricular haemorrhage versus placebo (RR 0.77, 95% CI 0.33 to 1.76; one RCT; 299 children).

Authors' conclusions

This overview summarises evidence from Cochrane reviews on the effects of antenatal and intrapartum interventions on cerebral palsy, and can be used by researchers, funding bodies, policy makers, clinicians and consumers to aid decision-making and evidence translation. We recommend that readers consult the included Cochrane reviews to formally assess other benefits or harms of included interventions, including impacts on risk factors for cerebral palsy (such as the reduction in intraventricular haemorrhage for preterm babies following exposure to antenatal corticosteroids).

Magnesium sulphate for women at risk of preterm birth for fetal neuroprotection can prevent cerebral palsy. Prophylactic antibiotics for women in preterm labour with intact membranes, and immediate rather than deferred birth of preterm babies with suspected fetal compromise, may increase the risk of cerebral palsy. Repeat doses compared with a single course of antenatal corticosteroids for women at risk of preterm birth do not clearly impact the risk of cerebral palsy.

Cerebral palsy is rarely diagnosed at birth, has diverse risk factors and causes, and is diagnosed in approximately one in 500 children. To date, only a small proportion of Cochrane reviews assessing antenatal and intrapartum interventions have been able to report on this outcome. There is an urgent need for long-term follow-up of RCTs of interventions addressing risk factors for cerebral palsy, and consideration of the use of relatively new interim assessments (including the General Movements Assessment). Such RCTs must be rigorous in their design, and aim for consistency in cerebral palsy outcome measurement and reporting to facilitate pooling of data, to focus research efforts on prevention.

PLAIN LANGUAGE SUMMARY

Interventions during pregnancy and childbirth for preventing cerebral palsy: an overview of Cochrane reviews

What is the issue?

Cerebral palsy is a term that includes a group of conditions affecting people's ability to move, and is the most common physical disability in childhood. Cerebral palsy is usually due to events before, during, or after childbirth that lead to injury in babies' developing brains. There is no single cause of cerebral palsy. For many children, the cause of cerebral palsy is unclear, however, there are many known risk factors. The biggest risk factor is birth before 37 weeks of pregnancy (preterm birth). Other risk factors for mothers include some medical conditions (including thyroid problems), abnormalities of the placenta, pre-eclampsia (high blood pressure and protein in the urine), and some bacterial and viral infections. For babies, risk factors include congenital and genetic abnormalities, having a low birthweight or growth restricted as a fetus, being a twin or triplet, some infections, and prolonged loss of oxygen during birth.

Why is this important?

As there are different risk factors and causes for cerebral palsy, it is likely that various different interventions (treatments) may be needed to prevent cerebral palsy by reducing risk factors. This overview summarises the evidence about preventing cerebral palsy from Cochrane reviews of interventions during pregnancy and childbirth.

What evidence did we find?

We searched for evidence on 7 August 2016. We identified 15 Cochrane reviews that assessed interventions during pregnancy or childbirth that reported on cerebral palsy, with information from 27 randomised controlled trials involving 32,490 children. The reviews were all high quality, but the quality of the evidence about cerebral palsy ranged from very low to high.

The interventions assessed were for treating mild to moderate hypertension (two reviews), treating pre-eclampsia (two reviews), diagnosing or preventing fetal compromise (when the unborn baby may not be well) during labour (one review), preventing preterm birth (four reviews), maturing or protecting babies' lungs or brains before preterm birth (five reviews), and managing fetal compromise of preterm babies (one review).

We found high-quality evidence that one intervention was effective for cerebral palsy prevention: preterm children born to mothers who received magnesium sulphate before birth were less likely to develop cerebral palsy than children whose mothers received a placebo (five trials, 6145 children).

We found moderate-quality evidence that two interventions were probably ineffective, and could cause harm: (i) children born to mothers who had received antibiotics for preterm labour when their waters had not broken were more likely to develop cerebral palsy than children whose mothers did not receive antibiotics (one trial, 3173 children); and (ii) preterm children who were born immediately when there was suspected fetal compromise were more likely to develop cerebral palsy than those for whom birth was postponed (one trial, 507 children).

We found moderate-quality evidence that there was no clear difference in the chance of children to develop cerebral palsy whether their mothers received one or more courses of corticosteroids before preterm birth (four trials, 3800 children).

There was low-quality evidence as to whether the other interventions prevented, increased, or had no impact on cerebral palsy, although we did find that children born to mothers who received corticosteroids to help mature their lungs before preterm birth were potentially less likely to develop cerebral palsy than those born to mothers who received a placebo (five trials, 904 children).

What does this mean?

We identified one intervention that was effective in preventing cerebral palsy (magnesium sulphate before preterm birth), two that appeared to cause harm (preventive antibiotics for women in preterm labour when their waters have not broken, and immediate birth for preterm babies with suspected compromise), and one that did not appear to make a clear difference (more than one course of corticosteroids before preterm birth). For the other interventions assessed, there was not enough evidence to reach any conclusions. Further good quality randomised controlled trials, assessing interventions that might impact cerebral palsy risk factors, with long-term follow-up to measure cerebral palsy, are needed. We identified over 60 other Cochrane reviews that may provide more information in the future.

BACKGROUND

Description of the condition

Cerebral palsy: definition and prevalence

Cerebral palsy was originally defined by clinical description, at a time when there was little knowledge of causes, risk factors, or pathology. Discussion on the definition and classification was first recorded in English, French, and German medical literature in the nineteenth century; for over 150 years, there has been debate about what the term 'cerebral palsy' actually describes (Morris 2007). Definitions adopted by international cerebral palsy registries have commonly included those proposed by Bax in the 1960s (Bax 1964), Mutch and colleagues in the 1990s (Mutch 1992), and more recently, by Rosenbaum and colleagues (a revised version of Bax 1964): "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems" (Rosenbaum 2007).

Today, cerebral palsy is still a clinical description, but registries and surveillance programmes, such as those in Australia, the United Kingdom, and Europe, highlight five key elements that reflect the core features of cerebral palsy, provided in definitions, and proposed by the Surveillance of Cerebral Palsy in Europe (SCPE): (i) it is an 'umbrella term'; (ii) it is permanent but not unchanging; (iii) it involves a disorder of movement, posture, motor function, or a combination; (iv) it is due to a non-progressive interference, lesion, or abnormality; and (v) the interference, lesion, or abnormality arose in the developing or immature brain (Cans 2000; Mutch 1992; Rosenbaum 2007; Smithers-Sheedy 2014). As cerebral palsy is defined by clinical description, which may change over time, a longer time span for diagnosis is considered useful to confirm that the condition meets the criteria for cerebral palsy, and to accurately describe the motor impairment. Thus, final ascertainment for surveillance programmes across the world range from four to 12 years, with many considering data to be 'complete' at or near five years (Smithers-Sheedy 2014). While average age for diagnosis has been around 18 months, recent evidence has suggested that cerebral palsy may be reliably detected in high-risk infants as early as three to four months post-term age, using tests such as Prechtl's General Movements Assessment and medical resonance imaging (Bosanquet 2013; Morgan 2016).

Cerebral palsy can be described by its motor type and body parts distribution (topography). Primary and secondary motor types include spasticity, dyskinesia, ataxia, and hypotonia, which are determined by a combination of structured neurological and motor assessments, with observations sometimes corroborated by imaging findings (Cans 2000; Rosenbaum 2007; Sanger 2003). Spasticity is the predominant primary motor type. Frequently used terms to describe the topography are hemiplegia (unilateral involvement), diplegia (bilateral involvement), with the lower limbs more affected than the upper limbs, and quadriplegia (bilateral involvement), with the upper limbs more or equally involved. Monoplegia and triplegia are occasionally reported as separate entities, or grouped with hemiplegia and quadriplegia, respectively (Howard 2005; Sankar 2005).

Today, the Gross Motor Function Classification System (GMFCS) is used internationally as the principal way to classify gross motor function (Morris 2004; Palisano 1997; Wood 2000). It describes the gross movement ability of children in one of five ordinal levels, and provides descriptions for each level across five age bands: less than two years; two to four years; four to six years; six to 12 years; 12 to 18 years (Wood 2000). Unlike classifications based on motor type and topography, the GMFCS has been shown to be a valid, reliable, stable, and clinically relevant method for classification, and in conjunction with the Gross Motor Function Measure (GMFM), for prediction (after the age of two) of motor function in cerebral palsy (Palisano 1997; Wood 2000). The Manual Ability Classification System (MACS) provides a method analogous to the GMFCS for assessing the ability of children with cerebral palsy to handle objects (Eliasson 2006), and the Communication Function Classification System (CFCS) assists in evaluating the communication capacity in real-life situations for children with cerebral palsy (Hidecker 2011). One can draw a comprehensive picture of functional performance in daily life for individuals with cerebral palsy by using the GMFCS, MACS, and CFCS together, to inform both research and clinical practice (Compagnone 2014; Hidecker 2012).

Despite variation in definitions and classifications of cerebral palsy, there is wide agreement that it is the most common physical disability in childhood. In a recent meta-analysis of 19 studies, the global pooled birth prevalence was 2.11 per 1000 live births (95% confidence interval 1.98 to 2.25); a cumulative meta-analysis demonstrated stability in the prevalence over the past 10 years (Oskoui 2013). Similar trends and relative stability of rates over time have been shown in geographical regions "with CP Registers" that have used consistent methods of ascertainment, with most published estimates of total population birth prevalence around two per 1000 live births (Blair 2006). In low- and middle-income countries, birth prevalence estimates have tended to be in a similar range, or higher, but it is difficult to meaningfully compare rates, since very few of these countries use registries or surveillance programmes (Blair 2006; Cans 2000; Colver 2014). However, there is now emerging evidence, including from Australia and Europe,

that birth prevalence and severity of the condition are starting to decline for the first time (Reid 2016; Sellier 2015). Rate variations have also been observed, particularly when stratified by gestational age or birthweight. In the aforementioned meta-analysis, the prevalence was highest in children weighing 1000 to 1499 g at birth (59.18 per 1000 live births), and for children born before 28 weeks of gestation (111.80 per 1000 live births; Oskoui 2013).

Cerebral palsy: causes and risk factors

For approximately 6% of individuals with cerebral palsy, their brain injury is believed to have been acquired during a recognised event at least 28 days after birth and before the age of two to five; commonly, a cerebrovascular accident, spontaneous, associated with surgery or with complications of cardiac defects, or accidental and non-accidental head injuries (ACPR Group 2013). For the remaining 94% of individuals with cerebral palsy, their brain injury is believed to have occurred during the antenatal or the neonatal period of infant development, that is, during pregnancy, or within the first 28 days of life (ACPR Group 2013).

The pathogenesis of such brain injury is complex and multifactorial, with interrelated pathways contributing to cellular dysfunction and death, including accumulation of reactive oxygen species, the release of excitatory amino acids, energy depletion, and apoptosis (Inder 2000; Vexler 2001). There are multiple causes of brain injury, including hypoxia-ischaemia (characterised by reduced oxygen in the blood combined with reduced blood flow to the brain), haemorrhage, infection, maldevelopment, and metabolic derangement (Volpe 2000). Brain hypoxia (deficiency of oxygen) and ischaemia (insufficient blood supply) may lead to different neuropathology in infants born preterm and at term, with cerebral white matter injury predominating in preterm infants, and neuronal cell injury in term infants (Volpe 2000). Injury to the developing brain is known to be associated with long-term sequelae, including cerebral palsy, as well as hearing, sight, speech, and behavioural disorders, seizures, and intellectual disabilities (Vexler 2001).

Preterm birth is one of the principal risk factors for cerebral palsy and associated neurosensory disabilities (Himpens 2008; Oskoui 2013). The degree of prematurity is associated with vulnerability of cerebral white matter, and is predictive of an increasing risk of white matter injury (such as periventricular leukomalacia), and intraventricular haemorrhage (Larroque 2003), established risk factors for the development of cerebral palsy (Saliba 2001). Although preterm birth is acknowledged as a major risk factor for cerebral palsy, with over 40% of individuals with cerebral palsy being born preterm (compared with approximately 8% of the general population), most individuals with cerebral palsy (50% to 60%) are in fact, born at term (ACPR Group 2013).

Studies on possible risk factors for cerebral palsy for preterm- and term-born individuals are abundant (with some risk factors reported more consistently than others). Evidence now suggests that 70% to 80% of cerebral palsy cases are associated with antenatal factors, with birth asphyxia playing a relatively minor role (Blair 1988; Ellenberg 2013; MacLennan 2015). Risk factors, in additional to preterm birth, often reported in the literature include: (a) factors prior to conception, such as: young or advanced maternal age, high parity, nulliparity, a short or long inter-pregnancy interval, a history of stillbirth, multiple miscarriages, neonatal death, or premature birth, family history of cerebral palsy and other genetic predispositions, low socioeconomic status, and pre-existing maternal conditions (e.g. intellectual disability, and epilepsy); (b) factors in early pregnancy, such as: male gender, multiple gestation, congenital malformations or birth defects, and infections (i.e. TORCH complex: **t**oxoplasmosis (parasite), **o**ther infections, **r**ubella, **c**ytomegalovirus, **h**erpes simplex virus); (c) factors during pregnancy, such as: maternal disease (e.g. thyroid disorders), pregnancy complications (e.g. high blood pressure, pre-eclampsia, placenta praevia, placental abruption, and other placental abnormalities), intrauterine infection or inflammation and chorioamnionitis, intrauterine growth restriction, and other precursors to preterm birth; and (d) factors around the time of birth and neonatal period, such as: an acute intrapartum hypoxic event, meconium aspiration, stroke, seizures, hypoglycaemia, jaundice, and infection, along with inborn errors of metabolism (such as glucose-6-phosphate dehydrogenase deficiency), particular syndromes, or chromosomal abnormalities (Jacobsson 2004; McIntyre 2011; McIntyre 2013; Nelson 2008b; Smithers-Sheedy 2014).

In low- and middle-income countries, the causes and risk factors for cerebral palsy are known to differ considerably (Blair 2006). With few survivors of very preterm birth in such countries, common risk factors are birth asphyxia and maternal Rhesus alloimmunisation, or inherited disorders, such as glucose-6-phosphate dehydrogenase deficiency and subsequent bilirubin encephalopathy, and there are much higher proportions of children with postnatally acquired cerebral palsy, particularly associated with postinfectious brain damage following meningitis, septicaemia, and other conditions, such as malaria (Blair 2006; Lagunju 2009).

While a great number of potential risk factors for cerebral palsy have been identified, their commonality is that separately, or in combination, they may lead to injury to the developing brain. A growing body of evidence now suggests that genetic abnormalities may also contribute to the development of cerebral palsy (Moreno-De-Luca 2012; Oskoui 2015; O'Callaghan 2009). Previously, only 1% to 2% of cerebral palsy cases were linked to a causative genetic mutation, but recent studies have shown that up to 14% have single gene mutations and 31% have copy number variations that may be at fault (MacLennan 2015). Possible genetic mutations and variants associated with cerebral palsy are likely to be heterogeneous, but they both trigger pathways (either directly, or in the case of genetic susceptibility, when certain risk factors are present), leading to non-progressive neuropathology associated with motor dysfunction and cerebral palsy (MacLennan 2015). Though there is currently no known cure for cerebral palsy, increas-

ing knowledge of risk factors and causal pathways had increased the hope for the development and implementation of primary preventive strategies: "we are on the move… the vision of prevention and cure no longer seems an unattainable goal" (Badawi 2013).

Cerebral palsy: consequences

Cerebral palsy is the leading cause of physical disability in children. Though traditionally regarded as a paediatric condition, it is now recognised that cerebral palsy is a condition with life-long impact - a 'lifespan condition' - and thus, the outcomes of individuals with cerebral palsy across the life course are considered when planning and directing interventions in childhood (Colver 2014).

Most individuals with cerebral palsy will survive to adulthood, with some studies suggesting life expectancy can be broadly similar to that of the general population if a child reaches adolescence (Colver 2012). For known cases of antenatally- or neonatally-acquired cerebral palsy, the 20-year survival rate has been estimated to be approximately 90%, however, strong associations between increasing motor impairment, severe intellectual impairment, number of severe impairments, and early mortality have been shown (Blair 2001; Hemming 2005; Reid 2012). While a mixed picture in overall survival trends has been presented to date, some improvements in survival have been observed over time for two groups of individuals with cerebral palsy with the most severe disabilities - children who are largely immobile and fed by others, and adults who are dependent on gastrostomy feeding (Strauss 2008).

Today's frequently used definitions importantly acknowledge co-occurring impairments, diseases, and functional limitations, which are common among individuals with cerebral palsy, including hearing, sight, and speech disorders, intellectual disability and epilepsy (Rosenbaum 2007). A recent systematic review estimated, for example, that among children with cerebral palsy, "1 in 2 had an intellectual disability… 1 in 4 could not talk; 1 in 4 had epilepsy; 1 in 4 had a behaviour disorder… 1 in 10 were blind… and 1 in 25 were deaf" (Novak 2012).

Economic studies have estimated lifetime costs of cerebral palsy, including healthcare costs (such as primary health care, hospital care, and pharmaceuticals), social care costs (such as specialised education and housing), and productivity costs (the cost for society when an individual never enters the labour market, or leaves it) as EUR860,000 for men and EUR800,000 for women in Denmark (in 2000; Kruse 2009), and USD921,000 for individuals in the United States (in 2003; CDC 2004). In Australia, the financial cost of cerebral palsy was estimated AUD1.47 billion (in 2007); the value of lost well-being (disability and premature death) was a further AUD2.4 billion (Access Economics 2008).

The impacts of cerebral palsy are considerable, not only for individuals, but for families, carers, communities, and societies (Davis 2010). Accordingly, individuals with cerebral palsy and their families, clinicians and researchers recognise that identification of primary preventive measures continues to be a key priority (McIntyre 2010).

Description of the interventions

Antenatal or intrapartum approaches to prevention of cerebral palsy

Research efforts aimed at moving towards a future without cerebral palsy have increasingly focused on understanding the causes of cerebral palsy. As it is now widely recognised that causes differ, for example, by gestational age (i.e. for preterm- and term-born children), and clinical subtype of cerebral palsy (Nelson 2008), it is reasonable to consider that successful primary preventive interventions may also vary according to different aetiologies and causal factors. For example, spastic diplegia is the most common subtype of cerebral palsy in preterm infants, most often caused by white matter injury initiated by cerebral ischaemia, maternal intrauterine infection, or fetal systemic inflammation; quadriplegic cerebral palsy, especially with dyskinesia, is a subtype of cerebral palsy sometimes related to acute asphyxia during the birth process (Nelson 2008).

Primary preventive interventions may include public health strategies for the general population (e.g. periconceptional folate supplementation to reduce birth defects), strategies directed at preventing distal components on a causal pathway to cerebral palsy (e.g. melatonin for small-for-gestational age in pregnancy), and strategies closer to the proximal cause of brain damage (e.g. magnesium sulphate for neuroprotection immediately prior to very preterm birth; IMPACT for CP 2011).

Therefore, we considered a broad range of antenatal and intrapartum interventions* in this overview, with varying primary aims and indications, which may mediate the risk of cerebral palsy. The examples presented below are not an exhaustive list, but include:

- nutrition interventions in pregnancy, e.g. periconceptional folate supplementation; marine oil, and other prostaglandin precursors; vitamins C and E;
- behaviour or advice interventions in pregnancy, e.g. reducing alcohol and drug consumption; supporting smoking cessation; promoting hand-washing;
- interventions for predicting or preventing preterm birth (including subsequent management strategies), e.g. fetal fibronectin testing; cervical assessment by ultrasound; risk-scoring systems; transfer to a hospital with neonatal intensive care unit facilities; cervical cerclage; cervical pessary; prenatal administration of progesterone; acute tocolytic and maintenance therapy (i.e. magnesium sulphate; calcium channel blockers (nifedipine); oxytocin receptor antagonists (atosiban); betamimetics (terbutaline); cyclo-oxygenase (COX) inhibitors (indomethacin));

- interventions prior to preterm or term birth for fetal neuroprotection, e.g. antenatal corticosteroids; repeat doses of corticosteroids; thyrotropin-releasing hormone added to corticosteroids; magnesium sulphate; creatine; melatonin; phenobarbital; vitamin K;
- screening and management of fetal growth and well-being in pregnancy, e.g. fetal movement counting for assessment of well-being; symphysial fundal height (SFH) measurement for detecting abnormal fetal growth; ultrasound for fetal assessment in early pregnancy; routine ultrasound in late pregnancy; antenatal cardiotocography for fetal assessment; fetal and umbilical Doppler ultrasound; utero-placental Doppler ultrasound; interventions for impaired fetal growth;
- diagnosing and preventing fetal compromise in labour, e.g. intermittent auscultation (IA) of fetal heart rate; continuous cardiotocography (CTG) for electric fetal heart rate monitoring (EFM); fetal electrocardiogram (ECG); fetal pulse oximetry; patient safety programmes;
- interventions for infection during pregnancy, e.g. TORCH, urinary tract infections, other vaginal infections (i.e. bacterial vaginosis);
- interventions for preterm and term pre-labour rupture of membranes, e.g. planned early birth (versus expectant management); antibiotics; tocolytics;
- other specific interventions for medical problems in pregnancy and labour, e.g. screening and subsequent management for thyroid dysfunction; anti-D administration for preventing Rhesus alloimmunisation in Rh-negative women; interventions for the treatment of mild to moderate, or severe hypertension, and for the prevention (i.e. antioxidants; antiplatelet agents) and treatment of pre-eclampsia or eclampsia (i.e. magnesium sulphate; lytic cocktail; diazepam; phenytoin); interventions for placenta praevia or placental abruption; interventions for uterine rupture or cord prolapse.

*We will not consider interventions in the neonatal period (such as cooling for newborns with hypoxic ischaemic encephalopathy (Jacobs 2013)), as these interventions will be assessed in a separate overview which will be focused specifically on neonatal interventions for prevention of cerebral palsy (Shepherd 2016).

How the intervention might work

Advances in research into several factors that modify the risk of cerebral palsy in infants suggest many opportunities for prevention, with some of the main strategies focusing on the prevention of preterm birth, or protection of the developing fetal brain through antenatal administration of neuroprotective agents.

For example, because preterm birth and neurodevelopmental outcomes are so strongly associated (ACPR Group 2013; Oskoui 2013), it is possible that interventions to prolong gestation or reduce the risk of preterm birth will also reduce the risk of cerebral palsy (Chang 2015; O'Shea 2008). Specific approaches, supported by high level evidence, for prolonging pregnancy and preventing preterm birth include: interventions for primary prevention of preterm birth (e.g. smoking cessation programmes for the general population); interventions for secondary prevention of indicated preterm birth (e.g. antiplatelet drugs (low-dose aspirin) for the prevention of pre-eclampsia); interventions for secondary prevention of spontaneous preterm birth (e.g. progesterone and cervical cerclage for women at increased risk of preterm birth due to a prior preterm birth, or where a short cervix has been identified on ultrasound); and tertiary interventions, for women with immediate risk of preterm birth (e.g. antibiotics for women with preterm rupture of membranes; and calcium channel blockers and an oxytocin antagonist (atosiban) for women with preterm labour; Iams 2008; O'Shea 2008).

For women with immediate risk of preterm birth, it is possible that antenatal interventions aimed at protecting the developing fetal brain from injury will also reduce the risk of cerebral palsy. For example, antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth have also been shown to be neuroprotective, reducing the risk of intraventricular haemorrhage and periventricular leukomalacia (Chang 2015; Iams 2008; O'Shea 2008). Magnesium sulphate is another drug administered antenatally, with the potential to mediate the risk of cerebral palsy by protecting the developing fetal brain from injury, such as intraventricular haemorrhage (Chang 2015; Nelson 2008; O'Shea 2008). Beyond antenatal corticosteroids and magnesium sulphate, a range of other antenatally administered agents, such as melatonin, creatine, and allopurinol, may enhance the ability of the preterm or term developing fetal brain to withstand brain damage, and in doing so, reduce the risk of cerebral palsy (Chang 2015; Robertson 2012).

There are numerous other antenatal and intrapartum interventions with the potential to contribute to the prevention of cerebral palsy in preterm and term infants by modifying known risk factors for cerebral palsy, for example: identification and subsequent management of maternal thyroid dysfunction (both hypo- and hyperthyroidism) in pregnancy, identification and treatment of hypertension and pre-eclampsia in pregnancy, and identification and management of perinatal infections (including chorioamnionitis) in pregnancy.

Why it is important to do this overview

A multitude of individual studies and Cochrane reviews assessing a broad range of antenatal or intrapartum interventions (with varying primary aims and indications) recognise the potential for the interventions of interest to mediate the risk of cerebral palsy. With the acknowledgement that a multiplicity of risk factors impact on the risk of cerebral palsy, and that causes of cerebral palsy differ, there is a need to systematically consider all potentially relevant interventions for their ability to contribute to prevention. To our

knowledge, there is no published overview that has assembled and summarised the evidence from Cochrane reviews on interventions for the prevention of cerebral palsy in one coherent document, to be used by researchers, funding bodies, policy makers, clinicians, and consumers to aid decision making and evidence translation.

OBJECTIVES

The objective of this overview was to summarise the evidence from Cochrane reviews regarding the effects of antenatal and intrapartum interventions for preventing cerebral palsy, and to assess the effects of these interventions on associated outcomes, including severity and type of cerebral palsy.

METHODS

Criteria for considering reviews for inclusion

In this overview, we included Cochrane reviews of antenatal or intrapartum interventions, where cerebral palsy was reported as a primary or secondary outcome, or as part of a composite outcome, with data reported for cerebral palsy from at least one of the trials included in the review.

We identified relevant Cochrane protocols for future inclusion, and classified them as 'Ongoing reviews' (Appendix 1).

We listed reviews that pre-specified cerebral palsy as a primary or secondary outcome, but had no data reported from included trials as 'Reviews awaiting further classification', which will be reconsidered in future updates of the overview (Appendix 2).

We made note of the publication and search dates of the reviews, however, we did not attempt to update the individual reviews. We contacted the Cochrane Pregnancy and Childbirth Editorial Base to identify any relevant new reviews or review updates that were in progress, in order to include the most up-to-date versions of the reviews, if and where possible.

Participants

We considered reviews assessing interventions in pregnant women.

Interventions

We considered all types of interventions used in the antenatal or intrapartum period, compared with placebo, no treatment, or an alternative intervention.

We planned to include pharmacological, medical, nutritional, behavioural, and educational interventions (see Description of the interventions for further descriptions of possible interventions).

Outcomes of interest

Primary

- Cerebral palsy (however defined by review authors and trialists).

Secondary

- Cerebral palsy or death (e.g. in early childhood, and at the latest time point measured).
- Severity of cerebral palsy (e.g. according to: Gross Motor Function Classification System (GMFCS); Manual Ability Classification System (MACS); Communication Function Classification System (CFCS)).
- Other composite outcomes that included cerebral palsy as a component.
- Type of cerebral palsy (e.g. according to topography (diplegia; hemiplegia; quadriplegia; monoplegia; triplegia), or motor type (spastic; dyskinetic; ataxic)).
- Motor dysfunction (e.g. in infancy and early childhood, and at the latest time point measured; however defined by review authors and trialists)

Search methods for identification of reviews

We searched the *Cochrane Database of Systematic Reviews,* using the term 'cerebral palsy', on 7 August 2016. We searched 'all text', and did not limit our search to 'title, abstract, or keywords'. We did not apply any language or date restrictions. No other databases were searched. We managed citations retrieved through the search with Covidence (Covidence 2015).

Data collection and analysis

We followed the methodology for data collection and synthesis from Chapter 22 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). Where appropriate, we prepared the overview using Covidence and Review Manager 5 software (Covidence 2015; RevMan 2014).

Selection of reviews

Two overview authors independently assessed all potential reviews we identified. We resolved any disagreement through discussion, or if required, we consulted a third author.

Data extraction and management

Two overview authors independently extracted data from the reviews using a pre-defined data extraction form. We resolved discrepancies through discussion. Where any information from the reviews was unclear or missing, we accessed the published papers of the individual studies.

We extracted information on the following.

- Review characteristics:
  - review title and authors;
  - date that the review was last assessed as up-to-date;
  - number of included trials, number of participants (women and infants) in the trials and their characteristics (e.g. countries where the trials were conducted and inclusion criteria for the trials);
  - quality of the included trials (as reported by the review authors; see Assessment of methodological quality of included reviews);
  - interventions and comparisons relevant to this overview;
  - all pre-specified outcomes relevant to this overview;
  - any other characteristics required to assess and report on review quality (see Assessment of methodological quality of included reviews).
- Statistical summaries:
  - the summary intervention effects (including the pooled effects (e.g. risk ratios (RR), odds ratios (OR) or mean differences (MD) as reported in the individual reviews), 95% confidence intervals (CIs), and numbers of studies and participants contributing data to each pooled effect) for outcomes relevant to this overview (N.B. if the summary statistic (RR or OR) has been calculated using a random-effects analysis, the results are presented as the 'average' treatment effect);
  - information required to assess and report on the quality of the evidence for the intervention effects extracted above (see Assessment of methodological quality of included reviews);
  - results of any subgroup or sensitivity analyses conducted by the review authors, for our primary outcome.

If there were no meta-analyses in a review, and therefore, no statistical summaries, we extracted the narrative text relating to the results for our overview outcomes.

When cerebral palsy was reported as part of a composite outcome, we extracted any available data on cerebral palsy. Where it was not possible to extract only the cerebral palsy data, we reported the composite outcome data; however, we reported it separately, as a secondary outcome.

Assessment of methodological quality of included reviews

Quality of included reviews

We assessed the methodological quality of each systematic review using the AMSTAR (A Measurement Tool to Assess Reviews) instrument (Shea 2009). AMSTAR evaluates the methods used in a review against 11 distinct criteria and assesses the degree to which review methods are unbiased. Each item on AMSTAR is rated as yes (clearly done), no (clearly not done), cannot answer, or not applicable. These criteria are as follows.

1. Was an a priori design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

For all items except item 4, a rating of 'yes' was considered adequate. For item 4, a rating of 'no' was considered adequate. A review that adequately met all of the 11 criteria was considered to be a review of the highest quality. For this overview, we considered reviews that achieved scores of between 8 to 11 as high quality; scores of 4 to 7 as medium quality; and scores of 0 to 3 as low quality.

To further assess the risk of bias of the systematic reviews, we used the new ROBIS (Risk Of Bias In Systematic reviews) tool (Whiting 2014). The tool considers risk of bias across four key domains.

1. Study eligibility criteria.
2. Identification and selection of studies.
3. Data collection and study appraisal.
4. Synthesis and findings.

A series of questions within each of the domains elicits information about possible limitations of the systematic review, leading to a judgement about the concerns within that domain (low, high, or unclear). Assessors then consider the risk of bias of the review as a whole, with signalling questions and information to support the overall judgement of risk of low, high or unclear bias (Whiting 2014).

Two overview authors independently assessed the quality of the included reviews; another overview author verified this assessment. We resolved differences through discussion.

Quality of included studies within reviews

We did not reassess the quality of included studies within reviews but reported study quality according to the review authors' as-

sessment. When individual studies were included in two or more Cochrane reviews, we reported this, along with any variation in the review authors' assessments of study quality. We collected this information during the data extraction process.

Quality of evidence in included reviews

We assessed the quality of the evidence for our primary outcome (cerebral palsy) and secondary review outcomes using the GRADE approach, as outlined in the *GRADE Handbook* (Schünemann 2013). We reported the quality of evidence as assessed by the review authors (who were in the best position to assess quality given their familiarity with the study-level data), using 'Summary of findings' tables from the reviews if provided. Where necessary, we constructed tables using GRADEpro GDT software (GRADEpro GDT 2015). The GRADE system assesses the following features for the evidence found for important outcomes.

- Study limitations (risk of bias): internal validity of the evidence.
- Inconsistency: heterogeneity or variability in the estimates of effect across studies.
- Indirectness: degree of differences between population, intervention, comparator, for the intervention and outcome of interest.
- Imprecision (random error): extent to which confidence in the effect estimate is adequate to support a particular decision.
- Publication bias: degree of selective publication of studies.

The GRADE system rates the quality of the evidence as:

- High (further research is very unlikely to change confidence in the estimate of effect).
- Moderate (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate).
- Low (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate).
- Very low (any estimate of effect is very uncertain).

Data synthesis

We used a narrative description of the characteristics of the included Cochrane reviews.

We summarised the main results of the included reviews by categorising their findings in the following framework, organised by antenatal or intrapartum intervention, and by intervention topic. This approach was used in previous Cochrane and non-Cochrane overviews (i.e. Farquhar 2015; Lassi 2015). A similar approach was also used in Jones 2012, in which interventions were categorised as 'what works', 'what may work', and 'insufficient evidence to make a judgement'.

- Effective interventions: indicated that the review found high-quality evidence of effectiveness for an intervention.
- Possibly effective interventions: indicated that the review found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed.
- Ineffective interventions: indicated that the review found high-quality evidence of lack of effectiveness (or harm) for an intervention.
- Probably ineffective interventions: indicated that the review found moderate-quality evidence suggesting lack of effectiveness (or harm) for an intervention, but more evidence is needed.
- No conclusions possible: indicated that the review found low or very low-quality evidence, or insufficient evidence to comment on the effectiveness or safety of an intervention.

The choice of category was based on the quality of the evidence for cerebral palsy. We used separate assessments for different comparisons if required (e.g. where one intervention was compared with both placebo (or no treatment) and an alternative intervention).

RESULTS

Our search of the *Cochrane Database of Systematic Reviews* identified 500 protocols and reviews. Following our review of titles and abstracts, we excluded 381 protocols and reviews, and assessed the full-text of 119 protocols and reviews.

We excluded 33 reviews that did not pre-specify cerebral palsy as a primary or secondary review outcome (see Table 1: Characteristics of excluded studies).

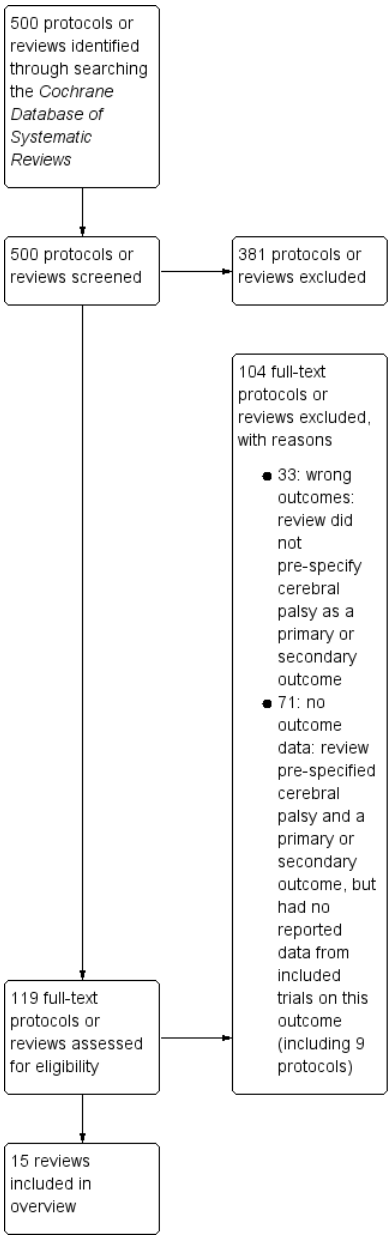
We listed 71 protocols and reviews in the appendices.

- Appendix 1, Ongoing reviews, lists nine Cochrane protocols that have pre-specified cerebral palsy as a primary or secondary outcome, and will be considered for inclusion in future updates of the overview when they are published as full reviews.

- Appendix 2, Reviews awaiting further classification, summarises the 62 Cochrane reviews that pre-specified cerebral palsy as a primary or secondary outcome, but the included trials had no data reported on this outcome; these reviews will again be considered for inclusion in future updates of the overview.

We included 15 reviews in this overview. See Figure 1. Review flow diagram, for details.

Figure 1. Review flow diagram.



Description of included reviews

Of the 15 included reviews:

- two focused on the treatment of mild to moderate hypertension:
  - antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Abalos 2014);
  - oral beta-blockers for mild to moderate hypertension during pregnancy (Magee 2003).
- two assessed interventions for the treatment of pre-eclampsia:
  - interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation (Churchill 2013);
  - magnesium sulphate and other anticonvulsants for women with pre-eclampsia (Duley 2010).
- one focused on interventions for the diagnosis and prevention of fetal compromise in labour:
  - continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour (Alfirevic 2013).
- four assessed interventions for the prevention of preterm birth:
  - prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth (Dodd 2013);
  - prophylactic antibiotics for inhibiting preterm labour with intact membranes (Flenady 2013);
  - magnesium sulphate for preventing preterm birth in threatened preterm labour (Crowther 2014);
  - betamimetics for inhibiting preterm labour (Neilson 2014).
- five focused on interventions prior to preterm birth for fetal maturation or neuroprotection:
  - vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010);
  - phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010a);
  - magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009);
  - repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Crowther 2015);
  - antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Roberts 2006).
- one focused on interventions for the management of preterm fetal compromise:
  - immediate versus deferred delivery of the preterm baby with suspected fetal compromise for improving outcomes (Stock 2016).

The number of randomised controlled trials (RCT) in the 15 reviews ranged from one (Stock 2016) to 49 (Abalos 2014). The number of women in each RCT ranged from 425 (Churchill 2013) to 37,715 (Alfirevic 2013). In total, there were 279 randomised trials, involving over 101,098 women and their babies.

One third (five) of the 15 reviews had conducted searches between August 2013 and August 2016, and were considered up-to-date (Crowther 2014; Crowther 2015; Flenady 2013; Neilson 2014; Stock 2016). The other 10 reviews had latest search dates ranging from August 2008 to April 2013.

See Table 2, Characteristics of included reviews and Table 3, Risk of bias assessments from included reviews, for further details of the characteristics of the 15 included reviews.

Methodological quality of included reviews

According to AMSTAR criteria:

1. all reviews pre-specified their design;
2. all reviews reported duplicate study selection and data extraction;
3. all reviews performed a comprehensive literature search;
4. all reviews considered grey literature;
5. all reviews provided lists of included and excluded studies;
6. all reviews provided the characteristics of the included studies;
7. all reviews assessed and documented the scientific quality of the included studies;
8. all reviews used scientific quality of the included studies appropriately in formulating conclusions;
9. 11 reviews combined the findings of studies using appropriate methods; in three reviews, fixed-effect meta-analyses were used despite the presence of substantial statistical heterogeneity; one review had only one included trial;
10. 11 reviews assessed the likelihood of publication bias (or pre-specified which methods they would use if 10 or more trials were included in a meta-analysis);
11. three reviews clearly reported conflict of interests or potential sources of support for both the review and included studies.

See Table 4: AMSTAR assessments for included reviews, for further details.

When assessed against the ROBIS domains, all reviews were considered at low risk of bias across the study eligibility criteria, identification and selection of studies, and data collection and study appraisal domains. Three of the reviews received an unclear risk of bias rating for the synthesis and findings domain (based on use of fixed-effect meta-analyses in the presence of substantial statistical heterogeneity). See Table 5: ROBIS assessments for included reviews, for further details.

Overall, all 15 included reviews were judged to be of high quality according to AMSTAR criteria, with scores ranging from 8 to 11, and at a low risk of bias, according to ROBIS domains.

Effect of interventions

We have summarised the main results of the included reviews below. They are organised by intervention topic and categorised in the framework discussed under Data synthesis, based on the quality of the evidence for the presence of cerebral palsy, the primary outcome.

For further details and 'Summary of findings' tables for the outcomes of interest, see Table 6, All comparisons measuring cerebral palsy; Table 7, Subgroup or sensitivity analyses of select comparisons for cerebral palsy; Table 8, All comparisons measuring cerebral palsy or death; Table 9, All comparisons measuring severity of cerebral palsy; Table 10, All comparisons measuring other composite outcomes that include cerebral palsy as a component; and Table 11, All comparisons measuring motor dysfunction.

Interventions for the treatment of mild to moderate hypertension

No conclusions possible: very low-quality evidence

Very low-quality evidence in both the Abalos 2014 and Magee 2003 reviews showed no clear difference for the presence of cerebral palsy at one year when any antihypertensive drug was compared with a placebo (Abalos 2014), or when an oral beta-blocker was compared with placebo (Magee 2003), in the treatment of mild to moderate hypertension during pregnancy (risk ratio (RR) 0.33, 95% confidence interval (CI) 0.01 to 8.01; one trial; 110 children; Table 6). The two reviews included the same trial, and made similar judgements regarding trial quality.

Interventions for the treatment of pre-eclampsia

No conclusions possible: low-quality evidence

Low-quality evidence in the Churchill 2013 review showed no clear difference for the presence of cerebral palsy at two years when interventionist care was compared with expectant (delayed delivery) care for severe pre-eclampsia between 24 and 34 weeks' gestation (RR 6.01, 95% CI 0.75 to 48.14; one trial; 262 children; Table 6).

Low-quality evidence in the Duley 2010 review showed no clear difference for the presence of severe cerebral palsy at 18 months when magnesium sulphate was compared with placebo for women with pre-eclampsia (RR 0.34, 95% CI 0.09 to 1.26; one trial; 2895 children; Table 6; Table 9).

Low-quality evidence in the Duley 2010 review also showed no clear difference in neurosensory disability (composite outcome that included cerebral palsy) at 18 months (RR 0.77, 95% CI 0.38 to 1.58; one trial; 3283 children; Table 10), or in death or neurosensory disability at 18 months (RR 1.06, 95% CI 0.90 to 1.25; one trial; 3283 children; Table 10) when magnesium sulphate was compared with placebo for women with pre-eclampsia.

Interventions for the diagnosis and prevention of fetal compromise in labour

No conclusions possible: low-quality evidence

Low-quality evidence in the Alfirevic 2013 review showed no clear difference for the presence of cerebral palsy in early childhood (between 18 months and four years) when continuous cardiotocography was compared with intermittent auscultation for fetal assessment during labour (average RR 1.75, 95% CI 0.84 to 3.63; two trials; 13,252 children; Table 6).

Alfirevic 2013 conducted subgroup analyses for the presence of cerebral palsy, based on pregnancy risk status, onset of labour, gestational age, number of babies, access to fetal blood sampling, parity, and and only high quality trials, however, did not identify any clear subgroup differences (Table 7).

Interventions for the prevention of preterm birth

Probably ineffective interventions: moderate-quality evidence of harm

Moderate-quality evidence in the Flenady 2013 review showed an increase in cerebral palsy in mid-childhood (at seven years) for children born to mothers who received any prophylactic antibiotics versus no antibiotics for inhibiting preterm labour with intact membranes (RR 1.82, 95% CI 0.99 to 3.34; one trial; 3173 children; Table 6).

Subgroup analysis for this outcome, based on type of antibiotic did not reveal clear subgroup differences (Table 7). Additional analyses were conducted for this outcome, comparing (i) any macrolide antibiotics (including macrolide antibiotics used as a single agent or in combination with other types of antibiotics) versus no macrolide antibiotics (including use of any non-macrolide antibiotics or no antibiotics), and (ii) any beta-lactam antibiotics (including beta-lactam antibiotics used as a single agent or in combination with other types of antibiotics) versus no beta-lactam antibiotics (including use of any non-beta-lactam antibiotics or no antibiotics). An increase in cerebral palsy in mid-childhood (at seven years) was observed for children born to mothers who received any macrolide versus no macrolide antibiotics, and any beta-lactam versus no beta-lactam antibiotics (Table 7).

No conclusions possible: low- to very low-quality evidence

Low-quality evidence in the Dodd 2013 review showed no clear difference for the presence of cerebral palsy at four years when prenatal administration of progesterone was compared with placebo for preventing preterm birth in women with a previous history of spontaneous preterm birth (RR 0.14, 95% CI 0.01 to 3.48; one trial; 274 children; Table 6). A subgroup analysis was planned for this outcome based on route of administration, however, only one trial was included, which used intramuscular administration (Table 7).

Low-quality evidence in the Neilson 2014 review showed no clear difference for the presence of cerebral palsy in children at 18 months when betamimetics were compared with placebo for inhibiting preterm labour (RR 0.19, 95% CI 0.02 to 1.63; one trial; 246 children; Table 6).

Very-low quality evidence in the Crowther 2014 review showed no clear difference for the presence of cerebral palsy in children at 18 months when magnesium sulphate was compared with other tocolytic agents for preventing preterm birth in threatened preterm labour (RR 0.13, 95% CI 0.01 to 2.51; one trial; 106 children; Table 6).

Very low-quality evidence in the Crowther 2014 review also showed no clear difference for serious infant outcomes (including cerebral palsy) when magnesium sulphate was compared with other tocolytic agents for preventing preterm birth in threatened preterm labour (RR 2.47, 95% CI 0.69 to 8.81; one trial; 106 children; Table 10).

There was also low-quality evidence in the Dodd 2013 review showing no clear difference in motor impairment for children at four years when prenatal administration of progesterone was compared with placebo for preventing preterm birth in women with a previous history of spontaneous preterm birth (RR 0.64, 95% CI 0.11 to 3.76; one trial; 274 children; Table 11).

Interventions prior to preterm birth for fetal maturation or neuroprotection

Effective interventions: high-quality evidence of effectiveness

High-quality evidence in the Doyle 2009 review showed a reduction in cerebral palsy at 18 months to two years for children born to women at risk of preterm birth who received magnesium sulphate compared with placebo for neuroprotection of the fetus (RR 0.68, 95% CI 0.54 to 0.87; five trials; 6145 children; Table 6). Subgroup analyses for cerebral palsy based on intent (neuroprotective, pre-eclampsia, tocolytic), single or multiple pregnancy, gestational age at randomisation, loading dose, maintenance dose, and whether re-treatment was permitted, showed no clear subgroup differences (Table 7); the results did not substantially change when they only included studies with high antenatal corticosteroid use, nor when they performed a sensitivity analysis based on trial quality (Table 7).

High-quality evidence from Doyle 2009 review also showed a reduction in moderate to severe cerebral palsy at two years (RR 0.64, 95% CI 0.44 to 0.92; three trials; 4387 children; Table 9), and in substantial gross motor dysfunction at 18 months to two years (RR 0.61, 95% CI 0.44 to 0.85; four trials; 5980 children; Table 11); though no clear differences were shown for death or cerebral palsy at 18 months to two years (average RR 0.94, 95% CI 0.78 to 1.12; five trials; 6145 children; Table 8), any neurologic impairment at 18 months to two years (RR 1.01, 95% CI 0.86 to 1.19; two trials; 2848 children; Table 10), death or any neurologic impairment (composite outcomes that included cerebral palsy) at 18 months to two years (RR 1.00, 95% CI 0.91 to 1.11; two trials; 2848 children; Table 10), or death or major neurological disability at 18 months to two years (RR 1.02, 95% CI 0.90 to 1.15; two trials; 2848 children; Table 10).

Moderate-quality evidence from Doyle 2009 showed no clear differences for mild cerebral palsy at two years (RR 0.74, 95% CI 0.52 to 1.04; three trials; 4387 children; Table 9), moderate cerebral palsy at two years (RR 0.66, 95% CI 0.34 to 1.28; two trials; 1943 children; Table 9), severe cerebral palsy at two years (RR 0.82, 95% CI 0.37 to 1.82; two trials; 1943 children; Table 9), major neurological disability at 18 months or two years (RR 1.07; 95% CI 0.82 to 1.40; two trials, 2848 children) (Table 10), or death or substantial gross motor dysfunction for children at 18 months to two years (average RR 0.92, 95% CI 0.75 to 1.12; four trials; 5980 children; Table 11) when magnesium sulphate was compared with placebo for women at risk of preterm birth for neuroprotection of the fetus.

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness

Moderate-quality evidence in the Crowther 2015 review showed no clear difference in cerebral palsy at 18 months to three years when repeat doses of corticosteroids were compared with a single course for women at risk of preterm birth (RR 1.03, 95% CI 0.71 to 1.50; four trials; 3800 children; Table 6).

High-quality evidence from the Crowther 2015 review also showed no clear differences for survival free of any disability at 18 months to two years (RR 1.01, 95% CI 0.97 to 1.05; two trials; 3155 children; Table 10), disability at two years (RR 0.98, 95% CI 0.83 to 1.16; one trial; 999 children; Table 10), or composite serious outcome at 18 months to two years (RR 0.99, 95% CI 0.87 to 1.12; two trials; 3164 children; Table 10) when repeat doses of corticosteroids were compared with a single course for women at risk of preterm birth;

Low-quality evidence from Crowther 2015 showed no clear differences for survival free of major neurosensory disability (a composite outcome that included cerebral palsy) for children at two to three years (average RR 1.01, 95% CI 0.92 to 1.11; two trials; 1317 children; Table 10) and major neurosensory disability at two to three years (average RR 1.08, 95% CI 0.31, 3.76; two trials;

1256 children; Table 10) when repeat doses of corticosteroids were compared with a single course for women at risk of preterm birth.

No conclusions possible: low- to very low-quality evidence

Low-quality evidence in the Crowther 2010a review, showed no clear difference in the presence of cerebral palsy in early childhood (between 18 months and three years) when phenobarbital was compared with placebo or no treatment, and given prior to preterm birth to prevent neonatal periventricular haemorrhage (RR 0.71, 95% CI 0.40 to 1.28; two trials; 517 children; Table 6). Crowther 2010a had planned to conduct a sensitivity analysis, excluding trials with inadequate concealment of allocation of treatment; the results did not change as the one included trial was retained in the analysis (Table 7).

Very low-quality evidence in the Crowther 2010a review also showed no clear difference in other neuromotor impairment for children at three years when phenobarbital was compared with no treatment prior to preterm birth for preventing neonatal periventricular haemorrhage (RR 0.67, 95% CI 0.13 to 3.49; one trial; 96 children; Table 11).

Very low-quality evidence from two reviews, showed no clear difference in the presence of cerebral palsy in mid-childhood (at seven years) when vitamin K was compared with placebo prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010), and when phenobarbital was compared with placebo prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010a; RR 0.77, 95% CI 0.33 to 1.76; one trial; 299 children; Table 6). These two reviews included the same trial (which assessed a combination intervention), and made similar judgements regarding trial quality. Both reviews planned to conduct a sensitivity analysis excluding trials with inadequate concealment of allocation of treatment; the results did not change as the one included trial was retained in the analysis (Table 7).

Low-quality evidence in the Roberts 2006 review showed a possible reduction in cerebral palsy between two and six years for children born to women at risk of preterm birth who received antenatal corticosteroids compared with placebo for accelerating fetal lung maturation (RR 0.60;,95% CI 0.34 to 1.03; five trials; 904 children; Table 6). A subgroup analysis for cerebral palsy, based on decade of recruitment, revealed no clear subgroup differences (Table 7).

Very low-quality evidence from Roberts 2006 review also showed no clear difference in neurodevelopmental delay at two years when antenatal corticosteroids were compared with placebo for accelerating fetal lung maturation for women at risk of preterm birth (RR 0.64, 95% CI 0.14 to 2.98; one trial; 82 children; Table 10).

Interventions for the management of preterm fetal compromise

Probably ineffective interventions: moderate-quality evidence of harm

Moderate-quality evidence in the Stock 2016 review showed an increase in cerebral palsy at or after two years for children, who as preterm babies with suspected fetal compromise,were born immediately, compared with those for whom birth was deferred (RR 5.88, 95% CI 1.33 to 26.02; one trial; 507 children; Table 6).

Low-quality evidence from the Stock 2016 review also showed no clear differences in death or disability at or after two years (RR 1.22, 95% CI 0.85 to 1.75; one trial; 573 children; Table 10), neurodevelopmental impairment at or after two years (RR 1.72, 95% CI 0.86 to 3.41; one trial; 507 children; Table 10), or death or severe disability at six to 13 years (RR 0.82, 95% CI 0.48 to 1.40; one trial; 302 children; Table 10) when immediate delivery of the preterm baby with suspected fetal compromise was compared with deferred delivery.

DISCUSSION

Summary of main results

This overview included 15 Cochrane reviews, involving 279 randomised controlled trials and 101,098 children. Data for cerebral palsy were available from 27 (10%) randomised controlled trials involving 32,490 (32%) children.

Effective interventions: high-quality evidence of effectiveness: high-quality evidence showed a reduction in cerebral palsy for children born to women at risk of preterm birth who received magnesium sulphate compared with placebo for neuroprotection of the fetus.

Probably ineffective interventions: moderate-quality evidence of harm: moderate-quality evidence showed an increase in cerebral palsy for children born to mothers who received any prophylactic antibiotics versus no antibiotics for inhibiting preterm labour with intact membranes. Moderate-quality evidence also showed an increase in cerebral palsy for children who, as preterm babies with suspected fetal compromise, were born immediately compared with those for whom birth was deferred.

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness: moderate-quality evidence showed no clear difference in cerebral palsy when repeat doses of corticosteroids were compared with a single course for women at risk of preterm birth.

No conclusions possible: low- to very low-quality evidence:

- Low-quality evidence showed a possible reduction in cerebral palsy for children born to women at risk of preterm birth who received antenatal corticosteroids compared with placebo for accelerating fetal lung maturation.
- Low-quality evidence showed no clear difference for cerebral palsy with interventionist care versus expectant care for

severe pre-eclampsia; magnesium sulphate versus placebo for pre-eclampsia; continuous cardiotocography versus intermittent auscultation for fetal assessment during labour; prenatal progesterone versus placebo for preventing preterm birth; and betamimetics versus placebo for inhibiting preterm labour.

- Very low-quality evidence showed no clear difference for cerebral palsy with any antihypertensive drug versus placebo, or with an oral beta-blocker versus placebo for mild to moderate hypertension; with magnesium sulphate versus other tocolytic agents for preventing preterm birth; and with vitamin K and phenobarbital versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage.

Overall completeness and applicability of evidence

This overview summarises published Cochrane reviews assessing antenatal and intrapartum interventions and their effects on cerebral palsy. Interventions in the neonatal period are the focus of a companion overview (Shepherd 2016).

We were only able to include 15 reviews (representing less than 3% of the 546 Pregnancy and Childbirth reviews in the *Cochrane Database of Systematic Reviews*), which reported data on our primary outcome, cerebral palsy. We identified an additional nine protocols that have pre-specified cerebral palsy as a primary or secondary outcome and will be considered for inclusion in future updates of the overview when they are published as full reviews. These protocols plan to assess a variety of interventions including: interventions for treating hypertension (guided imagery), preventing (with melatonin) or treating pre-eclampsia (melatonin; epidural therapy; planned caesarean section versus planned vaginal delivery), for preventing preterm labour or birth (progestogens for multiple pregnancy; hypnosis), for diagnosing and preventing fetal compromise in labour (intermittent auscultation of fetal heart rate in labour), and for induction of labour (amniotomy plus intravenous oxytocin). See Appendix 1, Ongoing reviews. We were unable to include an additional 62 reviews assessing a wide range of antenatal and intrapartum interventions, because although they recognised the potential impact of the interventions of interest on cerebral palsy (through pre-specifying cerebral palsy as a review outcome), none of the included trials within these reviews reported on this outcome. We have summarised the main conclusions of these reviews in Appendix 2, Reviews awaiting further classification, and will again consider them for inclusion in future updates of the overview.

Although the 15 reviews in this overview included 279 randomised trials, involving over 101,098 women and their babies, the body of evidence for our review was substantially reduced because the included reviews (and trials) did not report on our outcomes of interest. For our primary outcome, cerebral palsy, we have included data from all 15 reviews, but from 27 randomised trials, or only 10% of the trials within the included reviews.

The body of evidence for our secondary outcomes was further reduced, with six reviews reporting data on a composite outcome including cerebral palsy, three on motor dysfunction, two on severity of cerebral palsy, and one of the 15 reviews reporting data on cerebral palsy or death. None of our included reviews reported specifically on the type of cerebral palsy. For the majority of our outcomes, data were reported in the reviews by only one or two trials, up to a maximum of five trials, for the majority of interventions assessed. Thus, there were too few data to reach firm conclusions on the effects on cerebral palsy and our secondary outcomes. Unsurprisingly, for the majority of the reviews, data related to cerebral palsy was commonly shorter-term (reported at one to two years of age), with longer-term follow up less commonly reported (only three reviews reported on cerebral palsy at seven years). Definitions or criteria for a diagnosis of cerebral palsy, where reported, and assessment methods, varied substantially between and within trials; often this information was not reported in the reviews.

We did not attempt to make indirect comparisons in order to address questions concerning the relative performance of difference antenatal or intrapartum interventions. This would not have been appropriate, due to the variety of interventions (and control conditions) assessed in different populations, for various indications. Rather, we aimed to systematically consider all potentially relevant interventions for their ability to contribute to the prevention of cerebral palsy. Within this overview, we have not attempted to duplicate details of participants, interventions (and control conditions) in individual trials. Consulting the individual reviews and trials is encouraged to obtain more information on these factors.

The scope of this overview was limited to effects of interventions on cerebral palsy, and a restricted number of pre-specified secondary outcomes, including the composite outcome 'cerebral palsy or death', in recognition of the competing risks of death and survival with neurosensory disability. In order to assess the effects (benefits or harms) of the included interventions on other outcomes (including perinatal death), readers are encouraged to refer to the included Cochrane reviews themselves. For example, while this overview showed low-quality evidence of a possible reduction in cerebral palsy for children born to women at risk of preterm birth who received antenatal corticosteroids for accelerating fetal lung maturation, the recently updated Roberts 2017 review assessed additional outcomes, and has revealed reductions in perinatal death, neonatal death, respiratory distress syndrome, moderate to severe respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, need for mechanical ventilation, and systemic infections in the first 48 hours of life. The review concluded that the findings support "the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth" (Roberts 2017).

Quality of the evidence

All of the included reviews were assessed to be of high quality and at low risk of bias with the AMSTAR and ROBIS tools (Table 4; Table 5). Although the two tools differ in their approaches to assessing review quality or risk of bias, they led to similar assessments. All of the reviews assessed the risk of bias of the included randomised trials, the majority using current guidance as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The quality of the randomised trials was variable within and between the reviews (Table 3).

Two of the 15 reviews used the GRADE approach to assess the quality of evidence for review outcomes (Alfirevic 2013; Stock 2016). For the other reviews, we used the GRADE system to rate the quality of evidence, incorporating the assessments of study limitations (risk of bias) reported by the review authors. For our primary outcome, cerebral palsy, the quality of the evidence ranged from very low to high, similarly for our secondary outcomes. Downgrading of the quality was most commonly due to study limitations (risk of bias), and imprecision (small sample sizes, low number of events, and wide confidence intervals). As our overview outcomes were assessed through longer-term follow-up of antenatal or intrapartum interventions, the potential for bias relating to attrition (which could occur due to children lost to follow-up differing systematically from those followed-up), was an important consideration when rating the quality of evidence. The summary of findings for the quality of evidence for each outcome are set out in Table 6: Cerebral palsy; Table 8: Cerebral palsy or death; Table 9: Severity of cerebral palsy; Table 10: Other composite outcomes that include cerebral palsy as a component; and Table 11: Motor dysfunction.

Potential biases in the overview process

We were aware that there were risks of introducing bias at all stages of the overview process, and took a number of steps to minimise this. All included Cochrane reviews used a protocol that aimed to minimise bias; we also developed a protocol for our overview. At least two overview authors independently assessed reviews for inclusion, carried out data extraction and quality assessment, and assessed the quality of the evidence using the GRADE approach. One potential source of bias relates to authors of this overview being authors of some of the included reviews. As pre-specified in our protocol, data extraction and quality assessment for these reviews were carried out by two overview authors who were not authors of the individual reviews.

We undertook a comprehensive search of the *Cochrane Database of Systematic Reviews* without language or date restrictions, and identified published reviews, as well as planned and ongoing reviews (protocols). We did not search other databases, and thus it is possible that non-Cochrane systematic reviews assessing antenatal and intrapartum interventions, and reporting on cerebral palsy, have been conducted but not identified. It is also possible that Cochrane reviews assessing interventions that could have potential to impact cerebral palsy risk (see Description of the interventions for further discussion of various interventions) may not have acknowledged this by including cerebral palsy as a review outcome. Thus, data from relevant randomised trials assessing these interventions would not have been identified and included in this overview. Based on our search strategy, even Cochrane reviews that pre-specified outcomes such as 'impaired long-term growth and development in infancy and childhood' (e.g. Abalos 2014), but subsequently reported specifically on 'cerebral palsy' have been captured in our search, and included. However, reviews that reported on long-term neurodevelopmental outcomes without any mention of 'cerebral palsy' would not have been identified, which highlights the need for all Cochrane reviews to provide clear definitions accompanying any outcome measures reported.

While our included reviews were judged to be of high methodological quality and at low risk of bias, not all were considered 'up-to-date', with only one third conducting searches in the past four years; similarly, not all of the 'Reviews awaiting further classification' were 'up-to-date'. Thus, it is possible that additional trials assessing antenatal and intrapartum interventions and reporting on cerebral palsy have been published, but not yet included in the relevant Cochrane reviews; it is also possible that additional trials have been conducted but are not yet published. If and when such trials are included in the relevant Cochrane review, they will be incorporated into this overview.

Agreements and disagreements with other studies or reviews

We did not identify any other overviews or systematic reviews specifically designed to assess antenatal and intrapartum interventions for preventing cerebral palsy.

In regards to cerebral palsy prevention for children born preterm, World Health Organization (WHO) recommendations focused on improving the outcomes of preterm birth have recently been released, based on up-to-date systematic reviews for priority questions (WHO 2015). These guidelines assessed a number of interventions that were included in this review, and reached similar conclusions. Specifically, a strong recommendation was made for the use of magnesium sulphate for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy in the infant and child, which was based on which was based on high quality evidence for cerebral palsy. A strong recommendation was also made against the use of routine antibiotic administration for women in preterm labour with intact amniotic membranes and no clinical signs of infection, based on moderate-quality evidence for cerebral palsy (WHO 2015).

McIntyre 2013 conducted a systematic review of cohort and case-control studies focused on identifying risk factors for cerebral palsy in children born at term, with an aim to assess whether the potential for prevention of these risk factors has been adequately explored. They identified antenatal risk factors that included placen-

tal dysfunction or abnormalities, major and minor birth defects and low birthweight, while intrapartum risk factors were meconium aspiration, caesarean section, vacuum or breech delivery. Strategies for possible prevention of cerebral palsy in children born at term were only recognised to currently exist for two of these risk factors: reducing low birthweight (reducing heavy alcohol consumption during pregnancy), and reducing meconium aspiration (amnioinfusion in settings with limited perinatal surveillance; curtailment of post-term pregnancy). This review highlighted that prevention strategies for cerebral palsy in term born infants are urgently required, and called for heightened efforts focused on preventing identified risk factors, and thus, interrupting pathways to cerebral palsy.

A systematic review by Hines 2015 was designed to systematically review meta-analyses and randomised trials of interventions for infants at risk of cerebral palsy, to determine if consensus existed in study endpoints. The review identified that of the 685 Cochrane Pregnancy and Childbirth or Neonatal reviews published at the time, 177 addressed acknowledged risk factors for cerebral palsy (such as preterm birth, pre-eclampsia, or neonatal infection). A sample of 22 reviews, with 165 included randomised trials were selected, which addressed interventions such as fetal monitoring during labour; preventing preterm labour, hypertension, and pre-eclampsia; timing of umbilical cord clamping; maternal or neonatal infection, or both; minimising permanent brain injury; infant respiratory function; and glutamine supplementation. Hines 2015 identified that of the 22 reviews, 18 specified neurodevelopmental outcomes, such as cerebral palsy, blindness, deafness, or intellectual impairment, but of the 203 relevant randomised trials in those reviews, only 22 (11%) contributed data to meta-analyses for these outcomes. Similar to our overview, Hines 2015 identified an urgent need for long-term follow-up after such antenatal and intrapartum interventions, and concluded that "Variation in outcome measurement and long-term follow-up has hampered the ability of RCTs to contribute data on important outcomes for CP, resulting in lost opportunities to measure the impact of maternal and neonatal interventions".

AUTHORS' CONCLUSIONS

Implications for practice

This overview summarises the evidence from Cochrane reviews of randomised controlled trials regarding the effects of antenatal and intrapartum intervention on cerebral palsy, and can be used by researchers, funding bodies, policy makers, clinicians, and consumers to aid decision-making and evidence translation.

There is high-quality evidence that magnesium sulphate for neuroprotection of the fetus, given to women at risk of preterm birth, can prevent cerebral palsy better than placebo. Moderate-quality evidence shows that any prophylactic antibiotics for women in preterm labour with intact membranes may increase the risk of cerebral palsy more than no antibiotics. Moderate-quality evidence shows that immediate birth of preterm babies with suspected fetal compromise may increase the risk of cerebral palsy more than deferred birth. There is moderate-quality evidence showing no clear difference in the risk of cerebral palsy between repeat doses of corticosteroids and a single course for women at risk of preterm birth. No conclusions were possible for other interventions assessed in this overview, because of low- to very-low quality evidence.

The scope of this overview was limited to the effects of interventions on cerebral palsy, and pre-specified secondary review outcomes. Consultation of the included Cochrane reviews is required to formally assess additional benefits and harms of these interventions, including impacts on risk factors for cerebral palsy, (such as the reduction in intraventricular haemorrhage for preterm babies following exposure to antenatal corticosteroids).

Implications for research

This overview highlights areas where there was insufficient evidence to draw conclusions on the effects of several antenatal and intrapartum interventions on cerebral palsy, and it should be used to generate research questions and priorities. As cerebral palsy is rarely diagnosed at birth, has diverse risk and causal factors, and is diagnosed in approximately one in 500 children, it is a challenging outcome for investigators of such interventions to measure and report. To date, a small proportion of Cochrane reviews assessing antenatal and intrapartum interventions have been able to report on cerebral palsy, which may be due to a number of reasons, including: a lack of primary research (with few randomised trials of antenatal and intrapartum interventions conducting long-term follow-up of children), lack of reporting on cerebral palsy by randomised trials, lack of reporting on cerebral palsy by relevant Cochrane reviews (due to not pre-specifying it as an outcome of interest, not clearly defining long-term follow-up results, or not being 'up-to-date'), or the absence of Cochrane reviews assessing relevant interventions.

With greater understanding of the diverse risk factors and causes of cerebral palsy, there is an urgent need for long-term follow-up of interventions addressing risk factors for cerebral palsy, as well as a need to consider the use of relatively new interim assessments (such as the General Movements Assessment), to measure impact on cerebral palsy. Such studies must be rigorous in their design, and aim for consistency in cerebral palsy outcome measurement and reporting to facilitate pooling of outcome data, therefore, informing research efforts aimed at prevention of cerebral palsy.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Characteristics of excluded reviews

Review ID	Reason for exclusion
Abou El Senoun 2014	Secondary neonatal outcomes included: • Disability at time of childhood follow-up (as defined by authors). • Serious disability (as defined by authors) after two years. No outcome data for these outcomes.
Bricker 2015	Primary outcomes included: • Neurodevelopment at age two. No outcome data for this outcome.
Buchanan 2010	Secondary neonatal outcomes included: • Disability at time of childhood follow-up. No outcome data for this outcome.
Chapman 2014	No outcomes focused on development or disability at follow-up
Crowley 2016	Secondary infant outcomes included: • Neurodevelopmental delay at 12 months and 24 months.

Table 1. Characteristics of excluded reviews (*Continued*)

	No outcome data for this outcome.
Dare 2006	foetal, neonatal, and infant outcomes included: • Disability at time of childhood follow-up. No outcome data for this outcome
East 2014	Primary outcomes included: • Long-term neurodevelopmental outcome. No outcome data for this outcome.
Gomi 2015	No outcomes focused on development or disability at follow-up
Han 2013	Primary outcomes included: • Any neurological disability at follow-up. No outcome data for this outcome.
Hofmeyr 2015	Primary outcomes included: • Perinatal or infant death (excluding fatal anomalies) or disability in childhood. Secondary long-term infant outcomes included: • Disability in childhood, as defined by trial authors. No outcome data for these outcomes.
Hopkins 2002	No outcomes focused on development or disability at follow-up
Kenyon 2013	Secondary outcome included: • Long-term health outcomes (as defined by trial authors) after at least two years. Outcome data only reported for 'Serious childhood disability at seven years'
Khunpradit 2011	Secondary outcomes include: • Neonatal neurodevelopment. No outcome data for this outcome.
Kiiza 2015	Protocol. Secondary baby outcomes will include: • Long-term neurodevelopmental outcome.
Lewin 2010	No outcomes focused on development or disability at follow-up
Lutomski 2015	No outcomes focused on development or disability at follow-up
Mackeen 2014	No outcomes focused on development or disability at follow-up
Neilson 2003	No outcomes focused on development or disability at follow-up
Olsen 2012	No outcomes focused on development or disability at follow-up
Othman 2007	No outcomes focused on development or disability at follow-up
Sangkomkamhang 2015	No outcomes focused on development or disability at follow-up

Table 1. Characteristics of excluded reviews (*Continued*)

Say 1996	No outcomes focused on development or disability at follow-up
Say 1996a	No outcomes focused on development or disability at follow-up
Say 1996b	No outcomes focused on development or disability at follow-up
Say 1996c	No outcomes focused on development or disability at follow-up
Say 2001	No outcomes focused on development or disability at follow-up
Say 2003	No outcomes focused on development or disability at follow-up
Say 2003a	No outcomes focused on development or disability at follow-up
Say 2003b	No outcomes focused on development or disability at follow-up
Siegfried 2011	No outcomes focused on development or disability at follow-up
Siriwachirachai 2014	No outcomes focused on development or disability at follow-up
Stan 2013	Secondary outcomes included: • Long-term sequelae: neurologic impairment and chronic lung disease. No outcome data for this outcome.
Thomas 2007	Outcomes included: • Adverse neonatal outcomes in terms of longer-term neurological outcomes. No outcome data for this outcome.

Table 2. Characteristics of included reviews

Review ID	Date of search; date assessed as up-to-date	No. included trials; countries and years of publication	No. participants in included trials	Inclusion criteria for "Types of participants"	Relevant comparison interventions (no. trials and participants)	Overview outcomes for which data were reported (prespecified unless stated otherwise)
Abalos 2014	30 April 2013	49 RCTs 34 RCTs in industrialised countries (Australia, France, Hong Kong, Ireland, Israel, Italy, Sweden, UK and USA)	4723 women and their babies	women with mild to moderate hypertension during pregnancy, regardless of whether or not they had proteinuria, previous antihy-	any antihypertensive drug versus no drugs (29 RCTs, 3350 women)	cerebral palsy reported as a secondary outcome primary outcome was impaired long-term growth and development in in-

Table 2. Characteristics of included reviews (*Continued*)

		15 RCTs in low- or middle-income countries (Argentina, Brazil, Caribbean Islands, India, South Africa, Sudan and Venezuela) RCTs published in: 1960s: 1 1970s: 2 1980s: 22 1990s: 17 2000s: 5 2010s; 2		pertensive treatment, or whether the pregnancy was singleton or multiple		fancy and childhood
Alfirevic 2013	Search: 31 December 2012 Up-to-date: 31 January 2013	13 RCTs (1 qRCT) No. RCTs in: Australia: 2 Denmark: 1 Greece: 1 India: 1 Ireland: 2 Pakistan: 1 Sweden: 1 UK: 1 USA: 3 RCTs published in: 1970s: 4 1980s: 6 1990s: 2 2000s: 1	37,715 women and their babies	pregnant women in labour and their babies	continuous cardiotocography versus intermittent auscultation (12 RCTs, 33, 681 women)	cerebral palsy reported as a primary review outcome
Churchill 2013	Search: 28 February 2013 Up-to-date: 10 July 2013	4 RCTs No. RCTs in: Egypt: 1 Europe: 1 South Africa: 1 USA: 1 RCTs published in: 1990s: 2 2000s: 2	425 women and their babies	women with severe pre-eclampsia, up to and including 34 weeks' gestation	interventionist care versus expectant (delayed delivery) care (4 RCTs, 425 women)	cerebral palsy reported as a secondary review outcome pre-specified outcome was 'measures of long-term growth and development, such as important im-

Table 2. Characteristics of included reviews (*Continued*)

						pairment and cerebral palsy'
Crowther 2010	Search: 20 December 2010 Up-to-date: 15 February 2011	8 RCTs Countries of trials not reported RCTs published in: 1980s: 4 1990s: 3 2000s: 1	879 women and their babies	women at risk of imminent very preterm birth	vitamin K versus control (8 RCTs, 879 women)	cerebral palsy reported as a primary review outcome pre-specified outcome was long-term neurodevelopment
Crowther 2010a	Search: 20 December 2010 Up-to-date: 9 January 2011	9 RCTs Countries of trials not reported RCTs published in: 1980s: 4 1990s: 5	1752 women and their babies	women at risk of imminent very preterm birth (before 34 weeks' gestation)	phenobarbital versus control (9 RCTs, 1752 women)	cerebral palsy, motor dysfunction (other neuromotor impairment) reported as primary review outcomes pre-specified outcome was 'long-term neurodevelopment'
Crowther 2014	31 January 2014	37 RCTs (4 qRCTs) No. RCTs in: China: 3 Iran: 5 Italy: 1 Mexico: 1 Thailand: 1 Turkey: 1 USA: 25 RCTs published in: 1980s: 7 1990s: 18 2000s: 10 2010s: 2	3571 women and their babies	women considered to be in preterm labour given magnesium sulphate to reduce their risk of preterm birth	magnesium sulphate versus placebo, no treatment, or other tocolytic agent (37 RCTs, 3571 women)	cerebral palsy reported as a secondary review outcome primary review outcome was a composite outcome including cerebral palsy, listed as 'serious infant outcome' ("...death or chronic lung disease...grade three or four intraventricular haemorrhage or periventricular leukomalacia, major neurosensory disabil-

Table 2. Characteristics of included reviews (*Continued*)

						ity (legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment...))"
Crowther 2015	20 January 2015	10 RCTs No. RCTs in: Australia and New Zealand: 1 Canada: 1 Finland: 1 India: 1 USA: 5 20 countries: 1 RCTs published in: 2000s: 9 2010s: 1	4733 women and their babies	women considered to be at risk of preterm birth who had already received a single course of prenatal corticosteroid seven or more days previously	repeat doses of prenatal corticosteroids versus placebo or no treatment (10 RCTs, 4733 women)	cerebral palsy reported as a secondary review outcome; composite primary outcomes that included cerebral palsy • survival free of any disability (however defined by authors) • survival free of major disability (however defined by authors) • major neurosensory disability (not pre-specified) • disability at childhood follow-up (however defined by authors) • composite serious outcome (however defined by authors)

Table 2. Characteristics of included reviews (*Continued*)

Dodd 2013	14 January 2013	36 RCTs No. RCTs in: Albania: 1 Brazil: 1 Denmark and Austria: 1 Egypt: 3 Finland: 1 France: 3 India: 2 Iran: 5 Italy: 1 Netherlands: 1 Spain: 1 Turkey: 1 UK: 1 USA: 11 international: 3 RCTs published in: 1970s: 2 1980s: 2 2000s: 13 2010s: 19	8523 women and their babies	pregnant women considered to be at increased risk of preterm birth: • Past history of spontaneous preterm birth • Multiple pregnancy • Ultrasound identified short cervical length • fetal fibronectin testing • Following acute presentation with symptoms or signs of threatened preterm labour • Other reason considered to be at increased risk of preterm birth	progesterone versus placebo or no treatment (11 RCTs, 1899)	cerebral palsy reported as a secondary review outcome motor dysfunction, prespecified as motor impairment, reported as secondary review outcome
Doyle 2009	Search: 31 August 2008 Up-to-date: 5 November 2008	5 RCTs No. RCTs in: Australia and New Zealand: 1 France: 1 USA: 2 international; 1 (predominately in developing countries) RCTs published in: 2000s: 5	5560 women and their 6145 babies	women considered to be at risk of preterm birth	magnesium sulphate versus placebo (5 RCTs, 6145 babies)	cerebral palsy; cerebral palsy or death; severity of cerebral palsy (mild, moderate, moderate to severe, severe cerebral palsy); composite outcomes including cerebral palsy (any neurologic impairment; major neurological disability; death or any neurologic impairment; death or major neuro-

Table 2. Characteristics of included reviews (*Continued*)

						logical disability) ; motor dysfunction (substantial gross motor dysfunction; death or substantial gross motor dysfunction) reported as primary outcomes pre-specified outcomes were: neurological impairments (developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than one standard deviation (SD) below the mean) , cerebral palsy (abnormality of tone with motor dysfunction) , blindness (corrected visual acuity worse than 6/60 in the better eye) , or deafness (hearing loss requiring amplification or worse)); neurological disabilities (abnormal neurological function caused by any of the preceding impairments) at follow-up later

Table 2. Characteristics of included reviews (*Continued*)

						in childhood; substantial gross motor dysfunction (motor dysfunction such that the child was not walking at age two years or later, or the inability to grasp and release a small block with both hands); major neurological disability (legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than two SD below the mean)); paediatric mortality combined with cerebral palsy, substantial gross motor dysfunction, neurological impairment, or major neurological disability (these combined outcomes recognise the competing risks of death or survival with neurological problems)

Table 2. Characteristics of included reviews (*Continued*)

Duley 2010	Search: 4 June 2010 Up-to-date: 1 September 2010	15 RCTs No. RCTs in: Denmark: 1 India; 1 Malaysia: 1 Mexico: 2 South Africa: 2 Taiwan: 1 USA: 5 international: 2 (1 in 33 countries, with 85% recruitment in low- and middle-income countries; 1 in 8 countries) RCTs published in: 1990s: 10 2000s: 5	15,570 women and their babies	any women with pre-eclampsia, regardless of whether: before or after delivery, a singleton or multiple pregnancy, or whether an anticonvulsant had been given before trial entry	magnesium sulphate versus placebo or no anticonvulsant (6 RCTs, 11,444 women)	severe cerebral palsy; other composite outcomes including cerebral palsy (neurosensory disability; death or neurosensory disability) were all reported as secondary review outcomes pre-specified outcomes were 'long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay and cerebral palsy'
Flenady 2013	Search: 31 August 2013 Up-to-date: 3 October 2013	14 RCTs No. RCTs in: Canada: 1 Chile: 1 Denmark: 1 Germany: 1 Iran: 1 South Africa: 1 Uruguay: 1 USA: 6 international: 1 RCTs published in: 1980s: 1 1990s: 10 2000s: 3	7837 women and their babies	women thought to be in preterm labour with intact membranes, between 20 and 36 completed weeks of gestation	any antibiotics versus no antibiotics (14 RCTs, 7837 women)	cerebral palsy reported as a primary review outcome pre-specified outcome was 'major long-term infant neurosensory impairment'
Magee 2003	Search: 4 July 2012 (*results added to Studies awaiting classification*) Up-to-date: 30 January 2004	29 RCTs No. RCTs in: Argentina: 1 Australia: 2 Brazil: 1 England: 5 Fr Caribbean: 1 France: 3	2548 women and their babies	women with mild to moderate hypertension during pregnancy, however defined	beta-blockers versus placebo or no beta-blocker (13 RCTs, 1480 women)	Cerebral palsy reported as a review outcome, rather than primary or secondary pre-specified

Table 2. Characteristics of included reviews (*Continued*)

		Hong Kong: 1 India: 1 Israel: 4 Scotland: 4 Sweden: 3 USA: 2 Venezuela: 1 RCTs published in: 1970s: 1 1980s: 17 1990s: 11				outcome was 'measures of long-term health and development such as cerebral palsy'
Neilson 2014	31 December 2013	28 RCTs (20 RCTs contributed data) No. RCTs in: Australia: 1 Canada: 1 Europe: 6 Iran: 1 Italy: 1 Japan: 1 Sweden: 1 USA: 10 not reported: 6 RCTs published in: 1960s: 1 1970s: 5 1980s: 18 1990s: 3 2010s: 1	2715 women and their babies in 20 RCTs	pregnant women assessed as being in spontaneous preterm labour and considered suitable for tocolytic agents	betamimetics versus placebo (12 RCTs, 1367 women)	Cerebral palsy reported as a primary review outcome pre-specified outcome was 'abnormal long-term neurodevelopmental status at more than 12 months corrected age (moderate to severe developmental delay, cerebral palsy, sensory impairment, for example, blind and deaf, or a combination)'
Roberts 2006	Search: 30 April 2010 (added the search to Studies awaiting classification) Up-to-date: 15 May 2006	21 RCTs No. RCTs in: Brazil: 1 Canada: 1 Finland: 2 Jordan: 1 RCT Netherlands: 1 New Zealand: 1 South Africa: 1 Spain: 1 Tunisia: 1 UK: 1 USA: 10 RCTs published	over 3999 women (data available for 3885 women and their babies)	women with a singleton or multiple pregnancy, expected to deliver preterm as a result of either spontaneous preterm labour, preterm pre-labour rupture of the membranes, or elective preterm delivery	antenatal corticosteroids versus placebo or no treatment (21 RCTs, 3885 women)	cerebral palsy reported as a secondary review outcome other composite outcome including cerebral palsy (neurodevelopmental delay) reported as a primary review outcome pre-specified pri-

Table 2. Characteristics of included reviews (*Continued*)

		in: 1970s: 3 1980s: 8 1990s: 8 2000s: 2				mary outcome was 'neurodevelopmental disability' at follow-up (blindness, deafness, moderate/severe cerebral palsy (however defined by authors), or development delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than 2 SD below population mean))'
Stock 2016	30 April 2016	1 RCT 1 RCT in Belgium, Cyprus, Czech Republic, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Saudi Arabia, Slovenia, United Kingdom RCT published in 2000s	548 women and their babies	pregnant women at less than 36 weeks' gestation in whom there was clinical suspicion of fetal compromise as defined by trialists	Immediate delivery versus deferred delivery (1 RCT, 548 women)	cerebral palsy reported as a secondary outcome other composite outcomes including cerebral palsy (death or disability at or after two years of age) reported as a primary review outcome 'neurodevelopmental impairment at or after two years of age' reported as a secondary outcome 'death or severe disability in childhood' reported but not pre-specified

Abbreviation: RCT: randomised controlled trial

Table 3. Risk of bias assessments from included reviews

Review ID	Summary of trial limitations (risk of bias)
Abalos 2014	**Sequence generation:** 12 RCTs low risk; 35 RCTs unclear risk; 2 RCTs high risk **Allocation concealment:** 17 RCTs low risk; 32 RCTs unclear risk **Blinding (participants and personnel):** 10 RCTs low risk; 1 RCT unclear risk; 38 RCTs high risk **Blinding (outcome assessors):** 10 RCTs low risk; 2 RCTs unclear risk; 37 RCTs high risk **Incomplete outcome data:** 45 RCTs low risk; 4 RCTs high risk **Selective reporting:** 9 RCTs low risk; 40 RCTs unclear risk **Other:** 23 RCTs low risk; 24 RCTs unclear risk; 2 RCTs high risk **Overall:** "Overall, the quality of the studies included in this review is moderate to poor"
Alfirevic 2013	**Sequence generation:** 3 RCTs low risk; 8 RCTs unclear risk; 2 RCTs high risk **Allocation concealment:** 3 RCTs low risk; 6 RCTs unclear risk; 4 RCTs high risk **Blinding (participants and personnel):** 13 RCTs high risk **Blinding (outcome assessors):** 12 RCTs unclear risk; 1 RCT high risk **Incomplete outcome data:** 8 RCTs low risk; 3 RCTs unclear risk; 2 RCTs high risk **Selective reporting:** 13 RCTs high risk **Other:** 13 RCTs low risk **Overall:** Only 2 RCTs were judged to be of high quality. "The overall quality of the evidence can best be described as low to moderate"
Churchill 2013	**Sequence generation:** 3 RCTs low risk; 1 RCT unclear risk **Allocation concealment:** 3 RCTs low risk; 1 RCT unclear risk **Blinding (participants and personnel):** 1 RCT low risk; 3 RCTs unclear risk **Blinding (outcome assessors):** 1 RCT low risk; 3 RCTs unclear risk **Incomplete outcome data:** 1 RCT low risk; 2 RCTs unclear risk; 1 RCT high risk **Selective reporting:** 4 RCTs low risk **Other:** 1 RCT low risk; 2 RCTs unclear; 1 RCT high risk **Overall:** "Overall, two trials were judged to have a low risk of bias, one was unclear and one a high risk of bias"
Crowther 2010	**Sequence generation:** 2 RCTs low risk; 4 RCTs unclear risk; 2 RCTs high risk **Allocation concealment:** 7 RCTs unclear risk; 1 RCT high risk **Blinding:** 2 RCTs low risk; 1 RCT unclear risk; 5 RCTs high risk **Incomplete outcome data:** 3 RCTs low risk; 4 RCTs unclear risk; 1 RCT high risk **Selective reporting:** 6 RCTs low risk; 2 RCTs unclear risk **Other:** 5 RCTs low risk; 2 RCTs unclear risk; 1 RCT high risk **Overall:** "The trials were of variable quality."
Crowther 2010a	**Sequence generation:** 1 RCT low risk; 4 RCTs unclear risk; 4 RCTs high risk **Allocation concealment:** 7 RCTs unclear risk; 1 RCT high risk; 1 RCT: not reported **Blinding:** 4 RCTs low risk; 1 RCT unclear risk; 4 RCTs high risk **Incomplete outcome data:** 1 RCT low risk; 5 RCTs unclear risk; 3 RCTs high risk **Selective reporting:** 9 RCTs low risk **Other:** 6 RCTs low risk; 1 RCT unclear risk; 2 RCTs high risk **Overall:** "Poor-quality trials contribute excessively to the weight in the overall analysis due to the higher rate of adverse outcomes in those trials"

Table 3. Risk of bias assessments from included reviews (*Continued*)

Crowther 2014	**Sequence generation:** 15 RCTs low risk; 18 RCTs unclear risk; 4 RCTs high risk **Allocation concealment:** 6 RCTs low risk; 27 RCTs unclear risk; 4 RCTs high risk **Blinding (participants and personnel):** 4 RCTs low risk; 7 RCTs unclear risk; 26 RCTs high risk **Blinding (outcome assessors):** 1 RCT low risk; 35 RCTs unclear risk; 1 RCT high risk **Incomplete outcome data:** 20 RCTs low risk; 15 RCTs unclear risk; 2 RCTs high risk **Selective reporting:** 11 RCTs low risk; 19 RCTs unclear risk; 7 RCTs high risk **Other:** 17 RCTs low risk; 20 RCTs unclear risk **Overall: "**Overall, we judged the included trials to be of moderate to high risk of bias"
Crowther 2015	**Sequence generation:** 8 RCTs low risk; 2 RCTs unclear risk **Allocation concealment:** 10 RCTs low risk **Blinding (participants and personnel):** 9 RCTs low risk; 1 RCT high risk **Blinding (outcome assessors):** 4 RCTs low risk; 6 RCTs unclear risk **Incomplete outcome data:** 7 RCTs low risk; 3 RCTs unclear risk **Selective reporting:** 9 RCTs low risk; 1 RCT unclear risk **Other:** 7 RCTs low risk; 3 RCTs high risk **Overall:** "Overall, the included trials were assessed as having a low to moderate risk of bias"
Dodd 2013	**Sequence generation:** 23 RCTs low risk; 13 RCTs unclear risk **Allocation concealment:** 23 RCTs low risk; 13 RCTs unclear risk **Blinding (participants and personnel):** 24 RCTs low risk; 7 RCTs unclear risk; 4 RCTs high risk **Blinding (outcome assessors):** 15 RCTs low risk; 17 RCTs unclear risk; 4 RCTs high risk **Incomplete outcome data:** 31 RCTs low risk; 5 RCTs unclear risk **Selective reporting:** 25 RCTs low risk; 10 RCTs unclear risk; 1 RCT high risk **Other:** 21 RCTs low risk; 15 RCTs unclear risk **Overall:** "The overall quality of the included trials varied from good to fair"
Doyle 2009	**Sequence generation:** 4 RCTs low risk; 1 RCT unclear risk **Allocation concealment:** 4 RCTs low risk; 1 RCT unclear risk **Blinding:** 3 RCTs low risk; 2 RCT unclear risk **Incomplete outcome data:** 2 RCTs low risk; 3 RCT unclear risk **Selective reporting:** 4 RCTs low risk; 1 RCT unclear risk **Overall:** "Overall, the methodological quality of the trials was relatively good, with a low risk of bias. However, the quality was better, and the risk of bias lower, in some studies compared with others"
Duley 2010	**Sequence generation:** 6 RCTs low risk; 9 RCTs unclear risk **Allocation concealment:** 5 RCTs low risk; 9 RCTs unclear risk; 1 RCT high risk **Blinding:** 4 RCTs low risk; 3 RCTs unclear risk; 8 RCTs high risk **Incomplete outcome data:** 7 RCTs low risk; 3 RCTs unclear risk; 5 RCTs high risk **Overall:** "The quality of the studies included in this review ranged from excellent to poor. However, most of the poor quality studies were small. The large study comparing magnesium sulphate with placebo was of high quality"
Flenady 2013	**Sequence generation:** 7 RCTs low risk; 7 RCTs unclear risk **Allocation concealment:** 9 RCTs low risk; 5 RCTs unclear risk **Blinding (participants and personnel):** 12 RCTs low risk; 2 RCTs high risk **Blinding (outcome assessors):** 12 RCTs low risk; 2 RCTs high risk **Incomplete outcome data:** 13 RCTs low risk; 1 RCT unclear risk (long-term: 1 RCT low risk; 13 RCTs unclear risk)

Table 3. Risk of bias assessments from included reviews (*Continued*)

	Selective reporting: 12 RCTs low risk; 2 RCTs unclear risk **Other:** 13 RCTs low risk; 1 RCT unclear risk **Overall:** "Overall the quality of the included trials was good"
Magee 2003	**Allocation concealment:** adequate in 5 RCT **Double blinding (of physicians and patients) for outcome assessment:** 7 RCTs **For maternal and pregnancy outcomes, follow up of greater than 90%:** 20 RCTs **Overall:** "The quality of these trials was poor"
Neilson 2014	**Sequence generation:** 12 RCTs low risk; 16 RCTs unclear risk **Allocation concealment:** 7 RCTs low risk; 21 RCTs unclear risk **Blinding (participants and personnel):** 15 RCTs low risk; 1 RCTs unclear risk; 12 RCTs high risk **Blinding (outcome assessors):** 9 RCTs low risk; 8 RCTs unclear risk; 11 RCTs high risk **Incomplete outcome data:** 16 RCTs low risk; 10 RCTs unclear risk; 2 RCTs high risk **Selective reporting:** 1 RCT low risk; 26 RCTs unclear risk; 1 RCT high risk **Other:** 8 RCTs low risk; 19 RCTs unclear risk; 1 RCT high risk **Overall:** not detailed
Roberts 2006	**Allocation concealment:** 8 RCTs: A (adequate); 12 RCTs: B (unclear); 1 RCT: C (inadequate) **Overall:** not detailed
Stock 2016	**Sequence generation:** 1 RCT low risk **Allocation concealment:** 1 RCT low risk **Blinding (participants and personnel):** 1 RCT high risk **Blinding (outcome assessors):** 1 RCT low risk **Incomplete outcome data:** 1 RCT low risk (high for childhood outcomes) **Selective reporting:** 1 RCT low risk **Other:** 1 RCT high risk **Overall:** "large study of good quality"

Abbreviation: RCT: randomised controlled trial

Table 4. AMSTAR assessments for included reviews

Review ID	AMSTAR criteria											Total score
	A priori design	Duplicate selection and extraction	Comprehensive search	Grey literature considered	Included and excluded studies lists	Characteristics of included studies	Quality assessed and documented	Quality considered for conclusions	Methods for combining studies appropriate	Publication bias considered or assessed	Conflicts stated	
Abalos 2014	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY

Table 4. AMSTAR assessments for included reviews (*Continued*)

Alfire-vic 2013	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUAL-ITY
Churchill 2013	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUAL-ITY
Crowther 2010	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUAL-ITY
Crowther 2010a	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUAL-ITY
Crowther 2014	√	√	√	√	√	√	√	√	√	√	√	11/11 HIGH QUAL-ITY
Crowther 2015	√	√	√	√	√	√	√	√	√	√	√	11/11 HIGH QUAL-ITY
Dodd 2013	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUAL-ITY
Doyle 2009	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUAL-ITY
Duley 2010	√	√	√	√	√	√	√	√	?	×	×	8/11 HIGH QUAL-ITY
Flenady 2013	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUAL-ITY

Table 4. AMSTAR assessments for included reviews (*Continued*)

Magee 2003	√	√	√	√	√	√	√	√	?	×	×	8/11 HIGH QUALITY
Neilson 2014	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Roberts 2006	√	√	√	√	√	√	√	√	?	×	√	9/11 HIGH QUALITY
Stock 2016	√	√	√	√	√	√	√	√	N/A	√	×	9/10 HIGH QUALITY

√: item adequately addressed; ?: unclear whether item addressed; ×: item not adequately addressed

Table 5. ROBIS assessments for included reviews

Review ID	ROBIS domains				Overall risk of bias
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	
Abalos 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Alfirevic 2013	Low risk	Low risk	Low risk	Low risk	LOW RISK
Churchill 2013	Low risk	Low risk	Low risk	Low risk	LOW RISK
Crowther 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Crowther 2010a	Low risk	Low risk	Low risk	Low risk	LOW RISK
Crowther 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Crowther 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Dodd 2013	Low risk	Low risk	Low risk	Low risk	LOW RISK
Doyle 2009	Low risk	Low risk	Low risk	Low risk	LOW RISK
Duley 2010	Low risk	Low risk	Low risk	Unclear risk	LOW RISK

Table 5. ROBIS assessments for included reviews (*Continued*)

Flenady 2013	Low risk	Low risk	Low risk	Low risk	LOW RISK
Magee 2003	Low risk	Low risk	Low risk	Unclear risk	LOW RISK
Neilson 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Roberts 2006	Low risk	Low risk	Low risk	Unclear risk	LOW RISK
Stock 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK

Table 6. Summary of findings: all comparisons measuring cerebral palsy

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Interventions for the treatment of mild to moderate hypertension							
Any antihypertensive drug versus placebo for mild to moderate hypertension during pregnancy (Abalos 2014) and Oral beta-blockers versus placebo for mild to moderate hypertension during pregnancy (Magee 2003)	Cerebral palsy at 1 year (definition not clear; one child with 'spastic quadriparesis with a severe pseudobulbar palsy') assessed by clinical evaluation (assessment method taken from RCT manuscript as not detailed in reviews)	18 per 1000 (1/55)	6 per 1000 (0 to 146)	RR 0.33 (95% CI 0.01 to 8.01)	110 (1 RCT)	VERY LOW	study limitations (-1): 1 RCT with unclear sequence generation, allocation concealment, and selective reporting Imprecision (-2): Wide confidence intervals crossing line of no effect; 1 small RCT with few events
Interventions for the treatment of pre-eclampsia							
Interventionist care versus expectant (delayed delivery) care for severe pre-eclampsia (Churchill 2013)	Cerebral palsy at 2 years (definition not clear) assessed by family practitioner or paediatrician us-	8 per 1000 (1/121)	50 per 1000 (6 to 398)	RR 6.01 (95% CI 0.75 to 48.14)	262 (1 RCT)	LOW	imprecision (-2): wide confidence intervals crossing line of no effect; 1 small RCT with few

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	ing short questionnaire (assessment method taken from RCT manuscript as not detailed in review)						events
Magnesium sulphate versus placebo for women with pre-eclampsia (Duley 2010)	Severe cerebral palsy at 18 months defined as 'not walking or unlikely to walk unaided by 24 months; children screened with Ages and Stages Questionnaires; screen-positive and a sample of screen-negative children had clinical and neurodevelopmental assessments (using Bayley Scales of Infant Development; Griffiths Tests, or other); if this was not possible, clinical history and examination (using the Health Status Questionnaire) (definition and assessment method taken from RCT	6 per 1000 (9/1464)	2 per 1000 (1 to 8)	RR 0.34 (95% CI 0.09 to 1. 26)	2895 (1 RCT)	LOW	study limitations (-1): 1 RCT with unclear risk of attrition bias for this outcome (2895 of 6922 children included in original RCT) imprecision (-1): wide confidence intervals crossing line of no effect

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	manuscript as not detailed in review)						
Interventions for the diagnosis and prevention of fetal compromise in labour							
Continuous cardiotocography (CTG) versus intermittent auscultation (IA) for fetal assessment during labour (Alfirevic 2013)	Cerebral palsy at 18 months to 4 years • 1 RCT: defined as 'non-progressive disorder of movement or posture due to a defect in or damage to the developing brain'; a developmental paediatrician performed neurological examinations at 18 months • 1 RCT: definition not clear; children with abnormal neurological signs in the neonatal period underwent a general physical and detailed neurological examination by a paediatrician at 4 years; other cases identified from records of specialist	3 per 1000 (17/6643)	4 per 1000 (2 to 9)	average RR 1.75 (95% 0.84 to 3.63)	13,252 (2 RCTs)	LOW	quality of evidence (GRADE), taken from published review: "study limitations (-1): most of the pooled effect provided by studies "B" or "C" without a substantial proportion (i.e. < 40% (actual 0% weight) from studies "C" imprecision (-1): 95% confidence interval around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit favouring IA"

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	remedial clinics (definitions and assessment methods taken from RCT manuscripts as not detailed in review)						
Interventions for the prevention of preterm birth							
Prenatal administration of progesterone versus placebo for preventing preterm birth in women with a previous history spontaneous preterm birth (singletons) (Dodd 2013)	Cerebral palsy at 4 years, definition not clear; assessed by general physical examination by paediatrician or nurse practitioner, or from chart abstraction (age and assessment method taken from RCT manuscript as not detailed in review)	12 per 1000 (1/82)	2 per 1000 (0 to 42)	RR 0.14 (95% 0.01 to 3.48)	274 (1 RCT)	LOW	imprecision (-2): wide confidence intervals crossing line of no effect; 1 small RCT with few events
Any prophylactic antibiotics versus no antibiotics for inhibiting preterm labour with intact membranes (Flenady 2013)	Cerebral palsy at 7 years, definition not clear; measured using proxy information provided by parents through a postal questionnaire (or by telephone in a small num-	16 per 1000 (12/770)	28 per 1000 (15 to 52)	RR 1.82 (95% CI 0.99 to 3.34)	3173 (1 RCT)	MODERATE	imprecision (-1): wide confidence interval crossing the line of no effect

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	ber) using validated tools						
Betamimetics versus placebo for inhibiting preterm labour (Neilson 2014)	Cerebral palsy at 18 months, definition not clear; assessed by paediatrician examination (assessment method taken from RCT manuscript as not detailed in review)	41 per 1000 (5/121)	8 per 1000 (1 to 67)	RR 0.19 (95% CI 0.02 to 1. 63)	246 (1 RCT)	LOW	study limitations (-1): 1 RCT at unclear risk of attrition bias for this outcome imprecision (-1): wide confidence intervals crossing line of no effect; 1 small RCT
Magnesium sulphate versus other tocolytic agents for preventing preterm birth in threatened preterm labour (Crowther 2014)	Cerebral palsy at 18 months, definition not clear; assessed by neurodevelopment examinations at 4, 8, 12, and 18 months, with diagnoses made or verified by developmental paediatrician after 18 month examination (assessment method taken from RCT manuscript as not detailed in review)	59 per 1000 (3/51)	8 per 1000 (1 to 148)	RR 0.13 (95% CI 0.01 to 2. 51)	106 (1 RCT)	VERY LOW	study limitations (-1): 1 RCT with unclear risk of selection, attrition, and reporting bias, and high risk of performance bias imprecision (-2): wide confidence intervals crossing line of no effect; 1 small RCT with few events
Interventions prior to preterm birth for fetalmaturation or neuroprotection							
Phenobarbital versus placebo or no treatment prior to preterm birth for preventing neonatal periventric-	Cerebral palsy at 18 months to 3 years • 1 RCT: defined as presence of hypertonicity,	91 per 1000 (23/252)	61 per 1000 (37 to 117)	RR 0.71 (95% CI 0.40 to 1. 28)	517 (2 RCTs)	LOW	study limitations (-1) : 2 RCTs with limitations: 1 with high risk of selection bias, bias

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

ular haemorrhage (Crowther 2010a)	hyperreflexia, and dystonic or spastic movement quality in the affected extremity (including diplegia, hemiplegia, triplegia, or quadriplegia); assessed by certified examiners trained to perform neurologic examinations at 18 months • 1 RCT: described as cerebral palsy associated with motor delay (diplegia, monoplegia, quadriplegia, and hemiplegia); assessed by trained nurse practitioner using detailed physical and neurologic examination at 3 years (definitions and assessment methods taken from RCT manuscript as not detailed in review)						due to lack of blinding and attrition bias; 2 with unclear risk of selection bias imprecision (-1): wide confidence intervals crossing line of no effect

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

Vitamin K versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010) *and* Phenobarbital versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010a)	Cerebral palsy at 7 years, definition not clear; method of assessment not clear	79 per 1000 (12/151)	61 per 1000 (26 to 140)	RR 0.77 (95% CI 0.33 to 1.76)	299 (1 RCT)	VERY LOW	study limitations (-1): 1 RCT with unclear risk of selection bias, and high risk of attrition bias indirectness (-1): dual intervention of vitamin K and phenobarbital imprecision (-1): wide confidence intervals crossing line of no effect
Magnesium sulphate versus placebo for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009)	Cerebral palsy at 18 months to 2 years • 1 RCT: defined as abnormalities of tone and loss of motor function; assessed by developmental paediatrician at 2 years • 1 RCT: defined severe cerebral palsy as not walking or unlikely to walk unaided by 2 years; children screened with Ages and	50 per 1000 (154/3093)	34 per 1000 (27 to 43)	RR 0.68 (95% CI 0.54 to 0.87)	6145 (5 RCTs)	HIGH	Not downgraded

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	Stages Questionnaires; screen-positive and a sample of screen-negative children had clinical and neurodevelopmental assessments at 18 months (using Bayley Scales of Infant Development; Griffiths Tests; or other); if this was not possible, clinical history and examination (using the Health Status Questionnaire) was used • 1 RCT: used the European Cerebral Palsy Network definition; paediatricians evaluated motor function at 2 years; if examination was not possible, parent telephone interview was used						

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	• 1 RCT: definition not provided; assessed by neurodevelopment examinations at 4, 8, 12, and 18 months, with diagnoses made or verified by developmental paediatrician after the 18 month examination • 1 RCT: defined as presenting with 2 or more of the following three features: a delay of 30% or more in gross motor developmental milestones; abnormality in muscle tone, 4+ or absent deep tendon reflexes, or movement abnormality; or persistence of primitive reflexes or absence of protective reflexes; assessed by paediatrician or paediatric neurologist at 2 years						

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

Antenatal corticosteroids versus placebo for accelerating fetal lung maturation for women at risk of preterm birth (Roberts 2006)	Cerebral palsy at 2 to 6 years • 1 RCT: defined as any of hemiparesis, diplegia, tetra-, quadriplegia; assessed using detailed physical and neurologic examination (including of motor co-ordination) at 3 years • 1 RCT: defined as pathological muscle tonus, pre-existing primitive reflexes and delay in motor coordination; assessed using neurological examination by trial author (including evaluation of gross and fine motor) at 2 years • 3 RCTs: definition not clear (definitions and assessment methods taken, where possible, from RCT manuscripts as not detailed in review)	68 per 1000 (28/414)	41 per 1000 (23 to 70)	RR 0.60 (95% CI 0.34 to 1.03)	904 (5 RCTs)	LOW	study limitations (-1) : 2 RCTs with unclear and 1 RCT with inadequate allocation concealment imprecision (-1): wide confidence intervals crossing line of no effect

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

Repeat doses of corticosteroids versus single course for women at risk of preterm birth (Crowther 2015)	Cerebral palsy at 18 months to 3 years • 1 RCT: defined as abnormalities of muscle tone as well as loss of motor function; assessed by developmental paediatrician using neurological examinations at 2 years • 1 RCT: defined as non-progressive motor impairment characterised by abnormal muscle tone and decreased range of movements; assessed (by neonatologists, general paediatricians, developmental paediatricians, and trained nurses) using a standardised neurological assessment at 18 months to 2 years • 1 RCT: definition as described by	27 per 1000 (52/1891)	28 per 1000 (20 to 41)	RR 1.03 (95% CI 0.71 to 1.50)	3800 (4 RCTs)	MODERATE	imprecision (-1): wide confidence intervals crossing line of no effect

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

	Rosenbaum 2007; assessed by paediatric neurologist or paediatrician using specific neurological examination at 2 years • 1 RCT: defined as severe delay in gross motor milestones, failure to walk by 17 months of corrected age; abnormality of tone or reflexes; and aberration of primitive reflexes or postural reactions; assessed by paediatricians or paediatric neurologists using neurologic examination between 2 and 3 years (definitions and assessment methods taken from RCT manuscripts as not all detailed in review)						
Interventions for the management of preterm fetalcompromise							
Immediate versus deferred delivery	Cerebral palsy at or after 2 years	8 per 1000 (2/251)	47 per 1000 (11 to 207)	RR 5.88 (CI 95% 1.33 to 26.02)	507 (1 RCT)	MODERATE	study limitations (-1): 1 RCT at high

Table 6. Summary of findings: all comparisons measuring cerebral palsy (*Continued*)

of the preterm baby with suspected fetal compromise (Stock 2016)	definition not clear; assessed by family practitioner or paediatrician using short questionnaire (assessment method taken from RCT manuscript as not detailed in review)						risk of performance bias and other bias (did not account for non-independence of data for twin pregnancies)

Abbreviations: CI: confidence intervals; IA: intermittent auscultation; RCT: randomised controlled trial; RR: risk ratio; CI: confidence interval

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy

Intervention and comparison	Outcome	Subgroup or sensitivity analysis		Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Test for subgroup differences
Interventions for the diagnosis and prevention of fetalcompromise in labour								
Continuous cardiotocography (CTG) versus intermittent auscultation (IA) for fetal assessment during labour (Alfirevic 2013)	Cerebral palsy at 18 months to 4 years	Pregnancy risk status	High	77 per 1000	195 per 1000 (85 to 451)	RR 2.54 (95% CI 1. 10 to 5.86)	173 (1 RCT)	Chi² = 1.52, df = 1 (P = 0.22), I² = 34%
			Mixed or not specified	2 per 1000	2 per 1000 (1 to 4)	RR 1.20 (95% CI 0. 52 to 2.79)	13079 (1 RCT)	
		Onset of labour	Not specified	3 per 1000	4 per 1000 (2 to 8)	RR 1.74 (95% CI 0. 97 to 3.11)	13,252 (2 RCTs)	Not applicable
		Gestational age	Preterm labour	77 per 1000	195 per 1000 (85 to 451)	RR 2.54 (95% CI 1. 10 to 5.86)	173 (1 RCT)	Chi² = 1.52, df = 1 (P = 0.22), I² = 34%
			Both or gestation not specified	2 per 1000	2 per 1000 (1 to 4)	RR 1.20 (95% CI 0. 52 to 2.79)	13,079 (1 RCT)	

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy (*Continued*)

		Number of babies	Singleton	77 per 1000	195 per 1000 (85 to 451)	RR 2.54 (95% CI 1.10 to 5.86)	173 (1 RCT)	Chi² = 1.52, df = 1 (P = 0.22), I² = 34%
			Both or not specified	2 per 1000	2 per 1000 (1 to 4)	RR 1.20 (95% CI 0.52 to 2.79)	13,079 (1 RCT)	
		Access to fetal blood sampling	Yes	3 per 1000	4 per 1000 (2 to 8)	RR 1.74 (95% CI 0.97 to 3.11)	13,252 (2 RCTs)	Not applicable
		Parity	Both or not specified	3 per 1000	4 per 1000 (2 to 8)	RR 1.74 (95% CI 0.97 to 3.11)	13,252 (2 RCTs)	Not applicable
		Quality	High	2 per 1000	2 per 1000 (1 to 4)	RR 1.20 (95% CI 0.52 to 2.79)	13,079 (1 RCT)	Chi² = 1.52, df = 1 (P = 0.22), I² = 34%
			Unclear	77 per 1000	195 per 1000 (85 to 451)	RR 2.54 (95% CI 1.10 to 5.86)	173 (1 RCT)	
Interventions for the prevention of preterm birth								
Prenatal administration of progesterone versus placebo for preventing preterm birth in women with a previous history spontaneous preterm birth (singletons) (Dodd 2013)	Cerebral palsy at 4 years	Route of administration	Intramuscular	12 per 1000	2 per 1000 (0 to 42)	RR 0.14 (95% CI 0.01 to 3.48)	274 (1 RCT)	Not applicable
Prophylactic antibiotics versus no antibiotics for inhibit-	Cerebral palsy at 7 years	Type of antibiotic	Beta-lactam antibiotics alone	16 per 1000	19 per 1000 (6 to 57)	Average RR 1.22 (95% CI 0.41 to 3.63)	1049 (1 RCT)	Chi² = 1.41, df = 2 (P = 0.49), I² = 0.0%

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy (*Continued*)

ing preterm labour with intact membranes (Flenady 2013)			Macrolide antibiotics alone	16 per 1000	22 per 1000 (7 to 65)	Average RR 1.42 (95% CI 0.48 to 4.15)	1073 (1 RCT)	
			Macrolide and beta-lactam antibiotics	16 per 1000	44 per 1000 (16 to 123)	Average RR 2.83 (95% CI 1.02 to 7.88)	1052 (1 RCT)	
Any macrolide versus no macrolide for inhibiting preterm labour with intact membranes (Flenady 2013)		Any macrolide versus no macrolide antibiotics		17 per 1000	33 per 1000 (21 to 52)	RR 1.90 (95% CI 1.20 to 3.01)	3173 (1 RCT)	Not applicable
Any beta-lactam versus no beta-lactam for inhibiting preterm labour with intact membranes (Flenady 2013)		Any beta-lactam versus no beta-lactam antibiotics		19 per 1000	32 per 1000 (20 to 49)	RR 1.67 (95% CI 1.06 to 2.61)	3173 (1 RCT)	Not applicable
Interventions prior to preterm birth for fetal maturation or neuroprotection								
Phenobarbital versus placebo prior to preterm birth for prevent-	Cerebral palsy at 18 months to 3 years	Excluding trials with non-concealment at randomisation (C quality)		91 per 1000	61 per 1000 (37 to 117)	RR 0.71 (95% CI 0.40 to 1.28)	517 (2 RCTs)	Not applicable

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy (*Continued*)

ing neonatal periventricular haemorrhage (Crowther 2010a)								
Vitamin K versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010) and Phenobarbital versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage (Crowther 2010a)	Cerebral palsy at 7 years	Excluding trials with inadequate concealment of allocation of treatment		79 per 1000	61 per 1000 (26 to 140)	RR 0.77 (95% CI 0.33 to 1.76)	299 (1 RCT)	Not applicable
Magnesium sulphate versus placebo for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009)	Cerebral palsy between 18 and 2 years	neuroprotective intent	Neuroprotective	65 per 1000	46 per 1000 (36 to 59)	RR 0.71 (95% CI 0.55 to 0.91)	4446 (4 RCTs)	Chi^2 = 1.69, df = 2 (P = 0.43), I^2 = 0% (Performed by overview authors)
			Maternal neuropro-	6 per 1000	3 per 1000 (1 to 13)	RR 0.40 (95% CI 0.	1593 (1 RCT)	

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy (*Continued*)

			tective (pre-eclampsia)			08 to 2.05)		
			Tocolytic	59 per 1000	7 per 1000 (1 to 148)	RR 0.13 (95% CI 0. 01 to 2.51)	106 (1 RCT)	
		Single or multiple pregnancy	Single	28 per 1000	26 per 1000 (16 to 42)	RR 0.92 (95% CI 0. 57 to 1.49)	2321 (2 RCTs)	Chi² = 1.28, df = 1 (P = 0. 26), I² = 22.
			Multiple	53 per 1000	28 per 1000 (11 to 67)	RR 0.52 (95% CI 0. 21 to 1.25)	527 (2 RCTs)	
		Gestational age	Less than 34 weeks at randomisation	56 per 1000	39 per 1000 (30 to 50)	RR 0.69 (95% CI 0. 54 to 0.88)	5357 (5 RCTs)	Not applicable (subgroups not
			Less than 30 weeks at randomisation	56 per 1000	48 per 1000 (31 to 73)	RR 0.86 (95% CI 0. 56 to 1.31)	1537 (2 RCTs)	
		Loading dose	4 g (any or no maintenance)	43 per 1000	34 per 1000 (24 to 47)	RR 0.79 (95% CI 0. 56 to 1.10)	3595 (4 RCTs)	Chi² = 1.33, df = 1 (P = 0. 25), I² = 24.
			6 g (any or no maintenance)	59 per 1000	35 per 1000 (24 to 50)	RR 0.59 (95% CI 0. 40 to 0.85)	2444 (1 RCT)	
		Maintenance dose	No maintenance (any loading)	82 per 1000	113 per 1000 (15 to 879)	RR 1.37 (95% CI 0. 18 to 10.70)	747 (2 RCTs)	Chi² = 0.44, df = 1 (P = 0. 51), I² = 0%
			Any maintenance (any loading)	45 per 1000	31 per 1000 (23 to 41)	RR 0.68 (95% CI 0.51 to 0. 91)	5292 (3 RCTs)	
		Loading and maintenance dose	Loading dose (4 g) and no maintenance	82 per 1000	113 per 1000 (15 to 879)	average RR 1.37 (0.18, 10.70)	747 (2 RCTs)	Chi² = 2.94, df = 3 (P = 0. 40), I² = 0% *(Performed by overview authors)*
			Loading dose (4 g)	33 per 1000	27 per 1000 (18 to 41)	average RR 0.81 (95%	2848 (2 RCTs)	

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy (*Continued*)

			and lower-dose maintenance (1 g/hour)			CI 0.54 to 1.23)		
			Loading dose (4 g) and higher-dose maintenance (2 to 3 g/hour)	59 per 1000	8 per 1000 (1 to 148)	RR 0.13 (95% CI 0.01 to 2.51)	106 (1 RCT)	
			Loading dose (6 g) and higher-dose maintenance (2 to 3 g/hour)	59 per 1000	35 per 1000 (24 to 50)	RR 0.59 (95% CI 0.40 to 0.85)	2444 (1 RCT)	
		Retreatment permitted	Yes	59 per 1000	35 per 1000 (24 to 50)	RR 0.59 (95% CI 0.40 to 0.85)	2444 (1 RCT)	$Chi^2 = 1.26$, df = 2 (P = 0.53), $I^2 = 0\%$ *(Performed by overview authors)*
			No	44 per 1000	33 per 1000 (24 to 46)	RR 0.76 (95% CI 0.55 to 1.06)	3536 (3 RCTs)	
			Unclear	38 per 1000	35 per 1000 (8 to 170)	RR 0.94 (95% CI 0.20 to 4.53)	165 (1 RCT)	
		High antenatal corticosteroids		66 per 1000	44 per 1000 (35 to 56)	RR 0.67 (95% CI 0.53 to 0.86)	4493 (4 RCTs)	Not applicable
		Studies with lowest risk of bias only		62 per 1000	42 per 1000 (32 to 56)	RR 0.68 (95% CI 0.52 to 0.91)	3699 (2 RCTs)	Not applicable
Antenatal corticosteroids versus placebo for accelerating fetal lung maturation for women at risk of	Cerebral palsy at 2 to 6 years	In babies born from pregnancies complicated by hypertension syndromes		59 per 1000	16 per 1000 (2 to 177)	RR 0.28 (95% CI 0.03 to 3.01)	94 (1 RCT)	Not applicable

Table 7. Summary of findings: subgroup or sensitivity analyses of select comparisons for cerebral palsy (*Continued*)

preterm birth (Roberts 2006)								
		Main decade of recruitment	In babies from trials conducted in 1970s	28 per 1000	27 per 1000 (7 to 97)	RR 0.95 (95% CI 0. 26 to 3.45)	322 (2 RCTs)	Chi² = 1.05, df = 2 (P = 0. 59), I² = 0% (Performed by overview authors)
			In babies from trials conducted in 1980s	73 per 1000	45 per 1000 (20 to 100)	RR 0.62 (95% CI 0. 28 to 1.38)	406 (1 RCT)	
			In babies from trials conducted in 1990s	136 per 1000	57 per 1000 (22 to 149)	RR 0.42 (95% CI 0. 16 to 1.09)	176 (2 RCTs)	

Abbreviations: CI: confidence intervals; RCT: randomised controlled trial; RR: risk ratio

Table 8. Summary of findings: all comparisons measuring cerebral palsy or death

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Interventions prior to preterm birth for fetalmaturation or neuroprotection							
Magnesium sulphate versus placebo for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009)	Death or cerebral palsy between 18 months and 2 years (as above under cerebral palsy)	188 per 1000 (583/3093)	177 per 1000 (147 to 211)	Average RR 0. 94 (95% CI 0. 78 to 1.12)	6145 (5 RCTs)	HIGH	not downgraded

Abbreviations: CI: confidence intervals; RCT: randomised controlled trial; RR: risk ratio

Table 9. Summary of findings: all comparisons measuring severity of cerebral palsy

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Interventions for the treatment of pre-eclampsia							
Magnesium sulphate versus placebo for women with pre-eclampsia (Duley 2010)	Severe cerebral palsy at 18 months (definition: not walking or unlikely to walk unaided by 24 months) (definition taken from RCT manuscript as not detailed in review)	6 per 1000 (9/1464)	2 per 1000 (1 to 8)	RR 0.34 (95% CI 0.09 to 1.26)	2895 (1 RCT)	LOW	study limitations (-1): 1 RCT with unclear risk of attrition bias for this outcome (2895 of 6922 children in original RCT included) imprecision (-1): wide confidence intervals crossing line of no effect
Interventions prior to preterm birth for fetalmaturation or neuroprotection							
Magnesium sulphate (neuroprotective intent) versus placebo for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009)	Mild cerebral palsy at 2 years • 1 RCT: definition: walking at 2 years; assessed by developmental paediatrician at 2 years • 1 RCT: definition: Gross Motor Function Classification System of level 1; assessed by paediatrician or paediatric neurologist at 2 years	33 per 1000 (74/2218)	25 per 1000 (17 to 35)	RR 0.74 (95% CI 0.52 to 1.04)	4387 (3 RCTs)	MODERATE	imprecision (-1): wide confidence intervals crossing line of no effect

Table 9. Summary of findings: all comparisons measuring severity of cerebral palsy (*Continued*)

	• 1 RCT: definition not clear; paediatricians evaluated motor function at 2 years; if examination was not possible, parent telephone interview was used						
	Moderate cerebral palsy at 2 years • 1 RCT: definition: not walking at 2 years but likely to do so; assessed by developmental paediatrician at 2 years • 1 RCT: definition not clear; paediatricians evaluated motor function at 2 years; if examination was not possible, parent telephone interview was used	22 per 1000 (21/962)	14 per 1000 (7 to 28)	RR 0.66 (95% CI 0.34 to 1.28)	1943 (2 RCTs)	MODERATE	imprecision (-1): wide confidence intervals crossing line of no effect
	Moderate to severe cerebral palsy at 2 years • 1 RCT:	32 per 1000 (72/2218)	21 per 1000 (14 to 30)	RR 0.64 (95% CI 0.44 to 0.92)	4387 (3 RCTs)	HIGH	not downgraded

Table 9. Summary of findings: all comparisons measuring severity of cerebral palsy (*Continued*)

	definition: not walking at 2 years but likely to do so (moderate); not likely to walk (severe); assessed by developmental paediatrician at 2 years • 1 RCT: definition: Gross Motor Function Classification System level of 2 or 3 (moderate), or level 4 or 5 (severe); assessed by paediatrician or paediatric neurologist at 2 years • 1 RCT: definition not clear; paediatricians evaluated motor function at 2 years; if examination was not possible, parent telephone interview was used						
	Severe cerebral palsy at 2 years • 1 RCT: definition: not likely to walk; assessed by develop-	14 per 1000 (13/962)	11 per 1000 (5 to 25)	RR 0.82 (95% CI 0.37 to 1. 82)	1943 (2 RCTs)	MODERATE	imprecision (-1): wide confidence intervals crossing line of no effect

Table 9. Summary of findings: all comparisons measuring severity of cerebral palsy (*Continued*)

	mental paediatrician at 2 years • 1 RCT: definition not clear; paediatricians evaluated motor function a 2 years; if examination was not possible, parent telephone interview was used						

Abbreviations: CI: confidence intervals; RCT: randomised controlled trial; RR: risk ratio

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Interventions for the treatment of pre-eclampsia							
Magnesium sulphate versus placebo for women with pre-eclampsia (Duley 2010)	Neurosensory disability at 18 months (definition: functional blindness (binocular visual acuity < 6/60), deafness (severe enough to need a hearing aid), severe cerebral palsy, or DQ < 2 SD below the mean)	10 per 1000 (17/1648)	8 per 1000 (4 to 16)	RR 0.77 (95% CI 0.38 to 1.58)	3283 (1 RCT)	LOW	study limitations (-1): 1 RCT with unclear risk of attrition bias for this outcome (3283 of 6922 children in original RCT included) imprecision (-1): wide confidence intervals crossing line of no effect

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	Death or neurosensory disability at 18 months (definition as above for 'neursensory disability at 18 months')	141 per 1000 (233/1648)	150 per 1000 (127 to 177)	RR 1.06 (95% CI 0.90 to 1.25)	3283 (1 RCT)	LOW	study limitations (-1): 1 RCT with unclear risk of attrition bias for this outcome (3283 of 6922 children in original RCT included) imprecision (-1): wide confidence intervals crossing line of no effect
Interventions for the prevention of preterm birth							
Magnesium sulphate versus other tocolytic agents for preventing preterm birth in threatened preterm labour (Crowther 2014)	Serious infant outcome (definition: total perinatal and infant mortality; IVH 3/4 or PVL; cerebral palsy at 18 months; assessment method as above under 'cerebral palsy') (1 RCT included cerebral palsy in composite outcome)	59 per 1000 (3/51)	145 per 1000 (41 to 518)	RR 2.47 (95% CI 0.69 to 8.81)	106 (1 RCT)	VERY LOW	study limitations (-1): 1 RCT with unclear risk of selection, attrition, and reporting bias and high risk of performance bias imprecision (-2): wide confidence intervals crossing line of no effect; 1 small RCT with few events
Interventions prior to preterm birth for fetalmaturation or neuroprotection							
Magnesium sulphate versus placebo for women at risk of preterm birth for neuroprotection	Any neurologic impairment at 18 months or 2 years (definition: any of cerebral palsy,	141 per 1000 (200/1421)	142 per 1000 (121 to 167)	RR 1.01 (95% CI 0.86 to 1.19)	2848 (2 RCTs)	HIGH	not downgraded

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

of the fetus (Doyle 2009)	blindness, deafness, or developmental delay or intellectual impairment (DQ or IQ less than 1 SD below the mean))						
	Major neurological disability at 18 months or 2 years (definition: any of moderate or severe cerebral palsy, blindness, deafness, or an MDI less than 70)	64 per 1000 (91/1421)	69 per 1000 (53 to 90)	RR 1.07 (95% CI 0.82 to 1.40)	2848 (2 RCTs)	MODERATE	imprecision (-1): wide confidence intervals crossing the line of no effect
	Death or any neurologic impairment at 18 months or 2 years (definition as above for 'any neurological impairment')	348 per 1000 (495/1421)	348 per 1000 (317 to 387)	RR 1.00 (95% CI 0.91 to 1.11)	2848 (2 RCTs)	HIGH	not downgraded
	Death or major neurological disability at 18 months or 2 years (definition as above for 'major neurological disability')	272 per 1000 (386/1421)	277 per 1000 (244 to 312)	RR 1.02 (95% CI 0.90 to 1.15)	2848 (2 RCTs)	HIGH	not downgraded
Antenatal corticosteroids versus placebo for accelerating fetal	Neurodevelopmental delay at 2 years (definition: se-	94 per 1000 (3/32)	60 per 1000 (13 to 279)	RR 0.64 (95% CI 0.14 to 2.98)	82 (1 RCT)	VERY LOW	study limitations (-1): 1 RCT with unclear al-

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

lung maturation for women at risk of preterm birth (Roberts 2006)	vere disability: tetraplegic cerebral palsy and/or mental retardation (Bayley's mental index < 70)) (definition taken from RCT manuscript as not detailed in review)						location concealment imprecision (-2): wide confidence intervals crossing line of no effect; 1 small RCT with few events
Repeat doses of corticosteroids versus single course for women at risk of preterm birth (Crowther 2015)	Survival free of any disability 18 months to 2 years, defined as: • 1 RCT: definition: survival free of severe, moderate or mild neurosensory disability: severe neurosensory disability defined as severe cerebral palsy (child considered permanently non-ambulant), severe developmental delay (MDI score, > 3 SD below the mean), or blindness; moderate disability defined as moderate	773 per 1000 (1215/1571)	781 per 1000 (750 to 812)	RR 1.01 (95% CI 0.97 to 1.05)	3155 (2 RCTs)	HIGH	not downgraded

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	cerebral palsy (child non-ambulant at 2 years but likely to walk), moderate developmental delay (MDI score, > 2 SD to 3 SD below the mean), or deafness; mild disability defined as either mild cerebral palsy (walking at 2 years) or mild developmental delay (MDI score, > 1 SD to 2 SD below the mean) • 1 RCT: definition: survival free of neurological impairment (cerebral palsy or cognitive delay (2 SD below the normative value)) (definitions taken from RCT manuscripts as not clearly detailed in review)						
	Survival free of major neurosensory disability at 2 to 3 years, defined	847 per 1000 (572/675)	856 per 1000 (780 to 941)	Average RR 1.01 (95% CI 0.92 to 1.11)	1317 (2 RCTs)	LOW	study limitations (-1): 1 RCT with unclear risk of selection bias,

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	as: • 1 RCT: definition: survival being ambulant by 2 years of age and not having blindness, deafness, a developmental index score of more than 2 SD below the mean, or cerebral palsy • 1 RCT: definition: survival without severe neurodevelopmental impairment (cerebral palsy, MDI < 70, DQ < 70, deafness, or blindness) (definitions taken from RCT manuscripts as not clearly detailed in review)						attrition bias and high risk of other bias inconsistency (-1): substantial heterogeneity (I^2 = 88%)
	Major neurosensory disability at 2 to 3 years, defined as: • 1 RCT: definition: severe or moderate neurosensory disability: severe neurosensory	110 per 1000 (71/643)	119 per 1000 (34 to 415)	Average RR 1.08 (95% CI 0.31 to 3.76)	1256 (2 RCTs)	LOW	study limitations (-1): 1 RCT with unclear risk of selection bias, attrition bias, and high risk of other bias imprecision (-1): wide confidence intervals cross-

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	disability defined as severe cerebral palsy (child considered permanently non-ambulant), severe developmental delay (MDI score > 3 SD below the mean), or blindness; moderate disability defined as moderate cerebral palsy (child non-ambulant at 2 years but likely to walk), moderate developmental delay (MDI score > 2 SD to 3 SD below the mean), or deafness • 1 RCT: definition: severe neurodevelopmental impairment (cerebral palsy, MDI < 70, DQ < 70, deafness, or blindness) (definitions taken from RCT manuscripts as not clearly detailed in review)						ing line of no effect

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	Disability at 2 years, defined as: • 1 RCT: definition: severe, moderate, or mild neurosensory disability: severe neurosensory disability defined as severe cerebral palsy (child considered permanently non-ambulant), severe developmental delay (MDI score > 3 SD below the mean), or blindness; moderate disability defined as moderate cerebral palsy (child non-ambulant at 2 years but likely to walk), moderate developmental delay (MDI score > 2 SD to 3 SD below the mean), or deafness; mild disability was defined as either mild	361 per 1000 (182/504)	354 per 1000 (300 to 419)	RR 0.98 (95% CI 0.83 to 1.16)	999 (1 RCT)	HIGH	not downgraded

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	cerebral palsy (walking at 2 years) or mild developmental delay (MDI score > 1 SD to 2 SD below the mean) (definition taken from RCT manuscript as not clearly detailed in review)						
	Composite serious outcome at 18 months to 2 years, defined as: • 1 RCT: definition: death or any neurosensory disability: severe, moderate or mild neurosensory disability: severe neurosensory disability defined as severe cerebral palsy (child considered permanently non-ambulant), severe developmental delay (MDI score > 3 SD below the mean), or blindness;	227 per 1000 (356/1571)	224 per 1000 (197 to 254)	RR 0.99 (95% CI 0.87 to 1.12)	3164 (2 RCTs)	HIGH	not downgraded

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	moderate disability defined as moderate cerebral palsy (child non-ambulant at 2 years but likely to walk), moderate developmental delay (MDI score > 2 SD to 3 SD below the mean), or deafness; mild disability defined as either mild cerebral palsy (walking at 2 years) or mild developmental delay (MDI score > 1 SD to 2 SD below the mean) • 1 RCT: definition: death or neurologic impairment (cerebral palsy or cognitive delay (cognitive delay was defined as 2 SD below the normative value)) (definitions taken from RCT manuscripts as not clearly detailed in review)						

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

Interventions for the management of preterm fetalcompromise							
Immediate versus deferred delivery of the preterm baby with suspected fetal compromise (Stock 2016)	Death or disability at or after 2 years (definition: cerebral palsy, little or no vision, requirement for hearing aid, or Griffiths DQ of 70 or less)	155 per 1000 (44/283)	190 per 1000 (132 to 272)	RR 1.22 (95% CI 0.85 to 1.75)	573 (1 RCT)	LOW	study limitations (-1): 1 RCT at high risk of performance bias and other bias (did not account for non-independence of data for twin pregnancies) imprecision (-1): wide intervals crossing line of no effect
	Neurodevelopmental impairment at or after 2 years (definition: cerebral palsy, little or no vision, requirement for hearing aid, or Griffiths DQ of 70 or less)	48 per 1000 (12/251)	82 per 1000 (41 to 163)	RR 1.72 (95% CI 0.86 to 3.41)	507 (1 RCT)	LOW	study limitations (-1): 1 RCT at high risk of performance bias and other bias (did not account for non-independence of data for twin pregnancies) imprecision (-1): wide intervals crossing line of no effect
	Death or severe disability at 6 to 13 years (definition: classified severe blindness, severe deafness, cerebral palsy, or Kaufman Men-	168 per 1000 (25/149)	138 per 1000 (81 to 235)	RR 0.82 (95% CI 0.48 to 1.40)	302 (1 RCT)	LOW	study limitations (-1): 1 RCT at high risk of performance, attrition and other bias imprecision (-1): wide intervals cross-

Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component (*Continued*)

	tal Processing Component < 70 points) (definition taken from RCT manuscript as not detailed in review)						ing line of no effect

Abbreviations: CI: confidence intervals; DQ: developmental quotient; IQ: intelligence quotient; IVH: intraventricular haemorrhage; MDI: mental development index; PVL: periventricular leukomalacia; RCT: randomised controlled trial; RR: risk ratio; SD: standard deviation

Table 11. Summary of findings: all comparisons measuring motor dysfunction

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Interventions for the prevention of preterm birth							
Prenatal administration of progesterone versus placebo for preventing preterm birth in women with a previous history spontaneous preterm birth (singletons) (Dodd 2013)	Motor impairment at 4 years (definition: overall activity problems or co-ordination problems) (age and definition taken from RCT manuscript as not detailed in review)	24 per 1000 (2/82)	16 per 1000 (3 to 92)	RR 0.64 (95% CI 0.11 to 3.76)	274 (1 RCT)	LOW	imprecision (-2): wide confidence intervals crossing line of no effect; one small RCT with few events
Interventions prior to preterm birth for fetal maturation or neuroprotection							
Phenobarbital versus control prior to preterm birth for preventing neonatal periventricular	Other neuromotor impairment at 3 years (definition: tonal abnormalities with no delay in ambulation	73 per 1000 (4/55)	49 per 1000 (9 to 254)	RR 0.67 (95% CI 0.13 to 3.49)	96 (1 RCT)	VERY LOW	study limitations (-2) : 1 RCT with high risk of selection bias, bias due to lack of blind-

Table 11. Summary of findings: all comparisons measuring motor dysfunction (*Continued*)

haemorrhage (Crowther 2010a)	or other motor milestones) (definition taken from RCT manuscript as not detailed in review)						ing, and attrition bias imprecision (-2): wide confidence intervals crossing line of no effect; 1 small RCT with few events
Magnesium sulphate versus no placebo for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009)	Substantial gross motor dysfunction between 18 months and 2 years (definition: motor dysfunction such that the child was not walking at age 2 years or later, or the inability to grasp and release a small block with both hands)	31 per 1000 (94/3013)	19 per 1000 (14 to 27)	RR 0.61 (95% CI 0.44 to 0.85)	5980 (4 RCTs)	HIGH	not downgraded
	Death or substantial gross motor dysfunction between 18 months and 2 years (definition as above for 'substantial gross motor dysfunction')	174 per 1000 (523/3013)	160 per 1000 (130 to 194)	Average RR 0.92 (95% CI 0.75 to 1.12)	5980 (4 RCTs)	MODERATE	inconsistency (-1): substantial heterogeneity (I^2 = 65%)

Abbreviations: CI: confidence intervals; RCT: randomised controlled trial; RR: risk ratio

CONTRIBUTIONS OF AUTHORS

Emily Shepherd drafted the first version of the protocol for this review, with Sarah McIntyre, Maria Makrides, Philippa Middleton, and Caroline Crowther making comments and contributing to the final protocol.

Emily Shepherd and Rehana Salam assessed review eligibility and carried out all data extraction, quality assessment and data entry. Emily Shepherd authored initial drafts. Rehana Salam, Philippa Middleton, Maria Makrides, Sarah McIntyre, Nadia Badawi, and Caroline Crowther made comments and contributed to the final overview.

DECLARATIONS OF INTEREST

The overview authors were authors of some of the Cochrane systematic reviews that were considered for inclusion in this review. Assessment of eligibility of any and all of these reviews, and where included, data collection and analysis (including quality assessment) for these reviews, was carried out by two overview authors not involved in the individual Cochrane reviews.

Emily Shepherd, Philippa Middleton, and Caroline Crowther are investigators on a Project Grant from the Cerebral Palsy Alliance Research Foundation, Australia, which supported the conduct of this overview.

Maria Makrides has served on scientific advisory boards for Nestle and Fonterra. Associated honoraria were paid to the Women's and Children's Health Research Institute to support conference travel and continuing education for postgraduate students and early career researchers.

Sarah McIntyre is employed by Cerebral Palsy Alliance and the University of Sydney. She has also been invited to a number of international meetings where travel costs have been paid by the organisers of the meeting, e.g. Surveillance of Cerebral Palsy Europe.

Rehana Salam: none know.

Nadia Badawi: none known.

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MeSH check words

Female; Humans; Pregnancy

CHAPTER 3: NEONATAL INTERVENTIONS FOR PREVENTING CEREBRAL PALSY: AN OVERVIEW OF COCHRANE SYSTEMATIC REVIEWS

Statement of authorship

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Principal author

Principal author (candidate)	Emily Shepherd		
Contribution to the paper	Responsible for conception and design of the overview, including first draft of protocol, and revisions. Responsible for conduct of the overview, including conducting searches, assessing review eligibility, data extraction, quality assessment, data entry, analysis and interpretation. Responsible for first draft of overview manuscript and ongoing revisions of manuscript.		
Overall percentage (%)	75%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	10/10/2019

Co-author contributions

By signing the 'Statement of authorship', each author certified that:
The candidate's stated contribution to the publication is accurate (as detailed above);
Permission is granted for the candidate to include the publication in the thesis;
The sum of all co-authors is equal to 100% less the candidate's stated contribution.

Name of co-author	Rehana A Salam		
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Contribution to the paper	Input into conception and design of the overview, including critical revision of the protocol. Input into interpretation of the overview, including critical revision of the overview manuscript.		
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Cochrane Database of Systematic Reviews

Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews (Review)

Shepherd E, Salam RA, Middleton P, Han S, Makrides M, McIntyre S, Badawi N, Crowther CA

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TABLE OF CONTENTS

[Overview of Reviews]

Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews

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ABSTRACT

Background

Cerebral palsy is an umbrella term that encompasses disorders of movement and posture attributed to non-progressive disturbances occurring in the developing foetal or infant brain. As there are diverse risk factors and aetiologies, no one strategy will prevent cerebral palsy. Therefore, there is a need to systematically consider all potentially relevant interventions for prevention.

Objectives

Primary

To summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions for preventing cerebral palsy (reducing cerebral palsy risk).

Secondary

To summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions that may increase cerebral palsy risk.

Methods

We searched the *Cochrane Database of Systematic Reviews* (27 November 2016) for reviews of neonatal interventions reporting on cerebral palsy. Two review authors assessed reviews for inclusion, extracted data, and assessed review quality (using AMSTAR and ROBIS) and quality of the evidence (using the GRADE approach). Reviews were organised by topic; findings were summarised in text and were tabulated. Interventions were categorised as effective (high-quality evidence of effectiveness); possibly effective (moderate-quality evidence of effectiveness); ineffective (high-quality evidence of harm); probably ineffective (moderate-quality evidence of harm or lack of effectiveness); and no conclusions possible (low- to very low-quality evidence).

Main results

Forty-three Cochrane Reviews were included. A further 102 reviews pre-specified the outcome cerebral palsy, but none of the included randomised controlled trials (RCTs) reported this outcome. Included reviews were generally of high quality and had low risk of bias, as determined by AMSTAR and ROBIS. These reviews involved 454 RCTs; data for cerebral palsy were available from 96 (21%) RCTs involving 15,885 children. Review authors considered interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy (3); interventions for neonates born preterm and/or at low or very low birthweight (33); and interventions for other specific groups of 'at risk' neonates (7). Quality of evidence (GRADE) ranged from very low to high.

Interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy

Effective interventions: high-quality evidence of effectiveness

Researchers found a reduction in cerebral palsy following therapeutic hypothermia versus standard care for newborns with hypoxic ischaemic encephalopathy (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.54 to 0.82; seven trials; 881 children).

No conclusions possible: very low-quality evidence

One review observed no clear differences in cerebral palsy following therapeutic hypothermia versus standard care.

Interventions for neonates born preterm and/or at low or very low birthweight

Possibly effective interventions: moderate-quality evidence of effectiveness

Researchers found a reduction in cerebral palsy with prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants (RR 0.54, 95% CI 0.32 to 0.92; one trial; 644 children).

Probably ineffective interventions: moderate-quality evidence of harm

Researchers reported an increase in cerebral palsy (RR 1.45, 95% CI 1.06 to 1.98; 12 trials; 1452 children) and cerebral palsy in assessed survivors (RR 1.50, 95% CI 1.13 to 2.00; 12 trials; 959 children) following early (at less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants.

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness

Trial results showed no clear differences in cerebral palsy following ethamsylate versus placebo for prevention of morbidity and mortality in preterm or very low birthweight infants (RR 1.13, 95% CI 0.64 to 2.00; three trials, 532 children); volume expansion versus no treatment (RR 0.76, 95% CI 0.48 to 1.20; one trial; 604 children); gelatin versus fresh frozen plasma (RR 0.94, 95% CI 0.52 to 1.69; one trial, 399 children) for prevention of morbidity and mortality in very preterm infants; prophylactic indomethacin versus placebo for preventing mortality and morbidity in preterm infants (RR 1.04, 95% CI 0.77 to 1.40; four trials; 1372 children); synthetic surfactant versus placebo for respiratory distress syndrome in preterm infants (RR 0.76, 95% CI 0.55 to 1.05; five trials; 1557 children); or prophylactic phototherapy versus standard care (starting phototherapy when serum bilirubin reached a pre-specified level) for preventing jaundice in preterm or low birthweight infants (RR 0.96, 95% CI 0.50 to 1.85; two trials; 756 children).

No conclusions possible: low- to very low-quality evidence

No clear differences in cerebral palsy were observed with interventions assessed in 21 reviews.

Interventions for other specific groups of 'at risk' neonates

No conclusions possible: low- to very low-quality evidence

Review authors observed no clear differences in cerebral palsy with interventions assessed in five reviews.

Authors' conclusions

This overview summarises evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions on cerebral palsy, and can be used by researchers, funding bodies, policy makers, clinicians, and consumers to aid decision-making and evidence translation. To formally assess other benefits and/or harms of included interventions, including impact on risk factors for cerebral palsy, review of the included Reviews is recommended.

Therapeutic hypothermia versus standard care for newborns with hypoxic ischaemic encephalopathy can prevent cerebral palsy, and prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants may reduce cerebral palsy risk.

Early (at less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants may increase cerebral palsy risk.

Cerebral palsy is rarely identified at birth, has diverse risk factors and aetiologies, and is diagnosed in approximately one in 500 children. To date, only a small proportion of Cochrane Systematic Reviews assessing neonatal interventions have been able to report on this outcome. There is an urgent need for long-term follow-up of RCTs of such interventions addressing risk factors for cerebral palsy (through strategies such as data linkage with registries) and for consideration of the use of relatively new interim assessments (including the General Movements Assessment). Such RCTs must be rigorous in their design and must aim for consistency in cerebral palsy outcome measurement and reporting to facilitate pooling of data and thus to maximise research efforts focused on prevention.

PLAIN LANGUAGE SUMMARY

Interventions for babies from birth to one month of life for preventing cerebral palsy: an overview of Cochrane Systematic Reviews

What is the issue?

'Cerebral palsy' is a term that includes a group of conditions affecting people's ability to move; it is the most common physical disability in childhood. Cerebral palsy is usually due to events before, during, or after childbirth that lead to injury to babies' developing brains. No single cause of cerebral palsy is known. For many children, the cause of cerebral palsy is unclear, but many risk factors are known. The biggest risk factor is preterm birth (birth before 37 weeks of pregnancy). Other risk factors during the neonatal period (birth to one month of life) include prolonged loss of oxygen during birth; brain injury; strokes or seizures; disorders of the heart, blood vessels, airways, and lungs; prolonged mechanical assistance for breathing; some infections; jaundice (yellow discolouration of the skin and eyes due to excess bilirubin in the blood); and some syndromes or abnormalities of chromosomes (structures that hold genes).

Why is this important?

As there are different risk factors for and causes of cerebral palsy, it is likely that different interventions may be needed to prevent cerebral palsy by reducing risk factors. This overview summarises evidence about preventing cerebral palsy that has been presented in Cochrane Systematic Reviews of interventions during the neonatal period.

What evidence did we find?

We searched for evidence on 27 November 2016, and identified 43 Cochrane Reviews assessing interventions during the neonatal period that reported some information on cerebral palsy. These Reviews were all of moderate to high quality, but the quality of the evidence about cerebral palsy ranged from very low to high. Three Reviews assessed interventions for newborn babies who may have had a lack of oxygen at or around the time of birth; 33 Reviews assessed interventions for babies born preterm or at low birthweight; and seven Reviews assessed interventions for other groups of newborn babies at risk of injury to their brains (such as newborn babies with low blood sugar at birth).

We found that one intervention was effective for cerebral palsy prevention. Newborn babies who may have had a lack of oxygen at or around the time of birth who had induced hypothermia (cooling of their body or just their brain) were less likely to develop cerebral palsy than babies who did not receive hypothermia (seven trials; 881 children; high-quality evidence). We found that one intervention was possibly effective for cerebral palsy prevention. Preterm newborns who received methylxanthines (caffeine) when weaning from machine-assisted breathing (extubation from mechanical ventilation) was planned were less likely to develop cerebral palsy than babies who received a placebo (one trial; 644 children; moderate-quality evidence). We found one intervention that was probably ineffective and may cause harm: Preterm newborns who received early (at less than eight days of age) corticosteroids to prevent chronic lung disease were more likely to develop cerebral palsy than babies who received a placebo (12 trials; 959 children; moderate-quality evidence). We found that five other interventions were probably ineffective (did not prevent or increased the chance of cerebral palsy) (moderate-quality evidence). Review authors did not find enough evidence to say whether the other interventions prevented, increased, or had no impact on cerebral palsy (low- or very low-quality evidence).

What does this mean?

This overview identified one intervention that was effective in preventing cerebral palsy (induced hypothermia for newborn babies who may have had a lack of oxygen), one that was possibly effective for preventing cerebral palsy (caffeine for preterm babies weaning from machine-assisted breathing), one that appeared to cause harm (corticosteroids at less than eight days of age for preterm babies to prevent

chronic lung disease), and five that did not appear to make a difference. For the other interventions assessed, there was not enough evidence to allow conclusions. It is important that additional good quality trials assessing interventions that might impact cerebral palsy risk factors conduct long-term follow-up to measure the impact of these interventions. We identified over 100 other Cochrane Reviews that may in the future provide information on interventions during the neonatal period for preventing cerebral palsy if they include long-term follow-up.

BACKGROUND

Description of the condition

Cerebral palsy: definition and prevalence

'Cerebral palsy' was originally (and continues to be) defined by clinical description at a time when there was little knowledge of aetiology or pathology (Morris 2007). Today, many registries and surveillance programmes, including those in Australia, the United Kingdom, and Europe, highlight five key elements of cerebral palsy: It is an 'umbrella term'; it is permanent but not unchanging; it involves a disorder of movement or posture or both, and of motor function; it is due to a non-progressive interference, lesion, or abnormality; and the interference, lesion, or abnormality arose in the developing or immature brain (Cans 2000; Mutch 1992; Rosenbaum 2007; Smithers-Sheedy 2014). As cerebral palsy is defined by clinical description, which may change over time, a longer time span for diagnosis is considered useful to confirm that the condition meets criteria for cerebral palsy and to accurately describe the motor impairment. Thus, final ascertainment for surveillance programmes across the world ranges from four to 12 years, with many considering data to be 'complete' at or near five years (Smithers-Sheedy 2014). Although average age at diagnosis has been around 18 months, recent evidence has suggested that cerebral palsy may be reliably detected as early as three to four months' post term age via tests such as Prechtl's Qualitative Assessment of General Movements and medical resonance imaging (Bosanquet 2013; Morgan 2016).

Cerebral palsy is the most common physical disability in childhood. In a recent meta-analysis, including 19 studies (with varying ages of ascertainment), the global pooled prevalence was 2.11 per 1000 live births (95% confidence interval (CI) 1.98 to 2.25); a cumulative meta-analysis demonstrated stability over the past 10 years (Oskoui 2013). Similar rates have been reported in countries that have used consistent methods of ascertainment for over 20 years (such as Australia, Sweden, and England), with most published estimates in the region of 2 per 1000 (Blair 2006). In low- and middle-income countries, prevalence estimates have tended to be in a similar range or higher (Blair 2006; Cans 2000). However, emerging evidence, including rates from Australia and Europe, now shows that overall rates and severity of the condition are starting to decline for the first time (Reid 2015; Sellier 2015).

Cerebral palsy: causes and risk factors

Brain injury was acquired during an event more than 28 days after birth in approximately 6% of individuals with cerebral palsy (ACPR Group 2013). In the remaining 94% of individuals, brain injury occurred during pregnancy, at birth, or over the first 28 days of life (ACPR Group 2013). Preterm birth is one of the principal risk factors for cerebral palsy and associated neurosensory disabilities (Himpens 2008; Oskoui 2013), with over 40% of individuals with cerebral palsy born preterm (ACPR Group 2013). However, more than half of all individuals with cerebral palsy are born at term (ACPR Group 2013).

Studies on antenatal, intrapartum, and neonatal risk factors for cerebral palsy are abundant. Although a great number of risk factors have been identified, their commonality is that separately, or in combination, they influence potentially preventable pathways to brain injury. Risk factors commonly reported include (i) factors before conception (e.g. low or advanced maternal age, high parity, nulliparity, a short or long interpregnancy interval, a history of stillbirth, multiple miscarriages, neonatal death or preterm birth, family history of cerebral palsy and other genetic predispositions, low socioeconomic status, pre-existing maternal conditions (such as epilepsy or intellectual disability)); (ii) factors in early pregnancy (e.g. male sex, multiple gestation, congenital malformations or birth defects, infections (such as TORCH complex - **t**oxoplasmosis (parasite), **o**ther infections, **r**ubella, **c**ytomegalovirus, **h**erpes simplex virus)); (iii) factors during pregnancy (e.g. maternal disease (such as thyroid disorders), pregnancy complications (such as pre-eclampsia, placenta praevia, and placental abruption), intrauterine infection or inflammation and chorioamnionitis, intrauterine growth restriction, other precursors to preterm birth); and (iv) factors around the time of birth and the neonatal period (e.g. acute intrapartum hypoxic events and neonatal encephalopathy, neonatal brain injury (such as intraventricular haemorrhage, periventricular leucomalacia, and hydrocephalus), strokes or seizures, cardiovascular disorders (such as patent ductus arteriosus and hypotension),

respiratory disorders, associated prolonged ventilation (such as for respiratory distress syndrome or bronchopulmonary dysplasia), infection (such as sepsis and necrotising enterocolitis), metabolic or endocrine disorders (such as hypoglycaemia and hypothyroidism), neonatal jaundice along with inborn errors of metabolism, particular syndromes or chromosomal abnormalities) (Badawi 2005; Dixon 2002; Drougia 2007; Jacobsson 2004; McIntyre 2011; McIntyre 2013; Murphy 1997; Nelson 2008; Tran 2005; Walstab 2004).

Research has shown that contrary to previous beliefs, birth asphyxia is a relatively rare cause of cerebral palsy (Blair 1988; Ellenberg 2013). A growing body of evidence suggests that genetic abnormalities contribute in some cases (MacLennan 2015; Moreno-De-Luca 2012; O'Callaghan 2009; Oskoui 2015). Common risk factors in the post-neonatal period (some of which also contribute in the neonatal period) include infection (such as meningitis/encephalitis, or severe infection and subsequent severe dehydration), head injury (such as from traffic accidents, other traumatic injury, or non-accidental injury), vascular episodes (such as post cardiac or brain surgery), and other events (such as near drowning or near sudden infant death) (Cans 2004; Germany 2013).

Cerebral palsy: consequences

Cerebral palsy, the leading cause of physical disability for children, is a condition with lifelong impact. Most individuals will survive to adulthood, and some studies suggest that life expectancy can be similar to that of the general population (Colver 2012). For known cases of antenatally or neonatally acquired cerebral palsy, the 20-year survival rate has been estimated at 90%. However, strong associations between increasing motor impairment, severe intellectual impairment, number of severe impairments, and early mortality have been shown (Blair 2001; Hemming 2005; Reid 2012). Frequently used definitions for cerebral palsy acknowledge common co-occurring impairments, diseases, and functional limitations (Rosenbaum 2007). A recent systematic review estimated that among children with cerebral palsy, "1 in 2 had an intellectual disability…1 in 4 could not talk; 1 in 4 had epilepsy; 1 in 4 had a behavior disorder…1 in 10 were blind…and 1 in 25 were deaf" (Novak 2012).

Economic studies have estimated lifetime costs of cerebral palsy, including healthcare, social care, and productivity costs, as EUR 860,000 for men and EUR 800,000 for women in Denmark (in 2000) (Kruse 2009), and as USD 921,000 for individuals in the United States (in 2003) (CDC 2004). In Australia, the financial cost of cerebral palsy was estimated as AUD 1.47 billion (in 2007), and the value of lost well-being a further AUD 2.4 billion (Access Economics 2008).

The impact of cerebral palsy is considerable (Davis 2010). Accordingly, identification of primary preventive measures has been regarded as a key priority among individuals with cerebral palsy, their families, clinicians, and researchers (McIntyre 2010).

Description of the interventions

Neonatal approaches to prevention of cerebral palsy

Research efforts aimed at prevention of cerebral palsy have increasingly focused on understanding the causes of cerebral palsy. As it is now widely recognised that causes differ, for example, by gestational age (e.g. for preterm and term-born children) and by clinical subtype of cerebral palsy, it is reasonable to consider that successful primary preventive interventions will also vary according to different aetiologies or causal factors.

In this overview, therefore, we will include a broad range of neonatal interventions (with varying primary aims or indications) that may mediate cerebral palsy risk, including (but not limited to):

1. interventions for neonates following birth asphyxia or with evidence of encephalopathy (e.g. cooling; erythropoietin; darbepoetin; allopurinol; melatonin; magnesium sulphate; anticonvulsants; xenon; naloxone; dopamine; fluid restriction; acupuncture; umbilical cord stem cells);
2. interventions for neonates with neurological disorders, such as intracranial haemorrhage or post-haemorrhagic hydrocephalus (e.g. heparin; antithrombin; phenobarbital; diuretic therapy; erythropoietin; repeated lumbar or ventricular punctures); or those with seizures (anticonvulsants);
3. interventions for neonates requiring resuscitation (e.g. air or oxygen for positive-pressure ventilation; lower or higher oxygen concentrations titrated to target oxygen saturations; face mask, laryngeal mask airway, nasal airway or endotracheal intubation; positive end-expiratory pressure; respiratory function monitoring);
4. interventions for neonates with cardiovascular disorders, such as hypotension (e.g. corticosteroids; inotropes; early volume expansion; adrenaline; dopamine; dobutamine) or patent ductus arteriosus (e.g. ibuprofen; indomethacin; fluid restriction; surgical ligation);
5. interventions for neonates with respiratory disorders, such as apnoea of prematurity (e.g. kinaesthetic stimulation; methylxanthines (caffeine)); respiratory distress syndrome (e.g. early or delayed, prophylactic or selective, protein-containing or protein-free, animal-derived or synthetic pulmonary surfactant; thyroid hormones; continuous distending pressure); or bronchopulmonary dysplasia (chronic lung disease) (e.g. early or late, inhaled or systemic, postnatal corticosteroids);
6. interventions for gastrointestinal tract disorders, such as necrotising enterocolitis (e.g. lactoferrin; probiotics; antibiotics; immunoglobulin; peritoneal drainage; laparotomy);
7. interventions for neonates with infection, such as for control of general infection (e.g. chlorhexidine skin or cord care; patient isolation for infection; gowning by attendants and

visitors in newborn nurseries); fungal and protozoal infections (e.g. prophylactic antifungal agents; antifungal therapy for invasive fungal infection); viral infections (e.g. antiviral agents for treatment of herpes simplex virus or cytomegalovirus infection); or bacterial infections (e.g. intravenous immunoglobulin for prevention of infection, or for suspected or proven infection; antibiotics for suspected early- or late-onset sepsis; intraventricular antibiotics for meningitis; prophylactic antibiotics for ventilated newborns);

8. interventions for neonates with metabolic or endocrine disorders, such as disorders of carbohydrate metabolism (e.g. oral dextrose gel for hypoglycaemia; insulin for hyperglycaemia) or thyroid disorders (postnatal thyroid hormones);

9. interventions for neonates with jaundice and liver disorders (e.g. phototherapy);

10. interventions focused on nutrition or metabolism for high-risk neonates (i.e. preterm or low birthweight neonates, or both) including enteral nutrition interventions (e.g. high protein intake; donor breast milk; nutrient-enriched formula; multi-nutrient fortification of human breast milk; responsive or scheduled feeding), parenteral nutrition interventions (e.g. early or late, high or low amino acid administration), or vitamin or mineral supplementation (e.g. glutamine; arginine; iodine; vitamin E);

11. interventions for neurodevelopmental care or physical environment management (or both) for neonates (e.g. developmental care to reduce stressors in the neonatal nursery; kangaroo mother care; massage; co-bedding in the neonatal nursery; early developmental programmes post discharge to prevent motor and cognitive impairments); and

12. interventions for all neonates at birth, such as newborn screening for inborn errors of metabolism.

We will not consider interventions in the antenatal or intrapartum period (such as magnesium sulphate for foetal neuroprotection (Doyle 2009)), as these interventions will be assessed in a separate overview (Shepherd 2016, under review).

How the intervention might work

Advances in research into several factors that modify the risk of cerebral palsy suggest many opportunities for prevention, with the main neonatal strategies focusing on protection of the immature brain through administration of neuroprotective agents or therapies.

For many individuals born at or near term who develop cerebral palsy, their neonatal course has been seemingly unremarkable, with the exception of those following perinatal asphyxia and with neonatal encephalopathy (brain injury that may be due to cerebral hypoxia and ischaemia before birth) (Badawi 2005; O'Shea 2008). For these neonates, therapeutic hypothermia, applied selectively to the head (as a 'cooling cap') or to the whole body, is one such intervention that can mediate cerebral palsy risk (O'Shea 2008). Beyond cooling, a range of other interventions (including those used as adjuvant therapy with cooling) may contribute to cerebral palsy prevention by protecting against secondary cell death and brain damage following hypoxic-ischaemic insult (Robertson 2012), or by treating the underlying cause(s) of encephalopathy (such as infection or metabolic derangement).

For preterm and very low birthweight neonates, and for other groups of neonates (such as those with hypoglycaemia) who are at increased risk of brain injury, many pharmacological and non-pharmacological interventions in the neonatal period may mediate cerebral palsy risk (O'Shea 2008). Although these interventions differ in their primary aims (such as maintaining adequate ventilation (e.g. through treatment of apnoea of prematurity with caffeine); maintaining normal metabolic status (e.g. through treatment of neonatal hypoglycaemia with dextrose gel); or controlling neonatal seizures (e.g. through use of anticonvulsants)), each may contribute to cerebral palsy prevention by reducing the likelihood or severity of brain injury, and thus of long-term neurodevelopmental sequelae.

Why it is important to do this overview

A multitude of individual studies and Cochrane Systematic Reviews assessing a broad range of neonatal interventions (with varying primary aims or indications) acknowledge the potential for the intervention of interest to influence cerebral palsy risk. With awareness that there are many and varied risk factors for cerebral palsy, and that causes of cerebral palsy differ, there is a need to systematically consider all potentially relevant interventions for their ability to contribute to reducing cerebral palsy risk. As new data suggest possible declining rates and severity of cerebral palsy, it is important to examine the different interventions that may, together, contribute to these observations.

To our knowledge, to date, no 'overview' has brought together the evidence around neonatal interventions for cerebral palsy prevention from Cochrane Systematic Reviews into a single coherent document to be used by researchers, funding bodies, policy makers, clinicians, and consumers to aid decision-making and evidence implementation.

Although the objective of this overview is to summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions for preventing cerebral palsy, it is also important to consider whether such interventions may, instead, actually contribute to increasing cerebral palsy risk.

Is an overview the right approach?

We have followed the Editorial Decision Tree proposed by the Cochrane Comparing Multiple Interventions Methods Group to establish whether our review would better fit an overview format or an intervention review format, specifically:

1. we will review systematic reviews, instead of individual trials;
2. we will not compare multiple interventions with the intention of drawing inferences about the comparative effectiveness of these interventions; and
3. we intend to present a map of evidence from systematic reviews but with no attempt to rank the interventions.

On the basis of these points, the Editorial Decision Tree recommends an overview as the appropriate format for this review.

OBJECTIVES

Primary

To summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions for preventing cerebral palsy (reducing cerebral palsy risk).

Secondary

To summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions that may increase cerebral palsy risk.

METHODS

Criteria for considering reviews for inclusion

In this overview of systematic reviews, we included only published Cochrane Systematic Reviews of neonatal interventions for which cerebral palsy was reported as a primary or secondary review outcome. We identified Cochrane protocols and titles for future inclusion and classified them as 'Ongoing reviews' (in an Appendix). We made note of publication and search dates of the reviews; however, we did not attempt to update the individual systematic reviews.

Participants

We considered reviews that included:
1. neonates with perinatal asphyxia or with evidence of neonatal encephalopathy; and
2. neonates born preterm or at low or very low birthweight (or both preterm and low/very low birthweight neonates).

We also included reviews that included other groups of 'at risk' neonates (e.g. neonates with hypoglycaemia), so long as the intervention assessed in the Cochrane Systematic Review was recognised by the review authors as having the potential to influence cerebral palsy risk - cerebral palsy had to be pre-specified as a primary or secondary outcome in the review.

Interventions

We considered all types of interventions used in the neonatal period compared with placebo, no treatment, or an alternative intervention.

We included both pharmacological and non-pharmacological interventions (see Description of the interventions for further description of possible interventions).

Outcomes of interest

Primary

1. Cerebral palsy (regardless of criteria used for diagnosis by review authors or trialists, and regardless of age at diagnosis; however, we have reported any variation)

Secondary

1. Cerebral palsy or death (regardless of criteria used for diagnosis by review authors or trialists, and regardless of age at diagnosis; however, we have reported any variation)
2. Severity of cerebral palsy (e.g. according to Gross Motor Function Classification System (GMFCS); Manual Ability Classification System (MACS); Communication Function Classification System (CFCS))
3. Type of cerebral palsy (e.g. according to topography (diplegia; hemiplegia; quadriplegia; monoplegia; triplegia) or motor type (spastic; dyskinetic; ataxic))
4. Motor dysfunction (regardless of criteria used for diagnosis by review authors or trialists, and regardless of age at diagnosis; however, we have reported any variation)
5. Other composite outcomes that include cerebral palsy as a component (regardless of criteria used for diagnosis by review authors or trialists, and regardless of age at diagnosis; however, we have reported any variation)

To be included, a review had to pre-specify our overview's primary outcome - cerebral palsy (or a composite outcome that included cerebral palsy*) as a primary or secondary systematic review outcome - and must have reported data for this outcome from at least one of the included trials in the review.

We listed reviews that pre-specified cerebral palsy as a primary or secondary systematic review outcome but provided no reported data from included trials on this outcome as 'Reviews awaiting

further classification', and we will reconsider these reviews in future updates of the overview.

*When possible, we extracted data related to cerebral palsy from any composite outcomes that included cerebral palsy. When it was not possible to extract only cerebral palsy data from such composite outcomes, we reported the composite outcome data; however, we reported these separately from the data for our primary outcome (i.e. as a secondary outcome).

Search methods for identification of reviews

We searched the *Cochrane Database of Systematic Reviews* on 27 November 2016, using the term 'cerebral palsy'. We used the search term to search 'all text', not limited to 'title, abstract, or keywords'. We did not apply any language or date restrictions. We searched no other databases. We managed citations retrieved through the search by using Covidence (Covidence 2015).

Data collection and analysis

We based our data collection and synthesis methods on Chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When appropriate, we prepared the overview using Covidence (Covidence 2015) and Review Manager 5 software (RevMan 2014).

Selection of reviews

Two overview authors independently assessed for inclusion all potential systematic reviews identified by the search. We resolved disagreements through discussion, or, if required, we consulted a third member of the overview team.

Data extraction and management

Two overview authors independently extracted data from the reviews using a pre-defined data extraction form. We resolved discrepancies through discussion or, if needed, through consultation with a third overview author. When information regarding review outcomes was unclear or missing, we accessed the published papers of individual studies for further details.

We extracted information on the following.

1. Review characteristics.
   i) Review title and authors.
   ii) Date that the review was last assessed as up-to-date.
   iii) Number of included trials and numbers of participants (neonates) in the trials and their characteristics (e.g. countries in which the trials were conducted, trial inclusion criteria).
   iv) Quality of the included trials (as reported by the review authors; see 'Quality of studies included within reviews' below under Assessment of methodological quality of included reviews).
   v) Interventions and comparisons relevant to this overview.
   vi) All pre-specified outcomes relevant to this overview (their definitions, and whether they were primary or secondary outcomes in the included reviews).
   vii) Any other characteristics required to assess and report on review quality (see 'Quality of included reviews' under Assessment of methodological quality of included reviews).
2. Statistical summaries*.
   i) Summary intervention effects (including pooled effects (e.g. risk ratios (RRs), odds ratios (ORs), or mean differences (MDs) as reported in the individual reviews), 95% confidence intervals (CIs), and numbers of studies and participants contributing data to each pooled effect) from comparisons and for outcomes relevant to this overview.
   ii) Information required to assess and report on the quality of evidence for the intervention effects extracted above (see 'Quality of evidence in included reviews' under Assessment of methodological quality of included reviews).

*When review authors were not able to perform meta-analyses and therefore did not report statistical summaries, we extracted from those reviews the narrative text related to results for our overview outcomes.

Assessment of methodological quality of included reviews

Quality of included reviews

We assessed the methodological quality of each systematic review using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) instrument (Shea 2009). AMSTAR evaluates the methods used in a review against 11 distinct criteria and assesses the degree to which review methods are unbiased. Each item on AMSTAR is rated as 'yes' (clearly done), 'no' (clearly not done), 'cannot answer', or 'not applicable'. These criteria were as follows:

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was status of the publication used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of included studies provided?
7. Was the scientific quality of included studies assessed and documented?
8. Was the scientific quality of included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was conflict of interest stated?

For all items except item 4, we considered a rating of 'yes' as adequate. For item 4, we considered a rating of 'no' as adequate.

We considered a review that adequately met all of the 11 criteria to be a review of the highest quality (Shea 2009). For this overview, we considered reviews that achieved scores of 8 to 11 as high quality; scores of 4 to 7 as medium quality; and scores of 0 to 3 as low quality.

To further assess risk of bias of the systematic reviews, we additionally used the new ROBIS (Risk of Bias in Systematic Reviews) tool (Whiting 2015). This tool considers risk of bias across four key domains.

1. Study eligibility criteria.
2. Identification and selection of studies.
3. Data collection and study appraisal.
4. Synthesis and findings.

A series of questions within each domain elicited information about possible limitations of the systematic review, leading to a judgement about concerns within that domain (low, high, or unclear). We then considered risk of bias of the review as a whole, using signalling questions and information to support the overall judgement of risk of bias (low, high, or unclear) (Whiting 2015). Two overview authors independently assessed the quality of included reviews using AMSTAR and ROBIS, and another overview author verified this assessment. We resolved differences through discussion or, if needed, through consultation with a third overview author.

We also noted and reported for each review the publication and search dates.

Quality of studies included within reviews

We did not reassess the quality of studies included within reviews but instead reported study quality according to review authors' assessments. We collected this information during the data extraction process.

Quality of evidence in included reviews

We assessed/reported the quality of evidence for our primary outcome (cerebral palsy) and for secondary review outcomes using the GRADE approach, as outlined in the GRADE handbook. We reported the quality of evidence as assessed by systematic review authors (who were in the best position to assess quality, given their familiarity with study-level data) by using GRADEPro 'Summary of findings' tables from the reviews if provided (or when necessary, we constructed such tables using the GRADEpro Guideline Development Tool). The GRADE system assesses the following features for the evidence found for important outcomes.

1. Study limitations (risk of bias): internal validity of the evidence.
2. Inconsistency: heterogeneity or variability in estimates of effect across studies.
3. Indirectness: degrees of difference between populations, interventions, and comparators for the intervention and the outcome of interest.
4. Imprecision (random error): extent to which confidence in the effect estimate is adequate to support a particular decision.
5. Publication bias: degree of selective publication of studies.

The GRADE system rates the quality of evidence as follows.

1. High (further research is very unlikely to change confidence in the estimate of effect).
2. Moderate (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate).
3. Low (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate).
4. Very low (any estimate of effect is very uncertain).

Data synthesis

We prepared a narrative description of characteristics of the included Cochrane Reviews. We organised Review findings by groups of neonates when possible as follows: interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy; interventions for neonates born preterm and at low or very low birthweight; and interventions for other specific groups of 'at risk' neonates.

We summarised the main results of included reviews by categorising their findings in the following framework (as has been used within previous Cochrane and non-Cochrane overviews, such as Farquhar 2015 and Lassi 2015).

1. Effective interventions: indicating that the review found high-quality evidence of effectiveness for an intervention.
2. Possibly effective interventions (more evidence needed): indicating that the review found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed.
3. Ineffective interventions: indicating that the review found high-quality evidence of lack of effectiveness for an intervention.
4. Probably ineffective interventions (more evidence needed): indicating that the review found moderate-quality evidence suggesting lack of effectiveness for an intervention, but more evidence is needed.
5. No conclusions possible: indicating that the review found low- or very low-quality evidence, or insufficient evidence to comment on the effectiveness of an intervention.

We based the choice of category on quality of evidence for the primary overview outcome (cerebral palsy). We used separate assessments for different comparisons (e.g. when one intervention was compared both with placebo (or no treatment) and with an alternative intervention). This approach to summarising the evidence was based on an earlier Cochrane overview (Jones 2012), which categorised interventions as 'What works,' 'What may work', and 'Insufficient evidence to make a judgement'.

RESULTS

Our search of the *Cochrane Database of Systematic Reviews* yielded 513 protocols and reviews. Following title and abstract review, we excluded 303 protocols or reviews and assessed the full text of 210 protocols or reviews.

We excluded 25 reviews that did not pre-specify cerebral palsy as a primary or secondary review outcome (see Table 1, 'Characteristics of excluded studies').

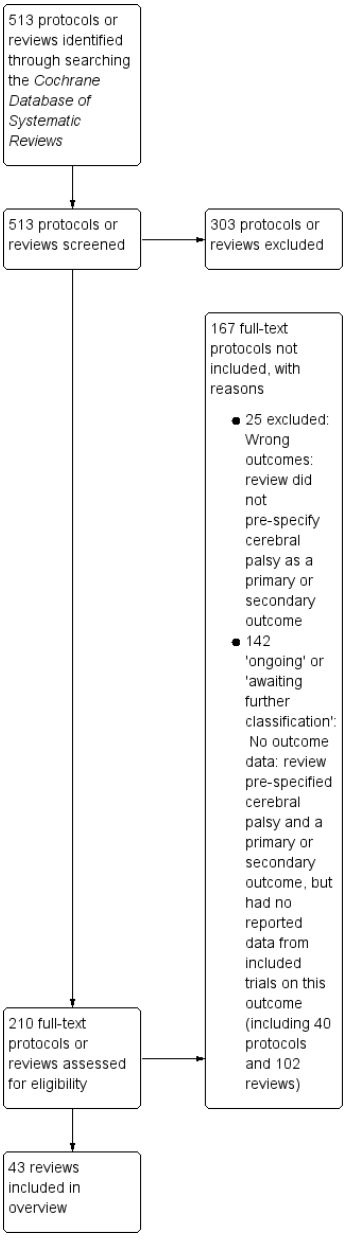
We listed an additional 142 protocols and reviews in the Appendices.

1. Appendix 1 ('Ongoing reviews') lists 40 Cochrane protocols that pre-specified cerebral palsy as a primary or secondary outcome; we will consider these protocols for inclusion in future updates of the overview when they have been published as full reviews.

2. Appendix 2 ('Reviews awaiting further classification') summarises the 102 Cochrane Reviews that pre-specified cerebral palsy as a primary or secondary outcome but reported no data from included trials on this outcome; again, we will consider these reviews for inclusion in future updates of the overview.

We therefore included 43 reviews in this overview. See Figure 1.

Figure 1. Study flow diagram.



Description of included reviews

Of the 43 included reviews:

1. Three reviews focused on interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy, categorised under the Cochrane Neonatal 'Neonatal care' topic.

i) *Asphyxia:* 'Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy' (Chaudhari 2012); 'Cooling for newborns with hypoxic ischaemic encephalopathy' (Jacobs 2013); 'Prophylactic barbiturate use for the prevention of morbidity and mortality following perinatal asphyxia' (Young 2016).

2. Thirty-three reviews focused on interventions for neonates born preterm and/or at low or very low birthweight, categorised under the following Cochrane Neonatal 'Neonatal care' topics.

i) *Haemorrhage: periventricular/intraventricular:* 'Ethamsylate for the prevention of morbidity and mortality in preterm or very low birth weight infants' (Hunt 2010); 'Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants' (Smit 2013).

ii) *Hypotension:* 'The effect of inotropes on morbidity and mortality in preterm infants with low systemic or organ blood flow' (Osborn 2007b).

iii) *Fluid therapy:* 'Early volume expansion for prevention of morbidity and mortality in very preterm infants' (Osborn 2004).

iv) *Patent ductus arteriosus*: 'Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants' (Fowlie 2010); 'Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants' (Ohlsson 2015).

v) *Blood disorders:* 'Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants' (Ohlsson 2014); 'Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants' (Whyte 2011).

vi) *Nitric oxide:* 'Inhaled nitric oxide for respiratory failure in preterm infants' (Barrington 2010).

vii) *Apneoa:* 'Methylxanthine treatment for apnoea in preterm infants' (Henderson-Smart 2010b); 'Prophylactic methylxanthine for prevention of apnoea in preterm infants' (Henderson-Smart 2010c).

viii) *Respiratory distress syndrome:* 'Inositol in preterm infants at risk for or having respiratory distress syndrome' (Howlett 2015); 'Animal derived surfactant extract for treatment of respiratory distress syndrome' (Seger 2009); 'Synthetic surfactant for respiratory distress syndrome in preterm infants' (Soll 2000); 'Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants' (Soll 2010).

ix) *Mechanical ventilation:* 'Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants' (Cools 2015); 'Continuous distending pressure for respiratory distress in preterm infants' (Ho 2015); 'Prophylactic methylxanthines for endotracheal extubation in preterm infants' (Henderson-Smart 2010).

x) *Bronchopulmonary dysplasia:* 'Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants' (Doyle 2014b); 'Moderately early (7 to 14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants' (Halliday 2003); 'Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants' (Doyle 2014); 'Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates' (Shah 2012); 'Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants' (Darlow 2016).

xi) *Necrotising enterocolitis:* 'Probiotics for prevention of necrotizing enterocolitis in preterm infants' (AlFaleh 2014); 'Arginine supplementation for prevention of necrotising enterocolitis in preterm infants' (Shah 2007).

xii) *Fungal infections:* 'Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants' (Cleminson 2015).

xiii) *Jaundice:* 'Prophylactic phototherapy for preventing jaundice in preterm or low birth weight infants' (Okwundu 2012).

xiv) *Parenteral feeding:* 'Glutamine supplementation to prevent morbidity and mortality in preterm infants' (Moe-Byrne 2016).

xv) *Other neonatal care (including thermal environment and developmental care):* 'Thyroid hormones for preventing neurodevelopmental impairment in preterm infants' (Osborn 2001); 'Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants' (Osborn 2007); 'Sound reduction management in the neonatal intensive care unit for preterm or very low birth weight infants' (Almadhoob 2015); 'Kangaroo mother care to reduce morbidity and mortality in low birthweight infants' (Conde-Agudelo 2016); 'Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants' (Spittle 2015).

3. Seven reviews focused on interventions for other specific groups of 'at risk' neonates, categorised under the following Cochrane Neonatal 'Neonatal care' topics.

i) *Pulmonary hypertension:* 'Endothelin receptor antagonists for persistent pulmonary hypertension in term and

late preterm infants' (More 2016).

ii) *Resuscitation:* 'Air versus oxygen for resuscitation of infants at birth' (Tan 2005).

iii) *Nitric oxide:* 'Nitric oxide for respiratory failure in infants born at or near term' (Finer 2006).

iv) *Mechanical ventilation:* 'Long versus short inspiratory times in neonates receiving mechanical ventilation' (Kamlin 2003); 'Volume-targeted versus pressure-limited ventilation in the neonate' (Wheeler 2010) (although in these reviews, relevant outcome data were from neonates born preterm and/or at low or very low birthweight only).

v) *Herpes simplex:* 'Antiviral agents for treatment of herpes simplex virus infection in neonates' (Jones 2009).

vi) *Hypoglycaemia:* 'Oral dextrose gel for the treatment of hypoglycaemia in newborn infants' (Weston 2016).

The 43 reviews included between one - as in Almadhoob 2015, Osborn 2007b, and Shah 2007 - and 33 - as in Ohlsson 2015 - randomised controlled trials, and between 34 - as in Almadhoob 2015 - and 5529 - as in AlFaleh 2014 - infants. In total, the 43 reviews included 454 randomised trials, involving 63,977 infants. One-third (14) of the 43 reviews had conducted searches (and were considered 'up-to-date') in the past three years (November 2013 to November 2016) (AlFaleh 2014; Almadhoob 2015; Cleminson 2015; Conde-Agudelo 2016; Cools 2015; Darlow 2016; Ho 2015; Howlett 2015; Moe-Byrne 2016; More 2016; Ohlsson 2015; Spittle 2015; Weston 2016; Young 2016). The other 29 reviews had latest search end dates ranging from May 1998 - in Soll 2000 - to August 2013 - in Doyle 2014b.

See Table 2 and Table 3 for further details of the characteristics of the 43 included reviews (including review IDs and titles, search dates and when the review was last assessed as up-to-date, numbers of randomised controlled trials and infants included, interventions and comparisons examined, overview outcomes reported, and summary of included trial limitations (risk of bias)).

Methodological quality of included reviews

We rated the quality of included reviews using the AMSTAR and ROBIS tools (Shea 2009 and Whiting 2015, respectively).

With regards to AMSTAR criteria:

1. 41/43 reviews clearly pre-specified their design; for two reviews, this was unclear, with no reference made/access given to pre-specified published protocols (Seger 2009; Soll 2000);
2. 40/43 reviews clearly reported duplicate study selection and data extraction; for three reviews, it was unclear as to whether two independent review authors were involved in study selection and data extraction (Halliday 2003; Osborn 2001; Soll 2000);
3. 42/43 reviews performed a comprehensive literature search; one review searched only one electronic database (in addition to electronic searching and handsearching of meeting abstracts) (Finer 2006);
4. all reviews considered grey literature;
5. 41/43 reviews provided lists of both included and excluded studies; two reviews did not mention excluded studies and therefore provided no list (Henderson-Smart 2010; Shah 2007);
6. all reviews provided the characteristics of included studies;
7. all reviews assessed and documented the scientific quality of included studies;
8. 42/43 reviews clearly used scientific quality of included studies appropriately in formulating conclusions; one review did not clearly incorporate the quality of included studies into the conclusions (Barrington 2010);
9. 35/38 reviews combined the findings of studies using appropriate methods; three reviews provided no/limited discussion and/or exploration of substantial statistical heterogeneity present in some review meta-analyses and did not use a random-effects model (Halliday 2003; Okwundu 2012; Soll 2000); for five reviews, review authors found this item to be 'not applicable' and conducted no meta-analyses (Almadhoob 2015; Jones 2009; More 2016; Osborn 2007b; Shah 2007);
10. 18/43 reviews assessed the likelihood of publication bias; 25 reviews did not assess publication bias likelihood and/or did not pre-specify methods to be used if 10 or more trials were included in meta-analyses (AlFaleh 2014; Barrington 2010; Cools 2015; Finer 2006; Fowlie 2010; Halliday 2003; Henderson-Smart 2010; Henderson-Smart 2010b; Henderson-Smart 2010c; Ho 2015; Hunt 2010; Jacobs 2013; Jones 2009; Kamlin 2003; Okwundu 2012; Osborn 2001; Osborn 2004; Osborn 2007; Seger 2009; Shah 2007; Soll 2000; Soll 2010; Spittle 2015; Tan 2005; Wheeler 2010);
11. 2/43 reviews clearly reported conflicts of interest/potential sources of support for both the review and the included studies (Jacobs 2013; Weston 2016); the remaining 41 reviews did not report conflicts of interests/sources of support for the included studies (AlFaleh 2014; Almadhoob 2015; Barrington 2010; Chaudhari 2012; Cleminson 2015; Conde-Agudelo 2016; Cools 2015; Darlow 2016; Doyle 2014; Doyle 2014b; Finer 2006; Fowlie 2010; Halliday 2003; Henderson-Smart 2010; Henderson-Smart 2010b; Henderson-Smart 2010c; Ho 2015; Howlett 2015; Hunt 2010; Jones 2009; Kamlin 2003; Moe-Byrne 2016; More 2016; Ohlsson 2014; Ohlsson 2015; Okwundu 2012; Osborn 2001; Osborn 2004; Osborn 2007; Osborn 2007b; Seger 2009; Shah 2007; Shah 2012; Smit 2013; Soll 2000; Soll 2010; Spittle 2015; Tan 2005; Wheeler 2010; Whyte 2011; Young 2016).

See Table 4 for further details.

With regards to ROBIS domains:

1. 40 reviews were considered to have 'low risk of bias' across study eligibility criteria, data collection and study appraisal, and synthesis and findings domains, and 39 were considered to have 'low risk of bias' for the identification and selection of studies domain;
2. three reviews were considered to have 'unclear risk of bias' for the study eligibility criteria domain; as above, two reviews

provided no reference/access to pre-specified published protocols (Seger 2009; Soll 2000); and one review made a notable protocol deviation related to the inclusion criteria (Almadhoob 2015);

3. three reviews were considered to have 'unclear risk of bias' for both the identification and selection of studies domain and the data collection and study appraisal domain because review authors did not clearly specify whether two independent review authors were involved in selection of studies, data collection, and study appraisal (Halliday 2003; Osborn 2001; Soll 2000); one further review was considered to have 'unclear risk of bias' for the identification and selection of studies domain, as above, owing to concern regarding comprehensiveness of the search (Finer 2006); and

4. finally, three reviews were considered to have 'unclear risk of bias' for the synthesis and findings domain owing to the presence of substantial statistical heterogeneity (with use of a fixed-effect model) in some review meta-analyses that was not clearly explained/explored (Halliday 2003; Okwundu 2012; Soll 2000). See Table 5 for additional details.

Overall, all 41 included reviews were judged to be of 'high quality' according to AMSTAR (with scores ranging from 8 to 11 out of 11, or from 7 to 9 out of 10), and two were judged to be of 'moderate quality' (with scores of 6 and 7 out of 11) (Halliday 2003; Soll 2000); according to ROBIS, 40 reviews were judged to have 'low risk of bias', and three to have 'unclear risk of bias' (Finer 2006; Osborn 2001; Soll 2000).

Effect of interventions

Below, we have summarised the main results of the included reviews by categorising their findings according to the framework discussed under Data synthesis, organised by groups of neonates and 'Neonatal care' topics.

For further details, including outcome definitions and judgements supporting the quality of the evidence for each outcome, see Table 6 (cerebral palsy); Table 7 (cerebral palsy: subgroup or sensitivity analyses); Table 8 (cerebral palsy or death); Table 9 (severity of cerebral palsy); Table 10 (other composite outcomes that include cerebral palsy); and Table 11 (motor dysfunction).

Interventions for neonates with perinatal asphyxia or evidence of neonatal encephalopathy

Effective interventions: high-quality evidence of effectiveness

Neonatal care: treating asphyxia

High-quality evidence from the Jacobs 2013 review showed a reduction in cerebral palsy among survivors assessed at 18 to 24 months following therapeutic hypothermia versus standard care for newborns with hypoxic-ischaemic encephalopathy (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.54 to 0.82; seven trials; 881 children) (Table 6). Subgroup analysis based on method of cooling (e.g. selective head cooling with mild hypothermia, whole body cooling) showed no clear subgroup differences ($Chi^2 = 0.01$, $df = 1$ ($P = 0.93$), $I^2 = 0.0\%$) (Table 7). Low-quality evidence from Jacobs 2013 also showed no clear differences for cerebral palsy at six to seven years following therapeutic hypothermia versus standard care (RR 0.60, 95% CI 0.31 to 1.18; one trial; 121 children) (Table 6). High-quality evidence from Jacobs 2013 showed reductions in death or major disability among survivors assessed at 18 to 24 months (RR 0.75, 95% CI 0.68 to 0.83; eight trials; 1344 children), major neurodevelopmental disability at 18 to 24 months (RR 0.77, 95% CI 0.63 to 0.94; eight trials; 1344 children), major neurodevelopmental disability among survivors assessed at 18 to 24 months (RR 0.67, 95% CI 0.55 to 0.80; eight trials; 917 children), and neuromotor delay among survivors assessed at 18 to 24 months (RR 0.75, 95% CI 0.59 to 0.94; six trials; 657 children) (Table 10; Table 11). Low-quality evidence suggested no clear differences for death or moderate to severe disability at six to seven years (RR 0.81, 95% CI 0.64 to 1.04; one trial; 190 children) nor for moderate to severe disability at six to seven years (RR 0.92, 95% CI 0.57 to 1.48; one trial; 119 children) following therapeutic hypothermia versus standard care (Table 10).

No conclusions possible: very low-quality evidence

Neonatal care: treating asphyxia

Very low-quality evidence from the Young 2016 review suggested no clear differences for cerebral palsy at three to six years with barbiturates (phenobarbital) versus conventional therapy for prevention of morbidity and mortality following perinatal asphyxia (RR 0.58, 95% CI 0.19 to 1.70; two trials; 69 children) (Table 6). Very low-quality evidence from Young 2016 also suggested a reduction in death or major neurodevelopmental disability at three years (RR 0.33, 95% CI 0.14 to 0.78; one trial; 31 children) and in major neurodevelopmental disability at three years (RR 0.24, 95% CI 0.06 to 0.92; one trial; 31 children) following barbiturates (phenobarbital) versus conventional therapy (Table 10).

Very low-quality evidence from the Chaudhari 2012 review suggested no clear differences for severe quadriplegia among survivors at 18 months or at four to eight years following allopurinol versus placebo or no drug for preventing mortality and morbidity among newborn infants with hypoxic-ischaemic encephalopathy (RR 0.59, 95% CI 0.28 to 1.27; three trials; 73 children) (Table 9). Very low-quality evidence from Chaudhari 2012 also suggested no clear differences for death or severe neurodevelopmental disability among survivors at 18 months or at four to eight years following allopurinol versus placebo (RR 0.78, 95% CI 0.56 to 1.08; three trials; 110 children) (Table 10).

Interventions for neonates born preterm and/or at low or very low birthweight

Possibly effective interventions: moderate-quality evidence of effectiveness

Neonatal care: mechanical ventilation

Moderate-quality evidence from the Henderson-Smart 2010 review showed a reduction in cerebral palsy at 18 to 21 months' corrected age with prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants (RR 0.54, 95% CI 0.32 to 0.92; one trial; 644 children) (Table 6). Moderate-quality evidence from Henderson-Smart 2010 also showed a reduction in death or major disability at 18 to 21 months' corrected age with prophylactic methylxanthines (caffeine) versus placebo (RR 0.85, 95% CI 0.73 to 0.99; one trial; 676 children) (Table 10).

Probably ineffective interventions: moderate-quality evidence of harm

Neonatal care: preventing bronchopulmonary dysplasia

Moderate-quality evidence from the Doyle 2014b review showed an increase in cerebral palsy at 11 months to seven to nine years (RR 1.45, 95% CI 1.06 to 1.98; 12 trials; 1452 children) and in cerebral palsy among survivors assessed at 11 months to seven to nine years (RR 1.50, 95% CI 1.13 to 2.00; 12 trials; 959 children) following early (less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants (Table 6). Subgroup analysis based on type of corticosteroid used (i.e. dexamethasone, hydrocortisone) suggested no clear subgroup differences for cerebral palsy at 11 months to seven to nine years (Chi^2 = 2.96, df = 1 (P = 0.09), I^2 = 66%); however, a possible subgroup difference was identified that was based on the type of corticosteroid used for cerebral palsy among survivors assessed at 11 months to seven to nine years (Chi^2 = 3.99, df = 1 (P = 0.05), I^2 = 75%), with an increase in risk specifically observed in the dexamethasone (not the hydrocortisone) subgroup (Table 7). Moderate-quality evidence from Doyle 2014b also showed no clear differences for cerebral palsy or death at 11 months to seven to nine years (RR 1.09, 95% CI 0.92 to 1.25; 12 trials; 1452 children) (Table 8) nor for death or major neurosensory disability at 18 to 22 months to 53 months (RR 1.05, 95% CI 0.93 to 1.17; seven trials; 1233 children) (Table 10); Bayley Scales of Infant Development Psychomotor Developmental Index less than minus two standard deviations below the mean at 18 to 22 months or at 25 months (RR 1.17, 95% CI 0.85 to 1.60; three trials; 842 children); or Bayley Scales of Infant Development Psychomotor Developmental Index less than minus two standard deviations below the mean among tested survivors at 18 to 22 months or at 25 months (RR 1.17, 95% CI 0.87 to 1.57; three trials; 528 children) with early postnatal corticosteroids versus placebo or no treatment (Table 11). Low-quality evidence from Doyle 2014b suggested no clear differences between major neurosensory disability at 18 to 22 months to 53 months (RR 1.16, 95% CI 0.94 to 1.43; seven trials; 1233 children) and major neurosensory disability among survivors examined at 18 to 22 months to 53 months (RR 1.14, 95% CI 0.94 to 1.38; seven trials; 799 children) with early postnatal corticosteroids versus placebo or no treatment (Table 10).

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness

Neonatal care: preventing haemorrhage: periventricular/intraventricular

Moderate-quality evidence from the Hunt 2010 review showed no clear differences for cerebral palsy among surviving children available for follow-up at two years up to 3.5 to 4.2 years following ethamsylate versus placebo for prevention of morbidity and mortality in preterm or very low birthweight infants (RR 1.13, 95% CI 0.64 to 2.00; three trials; 532 children) (Table 6), nor on further subgroup analysis of infants born at less than 31 completed weeks at less than 1500 grams (RR 0.82, 95% CI 0.38 to 1.75; two trials; 328 children) (Table 7). Moderate-quality evidence from Hunt 2010 also showed no clear differences for neurodevelopmental disability at two years of age among surviving children available for follow-up (RR 0.79, 95% CI 0.53 to 1.17; three trials; 532 children), and low-quality evidence suggested no clear differences for death or any disability by two years of age among children with known outcome at any point in time (RR 0.96, 95% CI 0.82 to 1.11; seven trials; 1334 children) following ethamsylate versus placebo (Table 10).

Neonatal care: fluid therapy

Moderate-quality evidence from the Osborn 2004 review showed no clear differences for cerebral palsy among survivors at two years following volume versus no treatment (RR 0.76, 95% CI 0.48 to 1.20; one trial; 604 children) and gelatin versus fresh frozen plasma (RR 0.94, 95% CI 0.52 to 1.69; one trial; 399 children) for prevention of morbidity and mortality in very preterm infants (Table 6). Formal subgroup analyses in Osborn 2004 were not applicable based on timing of treatment, types of infants enrolled, or methodological quality (with the one included trial for this outcome using early treatment (less than 24 hours of age) in unselected preterm infants (not selected on the basis of cardiovascular compromise) and providing complete follow-up for neurodevelopmental outcomes (RR 0.76, 95% CI 0.48 to 1.20; one trial;

604 children, as in main analysis)) (Table 7). Moderate-quality evidence from Osborn 2004 also showed no clear differences between volume versus no treatment for severe neurodevelopmental disability among survivors at two years (RR 0.80, 95% CI 0.52 to 1.23; one trial; 604 children) or for death or severe neurodevelopmental disability among survivors at two years (RR 1.00, 95% CI 0.80 to 1.24; one trial; 776 children); or between gelatin versus fresh frozen plasma for severe neurodevelopmental disability among survivors at two years (RR 0.99, 95% CI 0.57 to 1.72; one trial; 399 children) or for death or severe neurodevelopmental disability among survivors at two years (RR 1.11, 95% CI 0.86 to 1.43; one trial; 518 children) (Table 10).

Neonatal care: preventing/treating patent ductus arteriosus

Moderate-quality evidence from the Fowlie 2010 review showed no clear differences for cerebral palsy at 18 to 54 months (RR 1.04, 95% CI 0.77 to 1.40; four trials; 1372 children) or at eight years (RR 1.24, 95% CI 0.59 to 2.62; one trial; 304 children) following prophylactic indomethacin versus placebo for preventing mortality and morbidity in preterm infants (Table 6). Moderate-quality evidence from Fowlie 2010 also showed no clear differences for death or severe neurodevelopmental disability at 18 to 36 months following prophylactic indomethacin versus placebo (RR 1.02, 95% 0.90 to 1.15; three trials; 1491 children) (Table 10).

Neonatal care: treating respiratory distress syndrome

Moderate-quality evidence from the Soll 2000 review showed no clear differences in cerebral palsy among survivors examined at one year (RR 0.76, 95% CI 0.55 to 1.05; five trials; 1557 children) (Table 6) nor in moderate to severe cerebral palsy among survivors examined at one year following synthetic surfactant versus placebo for respiratory distress syndrome in preterm infants (RR 0.75, 95% CI 0.48 to 1.16; five trials; 1557 children) (Table 9).

Neonatal care: preventing jaundice

Moderate-quality evidence from the Okwundu 2012 review showed no clear differences for cerebral palsy in all infants (birthweight < 2500 grams) at one year or at 18 months following prophylactic phototherapy versus standard care (starting phototherapy when serum bilirubin reached a pre-specified level) for preventing jaundice in preterm or low birthweight infants (RR 0.96, 95% CI 0.50 to 1.85; two trials; 756 children) (Table 6). Very low-quality evidence suggested no clear differences for cerebral palsy among all infants (birthweight < 1000 grams) at 18 months (RR 0.29, 95% CI 0.04 to 2.27; one trial; 30 children) (Table 6). Okwundu 2012 reported in text that "Secondary reports emanating from Brown 1985 at six-year follow-up also showed that there was no significant difference in the rate of cerebral palsy between the phototherapy and control group" (not graded). Moderate-quality evidence from Okwundu 2012 did however show a reduction in neurodevelopmental impairment at 18 to 22 months following prophylactic phototherapy versus standard care (RR 0.85, 95% CI 0.74 to 0.99; one trial; 1804 children) (Table 10).

No conclusions possible: low-quality evidence

Neonatal care: preventing/treating blood disorders

Low-quality evidence from Ohlsson 2014 suggested no clear differences for cerebral palsy at 18 to 22 months' corrected age in children examined following darbepoetin alfa versus placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants (RR 0.08, 95% CI 0.00 to 1.40; one trial; 51 children) (Table 6).

Low-quality evidence from Whyte 2011 suggested no clear differences for cerebral palsy at 18 to 21 months' follow-up among survivors following transfusion at a restrictive (low haemoglobin) versus a liberal (high haemoglobin) threshold for preventing morbidity and mortality in very low birthweight infants (RR 1.29, 95% CI 0.55 to 3.03; one trial; 335 children) (Table 6). Low-quality evidence from Whyte 2011 also suggested no clear differences for any neurosensory impairment at 18 to 21 months' follow-up among survivors (RR 1.31, 95% CI 0.90 to 1.90; one trial; 328 children) nor for death or severe morbidity at 18 to 21 months' follow-up (Mental Development Index component defined < 70) (RR 1.17, 95% CI 0.94 to 1.47; one trial; 421 children); however, moderate-quality evidence showed a possible increase in death or severe morbidity at 18 to 21 months' follow-up (Mental Development Index component defined < 85) (RR 1.21, 95% CI 1.01 to 1.44; one trial; 421 children) with transfusion at a restrictive (low haemoglobin) versus a liberal (high haemoglobin) threshold (Table 10).

Neonatal care: nitric oxide

Low-quality evidence from Barrington 2010 suggested no clear differences following inhaled nitric oxide versus placebo or no treatment for respiratory failure in preterm infants for cerebral palsy at 18 to 22 months (trial entry before three days based on oxygenation) (RR 1.85, 95% CI 0.93 to 3.71; two trials; 209 children); cerebral palsy at two years' corrected age or at 30 months (trial entry after three days based on bronchopulmonary dysplasia risk) (RR 1.10, 95% CI 0.54 to 2.23; two trials; 498 children); or cerebral palsy at one or two years' corrected age (trials of routine use in intubated preterm infants) (RR 0.94, 95% CI 0.51 to 1.70; two trials; 593 children) (Table 6). Low- to very low-quality evidence from Barrington 2010 also suggested no clear differences for neurodevelopmental disability at 18 to 22 months (trial entry before three days based on oxygenation) (RR 1.05, 95% CI 0.78 to 1.40; two trials; 208 children), neurodevelopmental disability at two years' corrected age or at 30 months (trial entry after

three days based on bronchopulmonary dysplasia risk) (RR 0.90, 95% CI 0.74 to 1.09; two trials; 498 children), or neurodevelopmental disability at one or two years' corrected age (trials of routine use in intubated preterm infants) (RR 0.90, 95% CI 0.72 to 1.13; two trials; 593 children) following inhaled nitric oxide versus placebo or no treatment (Table 10). Moderate-quality evidence from Barrington 2010 also showed no clear differences for Bayley Mental or Psychomotor Developmental Index less than minus two standard deviations below the mean at two years' corrected age (trials of routine use in intubated preterm infants) following inhaled nitric oxide versus placebo (RR 0.56, 95% CI 0.33 to 0.93; one trial; 138 children) (Table 11).

Neonatal care: preventing/treating apnoea

Low-quality evidence from the Henderson-Smart 2010b review suggested no clear differences for cerebral palsy at 18 to 21 months' corrected age following caffeine versus placebo for treatment of apnoea in preterm infants (RR 0.60, 95% CI 0.29 to 1.25; one trial; 729 children) (Table 6). Low-quality evidence from Henderson-Smart 2010b also suggested no clear differences in death or major disability at 18 to 21 months' corrected age following caffeine versus placebo (RR 0.85, 95% CI 0.71 to 1.01; one trial; 767 children) (Table 10).

Low-quality evidence from the Henderson-Smart 2010c review suggested no clear differences for cerebral palsy at 18 to 21 months' corrected age following caffeine versus placebo for prevention of apnoea in preterm infants (RR 1.03, 95% CI 0.43 to 2.49; one trial; 415 children) (Table 6). Low-quality evidence from Henderson-Smart 2010c also suggested no clear differences in death or major disability at 18 to 21 months' corrected age following caffeine versus placebo (RR 1.00, 95% CI 0.80 to 1.24; one trial; 423 children) (Table 10).

Neonatal care: preventing respiratory distress syndrome

Low-quality evidence from the Soll 2010 review suggested no clear differences for cerebral palsy at one to two years following prophylactic protein-free synthetic surfactant versus placebo for preventing morbidity and mortality in preterm infants (RR 0.93, 95% CI 0.64 to 1.33; four trials; 670 children) (Table 6). Subgroup analyses were conducted that were based on surfactant product (Exosurf Neonatal, DPPC/HDL; Burroughs Wellcome, Research Triangle Park, North Carolina, USA); however, formal tests for subgroup differences were not applied in the review (Table 7). Low-quality evidence from Soll 2010 also suggested no clear differences for moderate or severe cerebral palsy at one or two years following prophylactic protein-free synthetic surfactant versus placebo (RR 0.92, 95% CI 0.53 to 1.59; four trials; 670 children) (Table 9).

Neonatal care: mechanical ventilation

Low-quality evidence from the Wheeler 2010 review suggested no clear differences for severe disability at six to 18 months and at 22 months (RR 0.86, 95% CI 0.47 to 1.59; two trials; 209 children), for severe disability at 22 months or at death (RR 0.54, 95% CI 0.27 to 1.06; one trial; 109 children) (Table 10), and for gross motor developmental issues (RR 1.00, 95% CI 0.47 to 2.14; one trial; 128 children) (Table 11) following volume-targeted versus pressure-limited ventilation in the neonate.

Neonatal care: preventing/treating bronchopulmonary dysplasia

Low-quality evidence from the Doyle 2014 review suggested no clear differences for cerebral palsy at one to three years (RR 1.06, 95% CI 0.76 to 1.50; 14 trials; 876 children), cerebral palsy at one to three years among survivors assessed (RR 1.05, 95% CI 0.75 to 1.47; 14 trials; 631 children), cerebral palsy at latest age reported (one year up to 17 years) (RR 1.12, 95% CI 0.79 to 1.60; 15 trials; 855 children), or cerebral palsy at latest age reported among survivors assessed (one year up to 17 years) (RR 1.12, 95% CI 0.79 to 1.58; 15 trials; 591 children) following late (more than seven days of age) postnatal corticosteroids versus placebo or no treatment for chronic lung disease in preterm infants (Table 6). Low-quality evidence from Doyle 2014 also suggested no clear differences for cerebral palsy or death at one to three years (RR 0.92, 95% CI 0.76 to 1.12; 14 trials; 876 children), cerebral palsy or death at latest age reported (one year up to 17 years) (RR 0.95, 95% CI 0.77 to 1.16; 15 trials; 855 children) (Table 8), major neurosensory disability at one year corrected age up to 11 years (RR 1.17, 95% CI 0.85 to 1.60; eight trials; 655 children), major neurosensory disability among survivors assessed at one year corrected age up to 11 years (RR 1.10, 95% CI 0.81 to 1.50; eight trials; 480 children), death or major neurosensory disability at one year corrected age up to 11 years (RR 1.10, 95% CI 0.81 to 1.50; eight trials; 655 children) (Table 10), Bayley Scales of Infant Development Psychomotor Development Index less than minus two standard deviations below the mean at one year corrected age (RR 0.78, 95% CI 0.34 to 1.80; one trial; 118 children), or Bayley Scales of Infant Development Psychomotor Development Index less than minus two standard deviations below the mean among survivors assessed at one year corrected age (RR 0.67, 95% CI 0.30 to 1.50; one trial; 90 children) (Table 11) with late postnatal corticosteroids versus placebo or no treatment.

Low-quality evidence from the Darlow 2016 review suggested no clear differences for neurodevelopmental impairment at 18 to 24 months following supplemental vitamin A versus a sham injection to prevent mortality and short- and long-term morbidity in very low birthweight infants (RR 0.89, 95% CI 0.74 to 1.08; one trial; 538 children) (Table 10). Moderate-quality evidence also showed no clear differences for death or neurodevelopmental impairment at 18 to 24 months following supplemental vitamin A versus a sham injection (RR 0.92, 95% CI 0.81 to 1.05; one trial; 687

children) (Table 10).

Neonatal care: preventing necrotising enterocolitis

Low-quality evidence from the Shah 2007 review suggested no clear differences for cerebral palsy at 36 months' post-menstrual age following arginine supplementation versus placebo for prevention of necrotising enterocolitis in preterm infants (RR 0.88, 95% CI 0.21 to 3.80; one trial; 135 children) (Table 6). Low-quality evidence from Shah 2007 also suggested no clear differences for major neurodevelopmental disability at 36 months' post-menstrual age following arginine supplementation versus placebo (RR 0.65, 95% CI 0.23 to 1.83; one trial; 132 children) (Table 10).

Neonatal care: preventing/treating fungal infection

Low-quality evidence from the Cleminson 2015 review suggested no clear differences for cerebral palsy at 18 to 22 months post term following use of a systemic antifungal agent versus placebo to prevent mortality and morbidity in very low birthweight infants (RR 0.96, 95% CI 0.45 to 2.03; one trial; 219 children) (Table 6). Low-quality evidence from Cleminson 2015 also suggested no clear differences for neurodevelopmental impairment (composite) at 18 to 22 months following use of a systemic antifungal agent versus placebo (RR 1.13, 95% CI 0.71 to 1.81; one trial; 171 children) (Table 10).

Neonatal care: parenteral feeding

Moe-Byrne 2016 assessed glutamine supplementation versus placebo to prevent morbidity and mortality in preterm infants and reported the following: "van den Berg 2005 reported neurodevelopmental outcomes for infants aged two years post term. Outcomes assessed included...incidence of cerebral palsy... No significant differences between the glutamine and the control groups were reported for any of these individual outcomes" (not graded) (Table 6). Low-quality evidence from the Moe-Byrne 2016 review also suggested no clear differences for neurodevelopmental impairment at two years post term following glutamine supplementation versus placebo (RR 1.07, 95% CI 0.59 to 1.92; one trial; 72 children) (Table 10).

Neonatal care: other

Low-quality evidence from both the Osborn 2001 and Osborn 2007 reviews suggested no clear differences for cerebral palsy at 5.7 years following prophylactic thyroid hormones versus placebo for prevention of morbidity and mortality in preterm infants (RR 0.72, 95% CI 0.28 to 1.84; one trial; 156 children) (Table 6). In Osborn 2007, subgroup analyses based on dosing strategy, timing, and methodological quality were not possible for this outcome, with the one included trial using T4 8 mcg/kg/d, on days 1 to 42, commencing within 48 hours, and being of adequate methodological quality (Table 7). Low-quality evidence from both Osborn 2001 and Osborn 2007 also suggested no clear differences for cerebral palsy or death at 5.7 years following prophylactic thyroid hormones versus placebo (RR 0.70, 95% CI 0.43 to 1.14; one trial; 200 children) (Table 8).

Low-quality evidence from the Conde-Agudelo 2016 review suggested no clear differences for cerebral palsy at 12 months' corrected age following kangaroo mother care versus conventional neonatal care to reduce morbidity and mortality among low birthweight infants (RR 0.65, 95% CI 0.21 to 2.02; one trial; 588 children) (Table 6).

Low-quality evidence from the Spittle 2015 review suggested no clear differences for cerebral palsy at 18 months to six years following early developmental intervention versus standard follow-up post hospital discharge to prevent motor and cognitive impairment in preterm infants (RR 0.82, 95% CI 0.52 to 1.27; seven trials; 985 children) (Table 6). Subgroup analyses based on commencement of intervention (inpatient, post hospital discharge), focus of intervention (parent-infant relationship and infant development, infant development), and quality of studies (high-quality studies, lower-quality studies) were performed for this outcome; however, formal subgroup interaction tests were not applied in the review (Table 7). Low-quality evidence from Spittle 2015 also suggested no clear differences for motor outcome at school age (five years) following early developmental intervention versus standard follow-up (RR 1.12, 95% CI 0.87 to 1.44; two trials; 333 children) (Table 11).

No conclusions possible: very low-quality evidence

Neonatal care: preventing haemorrhage: periventricular/intraventricular

Very low-quality evidence from the Smit 2013 review suggested no clear differences for severe neurodevelopmental impairment at 27 months (RR 1.44, 95% CI 0.41 to 5.04; one trial; 101 children) nor for mild neurodevelopmental impairment at 27 months (RR 0.57, 95% CI 0.15 to 2.17; one trial; 101 children) following phenobarbital versus no treatment for prevention of intraventricular haemorrhage in preterm infants (Table 10).

Neonatal care: treating hypotension

Very low-quality evidence from the Osborn 2007b review suggested no clear differences for cerebral palsy at three years among survivors assessed following dobutamine versus dopamine in preterm infants with low superior vena cava flow (RR 0.16, 95% CI 0.01 to 2.64; one trial; 13 children) (Table 6). Very low-quality evidence from Osborn 2007b also suggested no clear differences for disability at three years among survivors (RR 0.10, 95% 0.01 to 1.56; one trial; 13 children), for death or disability at three years

(RR 0.79, 0.57 to 1.11; one trial; 37 children), or for death or disability at latest follow-up (one to three years) (RR 0.95, 95% CI 0.66 to 1.38; one trial; 41 children) following dobutamine versus dopamine (Table 10).

Neonatal care: treating patent ductus arteriosus

Very low-quality evidence from Ohlsson 2015 suggested no clear differences for moderate or severe cerebral palsy at 18 to 24 months following oral ibuprofen versus intravenous ibuprofen for treatment of patent ductus arteriosus in preterm or low birthweight (or both) infants (RR 1.35, 95% CI 0.24 to 7.48; one trial; 57 children) (Table 6).

Neonatal care: preventing blood disorders

Very low-quality evidence from Ohlsson 2014 suggested no clear differences for cerebral palsy at 18 to 22 months' corrected age among children examined following erythropoietin versus placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants (RR 0.66, 95% CI 0.31 to 1.37; two trials; 153 children) (Table 6). Very low-quality evidence from Ohlsson 2014 also suggested no clear differences for any neurodevelopmental impairment at 18 to 22 months' corrected age among children examined (RR 0.97, 95% CI 0.62 to 1.51; one trial; 99 children) (Table 10) nor for Psychomotor Developmental Index less than 70 at 18 to 22 months' corrected age among children examined (RR 2.33, 95% CI 0.98 to 5.53; one trial; 90 children) following erythropoietin versus placebo (Table 11).

Neonatal care: preventing/treating respiratory distress syndrome

Very low-quality evidence from Howlett 2015 suggested no clear differences for major neural developmental impairment at one year corrected age (RR 0.53, 95% CI 0.24 to 1.16; one trial; 169 children) (Table 10) nor for minor neural developmental impairment at one year corrected age (RR 0.84, 95% CI 0.38 to 1.86; one trial; 169 children) following inositol supplementation (repeat doses) versus placebo in preterm infants at risk for or having respiratory distress syndrome (Table 11).

Very low-quality evidence from Seger 2009 suggested no clear differences for cerebral palsy at one and two years' corrected age following animal-derived surfactant extract versus no treatment for respiratory distress syndrome (RR 0.88, 95% CI 0.34 to 2.27; one trial; 73 children) (Table 6). Subgroup analysis based on surfactant product for this outcome was not applicable, with the one included trial using porcine surfactant extract (Table 7). Very low-quality evidence from Seger 2009 also suggested no clear differences for major developmental disability among survivors at one and two years' corrected age following animal-derived surfactant extract versus no treatment (RR 3.30, 95% 0.14 to 26.78; one trial; 73 children) (Table 10).

Neonatal care: mechanical ventilation

Very low-quality evidence from the Ho 2015 review suggested no clear differences for cerebral palsy at nine to 15 years following continuous distending pressure versus standard care for respiratory distress in preterm infants (RR 5.0, 95% CI 0.26 to 97.37; one trial; 36 children) (Table 6). Subgroup analysis based on type of continuous distending pressure was not possible for this outcome, with the only included trial using continuous negative pressure (Table 7). Very low-quality evidence from Ho 2015 also suggested no clear differences for death or severe disability at nine to 15 years (RR 1.33, 95% CI 0.34, 5.17; one trial; 38 children), for severe disability at nine to 15 years (RR 1.06, 95% CI 0.24 to 4.57; one trial; 37 children), or for any disability at nine to 15 years (RR 0.62, 95% CI 0.31 to 1.21; one trial; 37 children) following continuous distending pressure versus standard care (Table 10).

Very low-quality evidence from the Kamlin 2003 review suggested no clear differences for cerebral palsy among survivors at less than 33 weeks' gestation, at birth, and at 18 months following long versus short inspiratory times among neonates receiving mechanical ventilation (RR 2.9, 95% CI 0.97 to 8.65; one trial; 177 children) (Table 6).

Neonatal care: preventing bronchopulmonary dysplasia

Very low-quality evidence from the Halliday 2003 review suggested no clear differences for cerebral palsy at 12 months' corrected age up to 90 months (RR 1.03, 95% CI 0.47 to 2.24; four trials; 204 children) nor for cerebral palsy among survivors assessed at 12 months' corrected age up to 90 months (RR 0.83, 95% CI 0.39 to 1.74; four trials; 130 children) following moderately early (between seven and 14 days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants (Table 6). Very low-quality evidence from Halliday 2003 also suggested no clear differences for cerebral palsy or death at 12 months' corrected age up to 90 months (RR 0.83, 95% CI 0.55 to 1.23; four trials; 204 children) (Table 8), for major neurosensory disability at 15 months' corrected age up to 90 months (RR 1.26, 95% CI 0.45 to 3.49; two trials; 96 children), for major neurosensory disability among survivors assessed at 15 months' corrected age up to 90 months (RR 0.89, 95% CI 0.38 to 2.10; two trials; 56 children), or for death or major neurosensory disability at 15 months' corrected age up to 90 months (RR 1.02, 95% CI 0.66 to 1.56; two trials; 96 children) with moderately early postnatal corticosteroids versus placebo or no treatment (Table 10).

Very low-quality evidence from the Shah 2012 review suggested no clear differences in cerebral palsy at three years with early inhaled corticosteroids versus placebo for preventing chronic lung disease among ventilated very low birthweight preterm neonates (RR 1.33, 95% CI 0.33 to 5.42; one trial; 56 children) (Table 6). Very low-quality evidence from Shah 2012 also suggested no clear differences for mean developmental index less than two standard

deviations of the mean on the Bayley Scales of Infant Development with early inhaled corticosteroids versus placebo (RR 1.25, 95% CI 0.37 to 4.17; one trial; 56 children) (Table 11).

Neonatal care: preventing necrotising enterocolitis

Very low-quality evidence from the AlFaleh 2014 review suggested no clear differences for mental retardation and cerebral palsy at six years following probiotics versus control (distilled water) for prevention of necrotising enterocolitis in preterm infants (RR 1.02, 95% CI 0.15 to 6.94; one trial; 85 children) (Table 10).

Neonatal care: other

Very low-quality evidence from the Almadhoob 2015 review suggested no clear differences for cerebral palsy at 18 to 22 months' corrected age with use of silicone earplugs versus no earplugs in the neonatal intensive care unit for preterm or very low birthweight infants (RR 3.0, 95% CI 0.14 to 63.15; one trial; 14 children) (Table 6).

No conclusions possible: not graded

Neonatal care: mechanical ventilation

The Cools 2015 review assessed elective high-frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cools 2015 did not perform a meta-analysis for the outcome cerebral palsy, with age and methods of assessment varying between studies, and rather reported the results for three separate trials in text, as below (not graded) (Table 6).

1. "Neurodevelopmental status was assessed at 16 to 24 months' corrected age in 77% of survivors of the HIFI 1989 study (185 HFOV and 201 CV) using Bayley psychometric tests and central nervous system examinations... The rate of cerebral palsy was 11% in both groups".
2. "Moriette 2001 assessed neuromotor outcome at the corrected age of two years in 192 of 212 survivors (90%) using a physician questionnaire...the risk of spastic cerebral palsy was significantly lower for infants ventilated with HFOV (4% versus 17%; OR 0.87, 95% CI 0.79 to 0.96), even after adjustment for multiple factors. Survival without cerebral palsy was significantly more likely in the HFOV group than in the CV group (OR 1.89, 95% CI 1.04 to 3.44)".
3. "Sun 2014 assessed neurodevelopmental outcomes at 18 months' corrected age in 145 infants of the HFOV group (84% of survivors) and in 143 infants of the CV group (86% of survivors). Cerebral palsy occurred significantly less in the HFOV group (3% versus 10% in the CV group, P = 0.03)".

Interventions for other specific groups of 'at risk' neonates

No conclusions possible: low-quality evidence

Neonatal care: treating pulmonary hypertension

Low-quality evidence from the More 2016 review suggested no clear differences for cerebral palsy at six months following use of endothelin receptor antagonists versus placebo for persistent pulmonary hypertension in term and late preterm infants (RR 0.09, 95% CI 0.00 to 1.61; one trial; 37 children) (Table 6). Low-quality evidence from More 2016 also suggested no clear differences for adverse neurological outcomes at six months with use of endothelin receptor antagonists versus placebo (RR 0.07, 95% CI 0.00,1.20; one trial; 37 children) (Table 11).

Neonatal care: nitric oxide

Low-quality evidence from the Finer 2006 review suggested no clear differences for cerebral palsy among survivors at 13 or 18 to 24 months following inhaled nitric oxide versus placebo for respiratory failure in infants born at or near term (RR 1.02, 95% CI 0.49 to 2.14; two trials; 299 children) (Table 6). Finer 2006 also reported on an additional trial not included in the meta-analysis for this outcome: "This group [Wessel 1996] has now published follow up data, including neurodevelopmental outcomes, which were obtained by telephone interview of 60 of the 83 survivors of the original trial. The interview was conducted between one and four years of age... Although cerebral palsy [was] reported it is unclear how [it] was defined... It is not, therefore, possible to add any of these data to the meta-analysis, but they do appear to show no evidence of neurodevelopmental impairment due to inhaled nitric oxide therapy" (not graded). Low-quality evidence from Finer 2006 also suggested no clear differences for neurodevelopmental disability among survivors at 13 or 18 to 24 months (RR 0.97, 95% CI 0.66 to 1.44; two trials; 301 children) (Table 10) nor for Bayley Psychomotor Developmental Index more than two standard deviations below the mean at 13 or 18 to 24 months (RR 1.09, 95% CI 0.58 to 2.03; two trials; 283 children) (Table 11) following inhaled nitric oxide versus placebo.

No conclusions possible: very low-quality evidence

Neonatal care: resuscitation

Very low-quality evidence from the Tan 2005 review suggested no clear differences for cerebral palsy among those followed up at 18 to 24 months following room air versus 100% oxygen for resuscitation of infants at birth (RR 1.34, 95% CI 0.55 to 3.24;

one trial; 213 children) (Table 6). Very low-quality evidence from Tan 2005 also suggested no clear differences in not walking among those followed up at 18 to 24 months following room air versus 100% oxygen (RR 1.03, 95% CI 0.04 to 2.25; one trial; 213 children) (Table 11).

Neonatal care: nitric oxide

Very low-quality evidence from the Finer 2006 review suggested no clear differences for cerebral palsy among survivors at 18 to 24 months following inhaled nitric oxide versus placebo for respiratory failure among infants with diaphragmatic hernias born at or near term (RR 8.33, 95% CI 0.45 to 154.78; one trial; 22 children) (Table 6).

Neonatal care: treating herpes simplex

Very low-quality evidence from the Jones 2009 review suggested no clear differences in cerebral palsy in central nervous system herpes simplex virus (HSV) neonatal infection up to three years by HSV serotype: HSV-1 (no events, one trial, nine children) and HSV-2 (RR 1.07, 95% CI 0.49 to 2.33; one trial; 14 children) following acyclovir versus vidarabine for treatment of HSV infection in neonates (Table 6). Very low-quality evidence from Jones 2009 also suggested no clear differences for abnormal neurodevelopment at approximately one year of age (RR 1.50, 95% 0.62 to 3.65; one trial; 56 children) nor for abnormal neurodevelopment or death at approximately one year of age (RR 0.86, 95% CI 0.60 to 1.22; one trial; 56 children) following vidarabine versus placebo; and abnormal neurodevelopment at approximately one year of age (RR 0.82, 95% 0.50 to 1.34; one trial; 202 children) or abnormal neurodevelopment or death at approximately one year of age (RR 0.79, 95% CI 0.57 to 1.10; one trial; 202 children) following acyclovir versus vidarabine (Table 10).

Neonatal care: treating hypoglycaemia

Very low-quality evidence from the Weston 2016 review suggested no clear differences in cerebral palsy at age two years following dextrose gel versus placebo for treatment of hypoglycaemia in newborn infants (RR 5.16, 95% CI 0.25 to 106.12; one trial; 183 children) (Table 6). Very low-quality evidence from Weston 2016 also suggested no clear differences in major neurosensory disability at two years (RR 6.27, 95% CI 0.77 to 51.03; one trial; 184 children) nor in any developmental disability at two years (RR 1.11, 95% CI 0.75 to 1.63; one trial; 184 children) following dextrose gel versus placebo (Table 10).

DISCUSSION

Summary of main results

This review included 43 Cochrane Reviews with outcome data for cerebral palsy available from meta-analyses of data from 96 randomised controlled trials (RCTs) involving 15,885 children.

Interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy

1. **Effective interventions (high-quality evidence of effectiveness):** High-quality evidence showed a reduction in cerebral palsy following therapeutic hypothermia versus standard care for newborns with hypoxic ischaemic encephalopathy.
2. **No conclusions possible: very low-quality evidence:** Very low-quality evidence suggested no clear differences in cerebral palsy following barbiturates (phenobarbital) versus conventional therapy for prevention of morbidity and mortality following perinatal asphyxia.

Interventions for neonates born preterm and/or at low or very low birthweight

1. **Possibly effective interventions (moderate-quality evidence of effectiveness):** Moderate-quality evidence showed a reduction in cerebral palsy with prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants.
2. **Probably ineffective interventions (moderate-quality evidence of harm):** Moderate-quality evidence showed an increase in cerebral palsy and cerebral palsy among survivors assessed following early (less than eight days) postnatal corticosteroids versus control for preventing chronic lung disease in preterm infants.
3. **Probably ineffective interventions (moderate-quality evidence of lack of effectiveness):** Moderate-quality evidence showed no clear differences in cerebral palsy following ethamsylate versus placebo for prevention of morbidity and mortality in preterm or very low birthweight infants; volume versus no treatment and gelatin versus fresh frozen plasma for prevention of morbidity and mortality in very preterm infants; prophylactic indomethacin versus placebo or no drug for preventing mortality and morbidity in preterm infants; synthetic surfactant versus placebo for respiratory distress syndrome in preterm infants; or prophylactic phototherapy versus standard care (starting phototherapy when serum bilirubin reached a prespecified level) for preventing jaundice in preterm or low birthweight infants.
4. **No conclusions possible (low- to very low-quality evidence):** Low- to very low-quality evidence suggested no clear differences for cerebral palsy following dobutamine versus dopamine in preterm infants with low superior vena cava flow; oral ibuprofen versus intravenous ibuprofen for treatment of patent ductus arteriosus in preterm or low birthweight (or both) infants; darbepoetin alfa versus placebo and erythropoietin versus placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants; transfusion at a restrictive (low haemoglobin) versus a liberal (high haemoglobin)

threshold for preventing morbidity and mortality in very low birthweight infants; inhaled nitric oxide versus placebo or no treatment for respiratory failure in preterm infants; caffeine versus placebo for treatment of apnoea in preterm infants; caffeine versus placebo for prevention of apnoea in preterm infants; animal-derived surfactant extract versus no treatment for treatment of respiratory distress syndrome; prophylactic protein-free synthetic surfactant versus placebo for preventing morbidity and mortality in preterm infants; continuous distending pressure versus standard care for respiratory distress in preterm infants; long versus short inspiratory times in neonates receiving mechanical ventilation; moderately early (between seven and 14 days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants; late (more than seven days of age) postnatal corticosteroids versus placebo or no treatment for chronic lung disease in preterm infants; early inhaled corticosteroids versus placebo for preventing chronic lung disease in ventilated very low birthweight preterm neonates; arginine supplementation versus placebo for prevention of necrotising enterocolitis in preterm infants; systemic antifungal agents versus placebo for prevention of mortality and morbidity in very low birthweight infants; prophylactic thyroid hormones versus placebo for prevention of morbidity and mortality in preterm infants; use of silicone earplugs versus no earplugs in the neonatal intensive care unit for preterm or very low birthweight infants; kangaroo mother care versus conventional neonatal care to reduce morbidity and mortality in low birthweight infants; and early developmental intervention versus standard follow-up post hospital discharge to prevent motor and cognitive impairment in preterm infants.

Interventions for other specific groups of 'at risk' neonates

1. **No conclusions possible (low- to very low-quality evidence):** Low- to very low-quality evidence suggested no clear differences for cerebral palsy following endothelin receptor antagonists versus placebo for persistent pulmonary hypertension in term and late preterm infants; inhaled nitric oxide versus placebo for respiratory failure in infants born at or near term; room air versus 100% oxygen for resuscitation of infants at birth; acyclovir versus vidarabine for treatment of HSV infection in neonates; and dextrose gel versus placebo for treatment of hypoglycaemia in newborn infants.

Overall completeness and applicability of evidence

This overview summarises published Cochrane Systematic Reviews assessing neonatal interventions reporting on cerebral palsy and does not consider interventions in the antenatal or intrapartum period, which is the focus of a companion overview (Shepherd 2016).

We were able to include only 43 reviews (representing less than 13% of the 343 Neonatal reviews in the *Cochrane Database of Systematic Reviews*). We identified an additional 40 protocols that have pre-specified cerebral palsy as a primary or secondary outcome and will be considered for inclusion in future updates of the overview when they have been published as full reviews. These protocols plan to assess a variety of interventions (see Appendix 1: 'Ongoing reviews'). We were not able to include an additional 102 reviews assessing a wide range of neonatal interventions, although we recognised the potential impact of the intervention of interest on cerebral palsy (through pre-specifying cerebral palsy as a review outcome); none of the included trials within these reviews reported on this outcome. We summarised the main conclusions of these reviews in Appendix 2 ('Reviews awaiting further classification') and will again consider them for inclusion in future updates of the overview. In total, the 43 reviews included 454 RCTs involving infants.

Although the 43 reviews in this overview included 454 randomised trials involving over 63,977 infants, the body of evidence for our review was substantially reduced by the fact that the included reviews (and trials) did not report on our overview outcomes. For our primary outcome - cerebral palsy - we included data from meta-analyses of 35 reviews involving 96 randomised trials, or only 21% of the trials within the included reviews.

The body of evidence for our secondary outcomes was further reduced for the composite outcome including cerebral palsy (30 reviews), motor dysfunction (12 reviews), cerebral palsy or death (five reviews), and severity of cerebral palsy (three reviews). None of our included reviews reported specifically on type of cerebral palsy. For most of our outcomes, reviews reported data from only one or two trials, up to a maximum of 15 trials. Thus, review authors often presented too few data to permit firm conclusions on effects on cerebral palsy and on our secondary outcomes. For most of the included reviews, data related to cerebral palsy were commonly short term (reported at one to three years of age), and longer-term follow-up was less commonly reported (although follow-up to 17 years was reported). Included reviews often did not report information regarding definitions nor criteria for cerebral palsy diagnosis and assessment methods.

We did not attempt to make indirect comparisons to address questions concerning the relative performance of different neonatal interventions. Rather we aimed to systematically consider all potentially relevant interventions for their ability to contribute to prevention of cerebral palsy. Within this overview, we did not attempt to duplicate details of participants and interventions (and control conditions) in individual trials. The reader may refer to these individual reviews and trials for more information on these factors. Further, the scope of this overview was limited to effects of interventions on cerebral palsy (and a restricted number of pre-specified secondary review outcomes). To assess effects (benefits or harms) of the included interventions on other outcomes, readers are encouraged to refer to the included Cochrane Reviews themselves. For example, although low-quality evidence presented in this overview suggested no clear differences in cerebral palsy fol-

lowing kangaroo mother care, the Conde-Agudelo 2016 review reported moderate-quality evidence of benefit for outcomes including mortality, severe infection/sepsis, hypothermia, weight gain, and breastfeeding, and thus supports the use of kangaroo mother care for low birthweight infants as an alternative to conventional neonatal care (mainly in resource-limited settings). Similarly, although very low-quality evidence in this overview suggested no clear differences in cerebral palsy following dextrose gel for treatment of hypoglycaemia, the Weston 2016 review found moderate-quality evidence of benefit for outcomes including mother-infant separation and breastfeeding, and thus concluded that oral dextrose therapy should be considered first-line treatment for neonates with hypoglycaemia.

Although our overview could demonstrate high-quality evidence of a reduction in cerebral palsy following therapeutic hypothermia for newborns with hypoxic-ischaemic encephalopathy (Jacobs 2013), the incidence of death and disability, including cerebral palsy, remains high despite therapy. Thus, optimisation of hypothermia strategies or adjuvant therapies is urgently needed to further improve outcomes. A range of possible agents such as antiepileptic drugs (including topiramate), xenon, erythropoietin, melatonin, magnesium sulphate, and cord blood continue to be under investigation (AAP 2014; Robertson 2012).

Quality of the evidence

We assessed almost all of the included reviews to be of high quality and to have low risk of bias using the AMSTAR and ROBIS tools (see Table 4: AMSTAR assessments for included reviews; and Table 5: ROBIS assessments for included reviews). Although these two tools differ in their approaches to assessing review quality or risk of bias, findings of these assessments were similar. All of the included reviews assessed risk of bias of included randomised trials (most used current guidance as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)), and the quality of randomised trials was variable within and between reviews (see Table 3: Risk of bias assessments from included reviews). Six of the 43 reviews used the GRADE approach to assess the quality of evidence for overview outcomes (Darlow 2016; Moe-Byrne 2016; More 2016; Okwundu 2012; Weston 2016; Young 2016). For the other reviews, we used the GRADE system to rate the quality of evidence and incorporated assessments of study limitations (risk of bias) as reported by the review authors. For our primary review outcome - cerebral palsy - evidence ranged from very low to high quality, and for our secondary review outcomes, quality of evidence varied similarly. Downgrading of quality was most commonly due to study limitations (risk of bias) and imprecision (small sample sizes, low numbers of events, and wide confidence intervals). Findings regarding the quality of evidence for each outcome are set out in Table 6: Cerebral palsy; Table 8: Cerebral palsy or death; Table 9: Severity of cerebral palsy; Table 10: Other composite outcomes that include cerebral palsy as a component; and Table 11: Motor dysfunction.

Potential biases in the overview process

We were aware of risks of introducing bias at all stages of the overview process, and we took several steps to minimise this, including developing a Cochrane overview protocol. At least two overview authors independently assessed reviews for inclusion, carried out data extraction and quality assessment, and assessed the quality of evidence using the GRADE approach. A potential source of bias is related to the fact that one overview author (Nadia Badawi) is an author of one of the included reviews (Jones 2009). As pre-specified in our protocol, two other overview authors, who were not authors of this review, carried out data extraction and quality assessment for this review.

We undertook a comprehensive search of the *Cochrane Database of Systematic Reviews* without applying language or date restrictions, and we identified published reviews, as well as planned/ongoing reviews (protocols). We did not search other databases; thus it is possible that non-Cochrane systematic reviews assessing neonatal interventions and reporting on cerebral palsy have been conducted but were not identified. It is also the case that Cochrane Reviews assessing interventions that could have the potential to impact cerebral palsy risk (see Description of the interventions for further discussion of various interventions) may not have acknowledged this through inclusion of cerebral palsy as a review outcome. Thus, data from relevant randomised trials assessing these interventions will not have been identified and included in this overview. Based on our search strategy, even Cochrane Reviews that pre-specified outcomes such as 'long-term growth and neurodevelopment' (Cools 2015) but subsequently reported specifically on 'cerebral palsy' were captured in our search and were included in this overview. However, reviews that have reported on long-term neurodevelopmental outcomes without any mention of 'cerebral palsy' will not have been identified; this highlights the need for all Cochrane Reviews to provide clear definitions accompanying any reported outcome measures.

Although we judged almost all of our included reviews to be of high quality and to have low risk of bias, we did not consider all as 'up-to-date', with only approximately one-third conducting searches in the past three years; similarly, not all of the 'Reviews awaiting further classification' were 'up-to-date'. Thus, it is possible that additional trials assessing neonatal interventions and reporting on cerebral palsy have been published but have not yet been included in relevant Cochrane Reviews; it is also possible that additional trials have been conducted but have not yet been published. If/when such trials are included in relevant Cochrane Reviews, we will incorporate them into an update of this overview.

Agreements and disagreements with other studies or reviews

We have not identified any other overviews or systematic reviews specifically designed to assess neonatal interventions for preventing cerebral palsy.

McIntyre 2013 conducted a systematic review of cohort and case-control studies that focused on identifying risk factors for cerebral palsy in children born at term and aimed to assess whether the potential for prevention of these risk factors has been adequately explored. Intrapartum and neonatal risk factors identified included birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia, jaundice, and infections including meningitis and sepsis. It is recognised that a strategy for prevention of cerebral palsy currently exists for only one of these risk factors - hypothermia for birth asphyxia - as was identified in this overview. McIntyre 2013 highlighted that prevention strategies are urgently required. A further recent systematic review - Hadders-Algra 2016 - focused on early interventions in infants younger than 12 months' corrected age with or at very high risk for cerebral palsy (such as on the basis of a lesion of the brain - periventricular leucomalacia or intraventricular haemorrhage, or definitely abnormal general movements). This review included seven studies of moderate to high quality assessing interventions such as neurodevelopmental treatment only, multi-sensory stimulation, developmental stimulation, and multi-faceted interventions combining developmental stimulation, support of parent-infant interaction, and neurodevelopmental treatment (Hadders-Algra 2016). Hadders-Algra 2016 concluded that although two suggestions emerged (dosing may be critical for effectiveness; multi-faceted interventions may offer the best opportunities), current evidence is limited.

AUTHORS' CONCLUSIONS

Implications for practice

This overview summarises the evidence from Cochrane Systematic Reviews of randomised controlled trials regarding effects of neonatal interventions on cerebral palsy, and can be used by researchers, funding bodies, policy makers, clinicians, and consumers to aid decision-making and evidence translation.

High-quality evidence shows that therapeutic hypothermia versus standard care for newborns with hypoxic-ischaemic encephalopathy can reduce cerebral palsy. Moderate-quality evidence shows that prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants may also reduce cerebral palsy risk. Moderate-quality evidence shows that early (less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants may increase cerebral palsy risk. In addition, moderate-quality evidence shows no clear differences in cerebral palsy risk with ethamsylate versus placebo for prevention of morbidity and mortality in preterm or very low birthweight infants; volume versus no treatment and gelatin versus fresh frozen plasma for prevention of morbidity and mortality in very preterm infants; prophylactic indomethacin versus placebo for prevention of mortality and morbidity in preterm infants; synthetic surfactant versus placebo for respiratory distress syndrome in preterm infants; or prophylactic phototherapy versus standard care (starting phototherapy when serum bilirubin reached a pre-specified level) for preventing jaundice in preterm or low birthweight infants. No conclusions were possible for other interventions assessed in this overview because evidence was of low to very low quality.

The scope of this overview was limited to the effects of interventions on cerebral palsy (and pre-specified secondary overview outcomes); consultation of the included Cochrane Reviews is recommended to formally assess additional benefits and/or harms of these interventions.

Implications for research

This overview highlights areas for which evidence is insufficient to permit conclusions on the effects of several neonatal interventions on cerebral palsy. These topics can be used to generate research questions and priorities. As cerebral palsy is rarely identified at birth, has diverse risk factors and aetiologies, and is diagnosed in approximately one in 500 children, it is a challenging outcome for investigators of such interventions to measure and report on. To date, a small proportion of Cochrane Reviews assessing neonatal interventions have reported on cerebral palsy; this may be due to a number of factors, including lack of primary research (with few randomised trials of neonatal interventions conducting long-term follow-up of children), lack of reporting on cerebral palsy by randomised trials, lack of reporting on cerebral palsy by relevant Cochrane Reviews (i.e. not pre-specifying it as an outcome of interest, not clearly defining long-term follow-up results reported, or not being 'up-to-date'), and the absence of Cochrane Reviews assessing relevant interventions.

With greater understanding of the diverse risk factors and aetiologies of cerebral palsy, there is an urgent need for long-term follow-up of interventions to address risk factors for cerebral palsy. In light of the challenges associated with long-term follow-up of randomised trials, new strategies to measure impact on cerebral palsy, such as data linkage with cerebral palsy registries, should be applied. Additionally, there is a need to consider the use of relatively new interim assessments (such as the General Movements Assessment). Such studies must be rigorous in their design and should aim for consistency in cerebral palsy outcome measurement and reporting to facilitate pooling of outcome data and thus aid research efforts aimed at prevention of cerebral palsy.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Characteristics of excluded reviews

Review ID and title	Reason for exclusion
Atherton 2012 Email for clinical communication between patients/caregivers and healthcare professionals	Wrong participants (not neonates): 1. "We included all healthcare professionals, patients and caregivers regardless of age, gender and ethnicity. We considered participants originating the email communication, receiving the email communication and copied into the email communication"
Barlow 2015 Parent-infant psychotherapy for improving parental and infant mental health	Wrong participants (not neonates): 1. "We included studies involving parent-infant dyads in which the parent was experiencing mental health problems, domestic abuse or substance dependency, with or without the

Table 1. Characteristics of excluded reviews (*Continued*)

	infant showing signs of attachment or dysregulation problems, or both attachment and dysregulation problems. We included all infants irrespective of the presence of problems such as low birthweight, prematurity or disabilities. We included studies targeting infants and toddlers in which the mean age of the infant participants was 24 months or less at the point of referral. We included studies targeting all parents (i.e. including fathers, birth parents, adoptive and kinship parents, but not foster parents)"
Bredemeyer 2012 Body positioning for spontaneously breathing preterm infants with apnoea	Secondary outcomes pre-specified include the following: 1. Short-term motor development up to about 12 months' corrected age, as measured by a validated assessment tool 2. Longer-term motor development up to about 2 years' corrected age, as measured by a validated assessment tool 3. Neurodevelopment assessed at about 2 years' corrected age, as measured by a validated assessment tool No outcome data for these outcomes
Brown 2016 C-reactive protein for diagnosing late-onset infection in newborn infants	Protocol for diagnostic test accuracy review
Carr 2003 G-CSF and GM-CSF for treating or preventing neonatal infections	Secondary outcomes pre-specified include: 1. Long-term outcomes: death and disability at or > 1 year from birth No outcome data for cerebral palsy (single study results reported "cognition, language and social developmental performance scores were within the normal range for age and motor deficits were 'typical of high-risk, low birth weight neonates'. However there was no comparison made between G-CSF and control infants"
Davis 2001 Intravenous dexamethasone for extubation of newborn infants	No pre-specified outcome focused on development/disability at follow-up
Ethawi 2016 High-frequency jet ventilation vs high-frequency oscillatory ventilation for pulmonary dysfunction in preterm infants	Secondary neonatal outcomes pre-specified include: 1. Neurodevelopmental outcomes including motor, mental, and sensory outcomes at 2 years of age (study author defined) No outcome data for this outcome (no included trials)
Hancock 2013 Treatment of infantile spasms	Outcomes pre-specified include: 1. Long-term psychomotor development No outcome data for cerebral palsy (single-study results reported related to BSID; VABS; 'cognitive development'; Japanese Tumor Scale; DDST)
Jones 2003 Antiviral therapy for symptomatic congenital cytomegalovirus infection in neonates and infants up to 3 months of age	Protocol Primary outcomes pre-specified include: 1. Mortality at 1 year of life and the presence of cognitive,

Table 1. Characteristics of excluded reviews (*Continued*)

	developmental, audiological, motor, or visual impairment upon completion of therapy, at follow-up at 1 year of life, and in later childhood
Lewin 2010 Lay health workers in primary and community health care for maternal and child health and management of infectious diseases	No pre-specified outcome focused on development/disability at follow-up
Malviya 2013 Surgical vs medical treatment with cyclo-oxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants	Secondary outcomes pre-specified include: 1. Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardised and validated assessment tool, a child developmental specialist, or both) at any age (outcome data will be grouped at 6, 9, 12, 18, 24 months, if available) No outcome data for this outcome
Morag 2016 Cycled light in the intensive care unit for preterm and low birthweight infants	Secondary outcomes pre-specified include: 1. Long-term outcomes: growth and neurodevelopment, including visual and auditory outcomes at any age as reported by study authors using standardised and validated tests No outcome data for these outcomes
Okwundu 2014 Transcutaneous screening for hyperbilirubinaemia in neonates	Protocol No pre-specified outcome focused on development/disability at follow-up
Pammi 2011 Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropaenia	Primary outcomes pre-specified include: 1. Neurological outcome at 1 year of age or later (neurodevelopmental outcome as assessed by any validated test) No outcome data for this outcome
Pammi 2015 Molecular assays for diagnosis of sepsis in neonates	Protocol for diagnostic test accuracy review
Pammi 2015b Pentoxifylline for treatment of sepsis and necrotising enterocolitis in neonates	Secondary outcomes pre-specified include: 1. Neurological outcome at 2 or more years of age (neurodevelopmental outcome as assessed by a validated test) No outcome data for this outcome
Scholefield 2013 Hypothermia for neuroprotection in children after cardiopulmonary arrest	Primary outcomes pre-specified include: 1. Best neurological outcome at hospital discharge and within the first year as assessed by the Paediatric Cerebral Performance Category score and other validated outcome scores for use in children (e.g. VABS) No outcome data for these outcomes (no included trials)
Shah 2012 Intraventricular antibiotics for bacterial meningitis in neonates	Secondary outcomes pre-specified include: 1. Neurodevelopmental outcome (neurodevelopmental outcome as assessed by a standardised and validated assessment tool or a child developmental specialist, or both) at any age

Table 1. Characteristics of excluded reviews (*Continued*)

	(outcome data will be grouped at 12, 18, and 24 months, if available) No outcome data for this outcome
Suresh 2003 Metalloporphyrins for treatment of unconjugated hyperbilirubinaemia in neonates	Outcomes pre-specified include: 1. Presence of neurodevelopmental sequelae (i.e. any sensory, motor, cognitive, psychological, or behavioural impairment reported on follow-up any time after the neonatal period) 2. Degree of such neurodevelopmental impairment (expressed as mean or median scores on tests of neurodevelopmental function performed any time after the neonatal period) No outcome data for these outcomes
Thukral 2015 Periodic change of body position under phototherapy in term and late preterm neonates with hyperbilirubinaemia	Protocol Secondary outcomes pre-specified include: 1. Incidence of BIND (proportion). BIND or subtle encephalopathy shall be defined as neurological, cognitive, learning, or movement disorders; isolated hearing loss; or auditory dysfunction in the presence of hyperbilirubinaemia (Bergman 1985; Hyman 1969; Johnson 1974; Rubin 1979; Scheldt 1977)
Upadhyay 2016 Short-duration vs standard-duration antibiotic regimens for treatment of neonatal bacterial infection	Protocol Secondary outcomes pre-specified include: 1. Survival without major disability at 18 to 24 months' corrected age (proportion)
Ward 2003 Steroid therapy for meconium aspiration syndrome in newborn infants	Primary outcomes pre-specified include: 1. Long-term growth and neurodevelopmental outcomes assessed at age 1, 2, and 5 years with validated assessment tools No outcome data for this outcome
Whitelaw 2001 Diuretic therapy for newborn infants with post-haemorrhagic ventricular dilatation	Outcomes pre-specified include: 1. Moderate to severe long-term motor disability at 1 to 3 years of age 2. Combined outcome: death or (moderate to severe) long-term disability at 1 to 3 years of age Data reported for these outcomes; no outcome data for cerebral palsy. "The larger trial showed that acetazolamide and furosemide treatment resulted in a borderline increase in the risk for motor impairment at one year (RR 1.27, 95% CI 1.02 - 1.58; RD 0.16, 95% CI 0.02 - 0.31), but did not significantly affect the risk for the combined outcome of delay, disability or motor impairment among survivors, or the risk of the combined outcome of death, delay, disability or impairment at one year"
Whitelaw 2001b Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage	Outcomes pre-specified include: 1. Surviving with major disability for 12 months or longer in survivors 2. Surviving with multiple neurodevelopmental impairments

Table 1. Characteristics of excluded reviews (*Continued*)

	Data reported for these outcomes; no outcome data for cerebral palsy. "The tables and figures show that none of the trials found a significant effect of CSF tapping on a) need for shunt b) death c) major disability in survivors d) multiple disability in survivors e) death or disability. Similarly, meta-analysis of the results of all included trials shows no significant effect of CSF tapping on any of these outcomes"
Woodgate 2001 Permissive hypercapnia for prevention of morbidity and mortality in mechanically ventilated newborn infants	Outcomes pre-specified include: 1. Neurodevelopmental outcome No outcome data for this outcome

Abbreviations: BIND: bilirubin-induced neurological dysfunction; BSID: Bayley Scales of Infant Development; CI: confidence interval; CSF: cerebrospinal fluid; DDST: Denver Developmental Screening Test; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; RD: risk difference; RR: risk ratio; VABS: Vineland Adaptive Behavior Scales.

Table 2. Characteristics of included reviews

Review ID and title	Date of search and date assessed as up-to-date	No. included trials (countries and publication years)	No. participants in included trials	Inclusion criteria for 'Types of participants'	Relevant comparison interventions (no. trials and participants)	Overview outcomes for which data were reported (no. trials and participants)
Neonatal care: asphyxia						
Chaudhari 2012 Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy	Searches: March 2012 Up-to-date: 4 April 2012	3 RCTs (Countries: Netherlands, Turkey; Published: 1990s: 1 RCT; 2000s: 2 RCTs)	114 infants	Newborn infants (> 34 weeks' gestation) with hypoxic-ischaemic encephalopathy defined as clinical evidence of cardiorespiratory or neurological depression (Apgar score < 7 at 5 minutes and beyond after birth) and/or evidence of severe metabolic acidosis in intrapartum foetal, umbilical	Allopurinol vs control (3 RCTs, 114 neonates)	**Severity of cerebral palsy** ("Severe quadriplegia in surviving infants" (3 RCTs, 73 children); reported as a primary outcome) **Other composite outcome that includes cerebral palsy as a component** ("Death or severe neurodevelopmental disability in survivors" (3

Table 2. Characteristics of included reviews (*Continued*)

				arterial cord, or very early neonatal blood samples (pH < 7 or base deficit > 12 mmol/L) , and/or clinical or electro-encephalographic (multi-channel or amplitude integrated) evidence of neonatal encephalopathy (MacLennan 1999)		RCTs, 110 children); reported as a primary outcome)
Jacobs 2013 Cooling for newborns with hypoxic-ischaemic encephalopathy	1 May 2012	11 RCTs (Countries: China: 2 RCTs; New Zealand: 1 RCT; Turkey: 1 RCT; USA; 3 RCTs; international: 4 RCTs Published: 1990s: 1 RCT; 2000s: 7 RCTs; 2010s: 3 RCTs)	1505 infants	1. Newborn infants of 35 weeks' gestation or greater 2. Evidence of peripartum asphyxia, with each enrolled infant satisfying at least 1 of the following criteria: a. Apgar score of 5 or less at 10 minutes b. Mechanical ventilation or resuscitation at 10 minutes c. Cord pH < 7. 1, or arterial pH < 7.1, or base deficit of 12 or more within 60 minutes of birth 3. Evidence of encephalopathy according to Sarnat staging (Finer 1981; Sarnat 1976):	Therapeutic hypothermia vs standard care (11 RCTs, 1505 neonates)	**Cerebral palsy** ("Cerebral palsy in survivors assessed" (7 RCTs, 881 children) and "Outcome at 6 to 7 years of age: Cerebral palsy" (1 RCT, 121 children); reported as secondary outcomes) **Other composite outcomes that include cerebral palsy as a component** ("Death or major disability in survivors assessed" (8 RCTs, 1344 children); reported as a primary outcome) ("Major neurodevelopmental dis-

Table 2. Characteristics of included reviews (*Continued*)

				a. Stage 1 (mild) : hyperalertness, hyperreflexia, dilated pupils, tachycardia, absence of seizures b. Stage 2 (moderate) : lethargy, hyperreflexia, miosis, bradycardia, seizures, hypotonia with weak suck and Moro c. Stage 3 (severe): stupor, flaccidity, small to mid position pupils that react poorly to light, decreased stretch reflexes, hypothermia, and absent Moro No major congenital abnormalities recognisable at birth	ability" (8 RCTs, 1344 children); "Major neurodevelopmental disability in survivors assessed" (8 RCTs, 917 children); "Outcome at 6 to 7 years of age: death or moderate-to-severe disability" (1 RCT, 190 children); "Outcome at 6 to 7 years of age: moderate-to-severe disability" (1 RCT, 119 children); reported as secondary outcomes) **Motor dysfunction** ("Neuromotor delay (BSID PDI more than 2 SD below mean) in survivors assessed" (6 RCTs, 657 children); reported as a secondary outcome)
Young 2016 Prophylactic barbiturate use for the prevention of morbidity and mortality following perinatal asphyxia	30 November 2015	9 RCTs (Countries: Finland: 1 RCT; India: 2 RCTs; Mexico: 1 RCT; Romania: 1 RCT; South Africa: 1 RCT; Spain: 1 RCT; USA: 2 RCTs; Published: 1980s: 2 RCTs; 1990s: 2 RCTs;	456 infants	1. Term infants (37 weeks or greater) and late preterm infants (34 to 36+6 weeks' gestation) 3 days of age or less with perinatal asphyxia 2. Evidence of perinatal asphyxia,	Barbiturates vs control (8 RCTs, 439 neonates)	**Cerebral palsy** ("Cerebral palsy" (2 RCTs, 69 children); reported as a secondary outcome) **Other composite outcomes that include cerebral palsy as a compo-**

Table 2. Characteristics of included reviews (*Continued*)

		2000s: 2 RCTs; 2010s: 3 RCTs)		characterised by evidence of neonatal or foetal distress with each enrolled infant satisfying at least 1 of the following criteria: i) Cord gas or postnatal blood gas (within the first hour of life) with pH 7.0 or less or base deficit 12 mEq/L or greater ii) Apgar score 5 or less at 10 minutes iii) Need for mechanical ventilation or resuscitation at 10 minutes of life 3. With or without evidence of encephalopathy (moderate or severe) according to Sarnat staging (Sarnat 1976) 4. No evidence of seizures 5. No major congenital abnormalities recognisable at birth		**nent** ("Death or major neurodevelopmental disability" (1 RCT, 31 children); reported as a primary outcome) ("Major neurodevelopmental disability" (1 RCT, 31 children); reported as a secondary outcome)
Neonatal care: haemorrhage: periventricular/intraventricular						

Table 2. Characteristics of included reviews (*Continued*)

Hunt 2010 Ethamsylate for the prevention of morbidity and mortality in preterm or very low birth weight infants	Search: 24 August 2009 Up-to-date: 22 September 2009	7 RCTs (Countries: France, Greece, UK: 1 RCT; India: 1 RCT; Switzerland: 1 RCT; Taiwan: 1 RCT; Turkey: 1 RCT; UK: 2 RCTs; Published: 1980s: 3 RCTs; 1990s: 4 RCTs)	1410 infants	Preterm infants born before and including 34 weeks plus 6 days' completed gestation or with birthweight < 2000 g	Ethamsylate vs placebo (7 RCTs, 1410 neonates)	**Cerebral palsy** ("Cerebral palsy in surviving children available for follow-up" (3 RCTs, 532 children); reported as a primary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Neurodevelopmental disability at 2 years of age in surviving children available for follow-up" (3 RCTs, 532 children); "Death or any disability by 2 years of age in children with known outcome at any point in time" (7 RCTs, 1334 children); reported as primary outcomes)
Smit 2013 Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants	Search: 31 October 2012 Up-to-date: 17 December 2012	12 RCTs (Countries: not reported; Published: 1980s: 8 RCTs; 1990s: 1 RCT: 2000s: 3 RCTs)	982 infants	Newborn infants (less than 24 hours old) with gestational age < 34 weeks or birthweight < 1500 g. We included preterm infants with gestational age 33 to 36 weeks or birthweight up to 1750 g, if they were mechan-	Phenobarbital vs control (12 RCTs, 982 neonates)	**Other composite outcomes that include cerebral palsy as a component** ("Mild neurodevelopmental impairment" (1 RCT, 101 children); "Severe neurodevelopmental impairment" (1 RCT, 101 chil-

Table 2. Characteristics of included reviews (*Continued*)

				ically ventilated. We excluded infants with serious congenital malformations		dren); reported as secondary outcomes)
Neonatal care: hypotension						
Osborn 2007b The effect of inotropes on morbidity and mortality in preterm infants with low systemic or organ blood flow	19 May 2010	1 RCT (Country: not reported; Published: 2000s)	42 infants	Preterm infants (< 37 weeks' gestational age) with low SBF or organ blood flow in the neonatal period. Low SBF may be determined on the basis of echocardiographically measured ventricular outputs or surrogates for SBF such as SVC flow. Low organ blood flow may be determined on the basis of techniques including ultrasound Doppler, near infrared spectroscopy, or xenon clearance techniques when evidence in the literature suggests that measurement is associated with substan- tial clinical outcomes and/or actual organ blood flow. The review does not include studies that include surrogates	Dobutamine vs dopamine in preterm infants with low superior vena cava flow (1 RCT, 42 neonates)	**Cerebral palsy** ("Cerebral palsy at 3 years in survivors assessed" (1 RCT, 13 children); reported as a primary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Disability at 3 years in survivors assessed" (1 RCT, 13 children); "Death or disability at 3 years" (1 RCT, 37 children); "Death or disability at latest follow-up" (1 RCT, 41 children); reported as primary outcomes)

Table 2. Characteristics of included reviews (*Continued*)

				of flow such as BP, ultrasound Doppler-measured velocities, pulsatility, or resistive indices		
Neonatal care: fluid therapy						
Osborn 2004 Early volume expansion for prevention of morbidity and mortality in very preterm infants	30 July 2008	8 RCTs (Countries: not reported; Published: 1970s: 1 RCT; 1980s: 1 RCT; 1990s: 4 RCTs; 2000s: 2 RCTs)	1185 infants	Very preterm infants born ≤ 32 weeks' gestation or ≤ 1500 g and enrolled and treated the first 72 hours after birth. Trials were eligible if they enrolled unselected preterm infants, preterm infants with clinically suspected poor perfusion (e.g. low BP, poor cutaneous perfusion, metabolic acidosis), or preterm infants with low blood flow (e.g. determined by Doppler ultrasound). Low BP may be defined as BP less than a specified percentile of a standard chart, mean BP ≤ 30 mmHg in any preterm infant, or mean BP ≤ 1 mmHg per week of gestation	Volume vs no treatment in very preterm infants (5 RCTs, 978 neonates) Gelatin vs fresh frozen plasma in hypotensive infants (1 RCT, 519 neonates)	**Cerebral palsy** ("Cerebral palsy in survivors" (1 RCT, 604 children; and 1 RCT, 399 children); reported as a primary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Severe neurodevelopmental disability in survivors" (1 RCT, 604 children; and 1 RCT, 399 children); "Death or severe neurodevelopmental disability" (1 RCT, 776 children; and 1 RCT, 518 children); reported as primary outcomes)
Neonatal care: patent ductus arteriosus						

Table 2. Characteristics of included reviews (*Continued*)

Fowlie 2010 Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants	Searches: April 2010 Up-to-date: 19 May 2010	19 RCTs (Countries: North America: 13 RCTs; Latin America, Europe, Asia: 6 RCTs; Published: 1980s: 11 RCTs; 1990s: 7 RCTs; 2000s; 1 RCT)	2872 infants	Preterm neonates (less than 37 weeks' completed gestation)	Prophylactic IV indomethacin vs placebo or no drug (19 RCTs, 2872 neonates)	**Cerebral palsy** ("Neurological assessments (18-54 months: Cerebral palsy" (4 RCTs, 1372 children); "School age neurological assessments: Cerebral palsy aged 8 years" (1 RCT, 304 children); reported as primary outcomes) **Other composite outcome that includes cerebral palsy as a component** ("Death or severe neurosensory impairment" (3 RCTs, 1491 children); reported as a primary outcome)
Ohlsson 2015 Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants	7 May 2014	33 RCTs (Countries: Albania: 1 RCT; Belgium: 2 RCTs; Czech Republic: 1 RCT; China: 1 RCT; Egypt: 1 RCT; India: 1 RCT; Iran: 3 RCTs; Israel: 1 RCT; Italy: 6 RCTs; Poland: 1 RCT; Qatar: 1 RCT; Spain: 2 RCTs; Taiwan: 2 RCTs; Thailand: 2 RCTs; Tunisia:	2190 infants	Preterm infants less than 37 weeks' gestational age or LBW infants (less than 2500 g) with PDA diagnosed either clinically or by echocardiographically (ECHO) guided criteria in the neonatal period (less than 28 days)	Oral ibuprofen vs IV ibuprofen (data for maximum of 4 RCTs, 304 neonates)	**Cerebral palsy** ("Moderate/severe cerebral palsy at 18-24 months" (1 RCT, 57 children); reported as a secondary outcome)

Table 2. Characteristics of included reviews (*Continued*)

		1 RCT; Turkey: 3 RCTs; UK: 2 RCTs; USA: 2 RCTs; Published: 1990s: 4 RCTs; 2000s: 18 RCTs; 2010s: 11 RCTs)				
Neonatal care: blood disorders						
Ohlsson 2014 Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants	1 July 2013	27 RCTs (Countries: Austria: 2 RCTs; Bangladesh: 1 RCT; Chile: 1 RCT; China: 2 RCTs; Greece: 3 RCTs; Iran: 1 RCT; Italy: 2 RCTs; Mexico: 1 RCT; New Zealand: 1 RCT; Poland: 1 RCT; Singapore: 1 RCT; South Africa: 1 RCT; Switzerland: 1 RCT; Turkey: 1 RCT; USA: 5 RCTs; Europe: 3 RCTs; Published 1990s: 12 RCTs; 2000s: 13 RCTs; 2010s: 2 RCTs)	2209 infants	Preterm (< 37 weeks) and/or LBW (< 2500 g) neonates less than 8 days of age	Erythropoietin vs placebo or no treatment (27 RCTs, 2209 neonates) Darbepoetin alfa vs placebo or no treatment (1 RCT, 66 neonates)	**Cerebral palsy** ("Cerebral palsy at 18 - 22 months' corrected age (in children examined)" (2 RCTs, 153 children; and 1 RCT, 51 children); reported as secondary outcomes) **Other composite outcome that includes cerebral palsy as a component** ("Any neurodevelopmental impairment at 18-22 months' corrected age (in children examined)" (1 RCT < 99 children); reported as a secondary outcome) **Motor dysfunction** ("PDI < 70 at 18 - 22 months'

Table 2. Characteristics of included reviews (*Continued*)

						corrected age (in children examined)" (1 RCT, 90 children); reported as a secondary outcome)
Whyte 2011 Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants	Search: August 2011 Up-to-date: 1 September 2011	5 RCTs (Countries: Canada: 1 RCT; International (Canada, USA, Australia): 1 RCT; Taiwan: 1 RCT; USA: 2 RCTs; Published: 1980s: 1 RCT; 1990s: 1 RCT; 2000s: 3 RCTs)	670 infants	VLBW infants (i.e. of birthweight less than or equal to 1500 g, or less than 32 weeks' gestational age) admitted to NICU at less than 1 week of age. We aimed specifically to include studies of infants receiving all levels of intensive care	Transfusion at a low haemoglobin or haematocrit level (restrictive) vs transfusion at a high haemoglobin or haematocrit level (liberal) (4 RCTs, 614 neonates)	**Cerebral palsy** ("Neurosensory impairment at 18-21 months' follow-up among survivors: Cerebral palsy" (1 RCT, 335 children); reported as a secondary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Death or severe morbidity: at 18-21 months' follow-up with MDI < 70" (1 RCT, 421 children); "Death or severe morbidity: at 18-21 months' follow-up with MDI < 85" (1 RCT, 421 children) ; reported as primary outcomes) ("Neurosensory impairment at 18-21 months' follow-up among sur-

Table 2. Characteristics of included reviews (*Continued*)

						vivors: any neurosensory impairment" (1 RCT, 328 children); reported as a secondary outcome)
Neonatal care: pulmonary hypertension						
More 2016 Endothelin receptor antagonists for persistent pulmonary hypertension in term and late preterm infants	28 December 2015	2 RCTs (Countries: Saudi Arabia: 1 RCT; unclear (multi-centre): 1 RCT; Published: 2010s: 2 RCTs)	68 infants	Late preterm infants (born at 34+0 to 36+6 weeks), term infants (born at 37+0 to 41+6 weeks), and post-term infants (i.e. born after 41+6 weeks' gestation) until post-menstrual age (PMA) up to 44 weeks with PPHN were eligible for inclusion. The diagnosis of PPHN was clinical or was based on echocardiography. Clinical diagnosis of PPHN was considered when there was hypoxaemia refractory to oxygen therapy and mechanical ventilation (Roberts 1997). The echocardiographic diagnosis of PPHN was made by demonstrating the presence of extrapul-	Endothelin receptor antagonists vs placebo (1 RCT, 47 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 37 children); reported as a secondary outcome) **Motor dysfunction** ("Adverse neurodevelopmental outcome at 6 months" (1 RCT, 37 children); reported as a secondary outcome)

Table 2. Characteristics of included reviews (*Continued*)

				monary right-to-left shunting at the ductal or atrial level, near or suprasystemic pulmonary arterial pressures, and doppler evidence of tricuspid regurgitation (Dhillon 2012; Stayer 2010)		
Neonatal care: resuscitation						
Tan 2005 Air versus oxygen for resuscitation of infants at birth	Search: December 2003/ January 2004 Up-to-date: 15 February 2005	5 RCTs (Countries: India: 1 RCT; 6 countries: 1 RCT; not reported: 3 RCTs Published: 1990s: 2 RCTs; 2000s: 3 RCTs)	1302 infants	Term or preterm neonates requiring IPPV at birth	Room air vs 100% oxygen (5 RCTs, 1302 neonates)	**Cerebral palsy** ("Long-term neurodevelopmental outcome: cerebral palsy in those followed up at 18-24 months" (1 RCT, 213 children); reported as a post hoc outcome) **Motor dysfunction** ("Long-term neurodevelopmental outcome: not walking in those followed up at 18-24 months" (1 RCT, 213 children); reported as a post hoc outcome)
Neonatal care: nitric oxide						
Barrington 2010 Inhaled nitric oxide for respiratory failure in preterm infants	Search: June 2010 Up-to-date: 12 October 2010	14 RCTs (Countries: Europe: 3 RCTs; Taiwan: 1 RCT; USA: 1 RCT; not reported/un-	3430 infants	Premature infants (less than 35 weeks' gestation) with respiratory failure after ad-	Inhaled NO compared with control; analyses conducted based on: 1. Studies	**Cerebral palsy** ("Cerebral palsy"; reported as an outcome (2 RCTs, 209 children; 2 RCTs,

Table 2. Characteristics of included reviews (*Continued*)

		clear: 9 RCTs Published: 1990s: 3 RCTs; 2000s: 11 RCTs)		equate treatment with surfactant	with entry before 3 days based on oxygenation (9 RCTs, 1006 neonates) 2. Studies with entry after 3 days based on BPD risk (2 RCTs, 624 neonates) 3. Studies of routine use in intubated preterm infants (3 RCTs, 1800 neonates)	498 children; and 2 RCTs, 593 children) (not separated into primary/secondary)) **Other composite outcome that includes cerebral palsy as a component** ("Neurodevelopmental disability" (2 RCTs, 208 children; 2 RCTs, 498 children; and 2 RCTs, 593 children); reported as an outcome (not separated into primary/secondary)) **Motor dysfunction** ("Bayley MDI or PDI <-2SD" (1 RCT, 138 children); reported as an outcome (not separated into primary/secondary))
Finer 2006 Nitric oxide for respiratory failure in infants born at or near term	Search: November 2005 Up-to-date: 30 May 2006	14 RCTs (Countries: 33 French and Belgian Units: 1 RCT; not reported: 13 RCTs Published: 1990s: 11 RCTs; 2000s: 3 RCTs)	1715 infants	Newborn infants (< 1 month of age) with hypoxaemia suspected to be due to lung disease, pulmonary hypertension with right-to-left shunting, or both	Inhaled NO vs control (10 RCTs, 1068 infants) Inhaled NO vs control in infants with diaphragmatic hernia (2 RCTs, 84 neonates)	**Cerebral palsy** ("Cerebral palsy among survivors" (2 RCTs, 299 children; and 1 RCT, 22 children); reported as an outcome (not separated into primary/secondary)

Table 2. Characteristics of included reviews (*Continued*)

				Only studies in term and near-term infants (> 34 weeks' gestation) were included Efforts were made in all studies to exclude infants with intracardiac shunting due to structural congenital heart disease Infants with diaphragmatic hernia may respond differently from other near term infants (from preliminary data), and as far as possible results from infants with diaphragmatic hernias have been evaluated separately		) **Other composite outcome that includes cerebral palsy as a component** ("Neurodevelopmental disability at 18 to 24 months among survivors" (2 RCTs, 301 children); reported as an outcome (not separated into primary/secondary)) **Motor dysfunction** ("Bayley PDI more than 2 SD below the mean" (2 RCTs, 283 children); reported as an outcome (not separated into primary/secondary))
Neonatal care: apnoea						
Henderson-Smart 2010b Methylxanthine treatment for apnoea in preterm infants	Search: June 2010 Up-to-date: 4 July 2010	6 RCTs (Countries: not reported Published: 1980s: 3 RCTs; 1990s: 1 RCT; 2000s: 2 RCTs)	959 infants	Preterm infants with recurrent apnoea. There must have been an effort to exclude specific secondary causes of apnoea	Any methylxanthine vs control (placebo or no drug therapy) (6 RCTs, 959 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 729 children); reported as a secondary outcome) **Other composite outcome that includes cerebral palsy as a component** ("Death or major disabil-

Table 2. Characteristics of included reviews (*Continued*)

						ity by late infancy" (1 RCT, 767 children); reported as a secondary outcome)
Henderson-Smart 2010c Prophylactic methylxanthine for prevention of apnoea in preterm infants	Search: August 2010 Up-to-date: 29 September 2010	3 RCTs (Countries: not reported Published: 1980s: 2 RCTs; 2000s: 1 RCT)	557 infants	Preterm infants, particularly those born at less than 34 weeks' gestation, who are at risk of developing recurrent apnoea, bradycardia, and hypoxic episodes	Prophylactic methylxanthine vs control (3 RCTs, 557 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 415 children); reported as a secondary outcome) **Other composite outcome that includes cerebral palsy as a component** ("Death or major disability" (1 RCT, 423 children); reported as a secondary outcome)
Neonatal care: respiratory distress syndrome						
Howlett 2015 Inositol in preterm infants at risk for or having respiratory distress syndrome	14 September 2014	4 RCTs (Countries: Finland: 2 RCTs; USA: 2 RCTs Published: 1980s: 1 RCT; 1990s: 2 RCTs; 2010s: 1 RCT)	429 infants	Preterm infants (< 37 weeks' post-menstrual age) or LBW (< 2500 g) infants	Inositol supplementation (repeat doses) vs control (3 RCTs, 355 neonates)	**Other composite outcomes that include cerebral palsy as a component** ("Major neural developmental impairment at one year corrected age" (1 RCT, 169 children); reported as a secondary outcome) **Motor dysfunction** ("Minor neural developmental impair-

Table 2. Characteristics of included reviews (*Continued*)

						ment at one year corrected age" (1 RCT, 169 children); reported as a secondary outcome)
Seger 2009 Animal derived surfactant extract for treatment of respiratory distress syndrome	Search: December 2008 Up-to-date: 13 February 2009	13 RCTs (Countries: not reported Published: 1980s: 7 RCTs; 1990s: 6 RCTs)	1611 infants	Preterm infants (< 37 weeks' gestation) with clinical and/or radiological evidence of respiratory distress syndrome requiring assisted ventilation	Animal-derived surfactant extract treatment of respiratory distress (all infants) (13 RCTs, 1611 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 73 children); reported as a secondary outcome) **Other composite outcome that includes cerebral palsy as a component** ("Major neurodevelopmental disability in survivors" (1 RCT, 73 children); reported as a secondary outcome)
Soll 2000 Synthetic surfactant for respiratory distress syndrome in preterm infants	Search: not reported Up-to-date: 21 May 1998	6 RCTs (Countries: not clearly reported; Canada/USA/both: 3 RCTs Published; 1980s: 1 RCT; 1990s: 5 RCTs)	2358 infants	Neonates with clinical and radiological evidence of respiratory distress syndrome requiring assisted ventilation	Synthetic surfactant vs control (6 RCTs, 2358 neonates)	**Cerebral palsy** ("Cerebral palsy in survivors examined" (5 RCTs, 1557 children); reported as an outcome (not separated into primary/secondary)) **Severity of cerebral palsy** ("Moderate - severe cerebral palsy in survivors examined" (5 RCTs, 1557 children); reported as an out-

Table 2. Characteristics of included reviews (*Continued*)

						come (not separated into primary/secondary))
Soll 2010 Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants	Search: September 2009 Up-to-date: 27 October 2009	7 RCTs (Countries: 1: UK; 6 RCTs: not reported Published: 1980s: 3 RCTs; 1990s: 4 RCTs)	1583 infants	Premature infants with or without evidence of surfactant deficiency	Prophylactic synthetic surfactant vs control (7 RCTs, 1583 neonates)	**Cerebral palsy** ("Cerebral palsy, 1-2 years" (4 RCTs, 670 children); reported as a secondary outcome) **Severity of cerebral palsy** ("Cerebral palsy, moderate/severe" (4 RCTs, 670 children); reported as a secondary outcome)
Neonatal care: mechanical ventilation						
Cools 2015 Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants	30 November 2014	19 RCTs (Countries: not reported Published: 1980s: 1 RCT; 1990s: 6 RCTs; 2000s: 10 RCTs; 2010s: 2 RCTs)	4096 infants	Preterm or LBW infants with pulmonary dysfunction, mainly due to respiratory distress syndrome, who were considered to require IPPV	High-frequency oscillatory ventilation vs conventional ventilation (19 RCTs, 4096 neonates)	**Cerebral palsy** (reported in text as a secondary outcome (3 RCTs))
Ho 2015 Continuous distending pressure for respiratory distress in preterm infants	30 April 2015	6 RCTs (Countries: not reported Published: 1970s: 4 RCTs; 1990s: 1 RCT; 2000s: 1 RCT)	355 infants	Preterm infants with respiratory failure	Continuous distending pressure vs standard care (6 RCTs, 355 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 36 children); reported as a secondary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Death or severe disabil-

Table 2. Characteristics of included reviews (*Continued*)

						ity" (1 RCT, 38 children) ; "Severe disability" (1 RCT, 37 children) ; "Any disability" (1 RCT, 37 children); reported as secondary outcomes)
Henderson-Smart 2010 Prophylactic methylxanthines for endotracheal extubation in preterm infants	Search: July 2010 Up-to-date: 16 August 2010	7 RCTs (Countries: not reported Published: 1980s: 3 RCTs; 1990s: 3 RCTs; 2000s: 1 RCT)	916 infants	Preterm or LBW infants being weaned from IPPV	Methylxanthine vs control (7 RCTs, 914 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 644 children); reported as a secondary outcome) **Other composite outcome that includes cerebral palsy as a component** ("Death or major disability by 18-21 months" (1 RCT, 676 children); reported as a secondary outcome)
Kamlin 2003 Long versus short inspiratory times in neonates receiving mechanical ventilation	Search: April 2004 Up-to-date: 22 June 2003	5 RCTs (Countries: not reported Published: 1980s: 3 RCTs; 19980s; 2 RCTs)	694 infants	Term and preterm infants at less than 28 days of age and requiring conventional mechanical ventilation. No restrictions on underlying pathophysiology were applied	Long vs short inspiratory times (5 RCTs, 694 neonates)	**Cerebral palsy** ("Cerebral palsy in survivors less than 33 weeks' gestation at birth" (1 RCT, 177 children); reported as a secondary outcome)
Wheeler 2010 Volume-targeted versus pressure-limited	Search: January 2010 Up-to-date: 30 June 2010	12 RCTs (Countries: not reported Pub-	693 infants	All intubated infants of less than 28 days' corrected age who	Volume-targeted vs pressure-limited ventilation (12 RCTs, 693	**Other composite outcomes that include cerebral**

Table 2. Characteristics of included reviews (*Continued*)

ventilation in the neonate		lished: 1990s: 2 RCTs; 2000s: 10 RCTs)		were being mechanically ventilated with IPPV at the time of study entry. Infants of all gestational ages and both paralysed and non-paralysed infants were eligible	neonates)	**palsy as a component** ("Severe disability (any definition)" (2 RCTs, 209 children); "Severe disability (any definition) or death" (1 RCT, 109 children; reported as outcomes from post hoc meta-analyses) **Motor dysfunction** ("Gross motor developmental issue (any definition)" (1 RCT, 128 children); reported as an outcome from a post hoc meta-analysis)
Neonatal care: bronchopulmonary dysplasia						
Doyle 2014b Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants	Search: August 2013 Up-to-date: 18 February 2014	29 RCTs (Countries: not reported Published: 1970s: 1 RCT; 1990s: 17 RCTs; 2000s: 10 RCTs; 2010s: 1 RCT)	3750 infants	Preterm infants at risk of developing chronic lung disease, including those who were ventilator dependent	Early (< 8 days) postnatal corticosteroids vs control (29 RCTs, 3750 neonates)	**Cerebral palsy** ("Cerebral palsy" (12 RCTs, 1452 children); "Cerebral palsy in survivors assessed" (12 RCTs, 959 children); reported as primary outcomes) **Cerebral palsy or death** ("Death or cerebral palsy" (12 RCTs, 1452 children); reported as a primary outcome) **Other composite**

Table 2. Characteristics of included reviews (*Continued*)

						outcomes that include cerebral palsy as a component ("Major neurosensory disability (variable criteria - see individual studies)" (7 RCTs, 1233 children); "Major neurosensory disability (variable criteria) in survivors examined" (7 RCTs, 799 children); "Death or major neurosensory disability (variable criteria)" (7 RCTs, 1233 children); reported as primary outcomes) **Motor dysfunction** ("Bayley Psychomotor Developmental Index (PDI) <-2SD" (3 RCTs, 842 children); "Bayley PDI <-2SD in tested survivors" (3 RCTs, 528 children); reported as primary outcomes)
Halliday 2003 Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants	Search: October 2002 Up-to-date: 11 November 2008	7 RCTs (Countries: not reported Published: 1980s: 1 RCT; 1990s: 6 RCTs)	669 infants	Preterm babies developing chronic lung disease including those who were ventilator dependent	Moderately early (7-14 days) postnatal corticosteroids vs control (7 RCTs, 659 neonates)	**Cerebral palsy** ("Cerebral palsy" (4 RCTs, 204 children); "Cerebral palsy in survivors assessed" (4 RCTs, 130 children); reported

Table 2. Characteristics of included reviews (*Continued*)

						as review outcomes (not separated into primary and secondary)) **Cerebral palsy or death** ("Death or cerebral palsy" (4 RCTs, 204 children); reported as a review outcome) **Other composite outcomes that include cerebral palsy as a component** ("Major neurosensory disability (variable criteria - see individual studies)" (2 RCTs, 96 children); "Major neurosensory disability (variable criteria) in survivors assessed" (2 RCTs, 56 children); "Death or major neurosensory disability (variable criteria)" (2 RCTs, 96 children); reported as review outcomes)
Doyle 2014 Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants	Search: August 2013 Up-to-date: 18 February 2014	21 RCTs (Countries: Australia, Canada, New Zealand: 1 RCT; 6 countries: 1 RCT; not reported: 19 RCTs Published:	1424 infants	Preterm infants with evolving or established chronic lung disease, defined as oxygen-dependent, ventilator-dependent, or both, with	Late (> 7 days) postnatal corticosteroids vs control (21 RCTs, 1424 neonates)	**Cerebral palsy** ("Cerebral palsy: at 1 to 3 years" (14 RCTs, 876 children); "Cerebral palsy: at latest reported age" (15 RCTs, 855 chil-

Table 2. Characteristics of included reviews (*Continued*)

		1980s: 5 RCTs; 1990s: 12 RCTs; 2000s: 3 RCTs; 2010s: 1 RCT)		or without radiographic changes of BPD		dren); "Cerebral palsy in survivors assessed: at 1 to 3 years" (14 RCTs, 631 children); "Cerebral palsy in survivors assessed: at latest reported age" (15 RCTs, 591 children) ; reported as primary outcomes) **Cerebral palsy or death** ("Death or cerebral palsy: at 1 to 3 years" (14 RCTs, 876 children); "Death or cerebral palsy: at latest reported age" (15 RCTs, 855 children); reported as primary outcomes) **Other composite outcomes that include cerebral palsy as a component** ("Major neurosensory disability (variable criteria - see individual studies) " (8 RCTs, 655 children); "Major neurosensory disability (variable criteria) in survivors assessed" (8 RCTs,

Table 2. Characteristics of included reviews (*Continued*)

						480 children); "Death or major neurosensory disability (variable criteria)" (8 RCTs, 655 children); reported as primary outcomes) **Motor dysfunction** ("Bayley Psychomotor Developmental Index (PDI) < -2 SD" (1 RCT, 118 children); "Bayley PDI < -2 SD in survivors tested" (1 RCT, 90 children); reported as primary outcomes)
Shah 2012 Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates	29 July 2011	7 RCTs (Countries: Canada: 1 RCT; China: 1 RCT; Germany: 1 RCT; UK: 1 RCT; USA: 1 RCT; not reported: 2 RCTs Published: 1990s: 5 RCTs; 2000s: 2 RCTs)	495 infants	Ventilator-dependent preterm neonates with birthweight ≤ 1500 g and postnatal age < 2 weeks	Early inhaled steroids (< 2 weeks) vs placebo (7 RCTs, 495 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 56 children); reported as a secondary outcome) **Motor dysfunction** ("Mean developmental index on BSID-II < 2 SD of the mean" (1 RCT, 56 children); reported as a secondary outcome)
Darlow 2016 Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight in-	1 May 2016	11 RCTs (Countries: Greece: 1 RCT; South Africa: 1 RCT; Thailand: 1 RCT; UK: 2 RCTs; USA: 6 RCTs Published:	1580 infants	VLBW infants (defined as birthweight ≤ 1500 g or at less than 32 weeks' gestation)	Supplemental vitamin A vs no supplementation (10 RCTs, 1460 neonates)	**Other composite outcomes that include cerebral palsy as a component** ("Neurodevelopmental impairment at 18

Table 2. Characteristics of included reviews (*Continued*)

fants		1980s: 2 RCTs; 1990s: 4 RCTs; 2000s: 3 RCTs: 2010s: 2 RCTs)				to 22 months" (1 RCT, 538 children); "Death or neurodevelopmental impairment at 18 to 22 months" (1 RCT, 687 children); reported as secondary outcomes)
Neonatal care: infections: necrotising enterocolitis						
AlFaleh 2014 Probiotics for prevention of necrotising enterocolitis in preterm infants	1 October 2013	24 RCTs (Countries: Australia and New Zealand: 1 RCT; Brazil: 1 RCT; Colombia: 1 RCT; France: 1 RCT; Germany: 2 RCTs; Greece: 2 RCTs; India: 1 RCT; Israel: 1 RCT; Italy: 4 RCTs; Japan: 2 RCTs; Taiwan: 2 RCTs; Turkey: 1 RCT; UK: 1 RCT; USA: 1 RCT; not reported; 3 RCTs Published: 1980s: 1 RCT; 1990s: 2 RCTs; 2000s: 12 RCTs; 2010s: 9 RCTs)	5529 infants *(20 RCTs with reported outcomes)*	Preterm infants at < 37 weeks and birthweight < 2500 g, or both	Probiotics vs control (20 RCTs, 5529 neonates)	**Other composite outcome that includes cerebral palsy as a component** ("Mental retardation and cerebral palsy" (1 RCT, 85 children); reported as a secondary outcome)
Shah 2007 Arginine supplementation for prevention of necrotising enterocolitis in preterm infants	Search: August 2010 Up-to-date: 28 November 2010	1 RCT (Country: not reported Published; 2000s)	152 infants	Preterm infants less than 37 weeks' gestation at birth	Arginine supplementation vs placebo (1 RCT, 152 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 135 children); reported as a post hoc secondary outcome) **Other composite out-**

Table 2. Characteristics of included reviews (*Continued*)

						come that includes cerebral palsy as a component ("Major neurodevelopmental disability" (1 RCT, 132 children); reported as a post hoc secondary outcome)
Neonatal care: infections: fungal infections						
Cleminson 2015 Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants	Search: August 2015 Up-to-date: 1 September 2015	15 RCTs (Countries: India: 2 RCTs; Italy: 2 RCTs; Korea: 1 RCT; Saudi Arabia: 1 RCT; Turkey: 2 RCTs; USA: 7 RCTs Published: 2000s: 7 RCTs; 2010s: 8 RCTs)	1690 infants	Very preterm or VLBW infants with or without evidence of fungal colonisation but without evidence of invasive fungal infection at study entry	Systemic antifungal agent vs placebo or no drug (10 RCTs, 1371 neonates)	**Cerebral palsy** ("Cerebral palsy" (1 RCT, 219 children); reported as a primary outcome) **Other composite outcome that includes cerebral palsy as a component** ("Neurodevelopmental impairment (composite)" (1 RCT, 171 children); reported as a primary outcome)
Neonatal care: infections: herpes simplex						
Jones 2009 Antiviral agents for treatment of herpes simplex virus infection in neonates	Search: November 2008 Up-to-date: 14 March 2009	2 RCTs (Countries: USA: 2 RCTs Published: 1980s: 1 RCT; 1990s: 1 RCT)	273 infants	Hospitalised newborn infants less than 1 month of age with virologically confirmed HSV infection	Vidarabine vs placebo (1 RCT, 56 neonates) Aciclovir vs vidarabine (1 RCT, 202 neonates)	**Cerebral palsy** ("Cerebral palsy in CNS HSV neonatal infection up to three years by HSV serotype: HSV-1" (1 RCT, 9 children); "Cerebral palsy in CNS HSV

Table 2. Characteristics of included reviews (*Continued*)

						neonatal infection up to three years by HSV serotype: HSV-2" (1 RCT, 14 children) ; reported as primary outcomes) **Other composite outcomes that include cerebral palsy as a component** ("Abnormal neurodevelopment at one year" (1 RCT, 56 children; and 1 RCT, 202 children); "Abnormal neurodevelopment or death at approximately one year of age" (1 RCT, 56 children; and 1 RCT, 202 children) ; reported as primary outcomes)
Neonatal care: jaundice						
Okwundu 2012 Prophylactic phototherapy for preventing jaundice in preterm or low birth weight infants	31 March 2011	9 RCTs (Countries: USA: 6 RCTs; Brazil: 1 RCT; Canada: 1 RCT; India: 1 RCT Published: 1960s: 2 RCTs; 1970s: 1 RCT; 1980s: 2 RCTs; 2000s: 4 RCTs)	3449 infants	1. Preterm infants (< 37 weeks' gestation) 2. LBW infants (< 2500 g), within first 36 hours of birth Originally (in the protocol) , the focus of the review was narrower (to include VLBW infants; < 1500 g birthweight); how-	Prophylactic phototherapy vs control (9 RCTs, 3449 neonates)	**Cerebral palsy** ("Cerebral palsy" (2 RCTs, 756 children); reported as a primary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Neurodevelopmental impairment" (1 RCT, 1804 children); reported

Table 2. Characteristics of included reviews (*Continued*)

				ever, so as not to lose valuable information, we made a post hoc decision to include any study that involved LBW (< 2500 g birthweight) or preterm infants We excluded studies of infants with a known cause that can lead to significant hyperbilirubinaemia, such as ABO incompatibility, Rh incompatibility, minor blood group incompatibility, or G-6PD deficiency		as a primary outcome)
Neonatal care: hypoglycaemia						
Weston 2016 Oral dextrose gel for the treatment of hypoglycaemia in newborn infants	29 February 2016	2 RCTs (Countries: Ireland: 1 RCT; New Zealand: 1 RCT; Published: 2000s: 1 RCT; 2010s: 1 RCT)	317 infants	We included newborn infants from birth to discharge home who were hypoglycaemic (blood glucose concentrations below the normal range, investigator defined) for any reason. We excluded infants who had received prior IV treatment for maintenance of glucose control at the time of hypoglycaemia	Dextrose gel vs control (2 RCTs, 317 neonates)	**Cerebral palsy** ("Cerebral palsy and severity at age 2 years or older" (1 RCT, 183 children); reported as a secondary outcome) **Other composite outcomes that include cerebral palsy as a component** ("Major neurosensory disability (2-year follow-up)" (1 RCT, 184 children); reported

Table 2. Characteristics of included reviews (*Continued*)

						as a primary outcome) ("Developmental disability at age 2 years or older" (1 RCT, 184 children); reported as a secondary outcome)
Neonatal care: parenteral feeding						
Moe-Byrne 2016 Glutamine supplementation to prevent morbidity and mortality in preterm infants	18 December 2015	12 RCTs (Countries: China; 1 RCT; Greece: 1 RCT; Malaysia: 1 RCT; Netherlands: 1 RCT; Turkey: 1 RCT; UK: 1 RCT; USA: 4 RCTs; not reported; 2 RCTs; Published: 1990s: 2 RCTs; 2000s: 6 RCTs; 2010s: 4 RCTs)	2877 infants	We included preterm infants (gestational age < 37 weeks) admitted to neonatal intensive or special care units or comparable settings after birth. When participants in a trial included both term and preterm infants, we sought subgroup data from the report or from trial authors	Glutamine supplementation vs no supplementation (12 RCTs, 2877 neonates)	**Other composite outcome that includes cerebral palsy as a component** ("Neurodevelopmental impairment" (1 RCT, 72 children); reported as a primary outcome)
Neonatal care: other						
Osborn 2001 Thyroid hormones for preventing neurodevelopmental impairment in preterm infants	Search: June 2001 Up-to-date: 1 February 2009	5 RCTs (Countries: not reported; Published: 1980s: 2 RCTs; 1990s: 2 RCTs; 2000s; 1 RCT)	362 infants	Studies that enrolled and treated preterm infants in the neonatal period	Thyroid hormones vs control (5 RCTs, 362 neonates)	**Cerebral palsy** ("Cerebral palsy in survivors" (1 RCT, 156 children); reported as a primary outcome) **Cerebral palsy or death** ("Death or cerebral palsy" (1 RCT, 200 children); reported as a primary outcome)

Table 2. Characteristics of included reviews (*Continued*)

Osborn 2007 Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants	Search: March 2006 Up-to-date: 12 October 2006	4 RCTs (Countries: not reported; Published: 1990s: 2 RCTs; 2000s: 2 RCTs)	318 infants	Studies that enrolled preterm infants (born < 37 completed weeks' gestation) in the neonatal period. Trials that enrolled infants on the basis of results of abnormal thyroid function tests (known congenital hypothyroidism or transient hypothyroxinaemia), or with only respiratory distress syndrome, were excluded	Prophylactic thyroid hormones vs no thyroid hormones (4 RCTs, 318 neonates)	**Cerebral palsy** ("Cerebral palsy in survivors" (1 RCT, 156 children); reported as a primary outcome) **Cerebral palsy or death** ("Death or cerebral palsy" (1 RCT, 200 children); reported as a primary outcome)
Almadhoob 2015 Sound reduction management in the neonatal intensive care unit for preterm or very low birth weight infants	18 December 2014	1 RCT (Country: USA; Published: 2009)	34 infants	Preterm infants (< 32 weeks' postmenstrual age or < 1500 g birthweight) cared for in the resuscitation area, during transport, or once admitted to an NICU or a stepdown unit	Silicone earplugs vs no earplugs (1 RCT, 34 infants)	**Cerebral palsy** ("Cerebral palsy at 18 to 22 months' corrected age" (1 RCT, 14 children); reported as a primary outcome)
Conde-Agudelo 2016 Kangaroo mother care to reduce morbidity and mortality in low birthweight infants	30 June 2016	21 RCTs (Countries: 13 RCTs in low- or middle-income countries: Colombia: 1 RCT; Ecuador: 1 RCT; Ethiopia: 1 RCT; Indonesia, Mexico, Ethiopia: 1 RCT; Indonesia: 1 RCT; India: 8	3042 infants	LBW infants (defined as birthweight < 2500 g) regardless of gestational age	Kangaroo mother care vs conventional neonatal care (20 RCTs, 2969 neonates)	**Cerebral palsy** ("Cerebral palsy at 12 months' corrected age" (1 RCT, 588 children); reported as a primary outcome)

Table 2. Characteristics of included reviews (*Continued*)

		RCTs; Madagascar: 1 RCT; Malaysia: 1 RCT; Nepal: 1 RCT; 5 RCTs in high-income countries: Australia: 1 RCT; United Kingdom: 1 RCT; United States: 3 RCTs; Published: 1990s: 5 RCTs; 2000s: 10 RCTs; 2010s: 6 RCTs)				
Spittle 2015 Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants	15 August 2015	25 RCTs (Countries: not reported; Published: 1970s: 1 RCT; 1980s: 5 RCTs; 1990s: 3 RCTs; 2000s: 13 RCTs; 2010s: 3 RCTs)	3615 infants	Preterm infants born at < 37 weeks' gestational age (according to best obstetrical estimate at the time of delivery). We excluded studies that did not report outcomes for preterm infants separately from those for infants born at term	Early developmental intervention vs standard follow-up (25 RCTs, 3615 neonates)	**Cerebral palsy** ("Rate of cerebral palsy" (7 RCTs, 985 children); reported as a secondary outcome) **Motor dysfunction** ("Motor outcome at school age (low score on Movement ABC)" (2 RCTs, 333 children); reported as a secondary outcome)

Abbreviations: BP: blood pressure; BPD: bronchopulmonary dysplasia; BSID: Bayley Scales of Infant Development; CNS: central nervous system; ECHO: echocardiogram; g: grams; G-6PD: glucose-6-phosphate dehydrogenase; HSV: herpes simplex virus; IPPV: intermittent positive-pressure ventilation; IV: intravenous; LBW: low birthweight; MDI: Mental Development Index; Movement-ABC: Movement Assessment Battery for Children; NICU: neonatal intensive care unit; NO: nitric oxide; PDA: patent ductus arteriosus; PDI: Psychomotor Development Index; PMA: post-menstrual age; PPHN: persistent pulmonary hypertension of the newborn; RCT: randomised controlled trial; Rh: Rhesus; SBF: systemic blood flow; SD: standard deviation; SVC: superior vena cava; VLBW: very low birthweight.

Table 3. Risk of bias assessments from included reviews

Review ID and title	Summary of trial limitations (risk of bias)*
Neonatal care: asphyxia	
Chaudhari 2012 Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy	**Random sequence generation:** 2 RCTs low risk; 1 RCT unclear risk **Allocation concealment:** 3 RCTs low risk **Blinding:** 2 RCTs low risk; 1 RCT high risk **Incomplete outcome data:** 3 RCTs low risk **Overall:** "Although small, the trials were generally of good methodological quality"
Jacobs 2013 Cooling for newborns with hypoxic-ischaemic encephalopathy	**Random sequence generation:** 9 RCTs low risk; 1 RCT unclear risk; 1 RCT high risk **Allocation concealment:** 8 RCTs low risk; 2 RCTs unclear risk; 1 RCT high risk **Blinding (participants and personnel):** 11 RCTs high risk **Blinding (outcome assessors):** 10 RCTs low risk; 1 RCT unclear risk **Incomplete outcome data:** 6 RCTs low risk; 1 RCT unclear risk; 4 RCTs high risk **Selective reporting:** 11 RCTs low risk **Overall:** "Several limitations of the available evidence should be noted"
Young 2016 Prophylactic barbiturate use for the prevention of morbidity and mortality following perinatal asphyxia	**Random sequence generation:** 7 RCTs low risk; 2 RCTs unclear risk **Allocation concealment:** 4 RCTs low risk; 4 RCTs unclear risk; 1 RCT high risk **Blinding:** 4 RCTs unclear risk; 5 RCTs high risk **Incomplete outcome data:** 6 RCTs low risk; 2 RCTs unclear risk; 1 RCT high risk **Selective reporting:** 9 RCTs low risk
Neonatal care: haemorrhage: periventricular/intraventricular	
Hunt 2010 Ethamsylate for the prevention of morbidity and mortality in preterm or very low birth weight infants	**Adequate sequence generation:** 4 RCTs yes; 2 RCTs unclear; 1 RCT no **Allocation concealment:** 3 RCTs yes; 2 RCT unclear; 2 RCTs no **Blinding:** 4 RCTs yes; 3 RCTs unclear **Incomplete outcome data addressed:** 5 RCTs yes; 1 RCT unclear; 1 RCT no **Free of selective reporting:** 7 RCTs yes **Free of other bias:** 7 RCTs yes
Smit 2013 Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants	**Random sequence generation:** 5 RCTs low risk; 6 RCTs unclear risk; 1 RCT high risk **Allocation concealment:** 4 RCTs low risk; 7 RCTs unclear risk;

Table 3. Risk of bias assessments from included reviews (*Continued*)

	1 RCT high risk **Blinding (participants and personnel):** 2 RCTs low risk; 10 RCTs high risk **Blinding (outcome assessors):** 6 RCTs low risk; 6 RCTs unclear risk **Incomplete outcome data:** 8 RCTs low risk; 4 RCTs unclear risk **Selective reporting:** 2 RCTs low risk; 10 RCTs unclear risk
Neonatal care: hypotension	
Osborn 2007b The effect of inotropes on morbidity and mortality in preterm infants with low systemic or organ blood flow	**Adequate sequence generation:** 1 RCT yes **Allocation concealment:** 1 RCT yes **Blinding (outcomes):** 1 RCT yes **Blinding (intervention):** 1 RCT yes **Incomplete outcome data addressed:** 1 RCT yes **Free of selective reporting:** 1 RCT yes **Free of other bias:** 1 RCT yes **Overall:** "The study was of adequate methodology"
Neonatal care: fluid therapy	
Osborn 2004 Early volume expansion for prevention of morbidity and mortality in very preterm infants	**Adequate randomisation:** 7 RCTs yes; 1 RCT unclear **Allocation concealment:** 7 RCTs yes; 1 RCT unclear **Blinding of intervention:** 1 RCT yes; 7 RCTs no **Blinding of measurement:** 3 RCTs yes; 1 RCT unclear; 4 RCTs no **Losses to follow-up:** 5 RCTs none; 1 RCT unclear; 2 RCTs yes
Neonatal care: patent ductus arteriosus	
Fowlie 2010 Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants	**Blinding of randomisation:** 12 RCTs yes; 7 RCTs can't tell **Blinding of intervention:** 16 RCTs yes; 2 RCTs can't tell; 1 RCT no **Blinding of outcome assessment:** 16 RCTs yes; 2 RCTs can't tell; 1 RCT no **Complete follow-up (short-term outcomes):** 18 RCTs yes; 1 RCT no **Overall:** "Overall, the quality of the trials was good"
Ohlsson 2015 Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants	**Random sequence generation:** 9 RCTs low risk; 24 RCTs unclear risk **Allocation concealment:** 18 RCTs low risk; 14 RCTs unclear risk; 1 RCT high risk **Blinding:** 6 RCTs low risk; 7 RCTs unclear risk; 20 RCTs high risk **Incomplete outcome data:** 28 RCTs low risk; 3 RCTs unclear risk; 2 RCTs high risk **Selective reporting:** 5 RCTs low risk; 28 RCTs unclear risk **Other:** 29 RCTs low risk; 4 RCTs unclear risk

Table 3. Risk of bias assessments from included reviews (*Continued*)

	Overall: "Study quality was variable…we identified concerns about bias in most individual studies and therefore for the group of studies included as well"
Neonatal care: blood disorders	
Ohlsson 2014 Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants	**Random sequence generation:** 8 RCTs low: risk; 19 RCTs unclear risk **Allocation concealment:** 13 RCTs low risk; 14 RCTs unclear risk **Blinding:** 12 RCTs low risk; 3 RCTs unclear risk; 12 RCTs high risk **Incomplete outcome data:** 23 RCTs low risk; 2 RCTs unclear risk; 2 RCTs high risk **Selective reporting:** 1 RCT low risk; 26 RCTs unclear risk **Other:** 26 RCTs low risk; 1 RCT unclear risk
Whyte 2011 Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants	**Allocation concealment:** 4 RCTs low risk; 1 RCT unclear risk **Blinding:** 1 RCT unclear risk; 4 RCTs high risk **Incomplete outcome data:** 3 RCTs low risk; 1 RCT unclear risk; 1 RCT high risk **Selective reporting:** 1 RCT low risk; 3 RCTs unclear risk; 1 RCT high risk **Overall:** "This review consists of five randomised controlled trials in which there appears to be no allocation bias; the overall level of evidence is high"
Neonatal care: pulmonary hypertension	
More 2016 Endothelin receptor antagonists for persistent pulmonary hypertension in term and late preterm infants	**Random sequence generation:** 1 RCT low risk; 1 RCT unclear risk **Allocation concealment:** 2 RCT unclear risk **Blinding (participants and personnel):** 2 RCTs low risk **Blinding (outcome assessors):** 2 RCTs low risk **Incomplete outcome data:** 1 RCT low risk; 1 RCT high risk **Selective reporting:** 1 RCT low risk; 1 RCT unclear risk **Other:** 2 RCTs low risk **Overall:** "the quality of evidence was considered low because of the very small sample size and methodological issues in the included studies"
Neonatal care: resuscitation	
Tan 2005 Air versus oxygen for resuscitation of infants at birth	**Concealment of allocation:** 2 RCTs yes; 3 RCTs no **Blinding of intervention:** 2 RCTs yes; 3 RCTs no **Blinding of outcome assessment:** 2 RCTs yes; 3 RCTs no **Completeness of follow-up (short-term):** 4 RCTs yes; 1 RCT no **Completeness of follow-up (long-term):** 3 RCTs no; 2 RCTs unclear

Table 3. Risk of bias assessments from included reviews (*Continued*)

Neonatal care: nitric oxide	
Barrington 2010 Inhaled nitric oxide for respiratory failure in preterm infants	**Allocation concealment:** 12 RCTs low risk; 2 RCTs unclear risk **Blinding:** 7 RCTs low risk; 7 RCTs high risk **Incomplete outcome data:** 14 RCTs low risk **Selective reporting:** 8 RCTs low risk; 6 RCTs not reported **Other:** 3 RCTs low risk; 4 RCTs high risk; 7 RCTs not reported
Finer 2006 Nitric oxide for respiratory failure in infants born at or near term	**Masking of allocation:** 10 RCTs yes; 4 RCTs cannot tell **Masking of intervention:** 6 RCTs yes; 8 RCTs no **Masking of outcome assessment:** 6 RCTs yes; 1 RCT can't tell; 7 RCTs no **Completeness of follow-up:** 13 RCTs yes; 1 RCT can't tell **Overall:** "The overall quality of these studies is quite variable"
Neonatal care: apnoea	
Henderson-Smart 2010b Methylxanthine treatment for apnoea in preterm infants	**Random sequence generation:** 1 RCT high risk; 5 RCTs not reported **Allocation concealment:** 2 RCTs low risk; 2 RCTs unclear risk; 2 RCTs high risk **Blinding:** 4 RCTs low risk; 2 RCTs high risk **Incomplete outcome data:** 3 RCTs low risk; 1 RCT unclear risk; 2 RCTs high risk **Selective reporting:** 2 RCTs low risk; 1 RCT unclear risk; 2 RCTs high risk; 1 RCT not reported **Overall:** "There was variation in trial design"
Henderson-Smart 2010c Prophylactic methylxanthine for prevention of apnoea in preterm infants	**Allocation concealment:** 3 RCTs low risk **Blinding:** 3 RCTs low risk **Incomplete outcome data:** 3 RCTs low risk **Selective reporting:** 2 RCTs low risk; 1 RCT not reported **Overall:** "Three studies are generally of high quality"
Neonatal care: respiratory distress syndrome	
Howlett 2015 Inositol in preterm infants at risk for or having respiratory distress syndrome	**Random sequence generation:** 1 RCT low risk; 3 RCTs unclear risk **Allocation concealment:** 2 RCTs low risk; 2 RCTs unclear risk **Blinding:** 2 RCTs low risk; 2 RCTs unclear risk **Incomplete outcome data:** 4 RCTs low risk **Selective reporting:** 3 RCTs low risk; 1 RCT unclear risk **Other:** 3 RCTs high risk; 1 RCT low risk **Overall:** "Study quality varied and interim analyses had occurred in all trials"
Seger 2009 Animal derived surfactant extract for treatment of respiratory distress syndrome	**Blinding of randomisation:** 10 RCTs yes; 3 RCTs not described **Blinding of intervention:** 8 RCTs yes; 1 RCT not described; 4

Table 3. Risk of bias assessments from included reviews (*Continued*)

	RCTs no **Blinding of outcome measurement:** 6 RCTs yes; 4 RCTs not described; 2 RCTs no; 1 RCT not reported **Complete follow-up (short-term):** 13 RCTs yes **Complete follow-up (long-term):** 4 RCTs yes; 9 RCTs no **Overall:** "studies are of high methodological quality"
Soll 2000 Synthetic surfactant for respiratory distress syndrome in preterm infants	**Blinding of randomisation:** 6 RCTs yes **Blinding of intervention:** 5 RCTs yes; 1 RCT no **Blinding of outcome measurement:** 5 RCTs yes; 1 RCT no **Complete follow-up (short term):** 6 RCTs yes **Complete follow-up (long term):** 80 to 100%
Soll 2010 Prophylactic protein free synthetic surfactant for preventing morbidity and mortality in preterm infants	**Adequate sequence generation:** 6 RCTs unclear: 1 RCT not reported **Allocation concealment:** 7 RCTs yes **Blinding of intervention:** 5 RCTs yes; 1 RCT unclear; 1 RCT no **Blinding of outcome measurement:** 6 RCTs yes; 1 RCT no **Incomplete outcome data addressed:** 5 RCTs yes; 2 RCTs unclear **Free of selective reporting:** 7 RCTs yes **Free of other bias:** 7 RCTs yes
Neonatal care: mechanical ventilation	
Cools 2015 Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants	**Random sequence generation:** 11 RCTs low risk; 8 RCTs unclear risk **Allocation concealment:** 7 RCTs low risk; 12 RCTs unclear risk **Blinding of participants and personnel:** 19 RCTs high risk **Blinding of outcome assessment:** 7 RCTs low risk; 12 RCTs unclear risk **Incomplete outcome data:** 19 RCTs low risk **Overall:** "The quality of the studies was generally high"
Ho 2015 Continuous distending pressure for respiratory distress in preterm infants	**Random sequence generation:** 2 RCTs low risk; 3 RCTs unclear risk; 1 RCT high risk **Allocation concealment:** 4 RCTs low risk; 1 RCT unclear risk; 1 RCT high risk **Blinding (intervention):** 6 RCTs high risk **Blinding (short term outcomes):** 6 RCTs high risk (1 RCT low risk for long term outcomes) **Incomplete outcome data (short term outcomes):** 3 RCTs low risk; 3 RCTs unclear risk (1 RCT low risk for long-term outcomes) **Selective reporting:** 2 RCTs low risk; 4 RCTs unclear risk **Other:** 6 RCTs unclear risk **Overall:** "These data should be interpreted with caution as in the studies reviewed, the numbers of infants were small, blinding of treatment was not possible and blinding of the outcome assess-

Table 3. Risk of bias assessments from included reviews (*Continued*)

	ment was reported in only one study for the outcomes in childhood, thus possibly introducing bias"
Henderson-Smart 2010 Prophylactic methylxanthines for endotracheal extubation in preterm infants	**Sequence generation:** 1 RCT low risk; 6 RCTs not reported **Allocation concealment:** 6 RCTs low risk; 1 RCT unclear risk **Blinding:** 6 RCTs low risk; 1 RCT high risk **Incomplete outcome data:** 3 RCTs low risk; 3 RCTs high risk; 1 RCT not reported **Selective reporting:** 4 RCTs low risk; 2 RCTs high risk; 1 RCT not reported **Other:** 1 RCT low risk; 6 RCTs not reported
Kamlin 2003 Long versus short inspiratory times in neonates receiving mechanical ventilation	**Concealment of allocation:** 1 RCT yes; 1 RCT cannot tell; 3 RCTs no **Blinding of intervention:** 5 RCTs no **Blinding of outcome measurement:** 3 RCTs no; 2 RCTs some **Completeness of follow-up (short term outcomes):** 5 RCTs yes
Wheeler 2010 Volume-targeted versus pressure-limited ventilation in the neonate	**Sequence generation:** 6 RCTs low risk; 6 RCTs unclear risk **Allocation concealment:** 11 RCTs low risk; 1 RCT unclear risk **Blinding:** 12 RCTs high risk **Incomplete outcome data:** 12 RCTs low risk **Selective reporting:** 10 RCTs low risk; 1 RCT unclear risk; 1 RCT high risk **Other:** 5 RCTs low risk; 5 RCTs unclear risk; 2 RCTs high risk **Overall:** "There are no major concerns about the methodology used in the twelve trials included in this review"
Neonatal care: bronchopulmonary dysplasia	
Doyle 2014b Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants	**Random sequence generation:** 15 RCTs low risk; 14 RCTs unclear risk **Allocation concealment:** 27 RCTs low risk; 2 RCTs unclear risk **Blinding of participants and personnel:** 23 RCTs low risk; 2 RCTs unclear risk; 4 RCTs high risk **Blinding of outcome assessment:** 23 RCTs low risk; 2 RCTs unclear risk; 4 RCTs high risk **Incomplete outcome data:** 28 RCTs low risk; 1 RCT unclear risk **Overall:** "Overall the risk of bias was low for most studies"
Halliday 2003 Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants	**Blinding of randomisation/allocation concealment:** 7 RCTs yes/low risk **Blinding of intervention:** 5 RCTs yes; 2 RCTs no **Blinding of outcome measurement:** 5 RCTs yes; 1 RCT some; 1 RCT cannot tell **Complete follow-up:** 6 RCTs yes/almost; 1 RCT no **Overall:** "the methodological quality of the studies to determine long-term outcome is limited in some cases"

Table 3. Risk of bias assessments from included reviews (*Continued*)

Doyle 2014 Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants	**Random sequence generation:** 12 RCTs low risk; 9 RCTs unclear risk **Allocation concealment:** 17 RCTs low risk; 4 RCTs unclear risk **Blinding of participants and personnel:** 15 RCTs low risk; 4 RCTs unclear risk; 2 RCTs high risk **Blinding of outcome assessment:** 16 RCTs low risk; 4 RCTs unclear risk; 1 RCT high risk **Incomplete outcome data:** 20 RCTs low risk; 1 RCT unclear risk **Overall:** "Overall the risk of bias was low for most studies"
Shah 2012 Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates	**Random sequence generation:** 7 RCTs unclear risk **Allocation concealment:** 7 RCTs low risk **Blinding of participants and personnel:** 7 RCTs low risk **Blinding of outcome assessment:** 1 RCT low risk; 6 RCTs unclear risk **Incomplete outcome data:** 6 RCTs low risk; 1 RCT unclear risk **Overall:** "Overall, the studies included for this review were of high methodological quality"
Darlow 2016 Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants	**Random sequence generation:** 9 RCTs low risk; 2 RCTs unclear risk **Allocation concealment:** 8 RCTs low risk; 3 RCTs unclear risk **Blinding:** 6 RCTs low risk; 2 RCTs unclear risk; 3 RCTs high risk **Incomplete outcome data:** 9 RCTs low risk; 1 RCT unclear risk; 1 RCT high risk **Selective reporting:** 8 RCTs low risk; 2 RCTs unclear risk; 1 RCT high risk **Other:** 2 RCTs low risk; 6 RCTs unclear risk; 2 RCTs high risk; 1 RCT not reported
Neonatal care: infections: necrotising enterocolitis	
AlFaleh 2014 Probiotics for prevention of necrotising enterocolitis in preterm infants	**Random sequence generation:** 15 RCTs low risk; 8 RCTs unclear risk; 1 RCT high risk **Allocation concealment:** 11 RCTs low risk; 12 RCTs unclear risk; 1 RCT high risk **Blinding:** 15 RCTs low risk; 9 RCTs unclear risk **Incomplete outcome data:** 21 RCTs low risk; 2 RCTs unclear risk; 1 RCT high risk **Selective reporting:** 17 RCTs low risk; 6 RCTs high risk; 1 RCT not reported **Other:** 14 RCTs low risk; 10 RCTs not reported **Overall:** "Eleven of our included trials were classified as high quality trials"
Shah 2007 Arginine supplementation for prevention of necrotising enterocolitis in preterm infants	**Masking of randomisation:** 1 RCT yes **Masking of intervention:** 1 RCT yes **Masking of outcome assessment:** 1 RCT yes **Completeness of follow-up:** 1 RCT yes

Table 3. Risk of bias assessments from included reviews (*Continued*)

	Overall: "The methodological quality of the included study was good"
Neonatal care: infections: fungal infections	
Cleminson 2015 Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants	**Allocation concealment:** 12 RCTs low risk; 3 RCTs unclear risk **Blinding of participants and personnel:** 10 RCTs low risk; 3 RCTs unclear risk; 2 RCTs high risk **Blinding of outcome assessment:** 10 RCTs low risk; 3 RCTs unclear risk; 2 RCTs high risk **Incomplete outcome data:** 15 RCTs low risk **Overall:** "The included trials were generally of good methodological quality"
Neonatal care: infections: herpes simplex	
Jones 2009 Antiviral agents for treatment of herpes simplex virus infection in neonates	**Allocation concealment:** 1 RCT unclear; 1 RCT inadequate **Overall:** "The two trials... have a number of methodological flaws"
Neonatal care: jaundice	
Okwundu 2012 Prophylactic phototherapy for preventing jaundice in preterm or low birth weight infants	**Random sequence generation:** 4 RCTs low risk; 3 RCTs unclear risk; 2 RCTs high risk **Allocation concealment:** 3 RCTs low risk; 4 RCTs unclear risk; 2 RCTs high risk **Blinding:** 1 RCT low risk; 2 RCTs unclear risk; 6 RCTs high risk **Incomplete outcome data:** 8 RCTs low risk; 1 RCT high risk **Selective reporting:** 2 RCTs low risk; 7 RCTs unclear risk **Other:** 7 RCTs low risk **Overall:** "In general, the overall methodological quality of the included studies was acceptable"
Neonatal care: hypoglycaemia	
Weston 2016 Oral dextrose gel for the treatment of hypoglycaemia in newborn infants	**Random sequence generation:** 1 RCT low risk; 1 RCT unclear risk **Allocation concealment:** 1 RCT low risk; 1 RCT unclear risk **Blinding of participants and personnel:** 1 RCT low risk; 1 RCT unclear risk **Blinding of outcome assessors:** 1 RCT low risk; 1 RCT unclear risk **Incomplete outcome data:** 1 RCT low risk; 1 RCT high risk **Selective reporting:** 1 RCT low risk; 1 RCT unclear risk **Other:** 1 RCT low risk; 1 RCT unclear risk
Neonatal care: parenteral feeding	

Table 3. Risk of bias assessments from included reviews (*Continued*)

Moe-Byrne 2016 Glutamine supplementation to prevent morbidity and mortality in preterm infants	**Random sequence generation:** 8 RCTs low risk; 3 RCTs unclear risk; 1 RCT high risk **Allocation concealment:** 8 RCTs low risk; 2 RCTs unclear risk; 2 RCTs high risk **Blinding:** 10 RCTs low risk; 2 RCTs unclear risk **Incomplete outcome data:** 8 RCTs low risk; 2 RCTs unclear risk; 2 RCTs high risk **Overall:** "in general the trials were of good quality"
Neonatal care: other	
Osborn 2001 Thyroid hormones for preventing neurodevelopmental impairment in preterm infants	**Blinding of randomisation/allocation concealment:** 4 RCTs yes; 1 RCT no **Blinding of intervention:** 4 RCTs yes; 1 RCT no **Blinding of outcome assessment:** 4 RCTs yes; 1 RCT not stated **Complete follow-up:** 2 RCTs yes; 3 RCTs no **Overall:** "four studies... were of good methodology"
Osborn 2007 Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants	**Allocation concealment:** 4 RCTs low risk **Blinding of intervention:** 4 RCTs yes **Blinding of outcome assessment:** 3 RCTs yes; 1 RCT probably **Complete follow-up:** 3 RCTs yes; 1 RCT no **Overall:** "All studies... were of adequate methodology"
Almadhoob 2015 Sound reduction management in the neonatal intensive care unit for preterm or very low birth weight infants	**Random sequence generation:** 1 RCT low risk **Allocation concealment:** 1 RCT low risk **Blinding of participants and personnel:** 1 RCT high risk **Blinding of outcome assessment:** 1 RCT low risk **Incomplete outcome data:** 1 RCT low risk **Selective reporting:** 1 RCT low risk **Other:** 1 RCT low risk **Overall:** "We considered the overall risk of bias to be low"
Conde-Agudelo 2016 Kangaroo mother care to reduce morbidity and mortality in low birthweight infants	**Random sequence generation:** 21 RCTs low risk **Allocation concealment:** 10 RCTs low risk; 11 RCTs unclear risk **Blinding of participants and personnel:** 21 RCTs high risk **Blinding of outcome assessment:** 2 RCTs low risk; 15 RCTs unclear risk; 4 RCTs high risk **Incomplete outcome data:** 14 RCTs low risk; 3 RCTs unclear risk; 4 RCTs high risk **Selective reporting:** 16 RCTs low risk; 3 RCTs unclear risk; 2 RCTs high risk **Other:** 15 RCTs low risk; 3 RCTs unclear risk; 3 RCTs high risk **Overall:** "The methodological quality of the included trials was mixed"
Spittle 2015 Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in	**Random sequence generation:** 11 RCTs low risk; 8 RCTs unclear risk; 5 RCTs high risk; 1 RCT not reported **Allocation concealment:** 11 RCTs low risk; 9 RCTs unclear risk;

Table 3. Risk of bias assessments from included reviews (*Continued*)

preterm infants	5 RCTs high risk **Blinding of participants and personnel:** 2 RCTs low risk; 4 RCTs unclear risk; 19 RCTs high risk **Blinding of outcome assessment:** 21 RCTs low risk; 3 RCTs unclear risk; 1 RCT high risk **Incomplete outcome data:** 12 RCTs low risk; 4 RCTs unclear risk; 9 RCT high risk **Selective reporting:** 3 RCTs unclear risk; 6 RCT high risk; 16 RCTs not reported **Overall:** "The methodological quality of included studies was variable"

Abbreviations: RCT: randomised controlled trial.
*We have reported only the risk of bias components assessed and reported in the included reviews.

Table 4. AMSTAR assessments for included reviews

Review ID	AMSTAR criteria											TOTAL SCORE
	'A priori' design	Duplicate selection and extraction	Comprehensive search	Grey literature considered	Included and excluded studies lists	Characteristics of included studies	Quality assessed and documented	Quality considered for conclusions	Methods for combining studies appropriate	Publication bias considered or assessed	Conflicts stated	
Neonatal care: asphyxia												
Chaudhari 2012	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Jacobs 2013	√	√	√	√	√	√	√	√	√	×	√	10/11 HIGH QUALITY
Young 2016	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal care: haemorrhage: periventricular/intraventricular												

Table 4. AMSTAR assessments for included reviews (*Continued*)

Hunt 2010	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Smit 2013	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal care: hypotension												
Osborn 2007b	√	√	√	√	√	√	√	√	N/A	√	×	9/10 HIGH QUALITY
Neonatal care: fluid therapy												
Osborn 2004	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Neonatal care: patent ductus arteriosus												
Fowlie 2010	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Ohlsson 2015	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal care: blood disorders												
Ohlsson 2014	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Whyte 2011	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal care: pulmonary hypertension												

Table 4. AMSTAR assessments for included reviews (*Continued*)

More 2016	√	√	√	√	√	√	√	√	N/A	√	×	9/10 HIGH QUALITY
Neonatal care: resuscitation												
Tan 2005	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Neonatal care: nitric oxide												
Barrington 2010	√	√	√	√	√	√	√	?	√	×	×	8/11 HIGH QUALITY
Finer 2006	√	√	×	√	√	√	√	√	√	×	×	8/11 HIGH QUALITY
Neonatal care: apnoea												
Henderson-Smart 2010b	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Henderson-Smart 2010c	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Neonatal care: respiratory distress syndrome												
Howlett 2015	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Seger 2009	?	√	√	√	√	√	√	√	√	×	×	8/11 HIGH QUALITY

Table 4. AMSTAR assessments for included reviews (*Continued*)

Soll 2000	?	?	√	√	√	√	√	√	?	×	×	6/11 MODERATE QUALITY
Soll 2010	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Neonatal care: mechanical ventilation												
Cools 2015	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Ho 2015	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Henderson-Smart 2010	√	√	√	√	×	√	√	√	√	×	×	8/11 HIGH QUALITY
Kamlin 2003	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Wheeler 2010	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Neonatal care: bronchopulmonary dysplasia												
Doyle 2014b	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Halliday 2003	√	?	√	√	√	√	√	√	?	×	×	7/11 MODERATE QUALITY

Table 4. AMSTAR assessments for included reviews (*Continued*)

Doyle 2014	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Shah 2012	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Darlow 2016	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal care: infections: necrotising enterocolitis												
AlFaleh 2014	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Shah 2007	√	√	√	√	?	√	√	√	N/A	×	×	7/10 HIGH QUALITY
Neonatal infections: fungal infections												
Clemenson 2015	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal infections: herpes simplex												
Jones 2009	√	√	√	√	√	√	√	√	N/A	×	×	8/10 HIGH QUALITY
Neonatal care: jaundice												
Okwundu 2012	√	√	√	√	√	√	√	√	?	×	×	8/11 HIGH QUALITY
Neonatal care: hypoglycaemia												

Table 4. AMSTAR assessments for included reviews (*Continued*)

Weston 2016	√	√	√	√	√	√	√	√	√	√	√	11/11 HIGH QUALITY
Neonatal care: parenteral feeding												
Moe-Byrne 2016	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Neonatal care: other												
Osborn 2001	√	?	√	√	√	√	√	√	√	×	×	8/11 HIGH QUALITY
Osborn 2007	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY
Almadhoob 2015	√	√	√	√	√	√	√	√	N/A	√	×	9/10 HIGH QUALITY
Conde-Agudelo 2016	√	√	√	√	√	√	√	√	√	√	×	10/11 HIGH QUALITY
Spittle 2015	√	√	√	√	√	√	√	√	√	×	×	9/11 HIGH QUALITY

Table 5. ROBIS assessments for included reviews

Review ID	ROBIS domains				OVERALL RISK OF BIAS
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	
Neonatal care: asphyxia					

Table 5. ROBIS assessments for included reviews (*Continued*)

Chaudhari 2012	Low risk	Low risk	Low risk	Low risk	LOW RISK
Jacobs 2013	Low risk	Low risk	Low risk	Low risk	LOW RISK
Young 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: haemorrhage: periventricular/intraventricular					
Hunt 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Smit 2013	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: hypotension					
Osborn 2007b	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: fluid therapy					
Osborn 2004	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: patent ductus arteriosus					
Fowlie 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Ohlsson 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: blood disorders					
Ohlsson 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Whyte 2011	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: pulmonary hypertension					
More 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: resuscitation					
Tan 2005	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: nitric oxide					
Barrington 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Finer 2006	Low risk	Unclear risk	Low risk	Low risk	UNCLEAR RISK
Neonatal care: apnoea					

Table 5. ROBIS assessments for included reviews (*Continued*)

Henderson-Smart 2010b	Low risk	Low risk	Low risk	Low risk	LOW RISK
Henderson-Smart 2010c	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: respiratory distress syndrome					
Howlett 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Seger 2009	Unclear risk	Low risk	Low risk	Low risk	LOW RISK
Soll 2000	Unclear risk	Unclear risk	Unclear risk	Unclear risk	UNCLEAR RISK
Soll 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: mechanical ventilation					
Cools 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Ho 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Henderson-Smart 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Kamlin 2003	Low risk	Low risk	Low risk	Low risk	LOW RISK
Wheeler 2010	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: bronchopulmonary dysplasia					
Doyle 2014b	Low risk	Low risk	Low risk	Low risk	LOW RISK
Halliday 2003	Low risk	Unclear risk	Unclear risk	Unclear risk	LOW RISK
Doyle 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Shah 2012	Low risk	Low risk	Low risk	Low risk	LOW RISK
Darlow 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal infections: necrotising enterocolitis					
AlFaleh 2014	Low risk	Low risk	Low risk	Low risk	LOW RISK
Shah 2007	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal infections: fungal infections					

Table 5. ROBIS assessments for included reviews (*Continued*)

Cleminson 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal infections: herpes simplex					
Jones 2009	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: jaundice					
Okwundu 2012	Low risk	Low risk	Low risk	Unclear risk	LOW RISK
Neonatal care: hypoglycaemia					
Weston 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: parenteral feeding					
Moe-Byrne 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK
Neonatal care: other					
Osborn 2001	Low risk	Unclear risk	Unclear risk	Low risk	UNCLEAR RISK
Osborn 2007	Low risk	Low risk	Low risk	Low risk	LOW RISK
Almadhoob 2015	Unclear risk	Low risk	Low risk	Low risk	LOW RISK
Conde-Agudelo 2016	Low risk	Low risk	Low risk	Low risk	LOW RISK
Spittle 2015	Low risk	Low risk	Low risk	Low risk	LOW RISK

Table 6. Cerebral palsy

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Neonatal care: asphyxia							
Therapeutic hypothermia vs standard care for newborns with hypoxic-ischaemic encephalopathy (Jacobs 2013)	Cerebral palsy in survivors assessed at 18 to 24 months	352 per 1000 (143/406)	232 per 1000 (190 to 289)	**RR 0.66 (0.54 to 0.82)**	881 (7 RCTs)	HIGH	Not downgraded

Table 6. Cerebral palsy (*Continued*)

	Cerebral palsy at 6 to 7 years	288 per 1000 (15/52)	173 per 1000 (89 to 340)	RR 0.60 (0.31 to 1.18)	121 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Barbiturates (phenobarbital) vs conventional therapy for prevention of morbidity and mortality following perinatal asphyxia (Young 2016)	Cerebral palsy at 3 to 6 years	242 per 1000 (8/33)	141 per 1000 (46 to 412)	RR 0.58 (0.19 to 1.70)	69 (2 RCTs)	VERY LOW	Study limitations (-1): unblinded studies; concern regarding performance bias and detection bias Imprecision (-1): 95% CIs were wide and imprecise Inconsistency (-1): clinically important heterogeneity noted *(GRADED by review authors themselves)*
Neonatal care: haemorrhage: periventricular/intraventricular							
Ethamsylate vs placebo for prevention of morbidity and mortality in preterm or very low birthweight infants (Hunt 2010)	Cerebral palsy in surviving children available for follow-up at 2 years up to 3.5 to 4.2 years (only cerebral palsy significant enough to cause moderate or severe impairment was included)	78 per 1000 (21/270)	88 per 1000 (50 to 156)	RR 1.13 (0.64 to 2.00)	532 (3 RCTs)	MODERATE	Imprecision (-1): wide CI crossing line of no effect

Table 6. Cerebral palsy (*Continued*)

Neonatal care: hypotension							
Dobutamine vs dopamine in preterm infants with low superior vena cava flow (Osborn 2007b)	Cerebral palsy at 3 years in survivors assessed	429 per 1000 (3/7)	69 per 1000 (4 to 1131)	RR 0.16 (0.01 to 2.64)	13 (1 RCT)	VERY LOW	Study limitations (-1): 5/18 surviving infants were not assessed at 3 years of age Imprecision (-2): wide CI crossing line of no effect; 1 RCT with very small sample size
Neonatal care: fluid therapy							
Volume vs no treatment for prevention of morbidity and mortality in very preterm infants (Osborn 2004)	Cerebral palsy in survivors at 2 years	132 per 1000 (27/205)	100 per 1000 (63 to 158)	RR 0.76 (0.48 to 1.20)	604 (1 RCT)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Gelatin vs fresh frozen plasma for prevention of morbidity and mortality in very preterm infants (Osborn 2004)		103 per 1000 (21/203)	97 per 1000 (54 to 175)	RR 0.94 (0.52 to 1.69)	399 (1 RCT)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Neonatal care: patent ductus arteriosus							
Prophylactic indomethacin vs placebo for preventing mortality and morbidity in preterm in-	Cerebral palsy at 18 to 54 months	111 per 1000 (77/694)	115 per 1000 (85 to 155)	RR 1.04 (0.77 to 1.40)	1372 (4 RCTs)	MODERATE	Imprecision (-1): wide CI crossing line of no effect

Table 6. Cerebral palsy (*Continued*)

fants (Fowlie 2010)							
	Cerebral palsy at 8 years	76 per 1000 (11/145)	94 per 1000 (45 to 199)	RR 1.24 (0.59 to 2.62)	304 (1 RCT)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Oral ibuprofen vs intravenous ibuprofen for treatment of patent ductus arteriosus in preterm or low birthweight (or both) infants (Ohlsson 2015)	Moderate or severe cerebral palsy at 18 to 24 months	74 per 1000 (2/27)	100 per 1000 (18 to 554)	RR 1.35 (0.24 to 7.48)	57 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection and reporting bias; high risk of performance, detection, and attrition bias Imprecision (-2): wide CI crossing line of no effect; small sample size and few events
Neonatal care: blood disorders							
Erythropoietin vs placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants (Ohlsson 2014)	Cerebral palsy at 18 to 22 months' corrected age (in children examined)	187 per 1000 (14/75)	123 per 1000 (58 to 256)	RR 0.66 (0.31 to 1.37)	153 (2 RCTs)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection bias and high risk of attrition bias (-73% follow-up) Inconsistency (-1): I^2 = 72% Imprecision (-2): wide CI crossing line of no effect; small sample sizes

Table 6. Cerebral palsy (*Continued*)

Darbepoetin alfa vs placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants (Ohlsson 2014)		208 per 1000 (5/24)	17 per 1000 (0 to 292)	RR 0.08 (0.00 to 1.40)	51 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size and few events
Transfusion at a restrictive vs a liberal haemoglobin threshold for preventing morbidity and mortality in very low birthweight infants (Whyte 2011)	Cerebral palsy at 18 to 21 months' follow-up among survivors	52 per 1000 (9/172)	68 per 1000 (29 to 159)	RR 1.29 (0.55 to 3.03)	335 (1 RCT)	LOW	Study limitations (-1): 1 RCT at high risk of performance bias and unclear risk of reporting bias Imprecision (-1): wide CI crossing line of no effect
Neonatal care: pulmonary hypertension							
Endothelin receptor antagonists vs placebo for persistent pulmonary hypertension in term and late preterm infants (More 2016)	Cerebral palsy at 6 months (delayed motor development and spasticity)	214 per 1000 (3/14)	19 per 1000 (0 to 345)	RR 0.09 (0.00 to 1.61)	37 (1 RCT)	LOW	Study limitation (-1): 8/23 infants in the placebo group were excluded from analysis Imprecision (-1): 1 RCT; small sample size *(GRADED by review authors themselves)*
Neonatal care: resuscitation							
Room air vs 100% oxygen for resuscitation of infants at birth (Tan 2005)	Cerebral palsy in those followed up at 18 to 24 months	74 per 1000 (9/122)	99 per 1000 (41 to 239)	RR 1.34 (0.55 to 3.24)	213 (1 RCT)	VERY LOW	Study limitations (-2): 1 qRCT with no blinding and < 70% follow-

Table 6. Cerebral palsy (*Continued*)

							up Imprecision (-1): wide CI crossing line of no effect
Neonatal care: nitric oxide							
Inhaled NO vs placebo for respiratory failure in preterm infants (entry before 3 days based on oxygenation) (Barrington 2010)	Cerebral palsy at 18 to 22 months (moderate/severe or disabling)	100 per 1000 (11/110)	185 per 1000 (93 to 371)	RR 1.85 (0.93 to 3.71)	209 (2 RCTs)	LOW	Imprecision (-2): wide CI crossing line of no effect; small sample sizes
Inhaled NO vs placebo or no treatment for respiratory failure in preterm infants (entry after 3 days based on BPD risk) (Barrington 2010)	Cerebral palsy at 2 years' corrected age or 30 months (1 RCT all severities; 1 RCT moderate/severe or disabling)	56 per 1000 (14/248)	62 per 1000 (30 to 126)	RR 1.10 (0.54 to 2.23)	498 (2 RCTs)	LOW	Study limitations (-1): 1 RCT with no blinding of intervention or outcome measurement Imprecision (-1): wide CI crossing line of no effect; small sample sizes
Inhaled NO vs placebo for respiratory failure in preterm infants (studies of routine use in intubated preterm infants) (Barrington 2010)	Cerebral palsy at 1 or 2 years' corrected age (1 RCT all severities; 1 RCT moderate/severe or disabling)	70 per 1000 (20/286)	66 per 1000 (36 to 119)	RR 0.94 (0.51 to 1.70)	593 (2 RCTs)	LOW	Study limitations (-1) : 2 RCTs with 74%-82% follow-up Imprecision (-1): wide CI crossing line of no effect

Table 6. Cerebral palsy (*Continued*)

Inhaled nitric oxide vs placebo for respiratory failure in infants born at or near term (Finer 2006)	Cerebral palsy among survivors at 13 or 18 to 24 months	89 per 1000 (16/179)	91 per 1000 (44 to 191)	RR 1.02 (0.49 to 2.14)	299 (2 RCTs)	LOW	Study limitations (-1) : 1 RCT masking of allocation, masking of outcomes. and completeness of follow-up Imprecision (-1): wide CI crossing line of no effect
	"This group has now published follow up data, including neurodevelopmental outcomes, which were obtained by telephone interview of 60 of the 83 survivors of the original trial. The interview was conducted between one and four years of age... Although cerebral palsy [was] reported it is unclear how [it] was defined... It is not, therefore, possible to add any of these data to the meta-analysis, but they do appear to show no evidence of neurodevelopmental impairment due to inhaled nitric oxide therapy"					NOT GRADED	
Inhaled nitric oxide vs placebo for respiratory failure in infants with diaphragmatic hernias born at or near term (Finer 2006)	Cerebral palsy among survivors at 18 to 24 months	(0/14)	(2/8)	RR 8.33 (0.45 to 154.78)	22 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with 76% follow-up of survivors Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: apnoea							
Caffeine vs placebo for treatment of apnoea in preterm infants (Henderson-Smart 2010b)	Cerebral palsy at 18 to 21 months' corrected age	50 per 1000 (18/361)	30 per 1000 (14 to 62)	RR 0.60 (0.29 to 1.25)	729 (1 RCT)	LOW	Study limitations (-1): results based on 1 RCT subgroup from post hoc subgroup analyses (randomisation not stratified according

Table 6. Cerebral palsy (*Continued*)

							to indication for inclusion) Imprecision (-1): wide CI crossing line of no effect
Caffeine vs placebo for prevention of apnoea in preterm infants (Henderson-Smart 2010c)	Cerebral palsy at 18 to 21 months' corrected age	45 per 1000 (9/200)	46 per 1000 (19 to 112)	RR 1.03 (0.43 to 2.49)	415 (1 RCT)	LOW	Study limitations (-1): results based on 1 RCT subgroup from post hoc subgroup analyses (randomisation not stratified according to indication for inclusion) Imprecision (-1): wide CI crossing line of no effect
Neonatal care: respiratory distress syndrome							
Animal-derived surfactant extract vs no treatment for treatment of respiratory distress syndrome (Seger 2009)	Cerebral palsy at 1 and 2 years' corrected age	207 per 1000 (6/29)	182 per 1000 (70 to 470)	RR 0.88 (0.34 to 2.27)	73 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with no blinding of intervention; and blinding of outcome measurement not reported Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Synthetic surfactant vs placebo for respiratory distress	Cerebral palsy in survivors examined at 1 year *(in 4 of the 5 RCTs)*	96 per 1000 (74/767)	73 per 1000 (53 to 101)	RR 0.76 (0.55 to 1.05)	1557 (5 RCTs)	MODERATE	Imprecision (-1): wide CI crossing the line of

Table 6. Cerebral palsy (*Continued*)

syndrome in preterm infants (Soll 2000)							no effect
Prophylactic protein-free synthetic surfactant vs placebo for preventing morbidity and mortality in preterm infants (Soll 2010)	Cerebral palsy at 1 or 2 years	153 per 1000 (49/320)	142 per 1000 (52 to 204)	RR 0.93 (0.64 to 1.33)	670 (4 RCTs)	LOW	Study limitations (-1): "Somewhat fewer infants who received surfactant failed to return for follow-up evaluation (typical relative risk 0.63, 95% CI 0.48, 0.82; typical risk difference -0.10, 95% CI -0.15, -0.04)" Imprecision (-1): wide CI crossing the line of no effect
Neonatal care: mechanical ventilation							
Elective high-frequency oscillatory ventilation vs conventional ventilation for acute pulmonary dysfunction in preterm infants (Cools 2015)	Cerebral palsy	1. "Neurodevelopmental status was assessed at 16 to 24 months corrected age in 77% of survivors of the HIFI 1989 study (185 HFOV & 201 CV) using Bayley psychometric tests and central nervous system examinations... The rate of cerebral palsy was 11% in both groups" 2. "Moriette 2001 assessed neuromotor outcome at the corrected age of two years in 192 of 212 survivors (90%) using a physician questionnaire... **the risk of spastic cerebral palsy was significantly lower for infants ventilated with HFOV** (4% versus 17%; OR 0.87, 95% CI 0.79 to 0.96), even after adjustment for multiple factors. **Survival without cerebral palsy was significantly more likely in the HFOV group than in the CV group** (OR 1.89, 95% CI 1.04 to 3.44)" 3. "Sun 2014 assessed neurodevelopmental outcomes at 18 months of corrected age in 145 infants of the HFOV group (84% of survivors) and in 143 infants of the CV group (86% of survivors). **Cerebral palsy occurred significantly less in the HFOV group** (3% versus 10% in the CV group, P = 0.03)"				NOT GRADED	"The age and methods of assessment varied between studies so the results were presented in the text and not included in a meta-analysis"

Table 6. Cerebral palsy (*Continued*)

Continuous distending pressure vs standard care for respiratory distress in preterm infants (Ho 2015)	Cerebral palsy at 9 to 15 years	(0/18)	(2/18)	RR 5.0 (0.26 to 97.37)	36 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection and attrition bias and high risk of performance bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Prophylactic methylxanthines (caffeine) vs placebo for endotracheal extubation in preterm infants (Henderson-Smart 2010)	Cerebral palsy at 18 to 21 months' corrected age	115 per 1000 (39/339)	62 per 1000 (37 to 106)	**RR 0.54 (0.32 to 0.92)**	644 (1 RCT)	MODERATE	Study limitations (-1): results based on 1 RCT subgroup from post hoc subgroup analyses (randomisation not stratified according to indication for inclusion)
Long vs short inspiratory times in neonates receiving mechanical ventilation (Kamlin 2003)	Cerebral palsy in survivors less than 33 weeks' gestation at birth at 18 months	133 per 1000 (12/90)	387 per 1000 (129 to 1153)	RR 2.9 (0.97 to 8.65)	177 (1 RCT)	VERY LOW	Study limitations: 1 RCT at high risk of performance bias; follow-up of subset (< 33 weeks only) Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: bronchopulmonary dysplasia							
Early (< 8 days) postnatal corticos-	Cerebral palsy at 11 months to 7 to 9 years	88 per 1000 (63/715)	128 per 1000 (93 to 174)	**RR 1.45 (1.06 to 1.98)**	1452 (12 RCTs)	MODERATE	Study limitations (-1): 4

Table 6. Cerebral palsy (*Continued*)

teroids vs placebo or no treatment for preventing chronic lung disease in preterm infants (Doyle 2014b)							RCTs at unclear risk of selection bias; 2 RCTs at high risk of performance and detection bias; 2 RCTs had 13%-53% follow-up overall
	Cerebral palsy in survivors assessed at 11 months to 7 to 9 years	134 per 1000 (63/470)	201 per 1000 (151 to 268)	**RR 1.50 (1.13 to 2.00)**	959 (12 RCTs)	MODERATE	Study limitations (-1): 4 RCTs at unclear risk of selection bias; 2 RCTs at high risk of performance and detection bias; 2 RCTs had 13%-53% follow-up overall
Moderately early (7-14 days) postnatal corticosteroids vs placebo or no treatment for preventing chronic lung disease in preterm infants (Halliday 2003)	Cerebral palsy at 12 months' corrected age up to 90 months	105 per 1000 (10/95)	108 per 1000 (49 to 236)	RR 1.03 (0.47 to 2.24)	204 (4 RCTs)	VERY LOW	Study limitations (-1) : 2 RCTs with 68%-70% follow-up; 1 RCT with unclear blinding of outcome assessment Imprecision (-2): wide CI crossing line of no effect; small sample sizes
	Cerebral palsy in survivors assessed at 12 months' corrected age up to 90 months	175 per 1000 (10/57)	146 per 1000 (68 to 305)	RR 0.83 (0.39 to 1.74)	130 (4 RCTs)	VERY LOW	Study limitations (-1) : 2 RCTs with 68%-70% follow-up; 1 RCT with unclear blinding of outcome as-

Table 6. Cerebral palsy (*Continued*)

							sessment Imprecision (-2): wide CI crossing line of no effect; small sample sizes
Late (> 7 days) postnatal corticosteroids vs placebo or no treatment for chronic lung disease in preterm infants (Doyle 2014)	Cerebral palsy at 1 to 3 years	127 per 1000 (55/433)	135 per 1000 (97 to 191)	RR 1.06 (0.76 to 1.50)	876 (14 RCTs)	LOW	Study limitations (-1): 5 RCTs unclear risk of selection bias; 5 RCTs with follow-up from 32% to 78% Imprecision (-1): wide CI crossing line of no effect
	Cerebral palsy at 1 to 3 years in survivors assessed	172 per 1000 (53/309)	180 per 1000 (129 to 252)	RR 1.05 (0.75 to 1.47)	631 (14 RCTs)	LOW	Study limitations (-1): 5 RCTs unclear risk of selection bias; 5 RCTs with follow-up between 32% and 78% Imprecision (-1): wide CI crossing line of no effect
	Cerebral palsy at latest reported age (from 1 year up to 17 years)	121 per 1000 (51/423)	135 per 1000 (95 to 193)	RR 1.12 (0.79 to 1.60)	855 (15 RCTs)	LOW	Study limitations (-1): 5 RCTs unclear risk of selection bias; 7 RCTs with follow-up between 32% and 78% Imprecision (-1): wide CI cross-

Table 6. Cerebral palsy (*Continued*)

							ing line of no effect
	Cerebral palsy at latest reported age in survivors assessed (from 1 year up to 17 years)	170 per 1000 (49/289)	190 per 1000 (134 to 268)	RR 1.12 (0.79 to 1.58)	591 (15 RCTs)	LOW	Study limitations (-1): 5 RCTs unclear risk of selection bias; 7 RCTs with follow-up between 32% and 78% Imprecision (-1): wide CI crossing line of no effect
Early inhaled corticosteroids vs placebo for preventing chronic lung disease in ventilated very low birthweight preterm neonates (Shah 2012)	Cerebral palsy (age not reported in review; *from trial manuscript:* 3 years)	107 per 1000 (3/28)	143 per 1000 (35 to 581)	RR 1.33 (0.33 to 5.42)	56 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection bias and detection bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: necrotising enterocolitis							
Arginine supplementation vs placebo for prevention of necrotising enterocolitis in preterm infants (Shah 2007)	Cerebral palsy at 36 months' post-menstrual age	55 per 1000 (4/73)	48 per 1000 (12 to 208)	RR 0.88 (0.21 to 3.80)	135 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: fungal infections							
Systemic antifungal agent vs placebo to prevent mortality	Cerebral palsy at 18 to 22 months	112 per 1000 (12/107)	108 per 1000 (50 to 228)	RR 0.96 (0.45 to 2.03)	219 (1 RCT)	LOW	Imprecision (-2): wide CI cross-

Table 6. Cerebral palsy (*Continued*)

and morbidity in very low birthweight infants (Cleminson 2015)	post term						ing line of no effect; 1 small RCT
Neonatal care: herpes simplex							
Aciclovir vs vidarabine for treatment of herpes simplex virus infection in neonates (Jones 2009)	Cerebral palsy in CNS HSV neonatal infection up to 3 years by HSV serotype: HSV-1	(0/4)	(0/5)	Not estimable	9 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with design limitations (inadequate allocation concealment) Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
	Cerebral palsy in CNS HSV neonatal infection up to 3 years by HSV serotype: HSV-2	625 per 1000 (5/8)	669 per 1000 (306 to 1456) (4/6)	RR 1.07 (0.49 to 2.33)	14 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with design limitations (inadequate allocation concealment) Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: jaundice							
Prophylactic phototherapy vs standard care for preventing jaundice in preterm or low birthweight infants	Cerebral palsy in all infants (birthweight < 2500 g) at 1 year or 18 months	**Medium risk population:** 84 per 1000 (18/394)	**Medium risk population:** 81 per 1000 (42 to 155)	RR 0.96 (0.50 to 1.85)	756 (2 RCTs)	MODERATE	Study limitations (-1): "There was no mention of blinding of the outcome assessors in two of the studies"

Table 6. Cerebral palsy (*Continued*)

(Okwundu 2012)							*(GRADED by review authors themselves)*
	Cerebral palsy in all infants (birthweight < 1000 g) at 18 months	250 per 1000 (4/16)	72 per 1000 (10 to 568)	RR 0.29 (0.04 to 2.27)	30 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with no blinding Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
	Cerebral palsy at 6 years	"Secondary reports emanating from Brown 1985 at six-year follow-up also showed that there was no significant difference in the rate of cerebral palsy between the phototherapy and control group"				NOT GRADED	
Neonatal care: hypoglycaemia							
Dextrose gel vs placebo for treatment of hypoglycaemia in newborn infants (Weston 2016)	Cerebral palsy at age 2 years	(0/93)	(2/90)	RR 5.16 (0.25 to 106.12)	183 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with 78% follow-up Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: parenteral feeding							
Glutamine supplementation vs placebo to prevent morbidity and mortality in preterm infants (Moe-Byrne 2016)	Cerebral palsy at 2 years	"van den Berg 2005 reported neurodevelopmental outcomes for infants aged two years post term. Outcomes assessed included... incidence of cerebral palsy... No significant differences between the glutamine and the control groups were reported for any of these individual outcomes"				NOT GRADED	
Neonatal care: other							

Table 6. Cerebral palsy (*Continued*)

Thyroid hormones vs placebo for preventing neurodevelopmental impairment in preterm infants (Osborn 2001)	Cerebral palsy at 5.7 years	120 per 1000 (9/75)	86 per 1000 (34 to 221)	RR 0.72 (0.28 to 1.84)	156 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Prophylactic thyroid hormones vs placebo for prevention of morbidity and mortality in preterm infants (Osborn 2007)							
Silicone earplugs vs no earplugs in the neonatal intensive care unit for preterm or very low birthweight infants (Almadhoob 2015)	Cerebral palsy at 18 to 22 months' corrected age	(0/7)	(1/7)	RR 3.0 (0.14 to 63.15)	14 (1 RCT)	VERY LOW	Study limitations (-1): "Because of funding restraints only the ELBW infants could be followed at 18 to 22 months corrected age" (14/24 survivors) Imprecision (-1): wide CI crossing line of no effect; 1 small RCT
Kangaroo mother care vs conventional neonatal care to reduce morbidity and mortality	Cerebral palsy at 12 months' corrected age	25 per 1000 (7/280)	16 per 1000 (5 to 51)	RR 0.65 (0.21 to 2.02)	588 (1 RCT)	LOW	Study limitation (-1): 1 RCT with unclear risk of selection bias; high risk of perfor-

Table 6. Cerebral palsy (*Continued*)

in low birthweight infants (Conde-Agudelo 2016)							mance and detection bias Imprecision (-1): wide CI crossing line of no effect
Early developmental intervention vs standard follow-up post hospital discharge to prevent motor and cognitive impairment in preterm infants (Spittle 2015)	Cerebral palsy at 18 months to 6 years	79 per 1000 (32/405)	65 per 1000 (41 to 100)	RR 0.82 (0.52 to 1.27)	985 (7 RCTs)	LOW	Study limitations (-1): 7 RCTs at unclear/high risk of performance bias; 2 RCTs at unclear/high risk of selection bias and unclear/high risk of attrition bias; 1 RCT at unclear risk of detection bias Imprecision (-1): wide CI crossing line of no effect

Abbreviations: BPD: bronchopulmonary dysplasia; CI: confidence interval; CNS: central nervous system; CV: conventional ventilation; ELBW: extremely low birthweight; g: grams; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; HFOV: high-frequency oscillatory ventilation; HSV: herpes simplex virus; NO: nitric oxide; OR: odds ratio; P: P value; qRCT: quasi-randomised controlled trial; RCT: randomised controlled trial; RR: risk ratio.

Table 7. Cerebral palsy: subgroup or sensitivity analyses

Intervention and comparison	Outcome	Subgroup or sensitivity analysis		Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Test for subgroup differences
Neonatal care: asphyxia								
Therapeutic hypothermia vs standard	Cerebral palsy in survivors assessed at 18	Method of cooling	Selective head cooling with mild hy-	338 per 1000 (49/145)	220 per 1000 (155 to 318)	**RR 0.65 (0.46 to 0.94)**	312 (3 RCTs)	Chi^2 = 0.01, df = 1 (P = 0.93), I^2 = 0.0%

Table 7. Cerebral palsy: subgroup or sensitivity analyses (*Continued*)

care for newborns with hypoxic-ischaemic encephalopathy (Jacobs 2013)	to 24 months		pothermia					
			Whole body cooling	360 per 1000 (94/261)	241 per 1000 (187 to 310)	**RR 0.67 (0. 52 to 0.86)**	569 (4 RCTs)	
Neonatal care: haemorrhage: periventricular/intraventricular								
Ethamsylate vs placebo for prevention of morbidity and mortality in preterm or very low birthweight infants (Hunt 2010)	Cerebral palsy in surviving children available for follow-up at 3 years up to 3.5 to 4.2 years	Infants < 31 completed weeks or < 1500 g		84 per 1000 (14/167)	69 per 1000 (32 to 147)	RR 0.82 (0. 38 to 1.75)	328 (2 RCTs)	Not applicable
Neonatal care: fluid therapy								
Volume vs no treatment for prevention of morbidity and mortality in very preterm infants (Osborn 2004)	Cerebral palsy in survivors at 2 years	Type of volume used	Fresh frozen plasma	132 per 1000 (27/205)	104 per 1000 (61 to 177)	RR 0.79 (0. 46 to 1.34)	408 (1 RCT)	Not performed *(as conducted as separate comparison)*
			Gelatin	132 per 1000 (27/205)	97 per 1000 (53 to 169)	RR 0.74 (0. 42 to 1.28)	401 (1 RCT)	
		Timing of treatment	Early treatment (< 24 hours age)	132 per 1000 (27/205)	100 per 1000 (63 to 158)	RR 0.76 (0. 48 to 1.20)	604 (1 RCT)	Not applicable
		Types of infant enrolled	Unselected preterm infants (not selected on the basis of cardiovascular compromise)					

Table 7. Cerebral palsy: subgroup or sensitivity analyses (*Continued*)

		Methodological quality	Complete follow-up for neurodevelopmental outcomes					
Neonatal care: respiratory distress syndrome								
Animal-derived surfactant extract vs no treatment for treatment of respiratory distress syndrome (Seger 2009)	Cerebral palsy at 1 and 2 years' corrected age	Surfactant product	Porcine surfactant extract	207 per 1000 (6/29)	182 per 1000 (70 to 470)	RR 0.88 (0.34 to 2.27)	73 (1 RCT)	Not applicable
Prophylactic protein-free synthetic surfactant vs placebo for preventing morbidity and mortality in preterm infants (Soll 2010)	Cerebral palsy at 1 or 2 years	Surfactant product	Exosurf Neonatal	158 per 1000 (44/279)	144 per 1000 (98 to 211)	RR 0.91 (0.62 to 1.34)	591 (3 RCTs)	Not applied in review
			DPPC/HDL	122 per 1000 (5/41)	132 per 1000 (41 to 420)	RR 1.08 (0.34 to 3.44)	79 (1 RCT)	
Neonatal care: mechanical ventilation								
Continuous distending pressure vs standard care for respiratory distress in preterm infants (Ho 2015)	Cerebral palsy at 9 to 15 years	Type of continuous distending pressure	Continuous negative pressure	(0/18)	(2/18)	RR 5.0 (0.26 to 97.37)	36 (1 RCT)	Not applicable
Neonatal care: bronchopulmonary dysplasia								

Table 7. Cerebral palsy: subgroup or sensitivity analyses (*Continued*)

Early (< 8 days) postnatal corticosteroids vs placebo or no treatment for preventing chronic lung disease	Cerebral palsy at 11 months to 7 to 9 years	Type of corticosteroid used	Dexamethasone	89 per 1000 (40/449)	156 per 1000 (107 to 227)	**RR 1.75 (1.20 to 2.55)**	921 (7 RCTs)	Chi² = 2.96, df = 1 (P = 0.09), I² = 66%
			Hydrocortisone	86 per 1000 (23/266)	84 per 1000 (48 to 146)	RR 0.97 (0.55 to 1.69)	531 (5 RCTs)	
	Cerebral palsy in survivors assessed at 11 months to 7 to 9 years	Type of corticosteroid used	Dexamethasone	139 per 1000 (40/288)	253 per 100 (179 to 357)	**RR 1.82 (1.29 to 2.57)**	586 (7 RCTs)	**Chi² = 3.99, df = 1 (P = 0.05), I² = 75%**
			Hydrocortisone	126 per 1000 (23/182)	120 per 1000 (71 to 206)	RR 0.95 (0.56 to 1.63)	373 (5 RCTs)	
Neonatal care: other								
Prophylactic thyroid hormones vs placebo for prevention of morbidity and mortality in preterm infants (Osborn 2007)	Cerebral palsy at 5.7 years	Dosing strategy	T4 8 mcg/kg/d, day 1 to 42	120 per 1000 (9/75)	86 per 1000 (34 to 221)	RR 0.72 (0.28 to 1.84)	156 (1 RCT)	Not applicable
		Timing	Commenced < 48 hours					
		Methodological quality	Studies with adequate methods					
Early developmental intervention vs standard follow-up post hospital discharge to prevent motor and cognitive impairment in preterm infants (Spittle 2015)	Cerebral palsy at 18 months to 6 years	Commencement of intervention	Inpatient	79 per 1000 (12/152)	74 per 1000 (36 to 152)	RR 0.94 (0.46 to 1.93)	354 (3 RCTs)	Not applied in review
			Post hospital discharge	79 per 1000 (20/253)	59 per 1000 (34 to 105)	RR 0.75 (0.43 to 1.33)	631 (4 RCTs)	
		Focus of intervention	Parent-infant relationship and Infant development	77 per 1000 (21/272)	52 per 1000 (29 to 90)	RR 0.67 (0.38 to 1.17)	716 (4 RCTs)	Not applied in review
			Infant development	83 per 1000 (11/133)	97 per 1000 (46 to 203)	RR 1.17 (0.56 to 2.46)	269 (3 RCTs)	
		Quality of studies	Higher-quality studies	82 per 1000 (25/304)	72 per 1000 (44 to 116)	RR 0.87 (0.53 to 1.41)	776 (5 RCTs)	Not applied in review

Table 7. Cerebral palsy: subgroup or sensitivity analyses (*Continued*)

			Lower-quality studies	69 per 1000 (7/101)	43 per 1000 (14 to 130)	RR 0.62 (0.20 to 1.87)	209 (2 RCTs)	

Abbreviations: CI: confidence interval; DPPC/HDL: dipalmitoylphosphatidylcholine/high-density lipoprotein; g: grams; P: P value; RCT: randomised controlled trial; RR: risk ratio; T4: thyroxine.

Table 8. Cerebral palsy or death

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Neonatal care: bronchopulmonary dysplasia							
Early (< 8 days) postnatal corticosteroids vs placebo or no treatment for preventing chronic lung disease in preterm infants (Doyle 2014b)	Cerebral palsy or death at 11 months to 7 to 9 years	352 per 1000 (252/715)	384 per 1000 (334 to 441)	RR 1.09 (0.95 to 1.25)	1452 (12 RCTs)	MODERATE	Study limitations (-1): 4 RCTs at unclear risk of selection bias; 2 RCTs at high risk of performance and detection bias; 2 RCTs had 13% to 53% follow-up overall
Moderately early (7-14 days) postnatal corticosteroids vs placebo or no treatment for preventing chronic lung disease in preterm infants (Halliday 2003)	Cerebral palsy or death at 12 months' corrected age up to 90 months	316 per 1000 (30/95)	262 per 1000 (174 to 388)	RR 0.83 (0.55 to 1.23)	204 (4 RCTs)	VERY LOW	Study limitations (-1) : 2 RCTs with 68% to 70% follow-up; 1 RCT with unclear blinding of outcome assessment Imprecision (-2): wide CI crossing line of no effect; small sample sizes
Late (> 7 days) postnatal corticosteroids vs placebo or no	Cerebral palsy or death at 1 to 3 years	328 per 1000 (142/433)	302 per 1000 (249 to 367)	RR 0.92 (0.76 to 1.12)	876 (14 RCTs)	LOW	Study limitations (-1): 5 RCTs unclear risk of selec-

Table 8. Cerebral palsy or death (*Continued*)

treatment for chronic lung disease in preterm infants (Doyle 2014)							tion bias; 5 RCTs with follow-up between 32% and 78% Imprecision (-1): wide CI crossing line of no effect
	Cerebral palsy or death at latest reported age (from 1 year up to 17 years)	312 per 1000 (132/423)	296 per 1000 (240 to 362)	RR 0.95 (0.77 to 1.16)	855 (15 RCTs)	LOW	Study limitations (-1): 5 RCTs unclear risk of selection bias; 7 RCTs with follow-up between 32% and 78% Imprecision (-1): wide CI crossing line of no effect
Neonatal care: other							
Thyroid hormones vs placebo for preventing neurodevelopmental impairment in preterm infants (Osborn 2001)	Cerebral palsy or death at 5.7 years	300 per 1000 (30/100)	210 per 1000 (129 to 342)	RR 0.70 (0.43 to 1.14)	200 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Prophylactic thyroid hormones vs placebo for prevention of morbidity and mortality in preterm infants (Osborn 2007)							

Abbreviations: CI: confidence interval; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; RCT: randomised controlled trial; RR: risk ratio.

Table 9. Severity of cerebral palsy

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Neonatal care: asphyxia							
Allopurinol vs placebo or no drug for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy (Chaudhari 2012)	Severe quadriplegia in surviving infants (18 months and 4 to 8 years)	343 per 1000 (12/35)	202 per 1000 (96 to 435)	RR 0.59 (0.28 to 1.27)	73 (3 RCTs)	VERY LOW	Study limitations (-1): 1 RCT with unclear risk of selection bias and high risk of performance/ detection bias Imprecision (-2): wide CI crossing line of no effect; small sample sizes with few events
Neonatal care: respiratory distress syndrome							
Synthetic surfactant vs placebo for respiratory distress syndrome in preterm infants (Soll 2000)	Moderate to severe cerebral palsy in survivors examined at 1 year *(in 4 of the 5 RCTs)*	55 per 1000 (42/767)	41 per 1000 (26 to 64)	RR 0.75 (0.48 to 1.16)	1557 (5 RCTs)	MODERATE	Imprecision (-1): wide CI crossing the line of no effect
Prophylactic protein-free synthetic surfactant vs placebo for preventing morbidity and mortality in preterm infants (Soll	Moderate/ severe cerebral palsy at 1 or 2 years	75 per 1000 (24/320)	69 per 1000 (40 to 119)	RR 0.92 (0.53 to 1.59)	670 (4 RCTs)	LOW	Study limitations (-1): "Somewhat fewer infants who received surfactant failed to return for follow-up evalu-

Table 9. Severity of cerebral palsy (*Continued*)

2010)							ation (typical relative risk 0. 63, 95% CI 0. 48, 0.82; typical risk difference -0.10, 95% CI -0.15, -0.04)" Imprecision (-1): wide CI crossing the line of no effect

Abbreviations: CI: confidence interval; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; RCT: randomised controlled trial; RR: risk ratio.

Table 10. Other composite outcomes that include cerebral palsy as a component

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Neonatal care: asphyxia							
Allopurinol vs placebo or no drug for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy (Chaudhari 2012)	Death or severe neurodevelopmental disability in survivors (18 months and 4 to 8 years) (defined as any 1 or combination of the following: non-ambulant cerebral palsy, severe developmental delay assessed via validated tools, auditory and visual impairment)	611 per 1000 (33/54)	477 per 1000 (342 to 660)	RR 0.78 (0.56 to 1.08)	110 (3 RCTs)	VERY LOW	Study limitations (-1): 1 RCT with unclear risk of selection bias and high risk of performance/ detection bias Imprecision (-2): wide CI crossing line of no effect; small sample sizes

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

Therapeutic hypothermia vs standard care for newborns with hypoxic-ischaemic encephalopathy (Jacobs 2013)	Death or major disability in survivors assessed at 18 to 24 months (defined as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification)	614 per 1000 (409/666)	461 per 1000 (418 to 510)	**RR 0.75 (0. 68 to 0.83)**	1344 (8 RCTs)	HIGH	Not downgraded
	Major neurodevelopmental disability at 18 to 24 months (defined as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineu-	249 per 1000 (166/666)	192 per 1000 (157 to 234)	**RR 0.77 (0. 63 to 0.94)**	1344 (8 RCTs)	HIGH	Not downgraded

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	ral deafness requiring amplification)						
	Major neurodevelopmental disability in survivors assessed at 18 to 24 months (defined as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification)	393 per 1000 (166/422)	264 per 1000 (216 to 315)	**RR 0.67 (0.55 to 0.80)**	917 (8 RCTs)	HIGH	Not downgraded
	Death or moderate to severe disability at 6 to 7 years (defined as IQ ≥ 2 SD below the mean, a GMF level of 3 or greater, bilateral deafness (with or without amplification), bilateral blindness, or refractory epilepsy)	645 per 1000 (60/93)	523 per 1000 (413 to 671)	RR 0.81 (0.64 to 1.04)	190 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	Moderate-to-severe disability at 6 to 7 years (defined as IQ ≥ 2 SD below the mean, a GMF level of 3 or greater, bilateral deafness (with or without amplification), bilateral blindness or refractory epilepsy)	380 per 1000 (19/50)	350 per 1000 (217 to 562)	RR 0.92 (0.57 to 1.48)	119 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Barbiturates (phenobarbital) vs conventional therapy for prevention of morbidity and mortality following perinatal asphyxia (Young 2016)	Death or major neurodevelopmental disability follow-up: > 12 months (3 years) (defined as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification)	813 per 1000 (13/16)	268 per 1000 (114 to 634)	**RR 0.33 (0.14 to 0.78)**	31 (1 RCT)	VERY LOW	Study limitations (-1): unblinded study; concern regarding performance bias, detection bias, and incomplete follow-up Imprecision (-2): 95% CIs were wide and imprecise *(graded by review authors themselves)*
	Major neurodevelopmental disability follow-	563 per 1000 (9/16)	135 per 1000 (34 to 518)	**RR 0.24 (0.06 to 0.92)**	31 (1 RCT)	VERY LOW	Study limitations (-1): unblinded study;

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	up: > 12 months (3 years) (defined as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification)						concern regarding performance bias, detection bias, and incomplete follow-up Imprecision (-2): 95% CIs were wide and imprecise *(graded by review authors themselves)*
Neonatal care: haemorrhage: periventricular/intraventricular							
Ethamsylate vs placebo for prevention of morbidity and mortality in preterm or very low birthweight infants (Hunt 2010)	Neurodevelopmental disability at 2 years of age in surviving children available for follow-up (defined as cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on any standard test of development, or blindness (VA < 6/60), or deafness (any hearing impairment	170 per 1000 (46/270)	135 per 1000 (90 to 199)	RR 0.79 (0.53 to 1.17)	532 (3 RCTs)	MODERATE	Imprecision (-1): wide CI crossing line of no effect

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	requiring amplification) at any time after 2 years' corrected age)						
	Death or any disability by 2 years of age in children with known outcome at any point in time (not defined in review)	338 per 1000 (233/690)	324 per 1000 (277 to 375)	RR 0.96 (0.82 to 1.11)	1334 (7 RCTs)	LOW	Study limitations (-1): 4 RCTs at unclear risk of selection bias; 3 RCTs at unclear risk of bias due to lack of blinding Imprecision (-1): wide CIs crossing line of no effect
Phenobarbital vs no treatment for prevention of intraventricular haemorrhage in preterm infants (Smit 2013)	Severe neurodevelopmental impairment at 27 months (defined as clinical cerebral palsy or DQ below the range that can be measured)	74 per 1000 (4/54)	107 per 1000 (30 to 373)	RR 1.44 (0.41 to 5.04)	101 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at high risk of performance bias) and unclear risk of other bias Imprecision (-2): wide CI crossing line of no effect; small sample size, low event rate
	Mild neurodevelopmental impairment at 27 months (defined as DQ < 80 or motor abnormality on examination)	111 per 1000 (6/54)	63 per 1000 (17 to 241)	RR 0.57 (0.15 to, 2.17)	101 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at high risk of performance bias) and unclear risk of other bias Imprecision (-2): wide CI crossing line

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

							of no effect; small sample size, low event rate
Neonatal care: hypotension							
Dobutamine vs dopamine in preterm infants with low superior vena cava flow (Osborn 2007b)	Disability at 3 years in survivors (defined as GMDS quotient ≤ 70, cerebral palsy, blind (VA < 6/60) or deaf (hearing aids))	714 per 1000 (5/7)	71 per 1000 (7 to 1114)	RR 0.10 (0.01 to 1.56)	13 (1 RCT)	VERY LOW	Study limitations (-1): 5/18 surviving infants were not assessed at 3 years Imprecision (-2): wide CI crossing line of no effect; 1 RCT with very small sample size
	Death or disability at 3 years (defined as GMDS quotient ≤ 70, cerebral palsy, blind (VA < 6/60) or deaf (hearing aids))	882 per 1000 (15/17)	697 per 1000 (503 to 979)	RR 0.79 (0.57 to 1.11)	37 (1 RCT)	VERY LOW	Study limitations (-1): 5/18 surviving infants were not assessed at 3 years Imprecision (-2): wide CI crossing line of no effect; 1 RCT with very small sample size
	Death or disability at latest follow-up (1 to 3 years) (defined as GMDS quotient ≤ 70, cerebral palsy, blind (VA < 6/60) or deaf (hearing aids))	750 per 1000 (15/20)	713 per 1000 (495 to 1035)	RR 0.95 (0.66 to 1.38)	41 (1 RCT)	VERY LOW	Study limitations (-1): 5/18 surviving infants were not assessed at 3 years Imprecision (-2): wide CI crossing line of no effect;

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

							1 RCT with very small sample size
Neonatal care: fluid therapy							
Volume vs no treatment for prevention of morbidity and mortality in very preterm infants (Osborn 2004)	Severe neurodevelopmental disability in survivors at 2 years (defined as blind, dead, unable to walk, DQ > 3 SD below the mean, or another severe disability)	141 per 1000 (29/205)	113 per 1000 (74 to 174)	RR 0.80 (0.52 to 1.23)	604 (1 RCT)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Gelatin vs fresh frozen plasma for prevention of morbidity and mortality in very preterm infants (Osborn 2004)		113 per 1000 (23/203)	112 per 1000 (65 to 195)	RR 0.99 (0.57 to 1.72)	399 (1 RCT)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Volume vs no treatment for prevention of morbidity and mortality in very preterm infants (Osborn 2004)	Death or severe neurodevelopmental disability in survivors at 2 years (defined as blind, dead, unable to walk, DQ > 3 SD below the mean, or another severe disability)	318 per 1000 (82/258)	318 per 1000 (254 to 394)	RR 1.00 (0.80 to 1.24)	776 (1 RCT)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Gelatin vs fresh frozen plasma for prevention of morbidity and mortality in very preterm in-		300 per 1000 (77/257)	333 per 1000 (258 to 428)	RR 1.11 (0.86 to 1.43)	518 (1 RCT)	MODERATE	Imprecision (-1): wide CI cross-

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

fants (Osborn 2004)							
Neonatal care: patent ductus arteriosus							
Prophylactic indomethacin vs placebo for preventing mortality and morbidity in preterm infants (Fowlie 2010)	Death or severe neurodevelopmental disability at 18 to 36 months (defined as any 1 or a combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment)	400 per 1000 (299/748)	407 per 1000 (360 to 460)	RR 1.02 (0.90 to 1.15)	1491 (3 RCTs)	MODERATE	Study limitations (-1): 2 RCTs at unclear risk of attrition bias (> 25% loss to follow-up)
Neonatal care: blood disorders							
Erythropoietin vs placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants (Ohlsson 2014)	Any neurodevelopmental impairment at 18 to 22 months' corrected age (in children examined) (not defined in review; *definition from trial manuscript:* 1 of the following: MDI < 70, PDI < 70, moderate or severe cerebral palsy, blindness, or deafness)	451 per 1000 (23/51)	437 per 1000 (280 to 681)	RR 0.97 (0.62 to 1.51)	99 (1 RCT)	VERY LOW	Study limitations: 1 RCT at unclear risk of selection bias and high risk of attrition bias (-73% follow-up) Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Transfusion at a restrictive vs a liberal haemoglo-	Any neurosensory impairment at 18	220 per 1000 (37/168)	289 per 1000 (198 to 418)	RR 1.31 (0.90 to 1.90)	328 (1 RCT)	LOW	Study limitations (-1): 1 RCT at high

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

bin threshold for preventing morbidity and mortality in very low birthweight infants (Whyte 2011)	to 21 months' follow-up among survivors (defined as cognitive delay (MDI < 70), cerebral palsy, severe visual impairment, severe hearing impairment)						risk of performance bias and unclear risk of reporting bias Imprecision (-1): wide CI crossing line of no effect
	Death or severe morbidity at 18 to 21 months' follow-up (defined as cognitive delay (MDI < 70), cerebral palsy, severe visual impairment, severe hearing impairment)	385 per 1000 (82/213)	450 per 1000 (362 to 566)	RR 1.17 (0.94 to 1.47)	421 (1 RCT)	LOW	Study limitations (-1): 1 RCT at high risk of performance bias and unclear risk of reporting bias Imprecision (-1): wide CI crossing line of no effect
	Death or severe morbidity at 18 to 21 months' follow-up (defined as cognitive delay (MDI < 85), cerebral palsy, severe visual impairment, severe hearing impairment)	498 per 1000 (106/213)	602 per 1000 (503 to 717)	**RR 1.21 (1.01 to 1.44)**	421 (1 RCT)	MODERATE	Study limitations (-1): 1 RCT at high risk of performance bias and unclear risk of reporting bias
Neonatal care: nitric oxide							
Inhaled NO vs placebo for respiratory	Neurodevelopmental disability at 18	455 per 1000 (50/110)	477 per 1000 (355 to 636)	RR 1.05 (0.78 to 1.40)	208 (2 RCTs)	LOW	Imprecision (-2): wide CI

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

failure in preterm infants (entry before 3 days based on oxygenation) (Barrington 2010)	to 22 months (defined as moderate or severe cerebral palsy, blind, deaf, BSID MDI < 70, or PDI < 70)						crossing line of no effect; small sample sizes
Inhaled NO vs placebo or no treatment for respiratory failure in preterm infants (entry after 3 days based on BPD risk) (Barrington 2010)	Neurodevelopmental disability at 2 years' corrected age or 30 months (defined as 1 RCT: moderate or severe cerebral palsy, blind, deaf, BSID MDI < 70, or PDI < 70; 1 RCT: cerebral palsy, BSID MDI or PDI < 71, or sensorineural impairment)	480 per 1000 (119/248)	432 per 1000 (355 to 523)	RR 0.90 (0.74 to 1.09)	498 (2 RCTs)	LOW	Study limitations (-1): 1 RCT with no blinding of intervention or outcome measurement Imprecision (-1): wide CI crossing line of no effect; small sample sizes
Inhaled NO vs placebo for respiratory failure in preterm infants (studies of routine use in intubated preterm infants) (Barrington 2010)	Neurodevelopmental disability at 1 or 2 years' corrected age (defined as 1 RCT: cerebral palsy, blind, severe hearing loss, BSID MDI < 70, or PDI < 70; 1 RCT: cerebral palsy, bilateral blindness, bilateral hearing loss, or BSID score > 2 SD below	364 per 100 (104/286)	327 per 1000 (262 to 411)	RR 0.90 (0.72 to 1.13)	593 (2 RCT)	VERY LOW	Study limitations (-1) : 2 RCTs with 74% to 82% follow-up Imprecision (-1): wide CI crossing line of no effect Inconsistency (-1): substantial heterogeneity I^2 = 83%

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	the mean)						
Inhaled nitric oxide vs control for respiratory failure in infants born at or near term (Finer 2006)	Neurodevelopmental disability among survivors at 13 or 18 to 24 months (defined as 1 RCT: cerebral palsy, BSID MDI or PDI < 2 SD below the mean, blind or hearing impaired; or 1 RCT: cerebral palsy, > 2 mild (mild neurological abnormalities; mild reductions in BSID scores 1 to 2 SD below the mean), or at least 1 severe impairment)	265 per 1000 (48/181)	257 per 1000 (175 to 382)	RR 0.97 (0.66 to 1.44)	301 (2 RCTs)	LOW	Study limitations (-1) : 1 RCT masking of allocation, masking of outcomes, and completeness of follow-up 'can't tell' Imprecision (-1): wide CI crossing line of no effect
Neonatal care: apnoea							
Caffeine vs placebo for apnoea in preterm infants (Henderson-Smart 2010b)	Death or major disability at 18 to 21 months' corrected age (defined as cognitive delay, cerebral palsy, deafness, or blindness)	417 per 1000 (153/367)	354 per 1000 (296 to 421)	RR 0.85 (0.71 to 1.01)	767 (1 RCT)	LOW	Study limitations (-1): results based on 1 RCT subgroup from post hoc subgroup analyses (randomisation not stratified according to indication for inclusion) Imprecision (-1): wide CI crossing line of no effect

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

Caffeine vs placebo for prevention of apnoea in preterm infants (Henderson-Smart 2010c)	Death or major disability at 18 to 21 months' corrected age (not defined in review; *definition from trial manuscript*: cerebral palsy, cognitive delay, severe hearing loss, or bilateral blindness)	431 per 1000 (88/204)	431 per 1000 (345 to 535)	RR 1.00 (0.80 to 1.24)	423 (1 RCT)	LOW	Study limitations (-1): results based on 1 RCT subgroup from post hoc subgroup analyses (randomisation not stratified according to indication for inclusion) Imprecision (-1): wide CI crossing line of no effect
Neonatal care: respiratory distress syndrome							
Inositol supplementation (repeat doses) vs placebo in preterm infants at risk for or having respiratory distress syndrome (Howlett 2015)	Major neural developmental impairment at 1 year corrected age (defined as sensory deficit, cerebral palsy, developmental delay, severe hypotonia)	178 per 1000 (13/73)	94 per 1000 (43 to 207)	RR 0.53 (0.24 to 1.16)	169 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection, performance, detection, and reporting bias, and at high risk of other bias Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Animal-derived surfactant extract vs no treatment for treatment of respiratory distress syndrome (Seger 2009)	Major developmental disability in survivors at 1 and 2 years' corrected age (defined as severe forms of cerebral palsy, blindness,	34 per 1000 (1/29)	114 per 1000 (5 to 923)	RR 3.30 (0.14 to 26.78)	73 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with no blinding of intervention; and blinding of outcome measurement not

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	deafness requiring hearing aids, or GMDS DQ < 70)						reported Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: mechanical ventilation							
Continuous distending pressure vs standard care for respiratory distress in preterm infants (Ho 2015)	Death or severe disability at 9 to 15 years (not defined in review; severe disability as defined below)	158 per 1000 (3/19)	210 per 1000 (54 to 816)	RR 1.33 (0.34 to 5.17)	38 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection and attrition bias and high risk of performance bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
	Severe disability at 9 to 15 years (not defined in review; *definition from trial manuscript:* unable to undertake activity without aids or assistance most of the time, or completely dependent on carer: WASI ≤ 69; GMF level 4 to 5, arms: needs assistance to feed and dress; VA <	158 per 1000 (3/19)	167 per 1000 (38 to 722)	RR 1.06 (0.24 to 4.57)	37 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection and attrition bias and high risk of performance bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	6/60, gross movement/ light and dark only or worse; hearing loss not corrected with age; parent and teacher overall difficulties (Q26), "Yes" and impact score 6 to 10 parent and 3 to 6 teacher; or other condition needs supervision/ aid constantly - includes continuous home oxygen; communication severely limited)						
	Any disability at 9 to 15 years (not defined in review; *definition from trial manuscript:* mild: some loss of function but able to function independently; moderate: aids or assistance needed for some tasks. Moderate difficulty in doing some activities; severe: unable to undertake activity with-	632 per 1000 (12/19)	392 per 1000 (196 to 764)	RR 0.62 (0.31 to 1.21)	37 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection and attrition bias and high risk of performance bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	out aids or assistance most of the time, or completely dependent on carer; includes neuromotor components includes GMF levels 1 to 5)						
Prophylactic methylxanthines (caffeine) vs placebo for endotracheal extubation in preterm infants (Henderson-Smart 2010)	Death or major disability at 18 to 21 months' corrected age (defined as cognitive delay, cerebral palsy, deafness, or blindness)	525 per 1000 (189/360)	446 per 1000 (383 to 520)	**RR 0.85 (0.73 to 0.99)**	676 (1 RCT)	MODERATE	Study limitations (-1): results based on 1 RCT subgroup from post hoc subgroup analyses (randomisation not stratified according to indication for inclusion)
Volume-targeted vs pressure-limited ventilation in the neonate (Wheeler 2010)	Severe disability (any definition) at 6 to 18 months and 22 months (definitions not reported in review; *definitions from trial manuscripts*: 1 RCT: abnormal neurological evaluation (gross or fine motor delay) or BSID MDI < 70; 1 RCT: cerebral palsy severe enough to hamper gross motor activity, deafness need-	176 per 1000 (18/102)	152 per 1000 (83 to 281)	RR 0.86 (0.47 to 1.59)	209 (2 RCTs)	LOW	Indirectness (-1): post hoc analysis including 2 RCTs with varied definitions Imprecision (-1): wide CI crossing line of no effect *(post hoc analysis in review)*

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	ing hearing aids, registered blind or partially sighted)						
	Severe disability (any definition) at 22 months or death (definition not reported in review; *definition from trial manuscript*: cerebral palsy severe enough to hamper gross motor activity, deafness needing hearing aids, registered blind or partially sighted)	327 per 1000 (17/52)	177 per 1000 (88 to 347)	RR 0.54 (0.27 to 1.06)	109 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small RCT *(post hoc analysis in review)*
Neonatal care: bronchopulmonary dysplasia							
Early (< 8 days) postnatal corticosteroids vs placebo or no treatment for preventing chronic lung disease in preterm infants (Doyle 2014b)	Major neurosensory disability at 18 to 22 months to 53 months (variable criteria reported in review: 1 RCT: non-ambulant cerebral palsy, global retardation (not specified), blindness, or deafness; 1 RCT: moderate or severe cerebral palsy,	199 per 1000 (121/607)	231 per 1000 (187 to 285)	RR 1.16 (0.94 to 1.43)	1233 (7 RCTs)	LOW	Study limitations (-1): 2 RCTs at unclear risk of selection bias; 1 RCT at high risk of performance and detection bias Imprecision (-1): wide CI crossing line of no effect

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	blindness, deafness, or BSID MDI or PDI < -2 SD; 1 RCT: cerebral palsy, BSID MDI or PDI < 71, blindness or deafness; 1 RCT: severe motor dysfunction (child non-ambulant), or BSID MDI or PDI <-2 SD; 2 RCTs: cerebral palsy, blindness, deafness, or developmental delay (BSID MDI < 70 (< -2 SD) or GMDS DQ < 70) ; 1 RCT: cerebral palsy, functional blindness, functional deafness, developmental delay (BSID MDI < 70 (<-2 SD)), or motor delay (BSID PDI < 70 (<-2 SD))						
	Major neurosensory disability in survivors examined at 18 to 22 months to 53 months (variable crite-	307 per 1000 (121/394)	350 per 1000 (289 to 424)	RR 1.14 (0.94 to 1.38)	799 (7 RCTs)	LOW	Study limitations (-1): 2 RCTs at unclear risk of selection bias; 1 RCT at high risk of perfor-

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	ria as above)						mance and detection bias Imprecision (-1): wide CI crossing line of no effect
	Death or major neurosensory disability at 18 to 22 months to 53 months (variable criteria as above)	466 per 1000 (283/607)	490 per 1000 (434 to 545)	RR 1.05 (0.93 to 1.17)	1233 (7 RCTs)	MODERATE	Study limitations (-1): 2 RCTs at unclear risk of selection bias; 1 RCT at high risk of performance and detection bias
Moderately early (7-14 days) postnatal corticosteroids vs placebo for preventing chronic lung disease in preterm infants (Halliday 2003)	Major neurosensory disability at 15 months' corrected age up to 90 months (variable criteria reported in review: 1 RCT: any of cerebral palsy or a BSID MDI or PDI < - 1 SD; 1 RCT: not specified)	98 per 1000 (4/41)	123 per 1000 (44 to 340)	RR 1.26 (0.45 to 3.49)	96 (2 RCTs)	VERY LOW	Study limitations (-1) : 1 RCT with 70% follow-up and unclear blinding of outcome assessment Imprecision (-2): wide CI crossing line of no effect; small sample sizes
	Major neurosensory disability in survivors assessed at 15 months' corrected age up to 90 months (variable criteria reported in review as above)	174 per 1000 (4/23)	155 per 1000 (66 to 365)	RR 0.89 (0.38 to 2.10)	56 (2 RCTs)	VERY LOW	Study limitations (-1) : 1 RCT with 70% follow-up and unclear blinding of outcome assessment Imprecision (-2): wide CI crossing line of no effect; small sample sizes

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	Death or major neurosensory disability at 15 months' corrected age up to 90 months (variable criteria reported in review as above)	366 per 1000 (15/41)	373 per 1000 (241 to 571)	RR 1.02 (0.66 to 1.56)	96 (2 RCTs)	VERY LOW	Study limitations (-1) : 1 RCT with 70% follow-up and unclear blinding of outcome assessment Imprecision (-2): wide CI crossing line of no effect; small sample sizes
Late (> 7 days) postnatal corticosteroids vs placebo or no treatment for chronic lung disease in preterm infants (Doyle 2014)	Major neurosensory disability at 1 year corrected age up to 11 years (variable criteria reported in review: 1 RCT: non-ambulant cerebral palsy, < 50% of age level on the Minnesota CDI, or predicted special schooling for sensory or other impairment; 1 RCT: abnormal neurological examination (i.e. cerebral palsy), cognitive delay (IQ < 71) or not in a regular classroom; 1 RCT: severe disability - bilateral	169 per 1000 (54/320)	197 per 1000 (143 to 270)	RR 1.17 (0.85 to 1.60)	655 (8 RCTs)	LOW	Study limitations (-1) : 3 RCTs with unclear risk of selection bias; 3 RCTs with follow-up rates 60% to 78% Imprecision (-1): wide CI crossing line of no effect

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	blindness, cerebral palsy with the child unlikely ever to walk or BSID MDI < 55 (< -3 SD)) or moderate disability - deafness, cerebral palsy in children not walking at 2 years but expected to walk, or MDI from 55 to < 70 (-3 SD to < -2 SD); 1 RCT: cerebral palsy, blindness, deafness requiring hearing aids or worse, or developmental delay (defined as BSID MDI < 70); 1 RCT: more than mild cerebral palsy, blindness, deafness, or needing extra help with schooling; 1 RCT: blindness, cerebral palsy or a BSID MDI < 70 OR cerebral palsy or mental retardation (IQ < 70 on either the DAS or the WISC-III						

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	and a VABS composite score < 70) ; 1 RCT: not specified; 1 RCT moderate or severe cerebral palsy, bilateral blindness, deafness or an MDI < 2 SD						
	Major neurosensory disability in survivors assessed at 1 year corrected age up to 11 years (variable criteria reported in review as above)	231 per 1000 (54/234)	254 per 1000 (187 to 346)	RR 1.10 (0.81 to 1.50)	480 (8 RCTs)	LOW	Study limitations (-1) : 3 RCTs with unclear risk of selection bias; 3 RCTs with follow-up rates 60% to 78% Imprecision (-1): wide CI crossing line of no effect
	Death or major neurosensory disability at 1 year corrected age up to 11 years (variable criteria reported in review as above)	375 per 1000 (120/320)	390 per 1000 (323 to 473)	RR 1.04 (0.86 to 1.26)	655 (8 RCTs)	LOW	Study limitations (-1) : 3 RCTs with unclear risk of selection bias; 3 RCTs with follow-up rates 60% to 78% Imprecision (-1): wide CI crossing line of no effect
Supplemental vitamin A vs a sham injection to prevent mortality and short-	Neurodevelopmental impairment at 18 to 24 months (defined as BSID-	481 per 1000 (128/266)	428 per 1000 (356 to 520)	RR 0.89 (0.74 to 1.08)	538 (1 RCT)	LOW	Imprecision (-2): "Concerning imprecision: does not met the optimal informa-

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

and long-term morbidity in very low birthweight infants (Darlow 2016)	II MDI < 70, PDI < 70, any cerebral palsy, blind in both eyes, or bilateral hearing aids)						tion size criteria" *(graded by review authors themselves)*
	Death or neurodevelopmental impairment at 18 to 24 months (defined as BSID-II MDI < 70, PDI < 70, any cerebral palsy, blind in both eyes, or bilateral hearing aids)	596 per 1000 (204/342)	549 per 1000 (483 to 626)	RR 0.92 (0.81 to 1.05)	687 (1 RCT)	MODERATE	Imprecision (-1): wide CIs crossing line of no effect
Neonatal care: necrotising enterocolitis							
Probiotics vs control (distilled water) for prevention of necrotising enterocolitis in preterm infants (AlFaleh 2014)	Mental retardation and cerebral palsy at 6 years	47 per 1000 (2/43)	47 per 1000 (7 to 323)	RR 1.02 (0.15 to 6.94)	85 (1 RCT)	VERY LOW	Study limitation (-1): 1 RCT at unclear risk for selection, performance, and detection bias; and high risk of attrition and reporting bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Arginine supplementation vs placebo for prevention of necrotising enterocoli-	Major neurodevelopmental disability at 36 months' postmen-	127 per 1000 (9/71)	82 per 1000 (29 to 232)	RR 0.65 (0.23 to 1.83)	132 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

tis in preterm infants (Shah 2007)	strual age (definition not reported in review; *definition from trial manuscript:* presence of 1 or more of cerebral palsy, cognitive delay (index < 70), bilateral blindness, bilateral hearing loss requiring aids)						RCT
Neonatal care: fungal infections							
Systemic antifungal agent vs placebo to prevent mortality and morbidity in very low birthweight infants (Cleminson 2015)	Neurodevelopmental impairment (composite) at 18 to 22 months (defined as at least 1 of (i) BSID-III cognition composite score < 70, (ii) cerebral palsy, (iii) deafness or, (iv) blindness)	274 per 1000 (23/84)	309 per 1000 (194 to 496)	RR 1.13 (0.71 to 1.81)	171 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: herpes simplex							
Vidarabine vs placebo for treatment of herpes simplex virus infection in neonates (Jones 2009)	Abnormal neurodevelopment at approximately 1 year of age (not defined in review; *definition from trial manuscript:* spasticity or hemiparesis only; or com-	214 per 1000 (6/28)	321 per 1000 (133 to 782)	RR 1.50 (0.62 to 3.65)	56 (1 RCT)	VERY LOW	Study limitations (-1) : 1 RCT with design limitations (method of randomisation not stated) Imprecision (-2): wide CIs crossing line

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	bina-tions of micro-cephaly, pare-sis, spas-ticity, seizures, blindness, or deafness)						of no effect; 1 small RCT
	Abnor-mal neurode-velopment or death at ap-proximately 1 year of age (not defined in review; *defini-tion from trial manuscript* as above)	750 per 1000 (21/28)	645 per 1000 (450 to 915)	RR 0.86 (0.60 to 1.22)	56 (1 RCT)	VERY LOW	Study limita-tions (-1) : 1 RCT with design limita-tions (method of randomisa-tion not stated) Imprecision (-2): wide CIs crossing line of no effect; 1 small RCT
Aciclovir vs vi-darabine for treatment of herpes simplex virus infection in neonates (Jones 2009)	Abnormal neurodevel-opment at approximately 1 year of age (not defined in review; *definition from trial manuscript:* mild impair-ment: only occular seque-lae; moderate neurological impairment: hemiparesis or a persistent seizure disor-der and no more than a 3-month de-velopmental delay; severe neurological sequelae:	263 per 1000 (25/95)	216 per 1000 (132 to 353)	RR 0.82 (0.50 to 1.34)	202 (1 RCT)	VERY LOW	Study limita-tions (-1): 1 RCT with de-sign lim-itations (inad-equate alloca-tion conceal-ment) Imprecision (-2): wide CIs crossing line of no effect; 1 small RCT

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

	microcephaly, spastic quadriplegia, chorioretinitis or blindness, and a serious developmental delay of > 3 months according to the DDST)						
	Abnormal neurodevelopment or death at approximately 1 year of age (not defined in review *definition from trial manuscript* as above)	463 per 1000 (44/95)	366 per 1000 (264 to 509)	RR 0.79 (0.57 to 1.10)	202 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with design limitations (inadequate allocation concealment) Imprecision (-2): wide CIs crossing line of no effect; 1 small RCT
Neonatal care: jaundice							
Prophylactic phototherapy vs standard care for preventing jaundice in preterm or low birthweight infants (Okwundu 2012)	Neurodevelopmental impairment at 18 to 22 months (defined as blindness, severe hearing loss, and moderate or severe cerebral palsy)	305 per 1000 (275/902)	259 per 1000 (226 to 302)	**RR 0.85 (0.74 to 0.99)**	1804 (1 RCT)	MODERATE	Study limitations (-1) : 1 RCT with high risk of attrition bias
Neonatal care: hypoglycaemia							
Dextrose gel vs placebo for treatment of hypoglycaemia in newborn infants (Weston	Major neurosensory disability at 2 years (defined as any of the following: le-	11 per 1000 (1/94)	67 per 1000 (8 to 543)	RR 6.27 (0.77 to 51.03)	184 (1 RCT)	VERY LOW	Study limitations (-1) : "Evidence is based on a single trial" Imprecision (-

Table 10. Other composite outcomes that include cerebral palsy as a component (*Continued*)

2016)	gal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay/intellectual impairment (defined as DQ < 2 SD below the mean))						2): "Wide confidence intervals, low event rates and small sample sizes are suggestive of imprecision: *(graded by review authors themselves)*
	Developmental disability at 2 years (defined as cognitive, language, or motor score below -1 SD, or cerebral palsy, blindness, or deafness)	32/94	34/90	RR 1.11 (0.75 to 1.63)	184 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT with 78% follow-up Imprecision: wide CI crossing line of no effect; 1 small RCT
Neonatal care: parenteral feeding							
Glutamine supplementation vs placebo to prevent morbidity and mortality in preterm infants (Moe-Byrne 2016)	Neurodevelopmental impairment at 2 years post term (defined as BSID-II MDI ≤ 85, PDI ≤ 85, cerebral palsy, blindness in 1 or both eyes, or hearing loss requiring amplification)	375 per 1000 (12/32)	401 per 1000 (221 to 720)	RR 1.07 (0.59 to 1.92)	72 (1 RCT)	LOW	Imprecision (-2): "Total sample size = 72" *(graded by review authors themselves)*

Abbreviations: BSID: Bayley Scales of Infant Development; CDI: Child Development Inventory; CI: confidence interval; DAS: Differential Ability Scales; DDST: Denver Developmental Screening Test; DQ: development quotient; GMDS: Griffiths Mental Development Scales; GMF: gross motor function; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; IQ: intelligence quotient; MDI: Mental Development Index; PDI: Psychomotor Development Index; RCT: randomised controlled

trial; RR: risk ratio; SD: standard deviation; VA: visual acuity; VABS: Vineland Adaptive Behaviour Scales; WASI: Wechsler Abbreviated Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children.

Table 11. Motor dysfunction

Intervention and comparison	Outcome	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
Neonatal care: asphyxia							
Therapeutic hypothermia vs standard care for newborns with hypoxic-ischaemic encephalopathy (Jacobs 2013)	Neuromotor delay (BSID PDI > 2 SD below mean) in survivors assessed at 18 to 24 months	349 per 1000 (104/298)	262 per 1000 (206 to 328)	**RR 0.75 (0.59 to 0.94)**	657 (6 RCTs)	HIGH	Not downgraded
Neonatal care: blood disorders							
Erythropoietin vs placebo for preventing red blood cell transfusion in preterm and/or low birthweight infants (Ohlsson 2014)	PDI < 70 at 18 to 22 months' corrected age (in children examined)	133 per 1000 (6/45)	311 per 1000 (131 to 737)	RR 2.33 (0.98 to 5.53)	90 (1 RCT)	VERY LOW	Study limitations: 1 RCT at unclear risk of selection bias and high risk of attrition bias (-73% follow-up) Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Neonatal care: pulmonary hypertension							
Endothelin receptor antagonists vs placebo for persistent pulmonary hypertension in term and late	Adverse neurological outcomes at 6 months (defined as clinical or electrographically proven	286 per 1000 (4/14)	20 per 1000 (0 to 343)	RR 0.07 (0.00 to 1.20)	37 (1 RCT)	LOW	Study limitation (-1): 8/23 infants in the placebo group were excluded from analysis Imprecision (-

Table 11. Motor dysfunction (*Continued*)

preterm infants (More 2016)	seizures, abnormal muscle tone, abnormal deep tendon reflexes, delayed motor milestones, or abnormal auditory brainstem response)						1): single RCT, small sample size *(graded by review authors themselves)*
Neonatal care: resuscitation							
Room air vs 100% oxygen for resuscitation of infants at birth (Tan 2005)	Not walking in those followed up at 18 to 24 months	107 per 1000 (13/122)	110 per 1000 (4 to 240)	RR 1.03 (0.04 to 2.25)	213 (1 RCT)	VERY LOW	Study limitations (-2): 1 qRCT with no blinding, and < 70% follow-up Imprecision (-1): wide CI crossing line of no effect
Neonatal care: nitric oxide							
Inhaled NO vs placebo for respiratory failure in preterm infants (studies of routine use in intubated preterm infants) (Barrington 2010)	BSID MDI or PDI < - 2 SD at 2 years' corrected age	412 per 1000 (28/68)	231 per 1000 (136 to 383)	RR 0.56 (0.33 to 0.93)	138 (1 RCT)	MODERATE	Study limitations (-1) : 1 small RCT with 82% follow-up
Inhaled nitric oxide vs control for respiratory failure in infants born at or near term (Finer 2006)	BSID PDI > 2 SD below the mean at 13 or 18 to 24 months	148 per 1000 (25/169)	161 per 1000 (86 to 300)	RR 1.09 (0.58 to 2.03)	283 (2 RCTs)	LOW	Study limitations (-1) : 1 RCT masking of allocation, masking of outcomes, and completeness of follow-

Table 11. Motor dysfunction (*Continued*)

							up 'can't tell' Inconsistency (-1): substantial heterogeneity (I^2 = 77%) *Note: error in review for Ninos 1996 data; intervention and control group data switched; this has been rectified in this analysis*
Neonatal care: respiratory distress syndrome							
Inositol supplementation (repeat doses) vs placebo in preterm infants at risk for or having respiratory distress syndrome (Howlett 2015)	Minor neural developmental impairment at 1 year corrected age (defined as sensorimotor abnormality and/or developmental delay)	137 per 1000 (10/73)	115 per 1000 (52 to 255)	RR 0.84 (0.38 to 1.86)	169 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection, performance, detection, and reporting bias, and at high risk of other bias Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Neonatal care: mechanical ventilation							
Volume-targeted vs pressure-limited ventilation in the neonate (Wheeler 2010)	Gross Motor Developmental Issue (any definition) at 6 to 18 months (defined as gross motor delay)	172 per 1000 (11/64)	172 per 1000 (81 to 368)	RR 1.00 (0.47 to 2.14)	128 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 small RCT *(post hoc analysis in review)*

Table 11. Motor dysfunction (*Continued*)

Neonatal care: bronchopulmonary dysplasia							
Early (< 8 days) postnatal corticosteroids vs placebo for preventing chronic lung disease in preterm infants (Doyle 2014b)	BSID PDI < -2 SD at 18 to 22 months or 25 months	146 per 1000 (61/419)	170 per 1000 (124 to 233)	RR 1.17 (0.85 to 1.60)	842 (3 RCTs)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
	BSID PDI < -2 SD in tested survivors at 18 to 22 months or 25 months	232 per 1000 (61/263)	271 per 1000 (202 to 364)	RR 1.17 (0.87 to 1.57)	528 (3 RCTs)	MODERATE	Imprecision (-1): wide CI crossing line of no effect
Late (> 7 days) postnatal corticosteroids vs placebo or no treatment for chronic lung disease in preterm infants (Doyle 2014)	BSID PDI < -2 SD at 1 year corrected age	180 per 1000 (11/61)	141 per 1000 (61 to 325)	RR 0.78 (0.34 to 1.80)	118 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
	BSID PDI < -2 SD in survivors assessed at 1 year corrected age	256 per 1000 (11/43)	171 per 1000 (77 to 384)	RR 0.67 (0.30 to 1.50)	90 (1 RCT)	LOW	Imprecision (-2): wide CI crossing line of no effect; 1 RCT with small sample size
Early inhaled corticosteroids vs placebo for preventing chronic lung disease in ventilated very low birthweight preterm neonates (Shah 2012)	Mean developmental index on BSID-II < 2 SD of the mean (age not reported in review;*from trial manuscript:* 3 years)	143 per 1000 (4/28)	179 per 1000 (53 to 596)	RR 1.25 (0.37 to 4.17)	56 (1 RCT)	VERY LOW	Study limitations (-1): 1 RCT at unclear risk of selection bias and detection bias Imprecision (-2): wide CI crossing line of no effect; 1 small RCT
Neonatal care: other							
Early developmental intervention vs stan-	Motor outcome at school age (5	378 per 1000 (51/135)	423 per 1000 (329 to 544)	RR 1.12 (0.87 to 1.44)	333 (2 RCTs)	LOW	Study limitations (-1): 2 RCTs at high

Table 11. Motor dysfunction (*Continued*)

dard follow-up post hospital discharge to prevent motor and cognitive impairment in preterm infants (Spittle 2015)	years) (defined as low score on Movement ABC)						risk of attrition bias and unclear risk of performance bias Imprecision (-1): wide CI crossing line of no effect

Abbreviations: BSID: Bayley Scales of Infant Development; CI: confidence interval; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; MDI: Mental Development Index; Movement ABC: Movement Assessment Battery for Children; PDI: Psychomotor Development Index; qRCT: quasi-randomised controlled trial; RCT: randomised controlled trial; RR: risk ratio; SD: standard deviation

CONTRIBUTIONS OF AUTHORS

Emily Shepherd, Rehana Abdus Salam, and Shanshan Han conducted screening, data extraction, and quality assessment of included reviews. Emily Shepherd drafted the first version of the overview, with Rehana Abdus Salam, Shanshan Han, Sarah McIntyre, Nadia Badawi, Maria Makrides, Philippa Middleton, and Caroline Crowther making comments and contributing to the final draft.

Emily Shepherd drafted the first version of the protocol for this review, with Sarah McIntyre, Nadia Badawi, Maria Makrides, Philippa Middleton, and Caroline Crowther making comments and contributing to the final draft.

DECLARATIONS OF INTEREST

Emily Shepherd, Rehana Abdus Salam, Shanshan Han, Sarah McIntyre, Maria Makrides, Philippa Middleton, Caroline Crowther: none known.

Nadia Badawi was an author of one of the included reviews (Jones 2009). As pre-specified in our protocol, data extraction and quality assessment for this review were carried out by two other overview authors, who were not authors of this review.

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CHAPTER 4: LINKING DATA FROM A LARGE CLINICAL TRIAL WITH THE AUSTRALIAN CEREBRAL PALSY REGISTER

Statement of authorship

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Contribution to the paper	Contributions to research design, the acquisition, analysis and interpretation of data; drafting and revising the paper critically; approval of the final version.		
Overall percentage (%)	80%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the 'Statement of authorship', each author certified that:
The candidate's stated contribution to the publication is accurate (as detailed above);
Permission is granted for the candidate to include the publication in the thesis;
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DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Linking data from a large clinical trial with the Australian Cerebral Palsy Register

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ABBREVIATIONS

ACPR	Australian Cerebral Palsy Register
ACTOMgSO$_4$	Australasian Collaborative Trial of Magnesium Sulphate

AIM To link data from a large maternal perinatal trial with the Australian Cerebral Palsy Register (ACPR) to identify children with cerebral palsy (CP).
METHOD Deidentified data from the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO$_4$) and the ACPR were linked. Children born from 1996 to 2000 at Australian hospitals who survived and had 2-year paediatric assessments were included. Children identified with CP in: (1) both the ACTOMgSO$_4$ (2y) and the ACPR (5y), (2) the ACTOMgSO$_4$ only, and (3) the ACPR only were compared.
RESULTS We included 913 children (492 males, 421 females; mean gestational age at birth 27.8wks [standard deviation 2.1wks]; range 23.0–40.0wks). Eighty-four children received a CP diagnosis: 35 by the ACTOMgSO$_4$ and the ACPR, 29 by the ACTOMgSO$_4$ only, and 20 by the ACPR only. The ACTOMgSO$_4$ diagnosed 76.2% (95% confidence interval [CI] 65.9–84.1) and the ACPR identified 65.5% (95% CI 54.7–74.9). Children born in states/territories with long-standing versus more recently established registers were more likely to be included on the ACPR (p<0.05).
INTERPRETATION Linking deidentified perinatal trial data with the ACPR was achieved. Limitations of both strategies for identifying children with CP in this era (late 1990s and early 2000s) probably explain many of the differences observed, and inform future linkage studies and evaluations of CP-preventive interventions.

Long-term follow-up of maternal perinatal interventions is crucial, with many neurodevelopmental disabilities and other morbidities associated with perinatal complications only becoming apparent in, or beyond, childhood.[1] However, only a minority of randomized trials assessing such interventions are able to report on long-term neurodevelopmental health, including cerebral palsy (CP). In a systematic review of 249 perinatal intervention trials, only 40 (16%) reported outcomes beyond the initial neonatal hospital discharge.[2] Although there is increasing recognition of the importance of assessing longer-term outcomes,[1,3] follow-up rates remain low.[2] In a systematic review of 22 Cochrane studies of interventions in infants at risk of CP, 'neurodevelopmental outcomes' (e.g. CP, blindness, deafness, intellectual impairment) were the second most frequently reviewed outcomes of interest.[4] Only a minority of included randomized trials (22 out of 203, 11%), however, reported these data.[4] Similarly, our own recent Cochrane overviews of reviews found that few relevant antenatal or intrapartum[5] (15 out of 77, 19%) and neonatal[6] (43 out of 145, 30%) randomized trials reported CP as an outcome.

Challenges associated with long-term follow-up are well recognized and numerous. Costs may be prohibitive or underestimated.[7] Loss to follow-up may compromise interpretation of outcomes, as the children most difficult to follow-up are known to have comparatively poorer neurodevelopmental outcomes.[8,9] Further, follow-up methods, ages of assessment, and outcome definitions vary within and between trials.[2,4–6] These hurdles in the meaningful evaluation of preventive strategies for adverse neurodevelopmental outcomes, including CP, have triggered growing interest in the use of alternative strategies to follow-up children from maternal perinatal intervention trials. One potential approach is linkage of trial data to routine/

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administrative data sets or disease-specific registries,[10] such as the Australian Cerebral Palsy Register (ACPR).

Thus, we aimed to assess the utility of linking data from a large maternal perinatal clinical trial with the ACPR to identify children with CP. The Australasian Collaborative Trial of Magnesium Sulphate ($ACTOMgSO_4$) was a randomized trial assessing magnesium sulphate before very preterm birth, for preventing paediatric mortality and CP, and was initially funded to follow-up children to these primary endpoints, at 2 years corrected age.[11]

What this paper adds

- Randomized trial data were linked with the Australian Cerebral Palsy Register.
- Trial (2y) and register (up to 5y) diagnoses of cerebral palsy (CP) differed.
- States with long-standing registers were more likely to include children with CP.

METHOD

Design

The current study was a deidentified linkage of existing data from the $ACTOMgSO_4$ and the ACPR.

Participants and setting

Full details of the $ACTOMgSO_4$ have been reported.[11] Briefly, 1062 females with a singleton, twin, triplet, or quadruplet pregnancy at less than 30 weeks' gestation, for whom birth was planned or expected within 24 hours, were randomized at 16 maternity hospitals in Australia or New Zealand, between 1996 and 2000, either to intravenous magnesium sulphate (n=535) or to saline placebo (n=527). The pregnant females, health professionals, and outcome assessors were blinded to allocation. Of 1262 fetuses, 1255 were alive at randomization, and 1061 children survived to 2 years corrected age, where the primary outcomes of (1) death, (2) CP, and (3) the combined outcome (death or CP) were determined. Surviving children were assessed by a developmental paediatrician and psychologist, and parents or caregivers completed questionnaires about their children's development. The criteria for CP included abnormalities of tone, deep tendon or Babinski reflexes, and impaired motor function. CP severity was described (before the Gross Motor Function Classification System[12]) as mild (disability in ambulant children interfering only slightly with normal daily activities), moderate (children attempting to walk at 2y, with or without assisted devices), or severe (children likely to remain non-ambulant).[13]

For data linkage, we included children at 13 Australian hospitals, who survived, and who had paediatric assessments at 2 years. We excluded children born at three hospitals in New Zealand, who died before 2 years, or who did not have 2-year paediatric assessments.

Data collection and linkage

Data from eligible children within the $ACTOMgSO_4$ database were linked with ACPR data. Established in 2008, the ACPR is an electronic database, securely uploaded from each state and territory CP register.[14] This includes data from long-standing CP registers in Western Australia (established in 1979), Victoria (1987), and South Australia (1998), and newer (as recently as 2006) registers in New South Wales/Australian Capital Territory, Queensland, Tasmania, and the Northern Territory. The processes for notification to add inclusion in the CP registers vary across states and territories in line with local ethics and legislative requirements. To be included in any CP register, a child's motor impairment must meet a definition for CP current at the time (as diagnosed by a health professional, commonly a paediatrician), which includes the following key elements: (1) an umbrella term for a group of disorders; (2) a condition that is permanent but not unchanging; (3) involves a disorder of movement and/or posture and of motor function; (4) caused by a non-progressive interference, lesion, or abnormality; (5) the interference, lesion, or abnormality originated in the immature brain.[15,16] Children's CP is again 'confirmed' when they reach 5 years of age; thereafter records are considered 'complete'. Where new information becomes available, cases may be updated, leading to inclusion or exclusion. Along with monitoring CP incidence and prevalence, one of the ACPR's key aims is to facilitate the evaluation of preventive strategies.[14]

For data linkage, the $ACTOMgSO_4$ coordinating centre provided the ACPR with a password-protected data set including the following variables for eligible children: (1) child's date of birth; (2) mother's date of birth; (3) child's hospital of birth; (4) child's birth order number (multiple births); (5) child's gestational age at birth (weeks and days); (6) child's birthweight (g). To ensure participant anonymity and confidentiality, personal details were not provided, and each child retained their unique $ACTOMgSO_4$ identifier. Using multiple-step deterministic linkage procedures,[17] the ACPR identified potential matches on the basis of the variables in the above order. Complete matches were individuals who matched on the first four variables. If there were missing data, the fifth and sixth variables were used. After extraction of the CP diagnoses from the register, the ACPR returned the data set.

Statistical analysis

CP diagnoses were grouped by: (1) diagnosis in both the $ACTOMgSO_4$ and on the ACPR, (2) in the $ACTOMgSO_4$ only, and (3) on the ACPR only. We assessed CP diagnoses for all children, and separately for children born in states with long-standing versus more recently established CP registers. We used univariate logistic regression models to explore whether birth state/territory register status, and movement- and/or posture-related outcomes at the $ACTOMgSO_4$ 2-year assessments, predicted later ACPR inclusion. Two-year outcomes included those from paediatric assessment (CP, including severity and type, not walking freely, decreased or increased limb tone, ankle clonus more than five beats, positive Babinski response, limited dorsiflexion of ankle, limited hip abduction, limited hip extension), psychological assessment (Psychomotor Developmental Index corrected score of the Bayley Scales of

Infant Development, Second Edition),[18] and parental questionnaire (receipt of care from physiotherapist or occupational therapist, difficulty walking, sitting, using hands, and with head control). The models were fitted separately according to CP status in the ACTOMgSO$_4$ and used generalized estimating equations to account for clustering due to multiple births. Associations were described using odds ratios with 95% confidence intervals (CIs). Data were analysed in SPSS version 21.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

Ethics approval and consent

Ethical approval was granted by the Women's and Children's Health Network Human Research Ethics Committee (HREC/16/WCHN/18), and research governance by the Women's and Children's Hospital (SSA/16/WCHN/057). As conditions of 2.3.10 of the National Statement on Ethical Conduct in Human Research were met, and all families had given written informed consent to participate in the ACTOMgSO$_4$,[11] a waiver of consent was approved. All state and territory CP register data custodians agreed to the use of ACPR data for linkage, and a waiver of consent was provided by the Cerebral Palsy Alliance Human Research and Ethics Committee (project waiver number 2016-03-01).

RESULTS

Of 1061 children who survived to 2 years corrected age, we excluded 135 born in New Zealand, and 13 who did not have 2-year paediatric assessments. We thus included 913 children. Their perinatal characteristics are presented in Table 1.

CP diagnoses

Of 913 eligible children, the ACTOMgSO$_4$ diagnosed 64 (7.0%) with CP at 2 years, and the ACPR identified 55 (6.0%) children with CP at 5 years. Some children with CP diagnoses were identified by both the ACTOMgSO$_4$ and the ACPR (n=35), others only by the ACTOMgSO$_4$ (n=29) or only by the ACPR (n=20). Thus 84 children were identified with CP by the ACTOMgSO$_4$ and/or the ACPR. The ACTOMgSO$_4$ diagnosed 76.2% (95% CI 65.9–84.1) of the 84 children, and the ACPR identified 65.5% (95% CI 54.7–74.9). The remaining 829 children did not have CP diagnoses either by the ACTOMgSO$_4$ or the ACPR (Table 2).

Of 46 children with a CP diagnosis (by the ACTOMgSO$_4$ and/or the ACPR) in states with long-standing CP registers, the ACTOMgSO$_4$ diagnosed 65.2% (95% CI 50.4–77.6) (n=30), and the ACPR 80.4% (95% CI 66.4–89.5) (n=37). Of 38 children with CP diagnoses (by the ACTOMgSO$_4$ and/or the ACPR) in states/territories with more recently established registers, the ACTOMgSO$_4$ diagnosed 89.5% (95% CI 75.1–96.0) (n=34), and the ACPR identified 47.4% (95% CI 32.3–63.0) (n=18) (Table 2).

Table 1: Perinatal characteristics of ACTOMgSO$_4$ children eligible for linkage

Characteristic	Eligible ACTOMgSO$_4$ children (n=913)
Mean gestational age (SD) at birth, completed wks	27.8 (2.1)
Preterm birth <30wks	872 (95.5)
Preterm birth <37wks	905 (99.1)
Mean birthweight (SD), g	1079.4 (375.4)
Male sex	492 (53.9)
Multiple pregnancy	262 (28.7)

Data are n (%) unless otherwise specified. ACTOMgSO$_4$, Australasian Collaborative Trial of Magnesium Sulphate; SD, standard deviation.

Children with a CP diagnosis in the ACTOMgSO$_4$

Of 64 children with a CP diagnosis at 2 years in the ACTOMgSO$_4$, those born in states with long-standing CP registers were more likely to be included on the ACPR (at 5y) than those born in states/territories with more recently established registers. Children judged to have a 'definitely yes' CP status at 2 years (vs a 'probably yes' CP status), with difficulty walking (paediatric assessment), and using their hands (parental assessment) were more likely to be included on the ACPR. No further associations between 2-year movement and/or posture outcomes assessed and ACPR inclusion at 5 years were observed (Table S1, online supporting information). Of the 29 children with a CP diagnosis in the ACTOMgSO$_4$, not included on the ACPR, at 2 years, 19 (65.5%) were judged to have 'mild', nine (31.0%) 'moderate', and one (3.4%) 'severe' CP; no clear association between CP severity and ACPR inclusion was observed, however.

Table 2: Diagnoses of cerebral palsy (CP) in ACTOMgSO$_4$ at 2 years, and on ACPR at 5 years

Australian children from ACTOMgSO$_4$ (n=913)	n (%)
CP diagnosis (any)	84 (9.2)
CP in ACTOMgSO$_4$ and on ACPR	35
CP in ACTOMgSO$_4$ only	29
CP on ACPR only	20
No CP diagnosis	829 (90.8)
Children born in states with long-standing CP registers from ACTOMgSO$_4$ (n=449)	**n (%)**
CP diagnosis (any)	46 (10.2)
CP in ACTOMgSO$_4$ and on ACPR	21
CP in ACTOMgSO$_4$ only	9
CP on ACPR only	16
No CP diagnosis	403 (89.8)
Children born in states/territories with more recently established CP registers from ACTOMgSO$_4$ (n=464)	**n (%)**
CP diagnosis (any)	38 (8.2)
CP in ACTOMgSO$_4$ and on ACPR	14
CP in ACTOMgSO$_4$ only	20
CP on ACPR only	4
No CP diagnosis	426 (91.8)

ACTOMgSO$_4$, Australasian Collaborative Trial of Magnesium Sulphate; ACPR, Australian Cerebral Palsy Register.

Children without a CP diagnosis in the ACTOMgSO$_4$

Of 849 children not diagnosed with CP at 2 years in the ACTOMgSO$_4$, those born in states with long-standing CP registers were more likely to be included on the ACPR (at 5y) than those born in states/territories with more recently established registers (Table S2, online supporting information). Children with a 'definitely no' CP status at 2 years (vs a 'probably no' CP status) were less likely to be included on the ACPR. Difficulty walking (paediatric and parental assessments) and using hands (parental assessment), decreased limb tone and limited dorsiflexion of the ankle (paediatric assessment), and receipt of care from a physiotherapist or occupational therapist (parental report) were all associated with ACPR inclusion. Bayley Scales of Infant Development, Second Edition Psychomotor Developmental Index corrected score was associated with ACPR inclusion; children included on the ACPR had a lower mean score overall than those not on the ACPR. For the remaining outcomes assessed, no clear associations with ACPR inclusion at 5 years were observed (Table S2).

DISCUSSION

With increasing challenges of long-term maternal perinatal intervention follow-up, there is growing interest in the use of routine data or registries to assess child health and development. This approach may have important advantages, including relatively low cost compared with primary data collection in costly trial follow-up assessments.[7,10] We report the first data linkage of a large maternal perinatal clinical trial (ACTOMgSO$_4$) with a nationwide CP register (ACPR) to identify children with CP.

Of almost 1000 Australian children included in this study (born 1996–2000), the ACTOMgSO$_4$ diagnosed 64 with CP at 2 years, and linkage with the ACPR identified 55 children to have CP up to 5 years. In total, 84 children were identified to have a CP diagnosis in the ACTOMgSO$_4$ and/or via the ACPR. Using these data, prevalence rates of CP ranged from 6.0% to 9.2%; comparable to recently reported Australian birth prevalence rates for similar gestational ages and years.[19]

Although we successfully linked these data, we did identify notable discrepancies in children diagnosed with CP through the ACTOMgSO$_4$ and those identified by the ACPR, with only 42% (n=35) of the 84 CP diagnoses considered 'matches'. Findings of exploratory analyses (assessing whether birth state/territory status, and movement and/or posture-related outcomes at the ACTOMgSO$_4$ 2-year assessments predicted later ACPR inclusion) should be interpreted with caution; small numbers led to relatively imprecise results. Limitations in both strategies for identifying children with CP in the late 1990s may account for the differences and warrant discussion.

The ACTOMgSO$_4$ diagnosed 29 children with CP who were not on the ACPR; there are a variety of potential reasons. While the three long-standing registers (established before 1998) have achieved population-level ascertainment, the remaining registers (established as recently as 2006—well after trial completion) are considered under-ascertained.[14] Although notable gains have been made in retrospective case ascertainment by these newer registers, for the relevant birth years, there are probably some 'missing' cases/matches.[14,19] In line with this, we observed an association between register status and ACPR inclusion, with children (with and without ACTOMgSO$_4$ CP diagnoses) born in states with long-standing CP registers being more likely to be included on the ACPR.

Missing ACPR data for variables used for linkage (such as gestational age at birth and birthweight) in these earlier birth years, and our obligation to ensure participant anonymity and confidentiality, precluded the determination of a small number (n=2) of potential 'matches'. From the under-ascertained registers, there were ACPR registrations with complete CP data, but missing data on all/many linkage variables, preventing any matching. Thus, linking with identifiable data would have facilitated this study. It is possible that some children with a diagnosis in the ACTOMgSO$_4$ were 'considered' for ACPR registration, but ultimately not included on the ACPR; deidentified linkage also precluded knowledge of this. Under-ascertainment by the ACPR could also relate to factors including relocation of families internationally; however, we were not able to quantify the impact of such losses to follow-up in this deidentified study. With continued improvements in ACPR ascertainment and considerably fewer missing data with prospective data collection, these factors may be less important in future linkages with contemporary trial cohorts.

Beyond ACPR data limitations for relevant birth years, possible reasons for differences observed relate to the descriptive nature of a CP diagnosis, and shortcomings of diagnostic methods used at the time. CP is an umbrella term, covering different clinical manifestations and aetiologies. Registers contributing to the ACPR only consider cases 'confirmed' when children reach 5 years of age,[14] acknowledging that new information (or different interpretation of information) may lead to alternative diagnoses or exclusion. The possibility of diagnosis reversal is well recognized, particularly for high risk children born preterm —'motor abnormalities detected in early childhood may subsequently lessen in degree, change in kind, or disappear altogether'.[20] Previous studies, including those from the South Australian[21] and Canadian[22] CP registers, have highlighted small proportions of children with CP notifications, later confirmed to have non-CP diagnoses, for example, progressive genetic conditions or syndromes and metabolic diseases excluded by definition, and developmental or gross motor delay. In 2016, Korzeniewski et al. described the 'transient' nature of a CP diagnosis, with 40% (17 out of 43) of children with 'non-disabling' CP at 2 years having CP at school age (6–9y), compared with 98% (47 out of 48) of those with 'disabling' CP.[23] In contrast, Chen et al. found no association between CP motor severity and loss of a diagnosis over time (between 2y and 5y) among 1683 children with a Canadian CP Registry

notification.[22] In our study, although we did not observe an association between CP severity at 2 years and later ACPR inclusion, of note 66% (19/29) of children diagnosed with CP in the ACTOMgSO$_4$, not subsequently on the ACPR, were considered to have mild CP.

An important further explanation for the differences observed relates to improvements in diagnostic methods used. Today, a CP diagnosis (including interim use of a 'high risk of CP' diagnosis) can be made according to recommendations within 2017 international clinical practice guidelines.[24] Where appropriate, including with congruence of findings, a diagnosis is possible under the age of 6 months using predictive tools. As there is no single diagnostic tool, a combination of clinical history, neuroimaging (magnetic resonance imaging, 86–89% sensitivity), standardized neurological assessments (such as the Hammersmith Infant Neurological Examination, 90% sensitivity), and standardized motor assessments (particularly Prechtl's Qualitative Assessment of General Movements before 5mo corrected age, 98% sensitivity) are suggested, to make the most accurate, earliest diagnosis.[24,25]

While the importance of early diagnosis, particularly for facilitating early intervention, is now recognized, traditionally a CP diagnosis was made much later.[24,25] A 'wait and see' approach was common (up to and beyond the perceived 'latent' period of 12–24mo, where it was believed CP could not be identified accurately[24]), providing time 'to rule out other diagnoses, delay the delivery of bad news, or provide time for the child to grow out of it'.[26] Within the ACTOMgSO$_4$, CP diagnoses were made at a single paediatric examination at 2 years.[13] While being the most accurate available approach, it has recognized limitations. We observed associations between CP status at 2 years in the ACTOMgSO$_4$ ('probably yes' vs 'definitely yes' for CP diagnoses; and 'probably no' vs 'definitely no' for non-CP diagnoses) and later ACPR inclusion at 5 years, emphasizing difficulties in making firm diagnoses in the late 1990s and early 2000s.

The ACPR identified 20 children with CP not diagnosed at 2 years in the ACTOMgSO$_4$. We found associations between a variety of possible indicators of movement and/or posture dysfunction at 2 years in the ACTOMgSO$_4$ and subsequent ACPR inclusion at 5 years. For example, children without CP diagnoses in the ACTOMgSO$_4$, but with parental reports of difficulty walking and using their hands, who received care from physiotherapists and/or occupational therapists, were more likely to be on the ACPR. This may represent the presence of 'milder' degrees of motor dysfunction among these children, not sufficient to flag CP diagnoses at the time of the trial, in the context of the previously discussed diagnostic limitations.

Our study provides a firm basis for further linkages of clinical trials with the ACPR for childhood follow-up. All ACPR contributing registers are expected to achieve population-level ascertainment in the coming years, and further research on the use of ACPR CP diagnoses for long-term outcome assessment in preventive trials is recommended. Future trials assessing preventive interventions for CP should consider pre-specification of linkage with CP register data in their protocols, participant information sheets, and consent forms, enabling the use of identifiable data. Maternal perinatal trials assessing CP are urged to follow the international clinical practice guidelines for early, accurate diagnosis.[24]

CONCLUSION

We have conducted the first deidentified data linkage of a large maternal perinatal randomized trial with the ACPR. Limitations of both strategies in the late 1990s and early 2000s for identifying children with CP probably explain many of the differences observed (with fewer than half of all CP diagnoses identified by both the trial and the ACPR). Further linkage studies, of contemporary trial cohorts, will progress our understanding of the 'criterion standard' strategy for assessing long-term follow-up of CP after maternal perinatal interventions; and, together with recent advances in early, accurate CP diagnosis, they will aid in the future evaluation of preventive strategies.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Birth state/territory CP register status and 2-year outcomes for children with a CP diagnosis in the ACTOMgSO$_4$

Table S2: Birth state/territory CP register status and 2-year outcomes for children without a CP diagnosis in the ACTOMgSO$_4$

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CHAPTER 5: ANTENATAL MAGNESIUM SULPHATE AND ADVERSE NEONATAL OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Principal author (candidate)	Emily Shepherd		
Contribution to the paper	Conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, writing – original, writing – review and editing.		
Overall percentage (%)	75%		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	10/10/2019

Co-author contributions

By signing the 'Statement of authorship', each author certified that:
The candidate's stated contribution to the publication is accurate (as detailed above);
Permission is granted for the candidate to include the publication in the thesis;
The sum of all co-authors is equal to 100% less the candidate's stated contribution.

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PLOS MEDICINE

RESEARCH ARTICLE

Antenatal magnesium sulphate and adverse neonatal outcomes: A systematic review and meta-analysis

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Abstract

Background

There is widespread, increasing use of magnesium sulphate in obstetric practice for pre-eclampsia, eclampsia, and preterm fetal neuroprotection; benefit for preventing preterm labour and birth (tocolysis) is unproven. We conducted a systematic review and meta-analysis to assess whether antenatal magnesium sulphate is associated with unintended adverse neonatal outcomes.

Methods and findings

CINAHL, Cochrane Library, LILACS, MEDLINE, Embase, TOXLINE, and Web of Science, were searched (inceptions to 3 September 2019). Randomised, quasi-randomised, and non-randomised trials, cohort and case–control studies, and case reports assessing antenatal magnesium sulphate for pre-eclampsia, eclampsia, fetal neuroprotection, or tocolysis, compared with placebo/no treatment or a different magnesium sulphate regimen, were included. The primary outcome was perinatal death. Secondary outcomes included pre-specified and non-pre-specified adverse neonatal outcomes. Two reviewers screened 5,890 articles, extracted data, and assessed risk of bias following Cochrane Handbook and RTI Item Bank guidance. For randomised trials, pooled risk ratios (RRs) or mean differences, with 95% confidence intervals (CIs), were calculated using fixed- or random-effects meta-analysis. Non-randomised data were tabulated and narratively summarised. We included 197 studies (40 randomised trials, 138 non-randomised studies, and 19 case reports), of mixed quality. The 40 trials (randomising 19,265 women and their babies) were conducted from 1987 to 2018 across high- (16 trials) and low/middle-income countries (23 trials) (1 mixed). Indications included pre-eclampsia/eclampsia (24 trials), fetal neuroprotection (7 trials), and tocolysis (9 trials); 18 trials compared magnesium sulphate with placebo/no treatment, and 22 compared different regimens. For perinatal death, no clear difference in randomised trials was observed between magnesium sulphate and placebo/no treatment

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CI, confidence interval; IM, intramuscular; IV, intravenous; MD, mean difference; RR, risk ratio.

(RR 1.01; 95% CI 0.92 to 1.10; 8 trials, 13,654 babies), nor between regimens. Eleven of 138 non-randomised studies reported on perinatal death. Only 1 cohort (127 babies; moderate to high risk of bias) observed an increased risk of perinatal death with >48 versus ≤48 grams magnesium sulphate exposure for tocolysis. No clear secondary adverse neonatal outcomes were observed in randomised trials, and a very limited number of possible adverse outcomes warranting further consideration were identified in non-randomised studies. Where non-randomised studies observed possible harms, often no or few confounders were controlled for (moderate to high risk of bias), samples were small (200 babies or fewer), and/or results were from subgroup analyses. Limitations include missing data for important outcomes across most studies, heterogeneity of included studies, and inclusion of published data only.

Conclusions

Our findings do not support clear associations between antenatal magnesium sulphate for beneficial indications and adverse neonatal outcomes. Further large, high-quality studies (prospective cohorts or individual participant data meta-analyses) assessing specific outcomes, or the impact of regimen, pregnancy, or birth characteristics on these outcomes, would further inform safety recommendations. PROSPERO: CRD42013004451.

Author summary

Why was this study done?

- Magnesium sulphate is widely used in pregnancy, considered effective for maternal neuroprotection in pre-eclampsia/eclampsia and for fetal neuroprotection (cerebral palsy prevention) in women at risk of preterm birth, and ineffective for preventing preterm birth or labour (tocolysis).
- It is important to understand whether this treatment, when given to women in pregnancy, is associated with any unintended adverse outcomes for babies.

What did the researchers do and find?

- This systematic review incorporates the findings of 197 studies (including 40 randomised controlled trials) that reported on adverse outcomes for babies whose mothers were treated with magnesium sulphate in pregnancy.
- Meta-analysis of randomised controlled trials showed no clear difference in the risk of perinatal death between babies whose mothers were treated with magnesium sulphate and those whose mothers received placebo/no treatment, or between different magnesium sulphate regimens.
- No clear adverse outcomes for babies were observed in randomised trials, and a very limited number of possible adverse outcomes warranting further consideration were identified in non-randomised studies.

What do these findings mean?

- Magnesium sulphate in pregnancy, when given for the beneficial indications of maternal or fetal neuroprotection, is not associated with an increased risk of perinatal death or other adverse outcomes for babies.
- Further investigation into specific adverse outcomes, and the impact of particular treatment regimen, pregnancy, and/or birth characteristics, would further inform safety recommendations.

Introduction

Antenatal magnesium sulphate is commonly used in obstetric practice. Systematic reviews and clinical practice guidelines support its use when given for maternal neuroprotection in pre-eclampsia or eclampsia [1–3] and for neuroprotection of the fetus in women at risk of preterm birth (for cerebral palsy prevention) [4–7]. Despite continued use in some countries [8], available evidence does not support its role in preventing preterm birth in women with, or following, threatened preterm labour (for tocolysis) [7,9].

Concerns surrounding possible unintended adverse outcomes for fetuses or neonates following exposure to antenatal magnesium sulphate emerged over 50 years ago [10,11], and uncertainty persists today. While the clinical consequences of hypermagnesemia, related to increased serum concentrations, are well known and documented (such as lethargy, drowsiness, flushing, nausea, vomiting, muscle weakness, loss of deep tendon reflexes, hypotension, apnoea, coma, cardiac arrest, and, ultimately, death [12]), whether neonates are at risk of such adverse outcomes following exposure to antenatal magnesium sulphate is unclear.

We have systematically reviewed the maternal adverse effects of different antenatal magnesium sulphate regimens [13], and a further systematic review has summarised the effects specifically on fetal heart rate [14]. To our knowledge, a broad evaluation of evidence surrounding potential unintended neonatal adverse outcomes, informed by current guidance [15–17], has not previously been conducted. Implementation of this treatment may be strengthened, and its safety improved, if guidelines and recommendations for practice can be based on such knowledge.

The aim of our study, therefore, was to conduct a comprehensive systematic review to assess whether antenatal magnesium sulphate is associated with perinatal death and other unintended adverse neonatal outcomes.

Methods

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline; the relevant checklist is provided in S1 PRISMA Checklist. Prior to conduct, this systematic review was registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42013004451) [18]. The Australian Cerebral Palsy Alliance Research Foundation–funded review protocol is available in S1 Text. Ethical approval was not required.

Search strategy

Comprehensive searches of the bibliographic databases CINAHL, Cochrane Library, LILACS, MEDLINE, Embase, TOXLINE, and Web of Science were undertaken from their respective inceptions to 3 September 2019, using combinations of MeSH and free text terms. The search strategies are available in S2 Text. No date or language restrictions were applied; however, because of logistical constraints, for non-English papers, only those with an available English abstract or full-text translation were retrieved. The reference lists of eligible articles were checked for additional reports.

Inclusion criteria

We included randomised and quasi-randomised controlled trials as well as non-randomised controlled studies (non-randomised trials, cohort studies, and case–control studies), and case reports. We excluded cross-sectional studies and case series. We included studies available as abstracts only, along with full-text publications.

We included neonates who were exposed to antenatal magnesium sulphate, regardless of their gestational age at exposure or birth. We included studies where antenatal magnesium sulphate was given for pre-eclampsia or eclampsia, for neuroprotection of the fetus, or for tocolysis. We excluded studies where magnesium sulphate was given as an adjuvant during obstetric anaesthesia. We included intervention studies in which magnesium sulphate was compared with no treatment, placebo, or a different magnesium sulphate regimen. We included observational studies where magnesium sulphate was assessed as an 'exposure'. We excluded studies where magnesium sulphate was compared with another therapy (for example, diazepam for pre-eclampsia or eclampsia, or nifedipine for tocolysis).

We included studies that reported on adverse outcomes for neonates, however defined. The primary outcome was perinatal death. Secondary outcomes included pre-specified adverse outcomes (based on non-systematic literature review: stillbirth, neonatal death or death up to hospital discharge, low Apgar scores at 1 and 5 minutes, need for active resuscitation at birth, respiratory depression, spontaneous intestinal perforation, patent ductus arteriosus, hypotension, lethargy, hypotonia or hyporeflexia, osteopenia or bone fractures, neonatal intensive care unit admission, and duration of neonatal care unit admission), along with other non-pre-specified adverse neonatal outcomes.

Study selection

After screening all titles and abstracts, we obtained full-text articles for studies that appeared to meet the inclusion criteria. All full-text articles were assessed for inclusion. Each stage was carried out by 2 reviewers, and we resolved any discrepancies through discussion, or, if required, we consulted a third reviewer.

Data extraction and management

For included studies, data were extracted using a standardised form, including information regarding design, participants, the magnesium sulphate regimen(s), the control/comparison if applicable, neonatal adverse outcomes reported, results relevant to the review, and the risk of bias. For all randomised trials, all case reports, and 60% of non-randomised studies, extraction was carried out by 2 reviewers (for 40% of non-randomised studies, extractions were checked by a second reviewer), and we resolved discrepancies through discussion, or, if required, we consulted a third reviewer.

Assessment of risk of bias

Quality appraisal of intervention studies was undertaken utilising established guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions [19]. The quality assessment of observational studies was guided by the RTI Item Bank [20].

Data synthesis and analysis

Data analyses were undertaken by study design. Statistical analyses for randomised trials were performed using Review Manager, version 5.3 [21]. We present quantitative data from individual studies as risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, with 95% confidence intervals (CIs). For all outcomes, we carried out analyses as far as possible on an intention-to-treat basis. Pooled estimates were calculated using fixed-effects meta-analysis (Mantel-Haenszel method) where there was a sufficient quantity of data, with clinical homogeneity. Where there was substantial statistical heterogeneity (where I^2 was greater than 30% and either T^2 was greater than 0 or there was a low P value [less than 0.10] in the χ^2 test), summary estimates were calculated using random-effects meta-analysis. Where there were 10 or more trials in a meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots, which we assessed visually.

Separate comparisons were performed for those studies assessing magnesium sulphate versus no treatment/placebo and those comparing different magnesium sulphate regimens. For our primary review outcome (perinatal death) and other mortality outcomes, we conducted subgroup analyses based on indication for use and characteristics of the magnesium sulphate loading and maintenance dose regimens, as these factors were considered likely to influence outcomes. It was not possible to conduct subgroup analyses based on other pregnancy or birth characteristics (gestational age at magnesium sulphate administration, birthweight, mode of birth, and concomitant maternal treatments) due to paucity of data. We assessed subgroup differences by interaction tests available within Review Manager, and, where applicable, we have quoted the χ^2 statistic and P value, and the interaction test I^2 value.

For observational studies (non-randomised trials, cohort studies, and case–control studies), we present effect estimates where possible as adjusted RRs or odds ratios if reported with 95% CIs, unadjusted RRs or odds ratios with 95% CIs, P values only, or percentages (rates), in tabular format; we used narrative synthesis to summarise the studies. Data from case reports were grouped according to common adverse outcomes, tabulated, and summarised narratively.

Results

Study selection

The results of the search strategy, including the sources of the studies, their assessment, and final inclusion are shown in Fig 1. The database searching identified 5,890 records, and other searching identified a further 11 records. Review of the titles and abstracts and exclusion of irrelevant and duplicate records yielded 777. Of these, we excluded 572 for the documented reasons (see S3 Text for list of records excluded due to absence of an English translation). We included a total of 205 articles, relating to 197 studies. See S4 Text for references for all included studies. In the case of multiple publications from the same study, we included the report with the most relevant data as the primary reference, and only included further publications as secondary references if they provided additional relevant data.

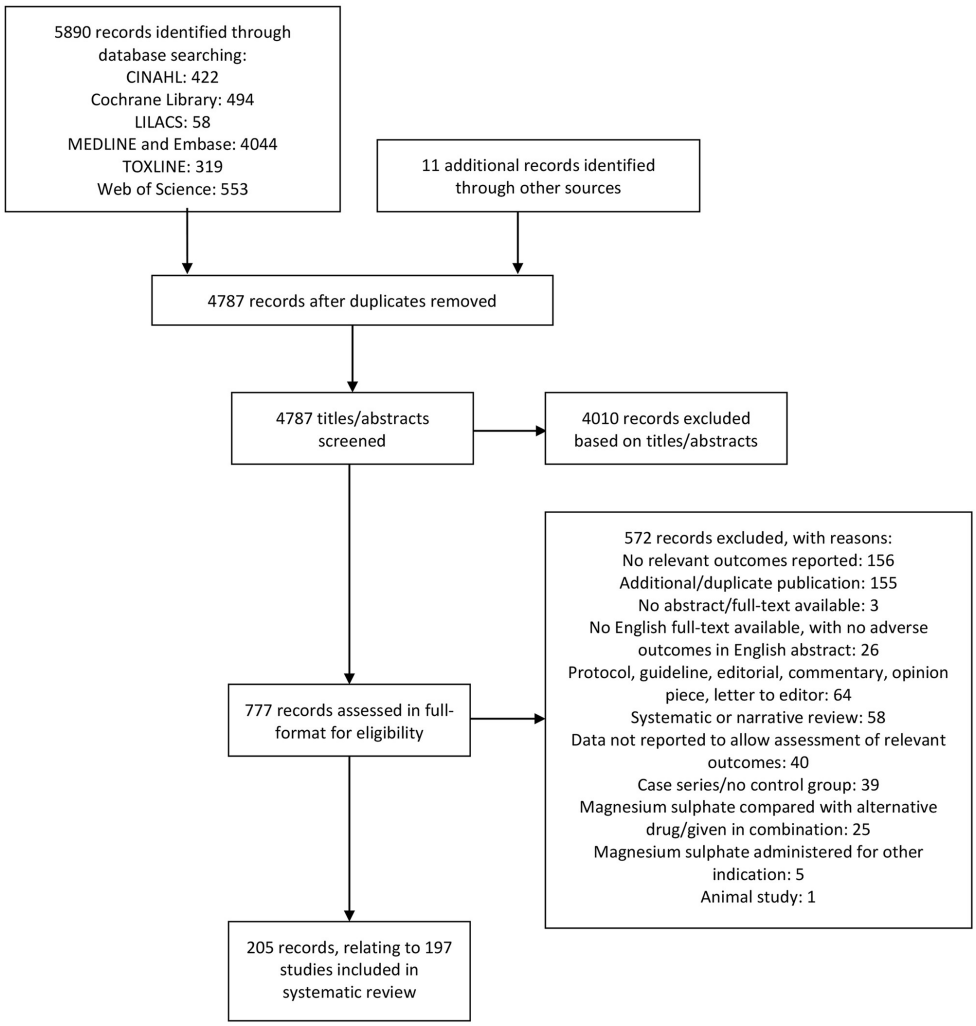

Fig 1. Flow diagram of included studies. Flow diagram showing the flow of records through the different phases of the review, indicating the number of records identified, included and excluded, and the reasons for exclusions.

https://doi.org/10.1371/journal.pmed.1002988.g001

Evidence from randomised controlled trials

Forty randomised trials were included, the characteristics of which are detailed in S1 Table, and the risk of bias assessments are summarised in Fig 2, S1 Fig, and S2 Table [22–61]. The trials assessed a range of different magnesium sulphate regimens with varying control groups, and are therefore assessed under 8 different comparisons:

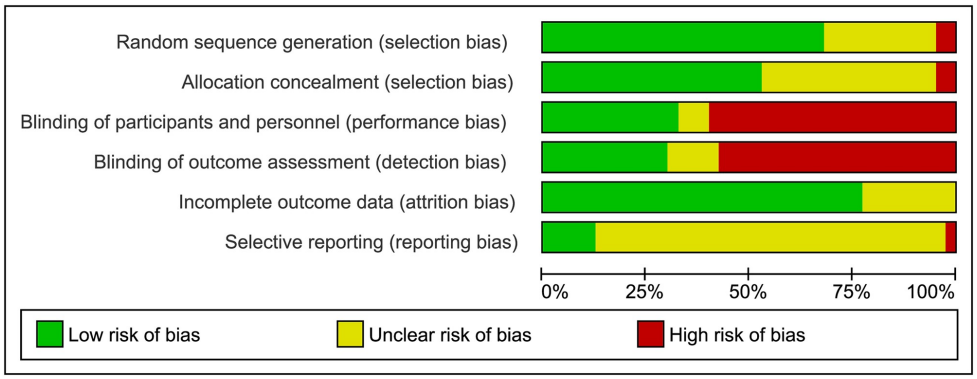

Fig 2. Risk of bias for randomised controlled trials. Risk of bias graph showing judgements about each risk of bias item presented as percentages across the 40 included randomised trials.

https://doi.org/10.1371/journal.pmed.1002988.g002

1. Magnesium sulphate versus placebo or no treatment (18 trials)
2. Lower versus higher dose regimens of magnesium sulphate (8 trials)
3. Intramuscular (IM) versus intravenous (IV) maintenance dose of magnesium sulphate (5 trials)
4. Loading versus loading and maintenance dose of magnesium sulphate (5 trials)
5. Serial IV boluses versus continuous IV infusion of magnesium sulphate (1 trial)
6. Short versus standard maintenance of magnesium sulphate (1 trial)
7. Slower versus standard rate of loading dose infusion of magnesium sulphate (1 trial)
8. Weaning versus no weaning of maintenance of magnesium sulphate (1 trial)

The methodological quality of the 40 trials varied considerably. Considering selection bias, 18 trials were at low risk, reporting adequate methods for sequence generation and allocation concealment. Twelve and 8 trials received an unclear judgement for 1 and 2 of the selection bias domains, respectively. Two trials appeared to be quasi-randomised and thus were at high risk of selection bias. Twelve trials were at low risk of performance and detection bias (with blinding of participants, personnel, and outcome assessors); 21 were at high risk of both performance and detection bias (all trials of different magnesium sulphate regimens, with no reported blinding), and the remaining 7 trials had an unclear judgement for 1 or 2 of the blinding domains. The majority of trials (31) were at low risk of attrition bias for neonatal outcome data, though for 9 trials, this was unclear. Only 5 trials were at low risk of reporting bias, 1 was at high risk of reporting bias, and for the remaining 34 trials, selective reporting was unclear.

Magnesium sulphate versus placebo or no treatment

This comparison included 18 trials. The indication for use of magnesium sulphate in 6 trials was the prevention of eclampsia [30,32,39,43,48,61]; in 6 trials, fetal neuroprotection [28,36,45,47,51,54]; and in 6 trials, the prevention of preterm birth (tocolysis) [33–35,38,40,46].

Magnesium sulphate regimens assessed varied considerably: 4-gram IV loading dose only (2 trials), 4-gram IV loading dose and 1-gram-per-hour IV maintenance dose (4 trials), 4-gram IV loading dose and 2-gram-per-hour IV maintenance (4 trials), 6-gram IV loading dose and 2-gram-per-hour IV maintenance dose (6 trials), and 4-gram IV and 10-gram IM loading dose and 5-gram IM maintenance dose every 4 hours (2 trials), with duration of treatment generally ranging from 12 to 24 hours. Fourteen trials compared magnesium sulphate with a placebo, while 4 trials had a no-treatment comparison (see Table 1 and S1 Appendix for effect estimates, forest plots, and funnel plots).

No clear difference was seen between magnesium sulphate and placebo/no treatment for the primary review outcome perinatal death (RR 1.01; 95% CI 0.92 to 1.10; 8 trials, 13,654 babies; analysis 1.1), nor for stillbirth, neonatal death (no obvious asymmetry observed on visual assessment of funnel plot), death later than 28 days but before discharge, early neonatal death, or late neonatal death (Table 1; S1 Appendix). When considering indication for use, the tocolysis subgroup showed an increase in perinatal death (RR 7.99; 95% CI 1.00 to 63.49; 2 trials, 257 babies; analysis 1.1.1) that was not observed in the pre-eclampsia or fetal neuroprotection subgroups. The subgroup interaction test, however, did not indicate a differential effect according to treatment indication ($\chi^2 = 4.07$, $P = 0.13$, $I^2 = 50.8\%$). For the remaining mortality outcomes, subgroup interaction tests did not indicate differential treatment effects according to indication for administration (see Tables 2 and 3 for effect estimates for individual subgroups and results from subgroup interaction tests).

Babies exposed to antenatal magnesium sulphate had a 67% relative increase in the risk of having an Apgar score less than 7 at 1 minute (RR 1.67; 95% CI 1.02 to 2.73; 2 trials, 199 babies; analysis 1.7), and over 2 times the risk of need for volume expansion compared with babies not exposed (RR 2.03; 95% CI 1.01 to 4.10; 1 trial, 87 babies; analysis 1.28). A subgroup of babies born less than 32 weeks gestation exposed to antenatal magnesium sulphate had a 62% relative reduction in the risk of intracerebral echodensity, compared with babies not exposed (RR 0.38; 95% CI 0.19 to 0.79; 1 trial, 1,613 babies; analysis 1.46). While a difference in intracerebral echolucency was not observed in all babies, a 39% relative reduction was seen for babies born less than 32 weeks exposed to antenatal magnesium sulphate (RR 0.61; 95% CI 0.38 to 0.97; 1 trial, 1,613 babies; analysis 1.47.2) (Table 1; S1 Appendix).

There were no clear differences between magnesium sulphate and placebo/no treatment for all remaining secondary outcomes reported (Table 1; S1 Appendix).

Lower versus higher dose regimens

This comparison included 8 trials, with 6 assessing magnesium sulphate for treatment of eclampsia or severe pre-eclampsia [22,23,44,52,56,59], and 2 for the prevention of preterm birth (tocolysis) [26,60]. Regimens assessed varied: lower dose regimens included a 4- to 10-gram loading dose with a 0.625- to 2-gram-per-hour maintenance dose; higher dose regimens assessed included a 4- to 14-gram loading dose with a 1.25- to 5-gram-per-hour maintenance dose (see Table 4 and S1 Appendix for effect estimates and forest plots).

No clear differences between the lower and higher dose regimens of magnesium sulphate were seen for the primary review outcome perinatal death (RR 1.01; 95% CI 0.75 to 1.36; 6 trials, 543 babies; analysis 2.1), nor for stillbirth or neonatal death (Table 4; S1 Appendix). For all mortality outcomes, subgroup interaction tests did not indicate differential treatment effects according to indication for administration of antenatal magnesium sulphate (see Table 5 for effect estimates for individual subgroups and results from subgroup interaction tests).

Babies exposed to the lower dose versus higher dose regimens of magnesium sulphate had an increased risk of neonatal intensive care unit admission (RR 1.75; 95% CI 1.06 to 2.88; 5

Table 1. Adverse outcome estimates from randomised controlled trials: Comparison 1—Magnesium sulphate versus placebo or no treatment.

Outcome	Studies	Participants	Method (I^2)	RR (95% CI)
1.1 Perinatal death	8	13,654	F (23%)	1.01 (0.92, 1.10)
1.2 Stillbirth	9	12,340	F (0%)	0.99 (0.87, 1.12)
1.3 Neonatal death	11	12,987	F (21%)	1.00 (0.86, 1.17)
1.4 Death > 28 days, before discharge	5	10,691	F (0%)	0.96 (0.60, 1.53)
1.5 Early neonatal death	1	9,024	F (NA)	1.09 (0.86, 1.37)
1.6 Late neonatal death	1	9,024	F (NA)	1.54 (0.95, 2.49)
1.7 Apgar score < 7 at 1 minute	2	199	F (17%)	**1.67 (1.02, 2.73)**
1.8 Apgar score < 7 at 5 minutes	5	12,729	F (0%)	1.02 (0.92, 1.14)
1.9 Meconium at birth	1	210	F (NA)	1.55 (0.89, 2.72)
1.10 Intubated at birth	3	11,364	F (30%)	0.95 (0.87, 1.04)
1.11 Resuscitation in the delivery room				
1.11.1 Any	1	2,416	F (NA)	0.99 (0.96, 1.03)
1.11.2 Oxygen bag, mask, or both	1	2,416	F (NA)	1.07 (0.98, 1.17)
1.11.3 Chest compressions	1	2,416	F (NA)	1.11 (0.73, 1.71)
1.12 Respiratory distress syndrome	7	3,639	R (46%)	0.95 (0.79, 1.14)
1.13 Transient tachypnoea of the newborn	2	243	F (0%)	0.96 (0.52, 1.77)
1.14 Surfactant	1	87	F (NA)	0.88 (0.62, 1.24)
1.15 Mechanical ventilation	5	12,751	R (63%)	1.01 (0.94, 1.09)
1.16 Non-invasive ventilation	1	688	F (NA)	1.03 (0.93, 1.15)
1.17 Oxygen required	1	153	F (NA)	0.95 (0.67, 1.35)
1.18 Chronic lung disease	5	4,513	F (0%)	1.06 (0.96, 1.17)
1.19 Apnoea and bradycardia	2	841	F (0%)	1.23 (0.98, 1.53)
1.20 Pneumothorax	1	87	F (NA)	2.44 (0.26, 22.52)
1.21 Pulmonary haemorrhage	1	87	F (NA)	2.44 (0.52, 11.41)
1.22 Necrotising enterocolitis	8	4,804	F (0%)	1.21 (0.98, 1.51)
1.23 Sepsis	4	2,694	R (31%)	0.83 (0.54, 1.28)
1.24 Hypoglycaemia on NICU admission	1	34	F (NA)	0.63 (0.06, 6.34)
1.25 Poor feeding	1	90	F (NA)	No events
1.26 Patent ductus arteriosus	3	2,536	F (26%)	0.97 (0.80, 1.17)
1.27 Hypotension	2	3,103	F (22%)	1.03 (0.89, 1.19)
1.28 Volume expansion	1	87	F (NA)	**2.03 (1.01, 4.10)**
1.29 Mean blood pressure < 10th centile in the first 24 hours	1	87	F (NA)	1.30 (0.67, 2.53)
1.30 Superior vena cava flow < 41 ml/kg/min in the first 24 hours	1	87	F (NA)	1.22 (0.62, 2.40)
1.31 Right ventricular output < 120 ml/kg/min in the first 24 hours	1	87	F (NA)	1.08 (0.51, 2.30)
1.32 Dobutamine	1	87	F (NA)	1.73 (0.84, 3.57)
1.33 Dopamine	1	87	F (NA)	2.17 (0.62, 7.62)
1.34 Any inotrope	1	87	F (NA)	1.54 (0.82, 2.92)
1.35 Retinopathy of prematurity	1	2,415	F (NA)	0.99 (0.85, 1.14)
1.36 Generalised hypotonicity	1	2,415	F (NA)	1.03 (0.77, 1.37)
1.37 Seizures	4	11,397	F (0%)	0.78 (0.57, 1.06)
1.38 Hyperbilirubinaemia	1	90	F (NA)	2.00 (0.19, 21.28)
1.39 Intraventricular haemorrhage	10	4,891	F (0%)	0.95 (0.85, 1.06)
1.40 Intraventricular haemorrhage, grade 3 or 4	6	3,769	F (19%)	0.81 (0.60, 1.09)
1.41 Periventricular leucomalacia	4	4,225	F (0%)	0.93 (0.68, 1.28)
1.42 Any white matter injury	1	665	F (NA)	0.87 (0.62, 1.22)
1.43 Severe white matter injury	1	688	F (NA)	0.85 (0.55, 1.32)
1.44 Severe white matter injury or death	1	688	F (NA)	0.92 (0.66, 1.28)

(*Continued*)

Table 1. (Continued)

Outcome	Studies	Participants	Method (I^2)	RR (95% CI)
1.45 Persistent parenchymal echogenicity	1	8,260	F (NA)	1.09 (0.66, 1.81)
1.46 Echodensity in children born < 32 weeks	1	1,613	F (NA)	**0.38 (0.19, 0.79)**
1.47 Echolucency				
1.47.1 In all children	1	1,776	F (NA)	0.62 (0.37, 1.03)
1.47.2 In children born < 32 weeks	1	1,613	F (NA)	**0.61 (0.38, 0.97)**
1.48 Ventriculomegaly	2	10,036	F (0%)	0.98 (0.68, 1.42)
1.49 Any of echodensity, echolucency, intraventricular haemorrhage, periventricular haemorrhage, or ventriculomegaly				
1.49.1 In all children	1	1,776	F (NA)	0.85 (0.69, 1.06)
1.49.2 In children born < 32 weeks	1	1,613	F (NA)	0.92 (0.78, 1.09)
1.50 Composite adverse outcome	1	1,776	F (NA)	0.62 (0.37, 1.03)
1.51 NICU admission	3	8,519	F (17%)	1.00 (0.95, 1.06)
1.52 Intensive care unit stay (days)	1	120	MD, F (NA)	0.02 (−0.17, 0.21)
1.53 Hospital stay (days)	2	257	MD, R (99%)	−2.75 (−8.92, 3.43)
1.54 Special care baby unit admission > 7 days or death	1	9,024	F (NA)	1.01 (0.95, 1.08)
1.55 Special care baby unit admission > 7 days	1	8,260	F (NA)	1.02 (0.93, 1.11)
1.56 Still in hospital at 6 weeks	1	9,024	F (NA)	0.99 (0.06, 15.80)

Statistically significant effect estimates in bold. Test for heterogeneity represented by I^2 statistic; where $I^2 > 30\%$, summary estimates were calculated using random-effects meta-analysis.

CI, confidence interval; F, fixed-effects; MD, mean difference; NA, not applicable; NICU, neonatal intensive care unit; R, random-effects; RR, risk ratio.

https://doi.org/10.1371/journal.pmed.1002988.t001

Table 2. Subgroup analyses based on indication for use from randomised controlled trials: Comparison 1—Magnesium sulphate versus placebo or no treatment.

Outcome and subgroup	Studies	Participants	Method (I^2)	RR (95% CI)	χ^2, *P* value, I^2
1.1 Perinatal death					
1.1.1 Tocolysis	2	257	F (NA)	**7.99 (1.00, 63.49)**	4.07, 0.13, 50.8%
1.1.2 Pre-eclampsia	2	9,259	F (0%)	1.01 (0.91, 1.13)	
1.1.3 Fetal neuroprotection	4	4,138	F (0%)	0.96 (0.80, 1.15)	
1.2 Stillbirth					
1.2.1 Tocolysis	2	257	F (NA)	5.70 (0.28, 116.87)	1.45, 0.49, 0%
1.2.2 Pre-eclampsia	3	9,961	F (8%)	0.99 (0.87, 1.12)	
1.2.3 Fetal neuroprotection	4	2,122	F (0%)	0.85 (0.40, 1.80)	
1.3 Neonatal death					
1.3.1 Tocolysis	4	445	R (61%)	0.78 (0.11, 5.67)	0.48, 0.79, 0%
1.3.2 Pre-eclampsia	2	9,259	R (35%)	1.03 (0.64, 1.65)	
1.3.3 Fetal neuroprotection	5	3,283	R (0%)	0.86 (0.68, 1.08)	
1.4 Death > 28 days, before discharge					
1.4.1 Tocolysis	3	412	F (0%)	0.76 (0.19, 3.09)	0.37, 0.83, 0%
1.4.2 Pre-eclampsia	1	9,024	F (NA)	1.13 (0.55, 2.31)	
1.4.3 Fetal neuroprotection	1	1,255	F (NA)	0.88 (0.44, 1.74)	

Statistically significant effect estimates in bold. Test for heterogeneity represented by I^2 statistic; where $I^2 > 30\%$, summary estimates were calculated using random-effects meta-analysis. Result of test subgroup differences represented by χ^2 statistic, *P* value, and I^2 statistic.

CI, confidence interval; F, fixed-effects; NA, not applicable; R, random-effects; RR, risk ratio.

https://doi.org/10.1371/journal.pmed.1002988.t002

Table 3. Subgroup analyses based on regimen characteristics from randomised controlled trials: Comparison 1—Magnesium sulphate versus placebo or no treatment.

Outcome or subgroup	Studies	Participants	Method (I^2)	RR (95% CI)	χ^2, *P* value, I^2
Subgroups based on LD					
1.1 Perinatal death					
1.1.4 4-g IV LD	5	2,259	R (42%)	0.96 (0.62, 1.49)	0.57, 0.75, 0%
1.1.5 6-g IV LD	1	2,136	R (NA)	1.12 (0.85, 1.47)	
1.1.6 4-g IV and 10-g IM LD	2	9,259	R (0%)	1.01 (0.91, 1.12)	
1.2 Stillbirth					
1.2.4 4-g IV LD	6	2,961	F (0%)	1.25 (0.85, 1.84)	1.57, 0.21, 36.1%
1.2.5 6-g IV LD	1	120	F (NA)	No events	
1.2.6 4-g IV and 10-g IM LD	2	9,259	F (0%)	0.96 (0.84, 1.10)	
1.3 Neonatal death					
1.3.4 4-g IV LD	6	2,294	R (7%)	0.86 (0.64, 1.16)	0.44, 0.80, 0%
1.3.5 6-g IV LD	3	1,434	R (2%)	0.83 (0.48, 1.44)	
1.3.6 4-g IV and 10-g IM LD	2	9,259	R (35%)	1.03 (0.64, 1.65)	
1.4 Death > 28 days, before discharge					
1.4.4 4-g IV LD	3	1,514	F (0%)	0.81 (0.43, 1.53)	0.81, 0.67, 0%
1.4.5 6-g IV LD	1	153	F (NA)	2.47 (0.10, 59.70)	
1.4.6 4-g IV and 10-g IM LD	1	9,024	F (NA)	1.13 (0.55, 2.31)	
Subgroups based on MD					
1.1 Perinatal death					
1.1.7 LD only	2	747	R (0%)	0.92 (0.59, 1.44)	2.73, 0.44, 0%
1.1.8 1-g/hour IV MD	1	1,255	R (NA)	0.81 (0.60, 1.09)	
1.1.9 2–5-g/hour IV MD	3	2,393	R (71%)	2.27 (0.35, 14.55)	
1.1.10 5-g/4-hour IM MD	2	9,259	R (0%)	1.01 (0.91, 1.12)	
1.2 Stillbirth					
1.2.7 LD only	2	747	F (0%)	0.96 (0.22, 4.17)	2.50, 0.48, 0%
1.2.8 1-g/hour IV MD	2	1,957	F (9%)	1.22 (0.81, 1.83)	
1.2.9 2–5-g/hour IV MD	3	377	F (0%)	5.70 (0.28, 116.87)	
1.2.10 5-g/4-hour IM MD	2	9,259	F (0%)	0.96 (0.84, 1.10)	
1.3 Neonatal death					
1.3.7 LD only	2	747	R (0%)	0.93 (0.58, 1.47)	0.72, 0.87, 0%
1.3.8 1-g/hour IV MD	1	1,255	R (NA)	0.81 (0.59, 1.11)	
1.3.9 2–5-g/hour IV MD	6	1,726	R (41%)	0.84 (0.30, 2.33)	
1.3.10 5-g/4-hour IM MD	2	9,259	R (35%)	1.03 (0.64, 1.65)	
1.4 Death > 28 days, before discharge					
1.4.7 1-g/hour IV MD	1	1,255	F (NA)	0.88 (0.44, 1.74)	0.37, 0.83, 0%
1.4.8 2–5-g/hour IV MD	3	412	F (0%)	0.76 (0.19, 3.09)	
1.4.9 5-g/4-hour IM MD	1	9,024	F (NA)	1.13 (0.55, 2.31)	

Test for heterogeneity represented by I^2 statistic; where $I^2 > 30\%$, summary estimates were calculated using random-effects meta-analysis. Result of test subgroup differences represented by χ^2 statistic, *P* value, and I^2 statistic.

CI, confidence interval; F, fixed-effects; g, gram; IM, intramuscular; IV, intravenous; LD, loading dose; MD, maintenance dose; NA, not applicable; R, random-effects; RR, risk ratio.

https://doi.org/10.1371/journal.pmed.1002988.t003

trials, 409 babies; analysis 2.17). On average, babies exposed to the lower dose regimen had a longer duration of stay in the neonatal intensive care unit compared with those exposed to the higher dose regimen (MD 3.10 days; 95% CI 0.78 to 5.42; 1 trial, 104 babies; analysis 2.18) (Table 4; S1 Appendix).

Table 4. Adverse outcome estimates from randomised controlled trials: Comparison 2—Lower versus higher dose regimens of magnesium sulphate.

Outcome	Studies	Participants	Method (I^2)	RR (95% CI)
2.1 Perinatal death	6	543	F (0)	1.01 (0.75, 1.36)
2.2 Stillbirth	5	471	F (0)	0.94 (0.61, 1.45)
2.3 Neonatal death	6	535	F (0)	1.12 (0.57, 2.22)
2.4 Apgar score < 7 at 1 minute	3	302	F (0)	0.96 (0.68, 1.35)
2.5 Apgar score < 7 at 5 minutes	3	302	R (35%)	1.41 (0.54, 3.65)
2.6 Resuscitation	1	64	F (NA)	1.00 (0.22, 4.59)
2.7 Respiratory distress syndrome	2	154	R (53%)	1.97 (0.76, 5.15)
2.8 Respiratory depression	1	50	F (NA)	0.33 (0.04, 2.99)
2.9 Respiratory disorders	1	64	F (NA)	1.08 (0.87, 1.33)
2.10 Mechanical ventilation	1	64	F (NA)	2.00 (0.39, 10.16)
2.11 Bradycardia	1	104	F (NA)	3.85 (0.45, 33.29)
2.12 Jaundice	1	50	F (NA)	1.25 (0.38, 4.12)
2.13 Hypoglycaemia	1	104	F (NA)	0.96 (0.06, 14.98)
2.14 Hypocalcaemia	1	104	F (NA)	2.89 (0.12, 69.32)
2.15 Hypotonia	1	50	F (NA)	0.14 (0.02, 1.08)
2.16 Requirement for calcium gluconate	1	50	F (NA)	0.25 (0.06, 1.06)
2.17 NICU admission	5	409	F (6%)	**1.75 (1.06, 2.88)**
2.18 NICU stay (days)	1	104	MD, F (NA)	**3.10 (0.78, 5.42)**

Statistically significant effect estimates in bold. Test for heterogeneity represented by I^2 statistic; where $I^2 > 30\%$, summary estimates were calculated using random-effects meta-analysis.

CI, confidence interval; F, fixed-effects; MD, mean difference; NA, not applicable; NICU, neonatal intensive care unit; R, random-effects; RR, risk ratio.

https://doi.org/10.1371/journal.pmed.1002988.t004

No clear differences were seen between the lower and higher dose regimens of magnesium sulphate for the remaining secondary outcomes reported (Table 4; S1 Appendix).

IM versus IV maintenance dose

This comparison included 5 trials, all assessing magnesium sulphate for the prevention or treatment of eclampsia [27,31,49,55,58]. Regimens assessed included Bhattacharjee's regimen

Table 5. Subgroup analyses based on indication for use from randomised controlled trials: Comparison 2—Lower versus higher dose regimens of magnesium sulphate.

Outcome and subgroup	Studies	Participants	Method (I^2)	RR (95% CI)	χ^2, *P* value, I^2
2.1 Perinatal death					
2.1.1 Tocolysis	1	104	F (NA)	2.25 (0.61, 8.21)	1.63, 0.20, 38.6%
2.1.2 Pre-eclampsia/eclampsia	5	439	F (0%)	0.94 (0.70, 1.28)	
2.2 Stillbirth					
2.2.1 Tocolysis	1	104	F (NA)	0.96 (0.06, 14.98)	0.00, 0.99, 0%
2.2.2 Pre-eclampsia/eclampsia	4	367	F (0%)	0.94 (0.60, 1.46)	
2.3 Neonatal death					
2.3.1 Tocolysis	1	104	F (NA)	2.89 (0.61, 13.65)	1.99, 0.16, 49.6%
2.3.2 Pre-eclampsia/eclampsia	5	431	F (0%)	0.82 (0.37, 1.82)	

Test for heterogeneity represented by I^2 statistic; where $I^2 > 30\%$, summary estimates were calculated using random-effects meta-analysis. Result of test subgroup differences represented by χ^2 statistic, *P* value, and I^2 statistic.

CI, confidence interval; F, fixed-effects; NA, not applicable; RR, risk ratio.

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(4-gram IV loading dose; 6-gram IV maintenance dose every 8 hours), Dhaka regimen (4-gram IV and 6-gram IM loading dose; 2.5-gram IM maintenance dose every 4 hours), Pritchard's regimen (4-gram IV and 10-gram IM loading dose; 5-gram IM maintenance dose every 4 hours), Zuspan's regimen (4-gram IV loading dose; 1-gram IV maintenance dose every hour), and Sibai's regimen (6-gram IV loading dose; 2-gram IV maintenance dose every hour) (all maintenance doses were for 24 hours after birth or last seizure) (see Table 6 and S1 Appendix for effect estimates and forest plots).

No clear differences were observed for

- Pritchard's versus Zuspan's regimen for the primary review outcome perinatal death (RR 0.94; 95% CI 0.66 to 1.32; 2 trials, 353 babies; analysis 3.1.1), nor for stillbirth or neonatal death;
- Pritchard's versus Sibai's regimen for the primary review outcome perinatal death (RR 0.90; 95% CI 0.53 to 1.53; 1 trial, 115 babies; analysis 3.1.2), nor for stillbirth or neonatal death;
- Pritchard's versus Bhattacharjee's regimen for the primary review outcome perinatal death (RR 1.28; 95% CI 0.61 to 2.65; 1 trial, 107 babies; analysis 3.1.3), nor for stillbirth or neonatal death;
- Dhaka versus Zuspan's regimen for the primary review outcome perinatal death (RR 0.57; 95% CI 0.16 to 2.08; 1 trial, 41 babies; analysis 3.1.4), nor for stillbirth or neonatal death (Table 6; S1 Appendix).

No clear differences were observed for Pritchard's versus Zuspan's regimen, Pritchard's versus Sibai's regimen, or Dhaka versus Zuspan's regimen for the remaining secondary outcomes reported (Table 6; S1 Appendix).

Loading dose versus loading and maintenance doses

This comparison included 5 trials, all assessing magnesium sulphate for the prevention or treatment of eclampsia [25,41,50,53,57]. Trials compared a cumulative 8-, 10-, or 14-gram loading dose (4 grams IV and 4 to 10 grams IM) with Dhaka or Pritchard's regimen (see descriptions above; and see Table 6 and S1 Appendix for effect estimates and forest plots).

No clear differences for loading dose only versus loading and maintenance dose regimens were seen for the primary review outcome perinatal death (average RR 0.94; 95% CI 0.33 to 2.72; 3 trials, 632 babies; analysis 4.1), nor for stillbirth, neonatal death, or neonatal death at less than 7 days (Table 6; S1 Appendix).

No clear differences for loading dose only versus loading and maintenance dose regimens were seen for the remaining secondary outcomes reported (Table 6; S1 Appendix).

Serial IV boluses versus continuous IV maintenance dose

This comparison included 1 trial, assessing magnesium sulphate for the treatment of severe pre-eclampsia, and compared a serial intravenous bolus regimen (6-gram IV loading dose, and 2-gram IV bolus over 10 minutes every 2 hours as maintenance) with a continuous infusion (4-gram IV loading dose, and 1-gram-per-hour continuous IV maintenance dose) [37] (see Table 6 and S1 Appendix for effect estimates and forest plots).

No clear differences between the serial bolus and continuous infusion regimens were seen for the primary review outcome perinatal death (RR 0.44; 95% CI 0.08 to 2.34; 1 trial, 197 babies; analysis 5.1), nor for stillbirth or neonatal death (Table 6; S1 Appendix).

No clear differences between the serial bolus and continuous infusion regimens were seen for the remaining secondary outcomes reported (Table 6; S1 Appendix).

Table 6. Adverse outcome estimates from randomised controlled trials: Comparisons 3–8.

Outcome and subgroup	Studies	Participants	Method (I^2)	RR (95% CI)
Comparison 3: IM versus IV maintenance dose of magnesium sulphate (pre-eclampsia/eclampsia)				
3.1 Perinatal death				
3.1.1 Pritchard's versus Zuspan's regimen	2	353	F (0%)	0.94 (0.66, 1.32)
3.1.2 Pritchard's versus Sibai's regimen	1	115	F (NA)	0.90 (0.53, 1.53)
3.1.3 Pritchard's versus Bhattacharjee's regimen	1	107	F (NA)	1.28 (0.61, 2.65)
3.1.4 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.57 (0.16, 2.08)
3.2 Stillbirth				
3.2.1 Pritchard's versus Zuspan's regimen	1	114	F (NA)	0.79 (0.44, 1.40)
3.2.2 Pritchard's versus Sibai's regimen	2	133	F (0%)	0.80 (0.46, 1.41)
3.2.3 Pritchard's versus Bhattacharjee's regimen	1	107	F (NA)	1.18 (0.38, 3.63)
3.2.4 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.24 (0.03, 1.95)
3.3 Neonatal death				
3.3.1 Pritchard's versus Zuspan's regimen	1	114	F (NA)	2.52 (0.27, 23.47)
3.3.2 Pritchard's versus Sibai's regimen	1	115	F (NA)	2.56 (0.27, 23.93)
3.3.3 Pritchard's versus Bhattacharjee's regimen	1	107	F (NA)	1.37 (0.47, 4.06)
3.3.4 Dhaka versus Zuspan's regimen	1	41	F (NA)	1.90 (0.19, 19.40)
3.4 Apgar score < 7 at 1 minute				
3.4.1 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.32 (0.10, 1.01)
3.5 Apgar score < 7 at 5 minutes				
3.5.1 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.38 (0.08, 1.74)
3.6 Respiratory distress syndrome				
3.6.1 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.76 (0.24, 2.44)
3.7 Jaundice				
3.7.1 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.76 (0.24, 2.44)
3.8 Hypotonia				
3.8.1 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.48 (0.10, 2.32)
3.9 NICU admission				
3.9.1 Pritchard's versus Zuspan's regimen	1	114	F (NA)	0.98 (0.35, 2.73)
3.9.2 Pritchard's versus Sibai's regimen	1	115	F (NA)	1.00 (0.36, 2.78)
3.9.3 Dhaka versus Zuspan's regimen	1	41	F (NA)	0.76 (0.24, 2.44)
Comparison 4: Loading dose versus loading and maintenance doses of magnesium sulphate (pre-eclampsia/eclampsia)				
4.1 Perinatal death	3	632	R (63%)	0.94 (0.33, 2.72)
4.2 Stillbirth	3	803	F (26%)	1.10 (0.77, 1.58)
4.3 Neonatal death	2	462	F (0%)	0.78 (0.43, 1.41)
4.4 Neonatal death < 7 days	1	402	F (NA)	0.73 (0.30, 1.77)
4.5 Apgar score < 7 at 0 minutes	1	52	F (NA)	1.07 (0.32, 3.54)
4.6 Apgar score < 7 at 1 minute	1	52	F (NA)	0.86 (0.06, 12.98)
4.7 Apgar score < 7 at 5 minutes	2	406	F (NA)	1.61 (0.72, 3.62)
4.8 NICU admission for respiratory distress	2	397	F (0%)	1.02 (0.63, 1.65)
4.9 NICU admission for early onset sepsis	1	80	F (NA)	1.00 (0.06, 15.44)
4.10 NICU admission for late onset sepsis	1	80	F (NA)	3.00 (0.13, 71.51)
4.11 NICU admission for meconium aspiration syndrome	1	80	F (NA)	1.00 (0.06, 15.44)
4.12 NICU admission for birth asphyxia	1	80	F (NA)	0.33 (0.01, 7.95)
4.13 NICU admission	3	435	F (0%)	0.94 (0.77, 1.15)
Comparison 5: Serial intravenous boluses versus continuous intravenous maintenance of magnesium sulphate (pre-eclampsia)				
5.1 Perinatal death	1	197	F (NA)	0.44 (0.08, 2.34)
5.2 Stillbirth	1	197	F (NA)	0.29 (0.01, 7.09)

(*Continued*)

Table 6. (Continued)

Outcome and subgroup	Studies	Participants	Method (I^2)	RR (95% CI)
5.3 Neonatal death	1	197	F (NA)	0.58 (0.10, 3.42)
5.4 Intubated at birth	1	197	F (NA)	0.88 (0.29, 2.62)
5.5 Mechanical ventilation	1	197	F (NA)	0.44 (0.11, 1.70)
5.6 Bradycardia (<110 bpm)	1	197	F (NA)	0.44 (0.08, 2.34)
5.7 Special care baby unit admission	1	197	F (NA)	0.84 (0.53, 1.35)
Comparison 6: Short versus standard maintenance course of magnesium sulphate (eclampsia)				
6.1 Stillbirth	1	98	F (NA)	0.87 (0.41, 1.82)
6.2 Birth asphyxia	1	98	F (NA)	0.83 (0.24, 2.92)
Comparison 7: Slower versus standard rate of loading dose of magnesium sulphate (fetal neuroprotection)				
7.1 Stillbirth	1	51	F (NA)	0.35 (0.01, 8.12)
Comparison 8: Weaning versus no weaning of magnesium sulphate (tocolysis)				
8.1 Apgar score < 7 at 5 minutes	1	141	F (NA)	0.65 (0.22, 1.90)

Test for heterogeneity represented by I^2 statistic; where $I^2 > 30\%$, summary estimates were calculated using random-effects meta-analysis. Bhattacharjee's regimen: 4-g IV LD; 6-g IV/8 hours MD. Dhaka regimen: 4-g IV and 6-g IM LD; 2.5-g IM/4-hour MD. Pritchard's regimen: 4-g IV and 10-g IM LD; 5-g IM/4-hour MD. Sibai's regimen: 6-g IV LD; 2-g IV/hour MD. Zuspan's regimen: 4-g IV LD; 1-g IV/hour MD. All MDs for 24 hours after birth/last seizure.

bpm, beats per minute; CI, confidence interval; F, fixed-effects; g, gram; IM, intramuscular; IV, intravenous; LD, loading dose; MD, maintenance dose; NA, not applicable; NICU, neonatal intensive care unit; R, random-effects; RR, risk ratio.

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Short versus standard maintenance course

This comparison included 1 trial, assessing magnesium sulphate for the treatment of eclampsia. Both groups received a 4-gram IV and 10-gram IM loading dose, followed by either a short maintenance course (2 doses of 5 grams IM 4 hours apart after birth or last seizure) or a standard maintenance course (5 grams IM every 4 hours for 24 hours after birth or last seizure) [29].

No clear difference between the short and standard maintenance course regimens was seen for stillbirth. No clear difference between the short and standard maintenance course regimens was seen for the only other secondary outcome reported, birth asphyxia (see Table 6 and S1 Appendix for effect estimates and forest plots).

Slower versus standard rate of loading dose

This comparison included 1 trial, assessing magnesium sulphate for fetal neuroprotection, and compared a slower (over 60 minutes) versus standard (over 20 minutes) rate of administering a 4-gram IV loading dose of magnesium sulphate (all women received a 1-gram-per-hour maintenance dose for 24 hours or until birth) [24].

No clear difference between a slower and standard rate of loading dose administration was seen for stillbirth (see Table 6 and S1 Appendix for effect estimate and forest plot).

Weaning versus no weaning

This comparison included 1 trial, assessing magnesium sulphate for the prevention of preterm birth (tocolysis), and compared weaning (by 1 gram IV per 4 hours) versus not weaning magnesium sulphate (all women received a 6-gram IV loading dose, and 2- to 3.5-gram IV maintenance dose per hour until tocolysis was achieved) [42].

No clear difference between weaning and no weaning was seen for Apgar score less than 7 at 5 minutes (see Table 6 and S1 Appendix for effect estimate and forest plot).

Evidence from non-randomised comparative studies

One hundred thirty-eight non-randomised studies were included: 5 non-randomised trials, 35 prospective cohort studies (7 with nested case–control analyses), 82 retrospective cohort studies (16 with nested case–control analyses), 8 non-concurrent cohort studies, and 8 case–control studies [62–199]. The characteristics of the studies and risk of bias assessments are detailed in S1 and S2 Tables.

There was substantial variation in the characteristics of these studies regarding participants, indications for use of magnesium sulphate (prevention or treatment of eclampsia: 30 studies; prevention of preterm birth (tocolysis): 28 studies; fetal neuroprotection: 25 studies; combination of aforementioned indications: 38 studies; unclear: 17 studies), comparison groups, outcomes assessed (and their definitions), and analysis methods employed. Methodological quality (specifically in relation to the risk of bias for reported review outcomes of interest) also differed across the studies, with overall judgements of unclear (specifically when only abstracts were available), high, moderate to high, and moderate risk of bias assigned to 43 studies, 49 studies, 35 studies, and 11 studies, respectively. The most common concerns across studies related to the potential for confounding (with no attempt to balance allocation between groups or match groups, and/or important confounding variables not taken into account in relevant outcome analyses), detection bias (with the consistent implementation of valid and reliable measures being unclear, and/or the absence of blinding of exposure or outcome assessors), and performance bias (with protocols not available to assess important variations).

The primary review outcome, perinatal death, was reported by 11 of the 138 non-randomised studies, 10 of which showed either a possible reduction (or lower rate) or no clear difference (or similar rate) in perinatal death among babies exposed to magnesium sulphate compared with no magnesium sulphate or a different magnesium sulphate regimen. A possible increase in perinatal death, specifically among babies exposed to >48 versus ≤48 grams of magnesium sulphate for tocolysis was shown in in the 11th study (retrospective cohort of 127 babies, moderate to high risk of bias) [183]. See Table 7 and S3 Table for summaries of individual study results.

For the majority of secondary pre-specified and non-pre-specified adverse neonatal outcomes reported, the results from non-randomised studies were consistent with those observed in randomised controlled trials, with no clear differences (and in some cases, possible benefits of magnesium sulphate) observed. The direction of the findings (no clear difference, possible benefit, possible harm, or mixed) from the non-randomised studies are summarised in Table 8, with the detailed individual study results provided in S3 Table.

Seventeen of the 138 non-randomised studies (14 at moderate or moderate to high risk of bias, and 3 at unclear risk of bias [abstracts only]) observed a possible increase in the risk of adverse neonatal outcomes with antenatal magnesium sulphate, with some consideration of important confounding variables in relevant outcome analyses [68,73,84,90,106,108,109,129,132,134,140,152,153,173,180,184,191]. Potential increased risks with antenatal magnesium sulphate of 4 outcomes (discussed below) were observed by more than 1 study. For the remaining outcomes (nosocomial infection [184], enteral feeding intolerance [68], respiratory disease composite [153], pulmonary interstitial emphysema [191], early germinal matrix/intraventricular haemorrhage [180], thalamostriate or mineralising vasculopathy [152], and a composite neonatal adverse outcome [73]), single studies reported possible harms.

Potential increased risk of neonatal death before intensive care unit discharge, and of a composite outcome of neonatal death before intensive care unit discharge and/or necrotising enterocolitis, was shown among a subgroup of babies born less than 26 weeks gestation with

Table 7. Perinatal death from non-randomised studies.

Study; design	Participants	Comparisons	Results summary
Adama-Hondegla 2013; RCS with CCS (N)	178 babies born to women with eclampsia	(1) Babies living at seventh day of life, $N = 147$ babies, versus (2) stillbirths and neonatal deaths in first 7 days, $N = 31$ babies	$MgSO_4$ exposure: aOR 1.04, $P > 0.05$
Alexander 2006; PCS	87 babies born to women with eclampsia	(1) No gestational hypertension, no $MgSO_4$, $N = 49$ babies, versus (2) gestational hypertension, $MgSO_4$, $N = 11$ babies, versus (3) gestational hypertension, no $MgSO_4$, $N = 27$ babies	Perinatal death: 6.1% (3/49) versus 0% (0/11) versus 11.1% (3/27)
Cawyer 2019; RCS	2,468 babies born to women with pre-eclampsia >32 weeks GA	(1) $MgSO_4$, $N = 1,353$ babies, versus (2) no $MgSO_4$, $N = 1,115$ babies	Perinatal or neonatal death: 0.1% (2/1,353) versus 0.2% (2/1,115), $P = 1.00$
Chowdhury 2009; PCS	529 babies born to women with eclampsia	(1) $MgSO_4$ Pritchard's regimen, $N = 406$ babies, versus (2) $MgSO_4$ low dose IV regimen, $N = 123$ babies	Perinatal death: OR 1.58, 95% CI 0.93–2.61, $P = 0.075$
Jung 2018; RCS	184 babies born to women with ROM <32 weeks GA	(1) $MgSO_4$ for tocolysis, $N = 143$ babies, versus (2) no $MgSO_4$, $N = 41$ babies	Perinatal death: Overall: 7.0% (10/143) versus 19.5% (8/41), $P = 0.0375$; ROM at 23 to 27+6 weeks GA: 14.3% (9/63) versus 36.8% (7/19), $P = 0.0651$; ROM at 28 to 31+6 weeks GA: 1.25% (1/80) versus 4.5% (1/22), $P = 0.9051$
Kamilya 2005; CCS (N)	1,205 babies born to women with eclampsia	(1) Birth year 2002–2004 (almost universal $MgSO_4$), $N = 481$ babies, versus (2) birth year 1995–1997 (no $MgSO_4$), $N = 724$ babies	Perinatal death: 24.3% (117/481) versus 54.8% (397/724)
Kamyar 2016a; RCS (secondary analysis RCT)	396 babies born to women with intrapartum clinical chorioamnionitis	(1) $MgSO_4$ for fetal neuroprotection, $N = 192$ babies, versus (2) placebo, $N = 204$ babies	Stillbirth or death by 1 year: Overall: aRR 1.68, 95% CI 0.85–3.32; ≤28 weeks GA: aRR 1.34, 95% CI 0.47–2.73
Mitani 2011; RCS	425 babies born between 22 and 31 weeks GA	(1) $MgSO_4$ for tocolysis, $N = 236$ babies, versus (2) no $MgSO_4$, $N = 189$ babies	Perinatal death: 5.5% (13/236) versus 9.0% (17/189), $P = 0.185$
Okusanya 2012; NRT	103 babies born to women with severe pre-eclampsia or eclampsia	Severe pre-eclampsia: (1) 10-g $MgSO_4$ LD, $N = 25$ babies, versus (2) 14-g $MgSO_4$ LD, $N = 30$ babies	Perinatal death, unclear reporting: Severe pre-eclampsia: (1) PMR 240 per 1,000 (6 deaths) versus (2) PMR 35 per 1,000 (1 death)
		Eclampsia: (1) 10-g $MgSO_4$ LD, $N = 29$ babies, versus (2) 14-g $MgSO_4$ LD, $N = 19$ babies	Perinatal death, unclear reporting: Eclampsia: (1) PMR 241 per 1,000 (6 deaths, all IUFD) versus (2) 0 deaths
Scudiero 2000; RCS with CCS(N)	127 babies born between 700 and 1,249 g, to women who received $MgSO_4$ for tocolysis	(1) Perinatal deaths, $N = 18$ babies, versus (2) survivors, $N = 109$ babies	$MgSO_4 > 48$ g: 72.2% (13/18) versus 45.0% (49/109), $P = 0.03$; $MgSO_4 \leq 48$ g versus >48 g (multivariable model): OR 4.72, 95% CI 1.12 to 19.97, $P = 0.035$
		(1) $MgSO_4 \leq 24$ g, $N = 43$ babies, versus (2) $MgSO_4 > 24$ to ≤ 48 g, $N = 25$ babies, versus (3) $MgSO_4 > 48$ g, $N = 59$ babies	Perinatal death (Cochrane–Armitage trend test, 1 versus 2 versus 3): 7.0% (3/43) versus 8.0% (2/25) versus 22.0% (13/59), $P = 0.03$; perinatal death (1 versus 2): 7.0% (3/43) versus 8.0% (2/25), $P = 1.0$
Young 1977; NRT	144 babies born to women with pre-eclampsia or eclampsia	(1) $MgSO_4$ IV bolus MD (2 g over 10 minutes every 1–2 hours), $N = 97$ babies, versus (2) $MgSO_4$ continuous IV MD (1 g per hour), $N = 47$ babies	Perinatal death: 2.1% (2/97) versus 2.1% (1/47)

The bold studies were judged to be of higher quality (moderate to high risk of bias) and presented results adjusted for confounders for the relevant outcome; other studies were judged to be at high or unclear risk of bias and/or did not present adjusted results for the relevant outcome.

aOR, adjusted odds ratio; aRR, adjusted risk ratio; CCS(N), nested case–control study; CI, confidence interval; g, gram; GA, gestational age; IUFD, intrauterine fetal demise; IV, intravenous; LD, loading dose; MD, maintenance dose; $MgSO_4$, magnesium sulphate; NRT, non-randomised trial; OR, odds ratio; PCS, prospective cohort study; PMR, perinatal mortality ratio; RCS, retrospective cohort study; RCT, randomised controlled trial; ROM, rupture of the membranes.

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the use of antenatal magnesium sulphate for fetal neuroprotection (293 babies, in a retrospective cohort of 697 babies born less than 28 weeks gestation) [129]. A possible increased risk of the composite outcome spontaneous intestinal perforation or neonatal death was also shown among a subgroup of babies born less than 25 weeks gestation with higher cumulative

Table 8. Summary of outcomes from non-randomised studies.

Outcome	Direction of effect for magnesium sulphate versus no magnesium sulphate or a different regimen		
	Studies showing no clear difference	**Studies showing possible benefit**	**Studies showing possible harm**
Stillbirth	Brazy 1982; Chowdhury 2009*; Jung 2018^	Jung 2018^; Shamsuddin 2005*	Das 2015*
Neonatal death or death before discharge	Alston 2016; Ambadkar 2019; Basu 2012; Bertello Grecco 2019*; Brazy 1982; Canterino 1999; Chowdhury 2009*; De Jesus 2015; del Moral 2007; de Veciana 1995; Drassinower 2015; **Elimian 2002***; Elliott 2003; **Farkouh 2001**; Gibbins 2013; Girsen 2015; Gonzalez-Quintero 2001; Hechtman 2002*; Hong 2019; James 2015; Jazayeri 2003; Jung 2018; Kamyar 2015a; Kamyar 2015b; **Kamyar 2016a**; **Kamyar 2016b**^; **Kimberlin 1998**; Lee 2013; Lloreda-Garcia 2016; Mikhael 2019*; Morag 2016; Narasimhulu 2017; Nassar 2006*; Özlü 2019; **Paneth 1997**; Rantonen 2001; **Shalabi 2017**^; Shokry 2010; Suh 2015; **Weisz 2015**^; Whitsel 2004; Yokoyama 2010	**Downey 2017**; Garcia Alonso 2018; **Grether 1998**; **Shalabi 2017**^; **Stockley 2018; Weisz 2015**^	Das 2015*;**Kamyar 2016b**^; Lipsitz 1971*; Rattray 2014; Rauf 2017
Apgar score < 7 at 1 minute (or ≤ 5)	Chun 2014^; Gibbins 2013; Lloreda-Garcia 2016; Mitani 2011; Morag 2016; Narasimhulu 2017		Chun 2014^; Das 2015*; Girsen 2015; Lipsitz 1971*
Apgar score < 7 at 5 minutes (or ≤5 or <6)	Canterino 1999; Chun 2014^; Cuff 2018*; de Veciana 1995; Drassinower 2015; Elimian 2002*; Gibbins 2013; Jung 2018; Lloreda-Garcia 2016; McPherson 2014*; Mitani 2011; Narasimhulu 2017; Nassar 2006*; Nelson 1995; Okusanya 2012*; Rhee 2012; Schanler 1997; Stockley 2018; Weisz 2015*	Jeanneteau 2014; Shalabi 2017	Chun 2014^; Das 2015*; Girsen 2015; Lipsitz 1971*; Morag 2016
Birth asphyxia	McGuiness 1980	Shamsuddin 2005*	
Meconium at birth	Greenberg 2013; Jazayeri 2003		
Intubation	Basu 2012; **De Jesus 2015**; Derks 2016; Morag 2016; Narasimhulu 2017; Weisz 2015*^	**Bajaj 2018;** Drassinower 2015; Weisz 2015^	Das 2015*; Rauf 2017; Weisz 2015*^
Intubation (duration)	de Veciana 1995	O Reilly 2016^	O Reilly 2016*^
Resuscitation	Basu 2012; Brookfield 2015*; De Jesus 2015; **Garcia Alonso 2018**; Gibbins 2013; Lloreda-Garcia 2016; McPherson 2014*; Narasimhulu 2017; Özlü 2019; **Weisz 2015***^	Bajaj 2018; **De Silva 2018**	Lipsitz 1971*; Weisz 2015^
Oxygen bag, mask, or both (resuscitation)	**Bajaj 2018**; Drassinower 2015; Riaz 1998; Weisz 2015*^	Weisz 2015*^	
Chest compressions (resuscitation)	Drassinower 2015; Stockley 2018; Weisz 2015*^	**Bajaj 2018**; Weisz 2015^	
Adrenaline (resuscitation)	Stockley 2018; Weisz 2015*^	Jeanneteau 2014; Weisz 2015^	
Score for Neonatal Acute Physiology > 10 or 20 in first 24 hours	Stockley 2018; Weisz 2015^	**Deering 2005**; Shalabi 2017; Weisz 2015*^	
Delayed adaptation	Lai 2017; Riaz 1998		Brazy 1982
Respiratory distress syndrome	Alston 2016; Ambadkar 2019; Bozkurt 2016; Brookfield 2016; Canterino 1999; De Jesus 2015; de Veciana 1995^; Drassinower 2015; Elimian 2002*; Girsen 2015; Gonzalez-Quintero 2001; Gursoy 2015; Imamoglu 2014; Jazayeri 2003; Jung 2018; Kamyar 2015a; Lee 2013; McPherson 2014*; Mitani 2011; Rantonen 2001; Schanler 1997; Shokry 2010; Suh 2015; Yokoyama 2010	de Veciana 1995^; Özlü 2019	

(*Continued*)

Table 8. (Continued)

Outcome	Direction of effect for magnesium sulphate versus no magnesium sulphate or a different regimen		
	Studies showing no clear difference	**Studies showing possible benefit**	**Studies showing possible harm**
Respiratory depression	Bertello Grecco 2019*		Das 2015*
Surfactant use	delValle 1998; Elimian 2002*; **Garcia Alonso 2018**; Lloreda-Garcia 2016; Rantonen 2001; Shokry 2010; Weisz 2015*		
Ventilation	Brookfield 2016; **De Jesus 2015**^; Drassinower 2015; Garcia Alonso 2018; Girsen 2015; Havranek 2011; James 2015; Lee 2013; Lloreda-Garcia 2016^; McPherson 2014*; Nunes 2018; Özlü 2019; Rantonen 2001; Schanler 1997; Shokry 2010	**De Jesus 2015**^; Lloreda-Garcia 2016^; Rauf 2017^; Shalabi 2017	Lipsitz 1971*; Lloreda-Garcia 2016^; Rauf 2017^
Ventilation (duration)	Black 2006; De Jesus 2015; Kimberlin 1998; Özlü 2019; Suh 2015		
Methylxanthine use or duration	Black 2006; Havranek 2011; Imamoglu 2014; Schanler 1997		
Chronic lung disease or bronchopulmonary dysplasia	Alston 2016; Basu 2012; Bozkurt 2016; De Jesus 2015; **Edwards 2018**; **Garcia Alonso 2018**; James 2015; Jung 2018; Kamyar 2015a; **Kamyar 2016a**; McPherson 2014*; Özlü 2019; **Shalabi 2017**; **Stockley 2018;** Suh 2015; **Weisz 2015**		Narasimhulu 2017; Stetson 2019
Oxygen use (at 28 days, 36 weeks, or discharge)	**Kimberlin 1998**; Morag 2016; Schanler 1997		
Oxygen use (duration)	De Jesus 2015; Özlü 2019; Suh 2015		
Steroid use (dexamethasone or hydrocortisone)	Mikhael 2019*; Rantonen 2001; Rattray 2014; Shalabi 2017		
Apnoea	Bozkurt 2016; Riaz 1998; Wutthigate 2017*		
Pulmonary haemorrhage	De Jesus 2015; James 2015		
Necrotising enterocolitis	Alston 2016; Bozkurt 2016; Brazy 1982; De Jesus 2015; delValle 1998; de Veciana 1995; **Downey 2017**; **Edwards 2018**; Elimian 2002*; Elliott 2003; Garcia Alonso 2018; **Ghidini 2001**; Gursoy 2015; Hong 2019; James 2015; Jazayeri 2003; Jung 2018; Kamyar 2015a; **Kamyar 2016a**; **Kamyar 2016b**; **Kimberlin 1998**; Lee 2013; Lloreda-Garcia 2016; McPherson 2014*; Mikhael 2019*; Morag 2016; Narasimhulu 2017; Özlü 2019; Schanler 1997; **Shalabi 2017**; **Stockley 2018;** Suh 2015; **Weisz 2015**; Yokoyama 2010	Moschos 2001; Wiswell 1996	
Spontaneous intestinal perforation	**Downey 2017**; Mikhael 2019*; **Shalabi 2017**		Rattray 2014
Composite of necrotising enterocolitis/spontaneous intestinal perforation or death	**Kamyar 2016b*^**; **Mikhael 2019*^**	**Downey 2017; Mikhael 2019*^**	**Kamyar 2016b*^; Rattray 2014***
Necrotising enterocolitis/ spontaneous intestinal perforation–associated death	Hong 2019; **Shalabi 2017**		
Sepsis	Alston 2016; Bozkurt 2016; De Jesus 2015; Elimian 2002*; Girsen 2015; James 2015; Jazayeri 2003; Jung 2018; **Kamyar 2016a**; Lloreda-Garcia 2016; Mikhael 2019*; Morag 2016; Özlü 2019; Rantonen 2001; Riaz 1998; **Stockley 2018;** Teng 2006; **Weisz 2015**		Whitsel 2004

(*Continued*)

Table 8. (Continued)

Outcome	Direction of effect for magnesium sulphate versus no magnesium sulphate or a different regimen		
	Studies showing no clear difference	**Studies showing possible benefit**	**Studies showing possible harm**
Antibiotic use	Elimian 2002*^; Greenberg 2013		Elimian 2002^
Hypoglycaemia	Bozkurt 2016; Grimbly 2015		
Feeding intolerance	Gursoy 2015; Özlü 2019; Riaz 1998		**Belden 2017***
Delayed stooling	Lloreda-Garcia 2016^	Lloreda-Garcia 2016^	Brazy 1982; Das 2015*
Meconium passage delay	Ambadkar 2019; Lloreda-Garcia 2016		
Ileus			Brazy 1982; Nakamura 1991*
Delayed voiding	Sahin 2001		Das 2015*
Patent ductus arteriosus	**Basu 2012**; Bozkurt 2016; delValle 1998; Elimian 2002*; Garcia Alonso 2018; Gursoy 2015; Imamoglu 2014; James 2015; Katayama 2011*^; Lee 2013*; Özlü 2019; Schanler 1997; Yokoyama 2010	Qasim 2017	Brazy 1982; **del Moral 2007**; Gonzalez-Quintero 2001; **Katayama 2011**^; Lee 2013; Narasimhulu 2017; Shokry 2010
Patent ductus arteriosus (treated)	**De Jesus 2015**; del Moral 2007; delValle 1998; Katayama 2011*; Lee 2013; Lloreda-Garcia 2016; Mikhael 2019*; Shalabi 2017; Suh 2015		Bonta 2000*
Hypotension	Brazy 1982; Derks 2016; Drassinower 2015; Gursoy 2015; Morag 2016; **Teng 2006**	**De Jesus 2015**	Narasimhulu 2017
Hypertension	Gursoy 2015	Brown 2019	
Inotrope use	Imamoglu 2014; James 2015; Shokry 2010		
Intravenous fluids and/or nutritional support needed			Greenberg 2013; Rasch 1982
Phototherapy	Greenberg 2013; Havranek 2011; Imamoglu 2014		
Retinopathy of prematurity	**Basu 2012**; Bozkurt 2016; Cuff 2018*; De Jesus 2015; Elliott 2003; **Garcia Alonso 2018**; Jung 2018; Kamyar 2015a; **Kimberlin 1998**; Lee 2013; McPherson 2014*; Narasimhulu 2017; Özlü 2019; **Shalabi 2017**^; **Stockley 2018;** Suh 2015; **Weisz 2015**; Yokoyama 2010	**Shalabi 2017**^	Rauf 2017
Hypotonia	Bertello Grecco 2019*; Drassinower 2015; Gibbins 2013; Girsen 2015; Nassar 2006*		Ambadkar 2019; Brazy 1982; Das 2015*; Rauf 2017; Riaz 1998
Seizure	Drassinower 2015; Girsen 2015; **Kimberlin 1998**; McPherson 2014*; Rauf 2017	Shokry 2010	
Encephalopathy	Girsen 2015; Rantonen 2001; Rauf 2017		
Intraventricular haemorrhage	Alston 2016; Black 2006; De Jesus 2015; delValle 1998; de Veciana 1995; Drassinower 2015; **Edwards 2018**; Elliott 2003; Gano 2016; Garcia Alonso 2018; Gasparyan 2017; Gonzalez-Quintero 2001; Gursoy 2015; Hom 2018; Imamoglu 2014; Jazayeri 2003; Jung 2018^; Kamyar 2015a; Lee 2013; **Leviton 1997**; Martin 1998; McPherson 2014*; Mitani 2011*; Nassar 2006*; Nelson 1995; Özlü 2019; **Paneth 1997**; Schanler 1997; Stetson 2019; **Stockley 2018;** Suh 2015; Yokoyama 2010	Jung 2018^; **Kuban 1992**; Perlman 1995; **Petrova 2012**; Rantonen 2001; Rauf 2017; Shokry 2010	**Salafia 1995**
Intraventricular haemorrhage grade 3 or 4	del Moral 2007; **Downey 2017**; Gano 2016; James 2015; Jung 2018; **Kamyar 2016a**; **Kimberlin 1998**; McPherson 2014*; Mikhael 2019*; Narasimhulu 2017; Özlü 2019; Rantonen 2001; **Stockley 2018; Weintraub 2001**	Gasparyan 2017; Perlman 1995; **Sarkar 2009**; Wiswell 1996	**Cuff 2018*; Khodapanahandeh 2008**

(*Continued*)

Table 8. (Continued)

Outcome	Direction of effect for magnesium sulphate versus no magnesium sulphate or a different regimen		
	Studies showing no clear difference	**Studies showing possible benefit**	**Studies showing possible harm**
Periventricular leucomalacia	Bozkurt 2016; De Jesus 2015; del Moral 2007; delValle 1998; Garcia Alonso 2018; Jung 2018^; Kamyar 2015a; **Kamyar 2016a**; Lee 2013; Mitani 2011*; Narasimhulu 2017; Rauf 2017; Suh 2015; Wiswell 1996	**FineSmith 1997**; Jung 2018^; **Murata 2005**	
Intraventricular haemorrhage or periventricular leucomalacia	Basu 2012; **Canterino 1999***; Elimian 2002*		
Intraventricular haemorrhage grade 3 or 4 and/or periventricular leucomalacia	Bozkurt 2016; **Canterino 1999***; Morag 2016; **Shalabi 2017**^; **Weisz 2015**	Koksal 2002; **Shalabi 2017**^; Wiswell 1996	
Hypocalcaemia	Cho 2014; Lee 2015; McGuiness 1980		Narasimhulu 2017
Bone abnormalities	Yokoyama 2010		Holcomb 1991*; Matsuda 1997*
Hearing impairment or hearing test failure	Jung 2018	**Leung 2016**	
Composite adverse outcomes	Drassinower 2015; Duffy 2012; Kamyar 2015a; Kamyar 2015b; Kamyar 2015c; **Kamyar 2016a**; **Mitani 2011***; Narasimhulu 2017; **Palatnik 2019**; Rizzolo 2019; Sakae 2017*^; **Weisz 2015**		Boyle 2018; Sakae 2017*^
NICU admission	Ambadkar 2019*^; Bertello Grecco 2019*; Cawyer 2019; Chun 2014^; Gibbins 2013; Lai 2017; McPherson 2014*; Rantonen 2001; Riaz 1998*		Ambadkar 2019*^; Chun 2014^; Das 2015*; **Girsen 2015**; **Greenberg 2011***; **Greenberg 2013***; Rhee 2012
NICU duration	Gibbins 2013; **Girsen 2015**; Greenberg 2013; Jazayeri 2003; Jung 2018; Kimberlin 1998; Rauf 2017		Narasimhulu 2017
Hospital stay duration	Alston 2016; **Basu 2012**; De Jesus 2015; de Veciana 1995; Özlü 2019; Riaz 1998; Schanler 1997; Suh 2015		Brazy 1982; Girsen 2015
Other (outcomes reported by single studies)	Black 2006; Blackwell 2002; Brazy 1982; Derks 2016; Gano 2016; Girsen 2015; Greenberg 2013; Havranek 2011; Hong 2019; Imamoglu 2014; Jeanneteau 2014; Jones 2018; Jung 2018; Katayama 2011*; Kelly 1992; **Kimberlin 1998**; Lai 2017; **Leviton 1997**; Lloreda-Garcia 2016; Mittendorf 2005*; Morag 2016; Nassar 2006*; Nunes 2018; Özlü 2019; **Paneth 1997**; Petrov 2013; Rantonen 2001; Riaz 1998; Sahin 2001; Schanler 1997; **Shalabi 2017**^	**Deering 2005**; Derks 2016; **Gano 2016**; Jeanneteau 2014; Kimberlin 1998; Mittendorf 2005*; Petrov 2013	**Belden 2017***; Brazy 1982; Das 2015*; **Katayama 2011**; Lai 2017; Lipsitz 1971*; Mittendorf 2009*; **Morag 2015**; Morag 2016; Rasch 1982; **Shalabi 2017**^; **Verma 2006***; Weisz 2015; Whitten 2015

The bold studies were judged to be of higher quality (moderate or moderate to high risk of bias) and presented results adjusted for confounders for the relevant outcomes; other studies were judged to be at high or unclear risk of bias and/or or did not present adjusted results for the relevant outcomes.

*Indicates where studies assessed different magnesium sulphate regimens or 1 or more characteristics of the regimen (such as dose, duration, timing, or indication for use).

^Indicates where studies demonstrated mixed findings (such as in different subgroups of the population).

NICU, neonatal intensive care unit.

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antenatal magnesium sulphate doses for fetal neuroprotection (non-concurrent cohort of 155 babies born less than 1,000 grams) [173].

A possible increased risk of patent ductus arteriosus was observed with magnesium sulphate given for pre-eclampsia (retrospective cohort of 81 'very low birthweight' babies; abstract

only) [140] or for pre-eclampsia or tocolysis (retrospective cohort of 941 babies born 500 to 1,000 grams) [90]. Further, a possible increased risk of patent ductus arteriosus in babies born 26 weeks gestation or later was shown with cumulative antenatal magnesium sulphate doses for pre-eclampsia or tocolysis of at least 50 grams (retrospective cohort of 941 babies born 500 to 1,000 grams) [90]. Potential increased risk of symptomatic patent ductus arteriosus, and of failure of early closure of the ductus arteriosus, was also observed with the use of antenatal magnesium sulphate for tocolysis (retrospective cohort of 160 babies born less than 28 weeks gestation, who all received indomethacin prophylaxis) [132].

A potential increased risk of intraventricular haemorrhage grade 3 or 4 was observed with antenatal magnesium sulphate for tocolysis (case–control study of 121 babies born less than 1,500 grams) [134], and with a higher dose regimen of antenatal magnesium sulphate for fetal neuroprotection (6-gram IV loading dose and 2-gram-per-hour IV maintenance dose for 12 hours versus 4-gram IV loading dose only) (retrospective cohort, including 54 babies exposed to magnesium sulphate within 12 hours of birth) [84].

A possible increased risk of neonatal intensive care unit admission with the use of antenatal magnesium sulphate for pre-eclampsia was observed (retrospective cohorts of 264 babies and 2,166 babies born at 37 weeks gestation or later) [106,109]. Further increased risks of neonatal intensive care unit and special care unit admission were observed with higher total hours, higher total doses, more than 12 hours, and more than 30 grams of antenatal magnesium sulphate for pre-eclampsia (retrospective cohort of 242 babies born at 35 weeks gestation or later) [108].

Evidence from case reports

Nineteen reports describing a total of 134 babies exposed to antenatal magnesium sulphate with adverse outcomes were included [200–218] (see Table 9; the detailed characteristics of cases are presented in S4 Table).

Clinical features of neonatal hypermagnesemia, magnesium 'toxicity', or magnesium 'intoxication' at birth were the focus of 5 reports (35 neonates), in which antenatal magnesium sulphate was given for pre-eclampsia/eclampsia (with exposure durations and doses ranging from 3.5 to 46 hours and 11 to 60.4 grams prior to birth, respectively) [202,205,206,213,218], and were variably described throughout the remaining reports. These included low Apgar scores, apnoea, cyanosis, hypotonia, and/or hyporeflexia, with or without the need for active resuscitation and calcium gluconate administration.

Table 9. Summary of main adverse outcomes from case reports.

Outcome	Indication for use: studies
Neonatal death	Tocolysis: Herschel 2001
	Pre-eclampsia/eclampsia: Kurtoglu 2000
Cardiopulmonary arrest after gentamicin exposure following hypermagnesemia at birth	Pre-eclampsia: L'Hommedieu 1983; Rasch 1981
Clinical features of magnesium 'toxicity' or 'intoxication' at birth (such as apnoea, cyanosis, hypotonia, and/or hyporeflexia)	Pre-eclampsia/eclampsia: Brady 1967; Cruz 2009; Lipsitz 1967; Teng 1989
	Not clear: Jashi 2014
Microcolon or 'meconium-plug syndrome'	Pre-eclampsia/eclampsia: Amodio 1986; Krasna 1996; Sokal 1972
Nonoliguric hyperkalaemia	Pre-eclampsia: Tanaka 2018
Bone abnormalities with prolonged magnesium sulphate for tocolysis	Tocolysis: Cumming 1989; Kaplan 2006; Kogan 2003; Lamm 1988; Malaeb 2004
	Not clear: Ahmad 2013

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Two reports described neonatal death following antenatal magnesium sulphate exposure. In the first report, death was considered to be related to 'the toxic effects of magnesium on the myocardium' when given for tocolysis (4-gram IV loading dose followed by 2.5-gram-per-hour IV maintenance dose for approximately 1 day: 51.4 grams total) [204], and in the second, 1 death (of 7) was attributed to 'overdose' (unclear dose/regimen) of magnesium sulphate when given for pre-eclampsia/eclampsia [210].

In the context of hypermagnesemia at birth (following exposure to a total of 24 to 28 grams of magnesium sulphate for pre-eclampsia), neonatal gentamicin administration for suspected sepsis was associated with respiratory arrest and cardiac arrest in 2 reports [211,215]. Other specific adverse outcomes attributed to antenatal magnesium sulphate exposure included

- Microcolon or meconium-plug syndrome (3 reports, 14 neonates, when given for pre-eclampsia/eclampsia: 25 to 41 grams in the day prior to birth in 1 report; regimen not described in 2 reports) [201,209,216];
- Nonoliguric hyperkalaemia (1 report, 1 neonate, when given for pre-eclampsia: 0.1 gram to 2 grams per hour IV for 12 days) [217];
- Bone abnormalities (commonly metaphyseal osteopenia, in some cases leading to fracture) (6 reports, 35 neonates, when given for tocolysis: ranging from 1 to 4 grams per hour for between 8 and 13 weeks) [200,203,207,208,212,214].

Discussion

Overall, no clear difference in our primary review outcome, perinatal death, was shown in the randomised trials comparing antenatal magnesium sulphate with placebo/no treatment, nor in regimen comparisons in randomised trials. While 11 of the 138 non-randomised studies reported on perinatal death, only 1 cohort study (at moderate to high risk of bias) observed a possible increased risk of perinatal death, with high-dose (more than 48 grams) antenatal magnesium sulphate exposure for tocolysis [183].

Results for secondary adverse neonatal outcomes were reassuring, with very few clear differences observed between antenatal magnesium sulphate and placebo/no treatment or between different magnesium sulphate regimens. Where possible harms of magnesium sulphate were seen, commonly no confounders were taken into account (and studies were judged to be at high risk of bias), study samples were small (less than 200 babies), and/or differences were observed in (non-formal) subgroup analyses only. Non-randomised studies identified a limited number of outcomes justifying further evaluation, such as from large, high-quality studies (prospective cohorts, individual participant data meta-analyses, or randomised trials of regimen comparisons). These included neonatal death and intestinal morbidity in very preterm neonates with exposure for fetal neuroprotection, patent ductus arteriosus in very preterm or very low birthweight neonates with exposure for pre-eclampsia or tocolysis, and intensive care unit admission in term neonates with exposure for pre-eclampsia. Case reports suggested an association between neonatal bone abnormalities and long-term, high-dose exposure to antenatal magnesium sulphate for tocolysis.

We are not aware of any other published systematic reviews with a focus on potential adverse outcomes for neonates following antenatal magnesium sulphate exposure, though we identified 3 review registrations focused specifically on magnesium sulphate for tocolysis and the outcomes neonatal respiratory depression (CRD42017058912), patent ductus arteriosus (CRD42017060049), and bone abnormalities (CRD42017062550) [18]. Three previous systematic reviews have assessed 'adverse events' [13], 'side effects' [219], and 'safety' [220] for

women, and a further systematic review has assessed the effects of antenatal magnesium sulphate specifically on fetal heart rate parameters, finding a small negative effect on rate, variability, and accelerative pattern, 'not sufficient clinically to warrant medical intervention' [14].

Our review findings are consistent with those from the relevant Cochrane reviews comparing antenatal magnesium sulphate with placebo/no treatment, or different magnesium sulphate regimens [1,2,4,9,221], though our review includes a wider range of outcomes. As was observed in our review's tocolysis subgroup for perinatal death, the Cochrane review assessing magnesium sulphate for tocolysis demonstrated a borderline increased risk of fetal, neonatal, or infant death with antenatal magnesium sulphate [9].

A recent non-systematic narrative review evaluated 'whether antenatal $MgSO_4$ is beneficial or harmful' in extremely and very preterm neonates [222]. Relevant systematic reviews, meta-analyses, randomised controlled trials, and observational studies were retrieved, with a broad search strategy focused on neuroprotection and cerebral palsy, necrotising enterocolitis, and spontaneous intestinal perforation. The narrative review suggested that current evidence supports the neuroprotective role of antenatal magnesium sulphate for preterm neonates, and that, while the effects are 'controversial' and 'not well established', a 'high index of suspicion of gastrointestinal complications in extremely preterms, particularly < 26 weeks of gestation' is recommended [222]. While our review similarly identified a possibility of harm, the relevant studies were of questionable methodological quality, and our systematic review included additional reports (of higher quality, and involving much larger cohorts) that indicated no increased risk of intestinal morbidity.

The findings of this review are reassuring and can be considered in conjunction with those from relevant reviews demonstrating a clear benefit of antenatal magnesium sulphate [1,2,4], and current international clinical practice guideline recommendations [3,7]. Our review findings of possible adverse outcomes with long-term, high-dose use for tocolysis have implications for settings with continued use for this indication [8] in spite of the absence of benefit shown in systematic reviews and international guidance [7–9].

Strengths and limitations

The main limitations of our review relate to missing data for important outcomes across most studies, the inclusion of published data only, and the heterogeneity of included studies.

Of the 40 randomised trials included in this review, our primary outcome (perinatal death) was reported by 22 (55%); it was reported by only 11 (8%) of the 138 included non-randomised studies. Aside from related mortality outcomes (stillbirth and neonatal death), all other adverse outcomes were reported sparsely, by less than a third of trials, with many outcomes reported by single trials only. While a broader range of adverse neonatal outcomes were reported by the non-randomised studies, apart from neonatal death (50 studies), intraventricular haemorrhage (39 studies), and necrotising enterocolitis (36 studies), all other outcomes were reported by less than a fifth of studies, again, with many reported by single studies only.

In addition to missing data for important outcomes across most studies, a further limitation includes the number of studies with relatively small sample sizes comparing different antenatal magnesium sulphate regimens. Moreover, many studies assessing antenatal magnesium sulphate for relevant indications were not included due to lack of reporting of adverse neonatal outcomes.

We searched extensively across multiple databases and reviewed reference lists for additional reports; however, we did not seek unpublished data. Recent evidence has suggested that while much adverse event information remains unpublished, inclusion of such data generally does not change the direction or statistical significance of pooled risk estimates [223]. While

we were not able to fully evaluate non-English publications without available translations for inclusion, we have provided a list of these for readers to consider (S3 Text).

As the aim of the review was to provide a comprehensive, general view of potential unintended adverse outcomes, we designed this review with broad scope [15,16]. This presented challenges, including the number of diverse outcomes, inconsistent reporting, and the vast quantities of heterogeneous data. The study characteristics (including designs, settings, participating women and neonates, and antenatal magnesium sulphate regimens) varied greatly, and reporting was commonly incomplete. The ability to conduct subgroup analyses for the randomised trials was limited, and we did not inappropriately pool data from non-randomised studies. We conducted this review in accordance with recommendations for systematic reviews of adverse events [15–17], and of randomised and non-randomised studies more generally [224]. Our evaluation thus provides a firm basis for any further, narrowly focused studies of specific outcomes and characteristics.

Conclusions

In conclusion, our findings do not support any clear associations between perinatal death or other adverse neonatal outcomes and antenatal magnesium sulphate exposure when given for the beneficial indications of maternal neuroprotection in pre-eclampsia/eclampsia and fetal neuroprotection in cerebral palsy prevention. To further inform safety recommendations of this widely used treatment in pregnancy, future research should be directed towards identified research gaps surrounding specific adverse neonatal outcomes and the impact of particular regimen, pregnancy, and/or birth characteristics.

Supporting information

S1 Appendix. Forest plots and funnel plots for comparisons 1–8.
(DOCX)

S1 Fig. Risk of bias for randomised controlled trials. Risk of bias summary showing judgements about each risk of bias item for the 40 included randomised trials. Green represents 'low risk of bias'; yellow, 'unclear risk of bias'; red, 'high risk of bias'.
(TIF)

S1 PRISMA Checklist. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.
(DOCX)

S1 Table. Characteristics of included studies.
(DOCX)

S2 Table. Risk of bias of included studies.
(DOCX)

S3 Table. Adverse outcomes from non-randomised studies.
(DOCX)

S4 Table. Adverse outcomes from case reports.
(DOCX)

S1 Text. Protocol.
(PDF)

S2 Text. Search strategies.
(DOCX)

S3 Text. Articles excluded at full-text screening due to absence of English translation.
(DOCX)

S4 Text. References for included studies.
(DOCX)

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CHAPTER 6: OVERALL CONCLUSIONS

Cerebral palsy (CP) remains the leading cause of physical disability in childhood. Despite emerging evidence from a number of countries that the birth prevalence of CP has begun to decline for the first time, CP continues to affect approximately one in 500 babies worldwide. While risk factors and causes of CP are well established, potential preventive interventions are under-researched.

The series of studies in Chapters 2, 3, 4 and 5 of this thesis, focused on CP prevention and antenatal magnesium sulphate, have addressed research gaps identified by literature review in Chapter 1. In concluding this thesis, the key findings of these studies are provided and the implications for practice and research summarised.

Summary of findings from studies within this thesis

Antenatal, intrapartum and neonatal interventions for preventing cerebral palsy: two overviews of Cochrane systematic reviews (Chapters 2 and 3)

To address the identified research question 'What is the current evidence regarding antenatal, intrapartum and neonatal preventive interventions for CP?' two overviews of Cochrane systematic reviews were conducted (Shepherd et al. 2018; Shepherd et al. 2017).

These overviews together included 58 moderate- to high-quality Cochrane reviews; data for CP were available from 123 randomised controlled trials (RCTs) and 48,375 children.

Effective interventions: high-quality evidence of effectiveness: Magnesium sulphate versus placebo given to women at risk of very preterm birth for neuroprotection of the fetus, and therapeutic hypothermia versus standard care for neonates with hypoxic-ischaemic encephalopathy, were shown to reduce the risk of CP.

Probably effective interventions: moderate-quality evidence of effectiveness: Prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm neonates were shown to probably reduce the risk of CP.

Probably ineffective interventions: moderate-quality evidence of harm: Any prophylactic antibiotics versus no antibiotics for women in preterm labour with intact membranes, immediate delivery versus deferred birth for preterm neonates with suspected fetal compromise, and early (at less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm neonates, were shown to probably increase the risk of CP.

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness: The following interventions were shown to probably not impact CP risk: repeat doses of corticosteroids versus a single course in women at risk of preterm birth; ethamsylate versus placebo for preventing morbidity in preterm or very low birthweight neonates; volume versus no treatment and gelatin versus fresh frozen plasma for preventing morbidity and mortality in very preterm neonates; prophylactic indomethacin versus placebo or no drug for preventing mortality and morbidity in preterm neonates; synthetic surfactant versus placebo for respiratory distress syndrome in preterm neonates; and prophylactic phototherapy versus standard care for preventing jaundice in preterm or low birthweight neonates.

No conclusions possible: low- to very low-quality evidence: The following interventions were shown to have an unclear impact on CP risk: continuous cardiotocography versus intermittent auscultation for fetal assessment during labour; any antihypertensive drug versus placebo in women with mild to moderate hypertension; oral beta-blockers versus placebo for women in mild to moderate hypertension; magnesium sulphate versus placebo in women with pre-eclampsia; interventionist care versus expectant care in women with severe pre-eclampsia; betamimetics versus placebo for inhibiting preterm labour; progesterone versus placebo for preventing preterm birth;

magnesium sulphate versus other tocolytic agents for preventing preterm birth; corticosteroids versus with placebo for accelerating fetal lung maturation in women at risk of preterm birth; vitamin K versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage; phenobarbital versus placebo prior to preterm birth for preventing neonatal periventricular haemorrhage; barbiturates (phenobarbital) versus conventional therapy for preventing morbidity and mortality following perinatal asphyxia in term and late preterm neonates; darbepoetin alfa versus placebo and erythropoietin versus placebo for preventing red blood cell transfusion in preterm or low birthweight neonates; transfusion at a restrictive (low haemoglobin) versus a liberal (high haemoglobin) threshold for preventing morbidity and mortality in very low birthweight neonates; dobutamine versus dopamine in preterm neonates with low superior vena cava flow; oral ibuprofen versus intravenous ibuprofen for treating patent ductus arteriosus in preterm or low birthweight (or both) neonates; endothelin receptor antagonists versus placebo for persistent pulmonary hypertension in term and late preterm neonates; room air versus 100% oxygen for resuscitation of neonates at birth; inhaled nitric oxide versus placebo or no treatment for respiratory failure in preterm neonates; inhaled nitric oxide versus placebo for respiratory failure in neonates born at or near term; caffeine versus placebo for preventing apnoea in preterm neonates; caffeine versus placebo for treating apnoea in preterm neonates; prophylactic protein free synthetic surfactant versus placebo for preventing morbidity and mortality in preterm neonates; animal-derived surfactant extract versus no treatment for treating respiratory distress syndrome in preterm neonates; continuous distending pressure versus standard care for respiratory distress in preterm neonates; long versus short inspiratory times in neonates receiving mechanical ventilation; early inhaled corticosteroids versus placebo for preventing chronic lung disease in ventilated very low birthweight preterm neonates; moderately early (between seven and 14 days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm neonates; late (more than seven days of age) postnatal corticosteroids versus placebo or no treatment for chronic lung disease in preterm neonates; arginine supplementation versus placebo for preventing necrotising enterocolitis in preterm neonates; systemic antifungal agents versus placebo for preventing mortality and morbidity in very low birthweight neonates; acyclovir versus vidarabine for treating herpes simplex virus infection in neonates; dextrose gel versus placebo for treating hypoglycaemia in neonates; prophylactic thyroid hormones versus placebo for preventing morbidity and mortality in preterm neonates; kangaroo mother care versus conventional neonatal care to reduce morbidity and mortality in low birthweight neonates; use of silicone earplugs versus no earplugs in the neonatal intensive care unit for preterm or very low birthweight neonates; early developmental intervention versus standard follow up post hospital discharge to prevent motor and cognitive impairment in preterm neonates.

Linking data from a large perinatal clinical trial with the Australian Cerebral Palsy Register for long-term follow up (Chapter 4)

To address the second identified research question ‘Can a nationwide CP registry be used for long-term RCT follow up?’ data from a large maternal perinatal RCT (Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO_4)) were linked with the Australian Cerebral Palsy Register (ACPR) (Shepherd et al. 2020).

Linkage of de-identified data from 913 ACTOMgSO_4 children (born 1996 to 2000) and the ACPR was achieved.

Notable discrepancies in children diagnosed with CP by ACTOMgSO_4 (up to two years) and the ACPR (up to five years), were identified – some children received a CP diagnosis by ACTOMgSO_4 and the ACPR, and others by ACTOMgSO_4 only, or by the ACPR only.

Children born in Australian states/territories with long-standing versus more recently established CP registers, and with a ‘definitely yes’ (versus ‘probably yes’) or ‘probably no’ (versus ‘definitely no’) CP status at two years in ACTOMgSO_4 were more likely to be included on the ACPR up to five years. For children without a CP diagnosis at two years in ACTOMgSO_4, a variety of indicators of motor dysfunction identified at two years (such as difficulty walking or using hands, decreased limb

tone, and receipt of physiotherapist or occupational therapist care) were also associated with ACPR inclusion up to five years.

Differences in the diagnoses observed were attributed to limitations of both strategies for identifying children with CP in this era (relating to diagnostic methods used at the time of ACTOMgSO_4, and under-ascertainment by more recently established ACPR contributing registers).

Antenatal magnesium sulphate and adverse neonatal outcomes: a systematic review and meta-analysis (Chapter 5)

To address the final identified research question 'Is antenatal magnesium sulphate associated with adverse neonatal outcomes?' a systematic review and meta-analysis was conducted (Shepherd et al. 2019).

The systematic review incorporated findings from 197 studies (40 RCTs randomising 19,265 women and their babies, 138 non-randomised studies, and 19 case reports; of mixed quality).

Overall, no clear difference in perinatal death was shown in the RCTs comparing antenatal magnesium sulphate with placebo or no treatment, nor in regimen comparisons used in the RCTs. Very few non-randomised studies reported perinatal death, and only one suggested a possible increased risk of perinatal death with high dose antenatal magnesium sulphate for tocolysis.

Findings for secondary adverse neonatal outcomes were reassuring, with no clear differences shown between antenatal magnesium sulphate and placebo or no treatment in RCTs. Non-randomised studies identified a limited number of adverse neonatal outcomes, warranting further consideration: neonatal death and intestinal morbidity in very preterm neonates with exposure for fetal neuroprotection, patent ductus arteriosus in very preterm or very low birthweight neonates with exposure for pre-eclampsia or tocolysis, and intensive care unit admission in term neonates with exposure for pre-eclampsia. Case reports suggested an association between neonatal bone abnormalities and long-term, high dose antenatal magnesium sulphate exposure for tocolysis.

Implications for practice and research from studies within this thesis

The main implications for practice and research from the studies conducted within this thesis are summarised below (Table 1).

Table 1: Research and practice implications from studies conducted within this thesis

Cochrane overviews of antenatal, intrapartum and neonatal interventions for CP prevention	
Practice	• Magnesium sulphate in women at risk of very preterm birth for neuroprotection of the fetus, and therapeutic hypothermia for neonates with hypoxic-ischaemic encephalopathy can reduce the risk of CP. • Prophylactic methylxanthines for endotracheal extubation in preterm neonates can probably reduce the risk of CP. • These overviews can be used by policy makers, health professionals and consumers to aid decision making and evidence translation. • As the scope of these overviews was limited to the effects of interventions on CP and pre-specified secondary outcomes, consultation of the included reviews is recommended to formally assess additional benefits and harms.
Research	• These overviews highlight areas where there is insufficient evidence to draw conclusions. o There was low- to very low-quality evidence on CP for interventions assessed in 37 included Cochrane reviews. o There was no evidence on CP for interventions assessed in 164 excluded Cochrane reviews (that pre-specified CP as a review outcome of interest, but had no CP data from RCTs included in the reviews). • These overviews can be used by researchers and funding bodies to generate research questions and priorities. • There is an urgent need for long-term follow up of RCTs addressing risk factors for CP. • Future studies must be rigorous in their design and aim for consistency in CP outcome measurement and reporting to facilitate pooling of outcome data, to maximise research efforts aimed at CP prevention. • In light of the challenges associated with long-term follow up, new strategies to measure impact on CP, such as data linkage with CP registries, should be further explored.
Linkage of ACTOMgSO$_4$ and ACPR data for long-term follow up	
Practice and research	• This study provides a firm basis for further linkage studies of data from participants in maternal perinatal RCTs with ACPR data for childhood CP assessment. • As all ACPR registers are expected to achieve population-level ascertainment in the coming years, further research on the use of ACPR CP diagnoses for long-term CP assessment in Australian preventive RCTs is recommended. • Future RCTs should consider pre-specification of linkage with CP registry data in their protocols, participant information sheets and consent forms, enabling the use of identifiable data. • Maternal perinatal clinicians and researchers assessing CP are urged to follow new international clinical practice guidelines for early, accurate diagnosis of CP.
Systematic review of antenatal magnesium sulphate and adverse neonatal outcomes	
Practice	• Antenatal magnesium sulphate, when given for the beneficial indications of maternal and fetal neuroprotection (for pre-eclampsia or eclampsia, and CP prevention respectively), does not increase the risk of perinatal death or other adverse outcomes for neonates. • Findings of possible adverse outcomes with long-term, high dose use for tocolysis has implications for settings with continued use for this indication, in spite of the absence of benefit of treatment.
Research	• Further large, high-quality studies (such as prospective cohort studies, individual participant data meta-analyses, or RCTs of regimen comparisons) assessing identified adverse neonatal outcomes, and the impact of regimen, pregnancy or birth characteristics on these outcomes, will further inform safety recommendations for the use of antenatal magnesium sulphate.

Abbreviations: ACPR: Australian Cerebral Palsy Register; ACTOMgSO$_4$: Australasian Collaborative Trial of Magnesium Sulphate; CP: cerebral palsy; RCT: randomised controlled trial

Final conclusions

This thesis has presented a series of studies addressing identified research gaps surrounding CP prevention and antenatal magnesium sulphate. Research methodologies used in this thesis included two overviews of Cochrane reviews, linkage of a large maternal perinatal RCT with a nationwide CP register, and a systematic review of both RCTs and non-randomised studies.

For CP prevention, evidence from this thesis supports the continued implementation of magnesium sulphate for fetal neuroprotection in women at risk of very preterm birth, and therapeutic hypothermia in neonates with hypoxic-ischaemic encephalopathy for CP prevention.

Based on the research findings presented in this thesis it is clear that current evidence to guide practice in the areas of antenatal, intrapartum and neonatal interventions for CP prevention is incomplete. Several priorities for future research have been identified, particularly relating to the unknown impacts of a range of relevant interventions on CP risk, and the related urgent need for further investment in strategies for follow up of participants from maternal perinatal RCTs to enable assessment and reporting of CP.

APPENDICES

Appendix 1: Other publications, presentations and grants during candidature related to thesis

Publications

Dickinson, H, **Bain, E**, Wilkinson, D, Middleton, P, Crowther, CA & Walker, DW 2014. 'Creatine for women in pregnancy for neuroprotection of the fetus', *Cochrane Database of Systematic Reviews*, Issue 12, Art. No.: CD010846.

Siwicki, K, **Bain, E**, Bubner, T, Ashwood, P, Middleton, P & Crowther, CA 2015. 'Nonreceipt of antenatal magnesium sulphate for fetal neuroprotection at the Women's and Children's Hospital, Adelaide 2010-2013.' *Australian and New Zealand Journal of Obstetrics and Gynaecology*, vol. 55, no. 3, pp. 233-238.

Bain, E, Bubner, T, Ashwood, P, Van Ryswyk, E, Simmonds, L, Reid, S, Middleton, P & Crowther, CA 2015. 'Barriers and enablers to implementing antenatal magnesium sulphate for fetal neuroprotection guidelines: a study using the theoretical domains framework' *BMC Pregnancy and Childbirth*, vol. 55, no. 1, p. 176.

Wilkinson, D, **Shepherd, E** & Wallace, EM 2016. 'Melatonin for women in pregnancy for neuroprotection of the fetus', *Cochrane Database of Systematic Reviews*, Issue 3, Art. No.: CD010527.

Martinello, KA, **Shepherd, E**, Middleton, P & Crowther, CA 2017. 'Allopurinol for women in pregnancy for neuroprotection of the fetus (Protocol).' *Cochrane Database of Systematic Reviews*, Issue 12, Art. No.: CD012881.

Presentations

Bain, E, Bubner, T, Middleton, P, Ashwood, P, Van Ryswyk, E, Simmonds, L, Reid, S & Crowther, CA. Barriers and enablers to implementing the magnesium sulphate for fetal neuroprotection guidelines: a study using the Theoretical Domains Framework. Perinatal Society of Australia and New Zealand Congress. April 2015: Melbourne, Australia.

Shepherd, E, Middleton, P & Crowther, CA. Challenges of overviews of reviews and how to overcome them. Cochrane Colloquium. October 2016: Seoul, Korea.

Grants

Crowther, CA, Middleton, P, **Bain, E,** Flenady, V, Morris, J, Beckmann, M, Groom, K & McIntyre, S. Research Foundation of Cerebral Palsy Alliance: IRG2213 – Working to improve the survival and good health for babies born preterm: The WISH project follow up study. 2014-2019. A$250,000.

Appendix 2: Appendices for Chapter 2 publication

Ongoing reviews

Protocol citation	Overview of pre-specified outcomes in protocol
Amorim MMR, Souza ASR, Katz L, Noronha Neto C. Planned caesarean section versus planned vaginal delivery for severe preeclampsia (Protocol). Cochrane Database of Systematic Reviews 2011, Issue 11.	Secondary pre-specified perinatal and neonatal outcomes include: • Long-term disability: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy
Bimbashi A, Duley L, Ndoni E, Dokle A. Amniotomy plus intravenous oxytocin for induction of labour (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 4.	Primary pre-specified outcomes for the baby include: • Serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood) Secondary pre-specified outcomes for the baby include: • Individual components of serious neonatal morbidity or perinatal death, as listed above (perinatal death, total baby death, seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood - such as neurodevelopmental delay, blind, deaf, cerebral palsy)
Dodd JM, Grivell RM, O'Brien CM, Dowswell T, Deussen AR. Prenatal administration of progestogens for preventing preterm birth in women with a multiple pregnancy (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 1.	Primary pre-specified outcomes for the infant include: • Major neurodevelopmental disability at childhood follow-up Secondary pre-specified outcomes for the child include: • Major sensorineural disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay, or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below mean)) • Cerebral palsy
Dutta D, Sule M, Ray A. Epidural therapy for the treatment of severe pre-eclampsia in non labouring women (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 1.	Secondary pre-specified outcome for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy
Eke AC, Ezebialu IU, Eleje GU. Hypnosis for preventing preterm labour (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 11.	Secondary pre-specified outcomes for the child include: • Major sensorineural disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay, or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below mean))

	• Cerebral palsy
Haruna M, Matsuzaki M, Ota E, Shiraishi M, Hanada N, Mori R. Guided imagery for treating hypertension in pregnancy (Protocol). Cochrane Database of Systematic Reviews 2014, Issue 10.	Secondary pre-specified outcomes for the neonate include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy
Hobson SR, Mockler JC, Lim R, Alers NO, Miller SL, Wallace EM. Melatonin for preventing pre-eclampsia (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 5.	Secondary pre-specified outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy
Hobson SR, Mockler JC, Lim R, Alers NO, Miller SL, Wallace EM. Melatonin for treating pre-eclampsia (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 3.	Secondary pre-specified outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy
Martis R, Emilia O, Nurdiati DS. Intermittent auscultation (IA) of fetal heart rate in labour for fetal well-being (Protocol). Cochrane Database of Systematic Reviews 2010, Issue 9.	Secondary pre-specified outcomes for the baby include: • Cerebral palsy

Reviews awaiting further classification

Review citation	Overview outcomes pre-specified in review with no outcome data	Main conclusion(s) of review
Abdel-Latif ME, Osborn DA, Challis D Cochrane Database of Systematic. Intra-amniotic surfactant for women at risk of preterm birth for preventing respiratory distress in newborns. Cochrane Database of Systematic Reviews 2010, Issue 1.	Primary outcomes include: • Neurodevelopmental disability at 18 months or more postnatal age, defined as neurological abnormality, including: cerebral palsy on clinical examination; developmental delay more than two standard deviations below population mean on any standard test of development; blindness (visual acuity less than 6/60); or deafness (any hearing impairment requiring amplification) at any time after term corrected age	No included trials. "We identified no randomised trials that evaluated the effect of intra-amniotic instillation of surfactant for women at risk of preterm birth. Evidence from animal and observational human studies suggest that intra-amniotic surfactant administration is potentially safe, feasible and effective. Well designed trials of intra-amniotic instillation of surfactant for women at risk of preterm birth are needed."
Bain E, Heatley E, Hsu K, Crowther CA. Relaxin for preventing preterm birth. Cochrane Database of Systematic Reviews 2013, Issue 8.	Secondary outcomes for the infant/child include: • Cerebral palsy	"There is limited randomised controlled trial evidence available on the effect of relaxin during pregnancy for preventing preterm birth for women in preterm labour. Evidence from one quasi-randomised trial suggested a reduction in birth within seven days of treatment for women receiving relaxin, compared with women in a control group, however this trial was at a high risk of bias and included only 30 women. Thus, there is insufficient evidence to support or refute the use of relaxin in women in preterm labour for preventing preterm birth."
Bain E, Middleton P, Crowther 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.	Primary outcomes for the infant/child include: • Cerebral palsy (abnormality of tone with motor dysfunction, or as defined by trialists) • Death or cerebral palsy (as they are competing outcomes, this combined outcome is often considered the most clinically relevant for assessing neuroprotection) Secondary outcomes for the infant/child include: • Cerebral palsy (mild, moderate or severe, evaluated separately, as defined by trialists) • Major neurologic disability (including: moderate or severe cerebral palsy (as defined by trialists))	No included trials. "Although strong evidence supports the use of antenatal magnesium sulphate for neuroprotection of the fetus prior to very preterm birth, no trials comparing different treatment regimens have been completed. Research should be directed towards comparisons of different dosages and other variations in regimens, evaluating both maternal and infant outcomes."
Bain E, Pierides KL, Clifton VL, Hodyl NA, Stark MJ,	Secondary outcomes for the infant, child, and for the child as an adult include:	"Based on eight included trials, of moderate quality overall, no firm conclusions about optimal interventions for managing asthma in

Crowther CA, et al. Interventions for managing asthma in pregnancy. Cochrane Database of Systematic Reviews 2014, Issue 10.	• Any neurodevelopmental disability (blindness, deafness, moderate or severe cerebral palsy (however defined by authors), or development delay or intellectual impairment (defined as developmental quotient or intelligence quotient more than two standard deviations below population mean)) • Cerebral palsy (however defined by authors)	pregnancy can be made. Five trials assessing pharmacological interventions did not provide clear evidence of benefits or harms to support or refute current practice. While inhaled magnesium sulphate for acute asthma was shown to reduce exacerbations, this was in one small trial of unclear quality, and thus, this finding should be interpreted with caution. Three trials assessing non-pharmacological interventions provided some support for the use of such strategies, however, were not powered to detect differences in important maternal and infant outcomes. While a FENO-based algorithm reduced exacerbations, the effects on perinatal outcomes were less certain, and thus, widespread implementation is not yet appropriate. Similarly, though positive effects on asthma control were shown with PMR and pharmacist-led management, the evidence to date is insufficient to draw definitive conclusions. In view of the limited evidence base, further randomised trials are required to determine the most effective and safe interventions for asthma in pregnancy. Future trials must be sufficiently powered, and well-designed, to allow differences in important outcomes for mothers and babies to be detected. The impact on health services requires evaluation. Any further trials assessing pharmacological interventions should assess novel agents or those used in current practice. Encouragingly, at least five trials have been identified as planned or underway."
Bricker L, Reed K, Wood L, Neilson JP. Nutritional advice for improving outcomes in multiple pregnancies. Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes for the child include: • Cerebral palsy	No included trials. "There is no robust evidence from randomised trials to indicate whether specialised diets or nutritional advice for women with multiple pregnancies do more good than harm. There is a clear need to undertake a randomised controlled trial."
Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane	Secondary outcomes for the neonate include: • Cerebral palsy at childhood follow-up	"Antibiotic treatment can eradicate bacterial vaginosis in pregnancy. The overall risk of PTB was not significantly reduced. This review provides little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent PTB and its consequences. When

Database of Systematic Reviews 2013, Issue 1.		screening criteria were broadened to include women with abnormal flora there was a 47% reduction in preterm birth, however, this is limited to two included studies."
Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2013, Issue 8.	Primary outcomes for the child include: • Neurodevelopmental disability at follow-up (blindness, deafness, moderate or severe cerebral palsy (however defined by authors), or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below population mean) or variously defined) Primary outcomes for the child as an adult include: • Neurodevelopmental disability at follow-up (blindness, deafness, moderate or severe cerebral palsy (however defined by authors), or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below population mean), or variously defined Secondary outcomes for the child include: • Cerebral palsy (however defined by authors)	"It remains unclear whether one corticosteroid (or one particular regimen) has advantages over another. Dexamethasone may have some benefits compared with betamethasone, such as less IVH, and a shorter length of stay in the NICU. The intramuscular route may have advantages over the oral route for dexamethasone, as identified in one small trial. Apart from the suggestion that 12-hour dosing may be as effective as 24-hour dosing of betamethasone, based on one small trial, we were unable to make few other conclusions about optimal antenatal corticosteroid regimens. No long-term results were available, except for a small subgroup of 18-month old children in one trial. Trials comparing the commonly used corticosteroids are most urgently needed, as are trials of dosages and other variations in treatment regimens."
Chawanpaiboon S, Laopaiboon M, Lumbiganon P, Sangkomkamhang US, Dowswell T. Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes. Cochrane Database of Systematic Reviews 2014, Issue 3.	Secondary outcomes for the neonate include: • Neurological sequelae (general intelligence, hearing, vision, cerebral palsy, and disability)	"We found no evidence that terbutaline pump maintenance therapy decreased adverse neonatal outcomes. Taken together with the lack of evidence of benefit, its substantial expense, and the lack of information on the safety of the therapy, the evidence does not support its use in the management of arrested preterm labour. Future use should only be in the context of well-conducted, adequately powered randomised controlled trials."
Cluett ER, Burns E. Immersion in water in labour and birth. Cochrane Database of	Primary outcomes for the neonate include: • Neurological pathology, e.g. seizures, cerebral palsy	"Evidence suggests that water immersion during the first stage of labour reduces the use of epidural or spinal analgesia and duration of the first stage of labour. There is limited information for other outcomes related to water use during the first and second stages of

Systematic Reviews 2009, Issue 2.		labour, due to intervention and outcome variability. There is no evidence of increased adverse effects to the fetus, neonate or woman from labouring in water or a water birth. However, the studies are very variable and considerable heterogeneity was detected for some outcomes. Further research is needed."
Devane D, Lalor JG, Daly S, McGuire W, Smith V. Cardiotocography versus intermittent auscultation of fetal heart on admission to labour ward for assessment of fetal well-being. Cochrane Database of Systematic Reviews 2012, Issue 2.	Primary outcomes for the infant include: • Severe neurodevelopmental disability assessed at greater than, or equal to, 12 months of age. We have defined severe neurodevelopmental disability as any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory, and visual impairment. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development (Psychomotor Developmental Index and Mental Developmental Index)	"Contrary to continued use in some clinical areas, we found no evidence of benefit for the use of the admission cardiotocograph (CTG) for low-risk women on admission in labour. We found no evidence of benefit for the use of the admission CTG for low-risk women on admission in labour. Furthermore, the probability is that admission CTG increases the caesarean section rate by approximately 20%. The data lacked power to detect possible important differences in perinatal mortality. However, it is unlikely that any trial, or meta-analysis, will be adequately powered to detect such differences. The findings of this review support recommendations that the admission CTG not be used for women who are low risk on admission in labour. Women should be informed that admission CTG is likely associated with an increase in the incidence of caesarean section without evidence of benefit."
Dickinson H, Bain E, Wilkinson D, Middleton P, Crowther CA, Walker DW. Creatine for women in pregnancy for neuroprotection of the fetus. Cochrane Database of Systematic Reviews 2014, Issue 12.	Primary outcomes for the infant and child include: • Death or any neurosensory disability (at latest time reported); this combined outcome recognises the potential for competing risks of death or survival with neurological problems • Neurosensory disability (any of cerebral palsy, blindness, deafness, developmental delay or intellectual impairment; at latest time reported) Secondary outcomes for the infant/child include: • Cerebral palsy (any, and graded as severe: including children who are non-ambulant and are likely to remain so; moderate: including those children who have substantial limitation of movement; mild: including those children walking with little limitation of movement)	No included trials. "As we did not identify any randomised controlled trials for inclusion in this review, we are unable to comment on implications for practice. Although evidence from animal studies has supported a fetal neuroprotective role for creatine when administered to the mother during pregnancy, no trials assessing creatine in pregnant women for fetal neuroprotection have been published to date. If creatine is established as safe for the mother and her fetus, research efforts should first be directed towards randomised trials comparing creatine with either no intervention (ideally using a placebo), or with alternative agents aimed at providing fetal neuroprotection (including magnesium sulphate for the very preterm infant). If appropriate, these trials should then be followed by studies comparing different creatine regimens (dosage and duration of exposure). Such trials should be high quality

	• Death or cerebral palsy • Major neurosensory disability (defined as any of: moderate or severe cerebral palsy, legal blindness, neurosensory deafness requiring hearing aids, or moderate or severe developmental delay, or intellectual impairment)	and adequately powered to evaluate maternal and infant short and longer-term outcomes (including neurodevelopmental disabilities, such as cerebral palsy), and should consider utilisation and costs of health care."
Dodd JM, Dowswell T, Crowther CA. Specialised antenatal clinics for women with a multiple pregnancy for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes for the infant include: • Disability at childhood follow-up (including deafness, blindness, neurodisability, or cerebral palsy)	"There is currently limited information available from randomised controlled trials to assess the role of 'specialised' antenatal clinics for women with a multiple pregnancy compared with 'standard' antenatal care in improving maternal and infant health outcomes. The value of 'specialised' multiple pregnancy clinics in improving health outcomes for women and their infants requires evaluation in appropriately powered and designed randomised controlled trials."
Drakeley AJ, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. Cochrane Database of Systematic Reviews 2003, Issue 1.	Neonatal outcomes include: • Infant and child development - such as cerebral palsy; mental retardation, hearing and vision as assessed by paediatric follow-up and attainment of developmental milestones (less than one year; less than two years; greater than two years	"The use of a cervical stitch should not be offered to women at low or medium risk of mid trimester loss, regardless of cervical length by ultrasound. The role of cervical cerclage for women who have short cervix on ultrasound remains uncertain as the numbers of randomised women are too few to draw firm conclusions. There is no information available as to the effect of cervical cerclage or its alternatives on the family unit and long term outcome."
Duckitt K, Thornton S, O'Donovan OP, Dowswell T. Nitric oxide donors for treating preterm labour. Cochrane Database of Systematic Reviews 2014, Issue 5.	Primary outcomes for the infant include: • Long-term neurological development (general intelligence, hearing, vision, cerebral palsy, and disability, (serious infant outcome))	"There is currently insufficient evidence to support the routine administration of nitric oxide donors in the treatment of threatened preterm labour."
Duley L, Gülmezoglu AM, Chou D. Magnesium sulphate versus lytic cocktail for eclampsia. Cochrane Database of Systematic Reviews 2010, Issue 9.	Secondary outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"Magnesium sulphate, rather than lytic cocktail, for women with eclampsia reduces the risk ratio of maternal death, of further seizures and of serious maternal morbidity (respiratory depression, coma, pneumonia). Magnesium sulphate is the anticonvulsant of choice for women with eclampsia; the use of lytic cocktail should be abandoned."

Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database of Systematic Reviews 2010, Issue 10.	Secondary outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"Magnesium sulphate, rather than phenytoin, for women with eclampsia reduces the risk ratio of recurrence of seizures, probably reduces the risk of maternal death, and improves outcome for the baby. Magnesium sulphate is the drug of choice for women with eclampsia. The use of phenytoin should be abandoned."
Duley L, Henderson-Smart DJ, Meher S. Altered dietary salt for preventing pre-eclampsia, and its complications. Cochrane Database of Systematic Reviews 2005, Issue 4.	Outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"In the absence of evidence that advice to alter salt intake during pregnancy has any beneficial effect for prevention of pre-eclampsia or any other outcome, salt consumption during pregnancy should remain a matter of personal preference."
Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2007, Issue 2.	Outcomes for the child include: • Infant and child development (such as cerebral palsy, cognitive delay, deafness, and blindness)	"Antiplatelet agents, largely low-dose aspirin, have moderate benefits when used for prevention of pre-eclampsia and its consequences. Further information is required to assess which women are most likely to benefit, when treatment is best started, and at what dose."
Duley L, Henderson-Smart DJ, Walker GJA, Chou D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database of Systematic Reviews 2010, Issue 12.	Secondary outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"Magnesium sulphate for women with eclampsia reduces the risk ratio of maternal death and of recurrence of seizures, compared with diazepam."
Duley L, Matar HE, Almerie MQ, Hall DR. Alternative magnesium sulphate regimens for women with pre-eclampsia and eclampsia. Cochrane Database of Systematic Reviews 2010, Issue 8.	Secondary outcomes for the baby include: • Development in childhood: including cerebral palsy and major neurodevelopmental delay	"Although strong evidence supports the use of magnesium sulphate for prevention and treatment of eclampsia, trials comparing alternative treatment regimens are too small for reliable conclusions."

Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database of Systematic Reviews 2013, Issue 7.	Secondary outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"Until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug; on what is known about adverse effects; and on women's preferences. Exceptions are nimodipine, magnesium sulphate (although this is indicated for women who require an anticonvulsant for prevention or treatment of eclampsia), diazoxide and ketanserin, which are probably best avoided."
Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of pre-eclampsia. Cochrane Database of Systematic Reviews 1999, Issue 4.	Outcomes for the baby include: • Measures of infant and child development (such as cerebral palsy)	"There is insufficient evidence for any reliable estimates of the effects of plasma volume expansion for women with pre-eclampsia."
Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DNM. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2014, Issue 6.	Primary outcomes include: • Serious infant outcome (defined as death or chronic lung disease (need for supplemental oxygen at 28 days of life or later), grade three or four intraventricular haemorrhage or periventricular leukomalacia, major neurosensory disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient (DQ) or intelligence quotient (IQ) less than two standard deviations below mean)))	"This review did not demonstrate superiority of oxytocin receptor antagonists (ORA; largely atosiban) as a tocolytic agent compared with placebo, betamimetics, or calcium channel blockers (CCB; largely nifedipine) in terms of pregnancy prolongation or neonatal outcomes, although ORA was associated with less maternal adverse effects than treatment with the CCB or betamimetics. The finding of an increase in infant deaths, and more births before completion of 28 weeks of gestation in one placebo-controlled study warrants caution. However, the number of women enrolled at very low gestations was small. Due to limitations of small numbers studied and methodological quality, further well-designed randomised controlled trials are needed. Further comparisons of ORA versus CCB (which has a better side-effect profile than betamimetics) are needed. Consideration of further placebo-controlled studies seems warranted. Future studies of tocolytic agents should measure all important short- and long-term outcomes for women and infants, and costs."
Flenady V, Wojcieszek AM, Papatsonis DNM, Stock OM, Murray L, Jardine LA, et al. Calcium channel blockers for	Primary outcomes include: • Serious infant outcome (defined as death or chronic lung disease (need for supplemental oxygen at 28 days of life or later), grade three or four intraventricular haemorrhage	"Calcium channel blockers (CCB; mainly nifedipine) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth, thus, theoretically allowing time for administration of antenatal corticosteroids and transfer to higher level

inhibiting preterm labour and birth. Cochrane Database of Systematic Reviews 2014, Issue 6.	(IVH) or periventricular leukomalacia (PVL), major neurosensory disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient (DQ) or intelligence quotient (IQ) less than two standard deviations below mean))) Secondary outcomes for the infant or child include: • Blindness, deafness, cerebral palsy	care. Calcium channel blockers were shown to have benefits over betamimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects. Calcium channel blockers may also have some benefits over ORAs and magnesium sulphate, although ORAs results in fewer maternal adverse effects. However, it must be noted that no difference was shown in perinatal mortality, and data on longer-term outcomes were limited. Further, the lack of blinding of the intervention diminishes the strength of this body of evidence. Further well-designed tocolytic trials are required to determine short- and longer-term infant benefit of CCBs over placebo or no treatment and other tocolytics, particularly ORAs. Another important focus for future trials is identifying optimal dosage regimens of different types of CCBs (high versus low, particularly addressing speed of onset of uterine quiescence), and formulation (capsules versus tablets). All future trials on tocolytics for women in preterm labour should employ blinding of the intervention and outcome assessment, include measurement of longer-term effects into early childhood, and also costs."
Grivell RM, Alfirevic Z, Gyte GML, Devane D. Antenatal cardiotocography for fetal assessment. Cochrane Database of Systematic Reviews 2015, Issue 9.	Secondary outcomes include: • Cerebral palsy at 12 months	"There is no clear evidence that antenatal CTG improves perinatal outcome, but further studies focusing on the use of computerised CTG in specific populations of women with increased risk of complications are warranted."
Grivell RM, Wong L, Bhatia V. Regimens of fetal surveillance for impaired fetal growth. Cochrane Database of Systematic Reviews 2012, Issue 6.	Secondary outcomes for the infant include: • Cerebral palsy	"There is limited evidence from randomised controlled trials to inform best practice for fetal surveillance regimens when caring for women with pregnancies affected by impaired fetal growth. More studies are needed to evaluate the effects of currently used fetal surveillance regimens in impaired fetal growth."
Haas DM, Morgan AM, Deans SJ, Schubert FP. Ethanol for preventing preterm birth in	Secondary outcomes for the fetus, neonate, or infant include: • Serious infant outcome (defined as death or chronic lung disease (need for supplemental oxygen at 28 days of life or	"This review is based on evidence from twelve studies, which were mostly low quality. There is no evidence to suggest that ethanol is an effective tocolytic compared to placebo. There is some evidence that

threatened preterm labor. Cochrane Database of Systematic Reviews 2015, Issue 11.	later), grade three or four intraventricular hemorrhage or periventricular leukomalacia, major neurosensory disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient (DQ) or intelligence quotient (IQ) less than two standard deviations below mean)))	ethanol may be better tolerated than other tocolytics (in this case betamimetics), but this result is based on few studies and small sample sizes and therefore, should be interpreted with caution. Ethanol appears to be inferior to betamimetics for preventing preterm birth in threatened preterm labor. Ethanol is generally no longer used in current practice, due to safety concerns for the mother and her baby. There is no need for new studies to evaluate the use of ethanol for preventing preterm birth in threatened preterm labour. However, it would be useful for long-term follow-up studies on the babies born to mothers from the existing studies, in order to assess the risk of long-term neurodevelopmental status."
Heazell AEP, Whitworth M, Duley L, Thornton JG. Use of biochemical tests of placental function for improving pregnancy outcome. Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes for the baby include: • Neurodevelopment in childhood (cerebral palsy, neurodevelopmental delay)	"There is insufficient evidence to support the use of biochemical tests of placental function to reduce perinatal mortality or increase identification of small-for-gestational-age infants. However, we were only able to include data from two studies that measured oestrogens and hPL. The quality of the evidence was low or very low. Two of the trials were performed in the 1970s, on women with a variety of antenatal complications, and this evidence cannot be generalised to women at low-risk of complications or groups of women with specific pregnancy complications (e.g. fetal growth restriction). Furthermore, outcomes described in the 1970s may not reflect what would be expected at present. For example, neonatal mortality rates have fallen substantially, such that an infant delivered at 28 weeks would have a greater chance of survival were those studies repeated; this may affect the primary outcome of the meta-analysis. With data from just two studies (740 women), this review is underpowered to detect a difference in the incidence of death of a baby or the frequency of a small-for-gestational-age infant, as these have a background incidence of approximately 0.75% and 10% of pregnancies, respectively. Similarly, this review is underpowered to detect differences between serious or rare adverse events, such as severe neonatal morbidity. Two of the three included studies were quasi-randomised, with significant risk of bias from group allocation. Additionally, there may be

		performance bias, as in one of the two studies contributing data, participants receiving standard care did not have venipuncture, so clinicians treating participants could identify which arm of the study they were in. Future studies should consider more robust randomisation methods and concealment of group allocation, and should be adequately powered to detect differences in rare adverse events. The studies identified in this review examined two different analytes: oestrogens and hPL. There are many other placental products that could be employed as surrogates of placental function, including: placental growth factor (PlGF), human chorionic gonadotrophin (hCG), plasma protein A (PAPP-A), placental protein 13 (PP-13), pregnancy-specific glycoproteins, and progesterone metabolites, and further studies should be encouraged to investigate these other placental products. Future randomised controlled trials should test analytes identified as having the best predictive reliability for placental dysfunction leading to small-for-gestational-age infants and perinatal mortality."
Jahanfar S, Jaafar SH. Effects of restricted caffeine intake by mother on fetal, neonatal and pregnancy outcomes. Cochrane Database of Systematic Reviews 2015, Issue 6.	Secondary outcomes include: • Cerebral palsy and cognitive impairment	"There is insufficient evidence to confirm or refute the effectiveness of caffeine avoidance on birthweight or other pregnancy outcomes. There is a need to conduct high-quality, double-blinded RCTs to determine whether caffeine has any effect on pregnancy outcome."
Khanprakob T, Laopaiboon M, Lumbiganon P, Sangkomkamhang US. Cyclo-oxygenase (COX) inhibitors for preventing preterm labour. Cochrane Database of Systematic Reviews 2012, Issue 10.	Secondary neonatal outcomes include: • Long-term outcomes, for example developmental delay, cerebral palsy, educational attainment, etc.	"There was very little evidence about using COX-inhibitors for preventing preterm labour. There are inadequate data to make any recommendation about using COX-inhibitor in practice to prevent preterm labour. Future research should include follow-up of the babies to examine the short-term and long-term effects of COX inhibitors."

Lalor JG, Fawole B, Alfirevic Z, Devane D. Biophysical profile for fetal assessment in high risk pregnancies. Cochrane Database of Systematic Reviews 2008, Issue 1	Outcomes for the infant include: • Disability to include non-ambulant cerebral palsy at or after 12 months of age, sensory impairment (visual, hearing), or both	"At present, there is insufficient evidence from randomised trials to support the use of biophysical profile (BPP) as a test of fetal well-being in high-risk pregnancies."
Li W, Tang L, Wu T, Zhang J, Liu GJ, Zhou L. Chinese herbal medicines for treating pre-eclampsia. Cochrane Database of Systematic Reviews 2006, Issue 2.	Secondary outcomes for the neonate include: • Measures of long-term growth and development, such as important impairment and cerebral palsy	No included trials. "The efficacy and safety of Chinese herbal medicines for treating pre-eclampsia remains unclear. There are no randomised controlled trials in this field. High-quality randomised controlled trials are urgently required."
Makrides M, Duley L, Olsen SF. Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. Cochrane Database of Systematic Reviews 2006, Issue 3.	Outcomes for the baby include: • Long-term follow-up included measures of neurological and developmental outcome (such as cerebral palsy)	"There is not enough evidence to support the routine use of marine oil, or other prostaglandin precursors, supplements during pregnancy to reduce the risk of pre-eclampsia, preterm birth, low birthweight, or small-for-gestational age."
McNamara HC, Crowther CA, Brown J. Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour. Cochrane Database of Systematic Reviews 2015, Issue 12.	Primary outcomes for the infant or child include: • Composite serious infant outcome (defined as death or chronic lung disease (oxygen requirement at 28 days of life or later); intraventricular haemorrhage (IVH; grade three or four), or periventricular leucomalacia (PVL); major neurosensory disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below the mean)) Secondary outcomes for the child include:	"There are limited data available (three studies, with data from only two studies) comparing different dosing regimens of magnesium sulphate given as single agent tocolytic therapy for the prevention of preterm birth. There is no evidence examining duration of therapy, timing of therapy, and the role for repeat dosing. Downgrading decisions for our primary outcome of fetal, neonatal, and infant death were based on wide confidence intervals (crossing the line of no effect), lack of blinding, and a limited number of studies. No data were available for any of our other important outcomes: birth less than 48 hours after trial entry; composite serious infant outcome; composite serious maternal outcome. The data are limited by volume and the outcomes reported. Only eight of our 45 pre-specified primary and

	• Cerebral palsy (mild, moderate, or severe, evaluated separately)	secondary maternal and infant health outcomes were reported on in the included studies. No long-term outcomes were reported. Downgrading decisions for the evidence on the risk of respiratory distress were based on wide confidence intervals (crossing the line of no effect), and lack of blinding. There is some evidence from a single study, suggesting a reduction in the length of stay in the neonatal intensive care unit and a reduced risk of respiratory distress syndrome, where a high-dose regimen of magnesium sulphate has been compared with a low-dose regimen. However, given that evidence has been drawn from a single study (with a small sample size), these data should be interpreted with caution. Magnesium sulphate has been shown to be of benefit in a wide range of obstetric settings, although it has not been recommended for tocolysis. In clinical settings where health benefits are established, further trials are needed to address the lack of evidence regarding the optimal dose (loading dose and maintenance dose), duration of therapy, timing of therapy, and role for repeat dosing, in terms of efficacy and safety for mothers and their children. Ongoing examination of different regimens with respect to important health outcomes is required."
Meher S, Duley L. Rest during pregnancy for preventing pre-eclampsia and its complications in women with normal blood pressure. Cochrane Database of Systematic Reviews 2006, Issue 2.	Outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"Daily rest, with or without nutrient supplementation, may reduce the risk of pre-eclampsia for women with normal blood pressure, although the reported effect may reflect bias, random error, or both, rather than a true effect. There is no information about outcomes such as perinatal mortality and morbidity, maternal morbidity, women's views, adverse effects, and costs. Current evidence is insufficient to support recommending rest or reduced activity to women for preventing pre-eclampsia and its complications. Whether women rest during pregnancy should therefore be a matter of personal choice."
Meher S, Duley L. Progesterone for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2006, Issue 4.	Secondary outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"There is insufficient evidence for reliable conclusions about the effects of progesterone for preventing pre-eclampsia and its complications. Therefore, progesterone should not be used for this purpose in clinical practice at present."

Meher S, Duley L. Nitric oxide for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2007, Issue 2.	Outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"There is insufficient evidence to draw reliable conclusions about whether nitric oxide donors and precursors prevent pre-eclampsia or its complications."
Meher S, Duley L. Garlic for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2006, Issue 3.	Outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"There is insufficient evidence to recommend increased garlic intake for preventing pre-eclampsia and its complications. Although garlic is associated with odour, other more serious side-effects have not been reported. Further large randomised trials evaluating the effects of garlic are needed before any recommendations can be made to guide clinical practice."
Meher S, Duley L. Exercise or other physical activity for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2006, Issue 2.	Outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"There is insufficient evidence for reliable conclusions about the effects of exercise on prevention of pre-eclampsia and its complications."
Naik Gaunekar N, Raman P, Bain E, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. Cochrane Database of Systematic Reviews 2013, Issue 10.	Primary outcomes include: • Any neurological disability at paediatric follow-up (impairment of vision, hearing, intelligence, or cerebral palsy)	"Based on the current available evidence, maintenance treatment with a calcium channel blocker after threatened preterm labour does not prevent preterm birth or improve maternal or infant outcomes."
Nanda K, Cook LA, Gallo MF, Grimes DA. Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth. Cochrane Database of	Outcomes for the infant include: • Neurological sequelae (general intelligence, hearing, vision, cerebral palsy, and disability)	"Terbutaline pump maintenance therapy has not been shown to decrease the risk of preterm birth by prolonging pregnancy. Furthermore, the lack of information on the safety of the therapy, as well as its substantial expense, argues against its role in the management of arrested preterm labor. Future use should only be in the context of well-conducted, adequately powered randomized controlled trials."

Systematic Reviews 2002, Issue 4.		
Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database of Systematic Reviews 2015, Issue 12.	Secondary outcomes for the fetus include: • Cerebral palsy	"The modest benefits of fewer fetal scalp samplings during labour (in settings in which this procedure is performed) and fewer instrumental vaginal births have to be considered against the disadvantages of needing to use an internal scalp electrode, after membrane rupture, for ECG waveform recordings. We found little strong evidence that ST-waveform analysis had an effect on the primary outcome measures in this systematic review. There was a lack of evidence showing that PR-interval analysis improved any outcomes; and a larger future trial may possibly demonstrate beneficial effects. There is little information about the value of fetal ECG waveform monitoring in preterm fetuses in labour. Information about long-term development of the babies included in the trials would be valuable."
Nguyen TMN, Crowther CA, Wilkinson D, Bain E. Magnesium sulphate for women at term for neuroprotection of the fetus. Cochrane Database of Systematic Reviews 2013, Issue 2.	Primary outcomes for the infant or child include: • Death or cerebral palsy • Cerebral palsy (abnormality of tone with motor dysfunction (as diagnosed at 18 months of age or later)) Secondary outcomes for the child include: • 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	"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."

	severe cerebral palsy, an intelligence quotient (IQ) less than 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 less than two SD below the mean. Mild disability will comprise mild cerebral palsy or an IQ from minus two SD to less than one SD below the mean • 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 or intellectual impairment (defined as developmental quotient or IQ less than two SD below the mean))	
Ohlsson A, Shah VS, Stade BC. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Cochrane Database of Systematic Reviews 2014, Issue 12.	Secondary intellectual impairment outcomes include: • Long-term neurological sequelae, which may include cognitive delay, cerebral palsy, cortical blindness, deafness, hydrocephalus, or a combination	"The quality of the four included trials varied, as did the risk of bias, and the quality of the evidence using GRADE, was very low. Vaginal chlorhexidine was not associated with reductions in any of the primary outcomes of early-onset GBS disease (sepsis, meningitis, or both), or GBS pneumonia. Vaginal chlorhexidine may reduce GBS colonization of neonates. The intervention was associated with an increased risk of maternal mild adverse effects. The review currently does not support the use of vaginal disinfection with chlorhexidine in labour for preventing early-onset disease. Results should be interpreted with caution as the methodological quality of the studies was poor. As early-onset GBS disease is a rare condition, trials with very large sample sizes are needed to assess the effectiveness of vaginal chlorhexidine, to reduce its occurrence. In the era of intrapartum antibiotic prophylaxis, such trials may be difficult to justify, especially in developed countries."
Papatsonis DNM, Flenady V, Liley HG. Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour.	Primary outcomes include: • Perinatal or infant mortality, or any neurological disability at long-term paediatric follow-up at two years of age (vision impairment, sensorineural deafness requiring hearing aids,	"There is insufficient evidence to support the use of oxytocin receptor antagonists to inhibit preterm birth after a period of threatened or actual preterm labour. Any future trials using oxytocin antagonists or other drugs as maintenance therapy for preventing preterm birth should examine a variety of important infant outcome measures,

Cochrane Database of Systematic Reviews 2013, Issue 10.	cerebral palsy, or developmental delay or intellectual impairment)	including reduction of neonatal morbidity and mortality, and long-term infant follow-up. Future research should also focus on the pathophysiological pathways that precede preterm labour."
Phipps H, de Vries B, Hyett J, Osborn DA. Prophylactic manual rotation for fetal malposition to reduce operative delivery. Cochrane Database of Systematic Reviews 2014, Issue 12.	Secondary outcomes for the neonate and infant include: • Severe neurodevelopmental disability in infants (assessed at 12 months of age or older), defined as any one or combination of the following: non-ambulant cerebral palsy, severe developmental delay assessed using validated tools, auditory and visual impairment	"Currently, there is insufficient evidence to determine the efficacy of prophylactic manual rotation early in the second stage of labour for prevention of operative delivery. One additional study is ongoing. Further appropriately designed trials are required to determine the efficacy of manual rotation."
Reinebrant HE, Pileggi-Castro C, Romero CLT, dos Santos RAN, Kumar S, Souza JP, et al. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database of Systematic Reviews 2015, Issue 6.	Primary outcomes include: • Serious infant outcome - death or major sensorineural disability at two years of age (defined as any one or more of the following: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below the mean))	"In this review, no clear benefit for COX inhibitors was shown over placebo or any other tocolytic agents. While some benefit was demonstrated in terms of postponement of birth for COX inhibitors over placebo and betamimetics, and also maternal adverse effects over betamimetics and MgSO4, due to the limitations of small numbers, minimal data on safety, lack of longer-term outcomes, and generally low quality of the studies included in this review, we conclude that there is insufficient evidence on which to base decisions about the role of COX inhibition for women in preterm labour. Further well-designed tocolytic studies are required to determine short- and longer-term infant benefit of COX inhibitors over placebo and other tocolytics, particularly CCBs and ORAs. Another important focus for future studies is identifying whether COX-2 inhibitors are superior to non-selective COX inhibitors. All future studies on tocolytics for women in preterm labour should assess longer-term effects into early childhood and also costs."
Rumbold A, Duley L, Crowther CA, Haslam RR. Antioxidants for preventing pre-eclampsia. Cochrane Database of Systematic Reviews 2008, Issue 1.	Secondary outcomes for the child include: • Disability during childhood (such as cerebral palsy, intellectual disability, hearing disability, and visual impairment)	"Evidence from this review does not support routine antioxidant supplementation during pregnancy to reduce the risk of pre-eclampsia and other serious complications in pregnancy."

Rumbold A, Ota E, Hori H, Miyazaki C, Crowther CA. Vitamin E supplementation in pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 9.	Secondary outcomes for the neonate include: • Disability at childhood follow-up (such as cerebral palsy, intellectual disability, hearing disability, and visual impairment)	"The data do not support routine vitamin E supplementation in combination with other supplements for the prevention of stillbirth, neonatal death, preterm birth, pre-eclampsia, preterm or term PROM, or poor fetal growth. Further research is required to elucidate the possible role of vitamin E in the prevention of placental abruption. There was no convincing evidence that vitamin E supplementation in combination with other supplements results in other important benefits or harms."
Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 9.	Secondary outcomes for the child include: • Disability at childhood follow-up (such as cerebral palsy, intellectual disability, hearing disability, and visual impairment)	"The data do not support routine vitamin C supplementation alone or in combination with other supplements, for the prevention of fetal or neonatal death, poor fetal growth, preterm birth, or pre-eclampsia. Further research is required to elucidate the possible role of vitamin C in the prevention of placental abruption and pre-labour rupture of membranes. There was no convincing evidence that vitamin C supplementation alone or in combination with other supplements results in other important benefits or harms."
Shub A, Walker SP. Planned early delivery versus expectant management for monoamniotic twins. Cochrane Database of Systematic Reviews 2015, Issue 4.	Secondary outcomes for the infant include: • Cerebral palsy	No included trials. "Monoamniotic twins are rare, and there is insufficient randomised controlled evidence on which to draw strong conclusions about the best management. In their absence, we can refer to historical case series and expert consensus. Management plans should take into consideration the availability of high-quality neonatal care if early delivery is chosen. Women and their families should be involved in the decision-making about these high-risk pregnancies. Ongoing, multicentre audits of maternal and perinatal outcomes for monoamniotic twins are needed in order to inform families and clinicians about up-to-date perinatal outcomes with contemporary obstetric practice. Research should consider the social and economic implications of planned interventions, as well as the perinatal outcomes."
Spencer L, Bubner T, Bain E, Middleton P. Screening and subsequent management for	Primary outcomes for the infant as a child include:	"Though universal screening versus no screening for hypothyroidism similarly increased diagnosis and subsequent treatment, no clear difference was seen for the primary outcome: neurosensory disability

thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. Cochrane Database of Systematic Reviews 2015, Issue 9.	• Neurosensory disability (any of: cerebral palsy, blindness, deafness, developmental delay, intellectual impairment, at latest time reported) Secondary outcomes for the infant as a child include: • Cerebral palsy	for the infant as a child (IQ less than 85 at three years); data were lacking for the other primary outcomes: pre-eclampsia and preterm birth, and for the majority of secondary outcomes, including miscarriage and fetal or neonatal death. For outcomes assessed using the GRADE approach, the evidence was considered to be moderate or high quality, with any downgrading of the evidence based on the presence of wide confidence intervals crossing the line of no effect. More evidence is needed to assess the benefits or harms of different screening methods for thyroid dysfunction in pregnancy, on maternal, infant and child health outcomes. Future trials should assess impacts on use of health services and costs, and be adequately powered to evaluate the effects on short- and long-term outcomes."
Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. Cochrane Database of Systematic Reviews 2015, Issue 6.	Secondary outcomes for the neonate pre-specified include: • Childhood cerebral palsy	"Antibiotic prophylaxis did not reduce the risk of preterm pre-labour rupture of membranes or preterm delivery (apart from in the subgroup of women with a previous preterm birth who had bacterial vaginosis). Antibiotic prophylaxis given during the second or third trimester of pregnancy reduced the risk of postpartum endometritis, term pregnancy with pre-labour rupture of membranes and gonococcal infection when given routinely to all pregnant women. Substantial bias possibly exists in the review's results because of a high rate of loss to follow-up, and the small numbers of studies included in each of our analyses. There is also insufficient evidence on possible harmful effects on the baby. Therefore, we conclude that there is not enough evidence to support the use of routine antibiotics during pregnancy to prevent infectious adverse effects on pregnancy outcomes."
Turnbull C, Osborn DA. Home visits during pregnancy and after birth for women with an alcohol or drug problem. Cochrane Database of Systematic Reviews 2012, Issue 1.	Outcomes for the infant or child include: • Disability (cerebral palsy, sensorineural impairment, or significant developmental delay)	"There is insufficient evidence to recommend the routine use of home visits for pregnant or postpartum women with a drug or alcohol problem. Further large, high-quality trials are needed."

Utama DP, Crowther CA. Transplacental versus direct fetal corticosteroid treatment for accelerating fetal lung maturation where there is a risk of preterm birth. Cochrane Database of Systematic Reviews 2011, Issue 9.	Secondary outcomes for the infant or child include: • Cerebral palsy (however defined by authors)	No included trials. "The available clinical studies carried out so far on animals and humans have shown that direct intramuscular injection of corticosteroid into the fetus under ultrasound guidance is feasible, but data on health outcomes are lacking. Therefore, uncertainty persists as to which method could provide better efficacy and safety profile. Randomised controlled trials are required, focusing on the benefits and harms of transplacental versus direct fetal corticosteroid treatment. Until the uncertainties have been answered, it is advisable to stay with the current standard of antenatal transplacental maternally administered corticosteroid treatment."
Vogel JP, Nardin JM, Dowswell T, West HM, Oladapo OT. Combination of tocolytic agents for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2014, Issue 7.	Primary outcomes include: • Short-term and long-term serious infant outcome (see definition below), determined by the presence of any of the following: death; chronic lung disease (use of supplemental oxygen therapy at 36 weeks' postmenstrual age, or at 28 days of life, or later); grade three or four intraventricular haemorrhage or periventricular leukomalacia; major sensorineural disability at two years of age, defined as any one or more of the following: severe or profound vision impairment, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below the mean)	"It is unclear whether a combination of tocolytic drugs for preterm labour is more advantageous for women, newborns, or both, due to a lack of large, well-designed trials including the outcomes of interest. There are no trials of combination regimens using widely used tocolytic agents, such as calcium channel blockers (nifedipine), oxytocin receptor antagonists (atosiban), or both. Further trials are needed before specific conclusions on use of combination tocolytic therapy for preterm labour can be made."
Waterfall H, Grivell RM, Dodd JM. Techniques for assisting difficult delivery at caesarean section. Cochrane Database of Systematic Reviews 2016, Issue 1.	Secondary outcomes for the infant include: • Cerebral palsy	"There is currently insufficient information available from randomised trials to support or refute the routine or selective use of tocolytic agents or instrument to facilitate infant birth at the time of difficult caesarean section. There is limited evidence that reverse breech extraction may improve maternal and fetal outcomes, though there was no difference in primary outcome of infant birth trauma. Further randomised controlled trials are needed to answer these questions."

Whitworth M, Quenby S. Prophylactic oral betamimetics for preventing preterm labour in singleton pregnancies. Cochrane Database of Systematic Reviews 2008, Issue 1.	Primary outcomes include: • Death at childhood follow-up at greater than, or equal to, 12 months of age (corrected for preterm birth), or severe neurodevelopmental disability defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70, or more than two standard deviations below the mean), severe auditory impairment (sensorineural deafness requiring hearing aids), or visual impairment (legal blindness)	"There is insufficient evidence to support or refute the use of prophylactic oral betamimetics for preventing preterm birth in women at high risk of preterm labour with a singleton pregnancy."
Whitworth M, Quenby S, Cockerill RO, Dowswell T. Specialised antenatal clinics for women with a pregnancy at high risk of preterm birth (excluding multiple pregnancy) to improve maternal and infant outcomes. Cochrane Database of Systematic Reviews 2011, Issue 9.	Secondary outcomes for the infant include: • Disability at childhood follow-up (including deafness, blindness, neurodisability, or cerebral palsy)	"Specialised antenatal clinics are now an accepted part of care in many settings, and carrying out further randomised trials may not be possible. Any future research in this area should include psychological outcomes, and should focus on which aspects of service provision are preferred by women. Such research could underpin further service development in this area."
Wilkinson D, Shepherd E, Wallace EM. Melatonin for women in pregnancy for neuroprotection of the fetus. Cochrane Database of Systematic Reviews 2016, Issue 3.	Primary outcomes for the infant or child include: • Death or any neurosensory disability (at latest time reported); this combined outcome recognises the potential for competing risks of death or survival with neurological problems • Neurosensory disability (any of: cerebral palsy, blindness, deafness, developmental delay or intellectual impairment), at latest time reported Secondary outcomes for the infant or child include: • Cerebral palsy (any, and graded as: severe: including children who are non-ambulant and are likely to remain so; moderate: including those children who have substantial	No included trials. "As we did not identify any randomised trials for inclusion in this review, we are unable to comment on implications for practice at this stage. Although evidence from animals studies has supported a fetal neuroprotective role for melatonin when administered to the mother during pregnancy, no trials assessing melatonin for fetal neuroprotection in pregnant women have been completed to date. However, there is currently one ongoing randomised controlled trial (with an estimated enrolment target of 60 pregnant women), which examines the dose of melatonin, administered to women at risk of imminent, very preterm birth (less than 28 weeks' gestation), required to reduce brain damage in the white matter of the babies that were born very preterm. Further high-quality research is needed, and

	limitation of movement; mild: including those children walking with little limitation of movement) • Death or cerebral palsy • Major neurosensory disability (defined as any of: moderate or severe cerebral palsy, legal blindness, neurosensory deafness requiring hearing aids, or moderate or severe developmental delay or intellectual impairment)	research efforts should be directed towards trials comparing melatonin with either no intervention (no treatment or placebo), or with alternative agents aimed at providing fetal neuroprotection (such as magnesium sulphate for the very preterm infant). Such trials should evaluate maternal and infant short- and longer-term outcomes (including neurosensory disabilities such as cerebral palsy), and consider the costs of care."
Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. Cochrane Database of Systematic Reviews 2010, Issue 9.	Secondary outcomes for the child include: • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy	"There was no clear evidence of any effect of corticosteroids on substantive clinical outcomes. Those receiving steroids showed significantly greater improvement in platelet counts, which was greater for those receiving dexamethasone than those receiving betamethasone. There is to date, insufficient evidence of benefits in terms of substantive clinical outcomes to support the routine use of steroids for the management of HELLP. The use of corticosteroids may be justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile."
Yamasmit W, Chaithongwongwatthana S, Tolosa JE, Limpongsanurak S, Pereira L, Lumbiganon P. Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 12.	Secondary outcomes for the neonate or infant include: • Abnormal neurodevelopmental status at more than 12 months corrected age (developmental delay, cerebral palsy, or both)	"There is insufficient evidence to support or refute the use of prophylactic oral betamimetics for preventing preterm birth in women with a twin pregnancy."

Abbreviations: CCB: calcium channel blockers; FENO-based: Fractional exhaled nitric oxide-based algorithm; GBS: Group B Streptococcus; hPL: human placental lactogen; MgSO4: magnesium sulphate; NICU: neonatal intensive care unit; PMR: progressive muscle relaxation; PROM: preterm rupture of membranes; PTB: preterm birth

Appendix 3: Appendices for Chapter 3 publication

Ongoing reviews

Protocol citation	Overview outcomes pre-specified in protocol
Abiramalatha T, Thomas N, Gupta V, Viswanathan A, McGuire W. High versus standard volumes of enteral feeds for preterm or low birth weight infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 10.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes assessed after 12 months post term: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of 1 or more of the following: non-ambulant cerebral palsy; developmental quotient > 2 SD below the population mean; and blindness (VA less than 6/60) or deafness (any hearing impairment requiring — or unimproved by — amplification)

Amari S, Shahrook S, Ota E, Mori R. Branched-chain amino acid supplementation for improving nutrition in term and preterm neonates (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 7.	Primary outcomes pre-specified include:
	• Neurological development
	  ○ Major neurodevelopmental disability after 18 months' post-term age
	  ▪ Cerebral palsy (yes/no)
	  ▪ Developmental delay (> 2 SD below the mean in a validated mental development test) or intellectual impairment (> 2 SD below the mean in a validated intelligence test) (yes/no)
	  ▪ Blindness (vision < 6/60 in both eyes) (yes/no)
	  ▪ Sensorineural deafness (requiring amplification) (yes/no)

Askie LM, Darlow BA, Davis PG, Finer N, Stenson B, Vento M, Whyte R. Effects of targeting higher versus lower arterial oxygen saturations on death or disability in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2014, Issue 7.	Primary outcomes pre-specified include: • Composite outcome of death or major disability by 18 to 24 months' corrected age (gestational age plus chronological age) Secondary outcomes pre-specified include: • Major disability by 18 to 24 months' corrected age (gestational age plus chronological age) • Cerebral palsy with GMFCS level 2 or higher, or MACS level 2 or higher at 18 to 24 months' corrected age (gestational age plus chronological age)
Choo YM, Ahmad Kamar A, Tengku Kamalden TAF, Looi ML, Tan K, Lai NM. Lutein and zeaxanthin for reducing morbidity and mortality in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 5.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome assessed at 18 months to 28 months (Newman 2012). We will accept any of the following outcomes alone or in combination: cerebral palsy, mental retardation (BSID MDI < 70), and hearing deficit (aided or < 60 dB on audiometric testing) or assessment via use of a validated cognitive/language/behavioural/social interaction/adaptive test (Albers 2007)

Dawson JA, Davis PG, Foster JP. Routine oro/nasopharyngeal suction versus no suction in the delivery room (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 1.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment; developmental delay, i.e. DQ > 2 SD < the mean on validated assessment tools, e.g. BSID MDI)
Foster JP, Buckmaster A, Sinclair L, Lees S, Guaran R. Nasal continuous positive airway pressure (nCPAP) for term neonates with respiratory distress (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes pre-specified include: • Neurodevelopmental disability (after at least 18 months' postnatal age) defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification)
Foster JP, Taylor C, Bredemeyer SL. Topical anaesthesia for needle-related pain in newborn infants (Protocol). Cochrane Database of Systematic Reviews 2013, Issue 1.	Secondary outcomes pre-specified include: • Neurodevelopmental disability (after at least 18 months' postnatal age) defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development
Good M, Jones LJ, Osborn DA, Abdel-Latif ME. Transfusion of fresh versus non-fresh (older) red blood cell in neonates (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes pre-specified include: • Neurodevelopmental disability to at least 18 months' postnatal age (defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after term corrected)
Gordon A, Greenhalgh M, McGuire W. Early planned removal versus expectant management of peripherally inserted central catheters to prevent infection in newborn infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes assessed after 12 months post term using validated tools: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of 1 or more of the following: non-ambulant cerebral palsy; DQ > 2 SD below the population mean; and blindness (VA < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification) • Death or neurological impairment assessed after 12 months post term
Gordon A, Greenhalgh M, McGuire W. Early planned removal of umbilical venous catheters to prevent infection in newborn infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes assessed after 12 months post term using validated tools: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of 1 or more of the following: non-ambulant cerebral palsy; DQ > 2 SD below the population mean; and blindness (VA < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification) • Death or neurological impairment assessed after 12 months post term

Green DS, Abdel-Latif ME, Jones LJ, Osborn DA. Pharmacological interventions for prevention and treatment of upper gastrointestinal bleeding in newborn infants (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 7.	Secondary outcomes pre-specified include: • Neurodevelopmental disability (defined as neurological abnormality including cerebral palsy on clinical examination or global developmental delay (2 or more SD below population mean on BSID or GMDS at any time after term corrected at 1 year, 18 months', 2 years', and 5 years' postnatal age)
Han S, Yu Z, Guo X, Dong X, Chen X, Soll R. Intratracheal instillation of corticosteroids using surfactant as a vehicle for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome (Protocol). Cochrane Database of Systematic Reviews 2011, Issue 4	Secondary outcomes pre-specified include: • Neurodevelopmental outcome at a later time point (> 1 year post-conceptional age). Neurodevelopmental impairment is defined as the presence of cerebral palsy and/or mental retardation (BSID MDI < 70) and/or legal blindness (< 20/200 VA) and or deafness (aided or < 60 dB on audiometric testing)
Hegarty JE, Harding JE, Crowther CA, Brown J, Alsweiler J. Oral dextrose gel for the prevention of hypoglycaemia in newborn infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 4.	Primary outcomes pre-specified include: • Major neurological disability at 2 years of age or greater (any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment (defined as a DQ or IQ lower than 2 SD below the mean)) Secondary outcomes pre-specified include: • Cerebral palsy and severity at 2 years of age or older

Hyttel-Sorensen S, Støy Saem L, Greisen G, Als-Nielsen B, Gluud C. Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 2.	Primary outcomes pre-specified include:
	• Major neurodevelopmental disability:
	  ○ Cerebral palsy
	  ○ Developmental delay or intellectual impairment:
	  ▪ BSID or GMDS assessment > 2 SD below the mean or intellectual impairment (IQ > 2 SD below mean)
	  ▪ Neuromotor development (BSID - PDI) assessed in survivors
	  ▪ Mental development (BSID - MDI) assessed in survivors
	  ○ Blindness (vision < 6/60 in both eyes)

Jauncey-Cooke J, Bogossian F, Hough JL, Schibler A, Davies MW, Grant CA, Gibbons K, East CE. Lung recruitment manoeuvres for reducing respiratory morbidity in mechanically ventilated neonates (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 7.	Secondary outcomes pre-specified include: • Neurodevelopmental impairment: cerebral palsy, sensorineural hearing loss, visual impairment or developmental delay (e.g. GMDS, BSID) assessed at 12 to 24 months' corrected age, 2 years, or 5 years

Kaempfen S, Neumann RP, Jost K, Schulzke SM. Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 9.	Secondary outcomes pre-specified include:
	• Adverse neurodevelopmental outcomes at 18 to 24 months' corrected age
	  o Cerebral palsy
	  o Moderate to severe developmental delay as assessed by validated neurodevelopmental tests such as BSID

Kent A, Kecskes Z. Magnesium sulfate for term infants following perinatal asphyxia (Protocol). Cochrane Database of Systematic Reviews 2003, Issue 2.	Primary outcomes pre-specified include: • Severe neurodevelopmental disability at or equal to 12 months of age or more. Severe neurodevelopmental disability is defined as cerebral palsy, developmental delay (DQ < 70), or blindness (VA < 6/60 in both eyes), or any combination of these disabilities
Kulasekaran K, Sargent PH, Flenady V. Milrinone for the treatment of cardiac dysfunction in neonates (Protocol). Cochrane Database of Systematic Reviews 2004, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardised and validated assessment tool and/or a child developmental specialist) at any age reported (outcome data will be grouped at 12, 18, 24 months if available) - cerebral palsy, developmental delay, blindness, sensorineural deafness
Lai NM, Ahmad Kamar A, Choo YM, Kong JY, Ngim CF. Fluid supplementation for neonatal unconjugated hyperbilirubinaemia (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 9.	Primary outcomes pre-specified include: • Proportion of infants with moderate or severe cerebral palsy, defined as a non-progressive disorder with abnormal muscle tone in at least 1 arm or leg that was associated with abnormal control of movement or posture and a modified GMFCS score (Palisano 2008) ≥ 2 (Rosenbaum 2007), measured at predefined intervals, e.g. at 6, 12, 18, and 24 months Secondary outcomes pre-specified include: • Proportion of infants with motor impairment, as indicated by a score of 2 or higher in the modified GMFCS evaluation (Palisano 2008)

Lui K, Foster JP, Davis PG, Ching SK, Oei JL, Osborn DA. Higher versus lower oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 11.	Primary outcomes pre-specified include:
	• Neurodevelopmental disability (after > 18 months' postnatal age):
	  o Neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on any standard test of development
	  o Blindness (VA < 6/60)
	  o Deafness (any hearing impairment requiring amplification)

Malhotra A, Veldman A. Recombinant activated Factor VII for prevention and treatment of intraventricular haemorrhage in neonates (Protocol). Cochrane Database of Systematic Reviews 2011, Issue 3.	Primary outcomes pre-specified include: • Severe neurodevelopmental disability as defined by cerebral palsy, low developmental scores (DQ < 2 SD or untestable), blindness, or any combination of these using validated assessment tools at 18 or 24 months: neurological examinations, developmental scores (BSID, etc.)

McCarthy LK, Davis PG, O'Donnell CPF. Nasal airways (single or double prong, long or short) for neonatal resuscitation (Protocol). Cochrane Database of Systematic Reviews 2011, Issue 5.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment; developmental delay, i.e. DQ > 2 SD < the mean on validated assessment tools, e.g. BSID MDI)
Molloy EJ, McCallion N, O'Donnell CPF, Davis PG. Heliox for prevention of morbidity and mortality in ventilated newborn infants (Protocol). Cochrane Database of Systematic Reviews 2008, Issue 3.	Secondary outcomes pre-specified include: • Death or long-term (< 18 months) major neurodevelopmental disability (cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification)
Neary E, Ni Ainle F, El-Khuffash A, Cotter M, Kirkham C, McCallion N. Plasma transfusion to prevent intraventricular haemorrhage in very preterm infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 9.	Primary outcomes pre-specified include: • Neurodevelopmental disability at 2 years' postnatal age, defined as neurological abnormality on clinical examination, including cerebral palsy, developmental delay > 2 SD below the population mean on any standard test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after 2 years' corrected age
O'Donnell CPF, Davis PG, Morley CJ. Endotracheal intubation versus face mask for newborns resuscitated with positive pressure ventilation at birth (Protocol). Cochrane Database of Systematic Reviews 2004, Issue 4.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment, developmental delay, i.e. IQ 2 SD < the mean on validated assessment tools, e.g. BSID MDI)
O'Donnell CPF, Davis PG, Morley CJ. Manual ventilation devices for neonatal resuscitation (Protocol). Cochrane Database of Systematic Reviews 2004, Issue 3.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment, developmental delay, i.e. IQ 2 SD < the mean on validated assessment tools, e.g. BSID MDI)
Onland W, De Jaegere APMC, Offringa M, van Kaam A. Systemic corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2014, Issue 1.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental sequelae, assessed after at least 1 year corrected gestational age and before a corrected gestational age of 4 years, and at the latest reported time point, including cerebral palsy and BSID (MDI)
Onyango AB, Suresh G, Were F. Intermittent phototherapy versus continuous phototherapy for neonatal jaundice (Protocol). Cochrane Database of Systematic Reviews 2009, Issue 4.	Primary outcomes pre-specified include: • Kernicterus defined as either the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei or acute or chronic neurological deficit including athetoid cerebral palsy, impaired upward gaze and deafness, isolated conditions like auditory neuropathy or dyssynchrony, and subtle bilirubin-induced neurological dysfunction

Pierro M, Thébaud B, Soll R. Mesenchymal stem cells for the prevention and treatment of bronchopulmonary dysplasia in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes pre-specified include: • Cerebral palsy at 18 to 24 months' corrected age • Neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, delayed neurodevelopment (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). We will define the composite outcome 'neurodevelopmental impairment' as having any 1 of the aforementioned deficits
Rivas-Fernandez M, Roqué i Figuls M, Tobias A, Balaguer A. Different strains of probiotics for preventing morbidity and mortality in preterm infants: a network meta-analysis (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 8.	Secondary outcomes pre-specified include: • Neurodevelopment impairment (i.e. rates of cerebral palsy, cognitive delay, deafness, blindness or their composite reported at 18 months' corrected age or later)
Romantsik O, Calevo MG, Bruschettini M. Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2016, Issue 9.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcomes (yes/no): cerebral palsy on physician assessment, developmental delay (i.e. IQ 2 SD below the mean on validated assessment tools such as BSID MDI) (Bayley 1993; Bayley 2006) • Major neurodevelopmental disability: cerebral palsy, developmental delay (BSID MDI (Bayley 1993; Bayley 2006) or GMDS (Griffiths 1954) assessment > 2 SDs below the mean), intellectual impairment (IQ > 2 SDs below the mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We plan to evaluate each of these components as a separate outcome and to extract data on each long-term outcome from studies that evaluated children after 18 months' chronological age. We will separately assess data on children 18 to 24 months of age and on those 3 to 5 years of age
Seliem W, Bhutta ZA, Soll R, McGuire W. Topical emollient therapy for preventing infection in preterm infants in low- or middle-income countries (Protocol). Cochrane Database of Systematic Reviews 2007, Issue 3.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes at > 12 months post term (measured using validated assessment tools) and classifications of disability, including auditory and visual disability. The composite outcome "severe neurodevelopmental disability" will be defined as any 1 or combination of the following: non-ambulant cerebral palsy, severe developmental delay, auditory and visual impairment
Shah D, Tracy M. Cutaneous antisepsis for prevention of intravascular catheter–associated infection in newborn infants (Protocol). Cochrane Database of Systematic Reviews 2014, Issue 3.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome: neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, significant mental developmental delay (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" was defined as having any 1 of the aforementioned deficits
Sinn JKH, Kumar K, Osborn DA, Bolisetty S. Higher versus lower amino acid intake in	Primary outcomes pre-specified include:

parenteral nutrition for newborn infants (Protocol). Cochrane Database of Systematic Reviews 2006, Issue 2.	• Neurodevelopmental disability at at least 18 months' postnatal age (defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after term corrected) Secondary outcomes pre-specified include: • Individual components of neurodevelopment at at least 18 months' postnatal age: o Cerebral palsy on clinical examination o Developmental delay > 2 SD below population mean on a standardised test of development o Blindness (VA < 6/60) o Deafness (any hearing impairment requiring amplification) at any time after term corrected
Van Rostenberghe H, Ho JJ, Quah BS, Noraida R. The effects of thyroxine on end organ damage in asphyxiated neonates (Protocol). Cochrane Database of Systematic Reviews 2009, Issue 4.	Primary outcomes pre-specified include: • Any neurodevelopmental disability assessed at 12 months or more of age: o Presence of no/minor or major disabilities o Presence of cerebral palsy o Any objective quantitative assessments of neurodevelopmental assessment that are internationally recognised
Xiong T, Chen H, Mu D. Effect of pre-exchange albumin infusion on neonatal hyperbilirubinaemia and long-term developmental outcomes (Protocol). Cochrane Database of Systematic Reviews 2014, Issue 2.	Primary outcomes pre-specified include: • Neurological deficits consistent with kernicterus at 2 years of age (including separate analysis of each component): athetoid cerebral palsy, impaired upward gaze and deafness, auditory neuropathy or dys-synchrony (ABR abnormality), dental dysplasia, and subtle bilirubin-induced neurological dysfunction
Xiong T, Li H, Zhao J, Dong W, Qu Y, Wu T, Mu D. Hyperbaric oxygen for term newborns with hypoxic ischemic encephalopathy (Protocol). Cochrane Database of Systematic Reviews 2011, Issue 8.	Primary outcomes pre-specified include: • Long-term (> 18 months) major neurodevelopmental disabilities among all participants or survivors (cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean), or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification)
Yu B, Li S, Zhou D, Davis PG. Subcutaneous reservoir drainage versus ventriculoperitoneal shunt for the treatment of posthemorrhagic hydrocephalus in preterm infants (Protocol). Cochrane Database of Systematic Reviews 2009, Issue 3.	Primary outcomes pre-specified include: • The incidence rates of death or neurodevelopmental disability in infancy (> 12 months' postnatal age). Neurodevelopmental disability includes developmental delay (e.g. the score of BSID < 2 SD below the mean indicates developmental delay), cerebral palsy, blindness, deafness, and any other neurodevelopmental abnormalities

Yu Z, Guo X, Han S, Lu J, Sun Q. Erythropoietin for term and late preterm infants with hypoxic ischemic encephalopathy (Protocol). Cochrane Database of Systematic Reviews 2010, Issue 1.	Primary outcomes pre-specified include: • The primary outcome measure will be either death or long-term (1 year or 18 months) major neurodevelopmental disability (cerebral palsy, developmental delay (BDIS or GMDS assessment > 2 SD below the mean), or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification) Secondary outcomes pre-specified include: • Each component of the primary outcome: o Cerebral palsy o Developmental delay or intellectual impairment o Blindness o Sensorineural deafness requiring amplification patient
Yu Z, Sun Q, Han S, Lu J, Ohlsson A, Guo X. Erythropoietin for preterm infants with hypoxic ischaemic encephalopathy (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 12.	Primary outcomes pre-specified include: • Either death (at 28 days and at discharge) or long-term (1 year or 24 months' corrected age) intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification Secondary outcomes pre-specified include: • Each component of the primary outcome: o Death at 28 days and at discharge o Cerebral palsy at > 1 year (the criterion for the diagnosis of cerebral palsy was a fixed motor deficit diagnosed by a neurologist) o Developmental delay (BSID or GMDS > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean) at 1 year or 24 months' corrected age o Blindness (vision < 6/60 in both eyes) at 1 year or 24 months' corrected age o Sensorineural deafness requiring amplification patient at 1 year or 24 months' corrected age

Abbreviations: ABR: auditory brainstem response; BSID: Bayley Scales of Infant Development; DQ: developmental quotient; GMDS: Griffith Mental Development Scales; GMFCS: Gross Motor Function Classification System; IQ; intelligence quotient; MACS: Manual Ability Classification System; MDI: Mental Development Index; PDI: Psychomotor Development Index; SD: standard deviation; VA: visual acuity

Reviews awaiting further classification

Review citation	Overview outcomes pre-specified in review with no outcome data	Main conclusion(s) of review
Abdel-Latif ME, Osborn DA. Intratracheal Clara cell secretory protein (CCSP) administration in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database of Systematic Reviews 2011, Issue 5.	Primary outcomes pre-specified include: • Neurodevelopmental disability ≥ 18 months' postnatal age (defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after term corrected)	"There are insufficient data to determine the role of rhCC10 in clinical practice. Further studies are required to determine if rhCC10 reduces lung inflammation in infants at risk of CLD, and to determine dose and dosing strategy."
Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database of Systematic Reviews 2011, Issue 7.	Primary outcomes pre-specified include: • Neurodevelopmental disability ≥ 18 months' postnatal age (defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after term corrected)	"There is evidence from a single small trial that LMA surfactant administration in preterm infants ≥ 1200 g with established RDS may have a short term effect in reducing oxygen requirements although the study is underpowered to detect important clinical effects. Adequately powered trials are required to determine the effect of LMA surfactant administration for prevention or treatment of RDS in preterm infants. LMA surfactant administration should be limited to clinical trials."
Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. Cochrane Database of Systematic Reviews 2011, Issue 3.	Primary outcomes pre-specified include: • Neurodevelopmental disability at ≥ 18 months' postnatal age, defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay of > 2 SD below the population mean on a standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after the age was term corrected	No included trials. "There were no data from randomised controlled or quasi-randomised trials that evaluated the effect of intrapartum instillation of pharyngeal surfactant before the first breath. Evidence from animal and observational human studies suggest that pharyngeal instillation of surfactant before the first breath is potentially safe, feasible and may be effective. Well designed trials are needed."
Abdel-Latif ME, Osborn DA. Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database of Systematic Reviews 2012, Issue 10.	Primary outcomes pre-specified include: • Neurodevelopmental disability assessed at 18 months' postnatal age or later defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a standardised test of development, blindness (VA < 6/60), or	"There are insufficient data to support or refute the use of nebulised surfactant in clinical practice. Adequately powered trials are required to determine the effect of nebulised surfactant administration for prevention or early treatment of RDS in preterm infants. Nebulised surfactant administration should be limited to clinical trials."

	deafness (any hearing impairment requiring amplification) at any time after term corrected	
Ainsworth S, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. Cochrane Database of Systematic Reviews 2015, Issue 10.	Primary outcomes pre-specified include: • Neurodevelopmental outcomes during infancy and beyond, using validated assessment tools, such as BSID, and classifications of disability, including auditory and visual disability. Severe neurodevelopmental disability was defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), or auditory and visual impairment	"Data from one small trial suggest that use of percutaneous central venous catheters to deliver parenteral nutrition increases nutrient input. The significance of this in relation to long-term growth and developmental outcomes is unclear. Three trials suggest that use of percutaneous central venous catheters decreases the number of catheters/cannulae needed to deliver nutrition. No evidence suggests that percutaneous central venous catheter use increases risks of adverse events, particularly invasive infection, although none of the included trials was large enough to rule out an effect on uncommon severe adverse events such as pericardial effusion."
Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database of Systematic Reviews 2002, Issue 3.	Outcomes pre-specified include: • Incidence of cerebral palsy	"Although the results show a significant reduction in the need for exchange transfusion in those treated with intravenous immunoglobulin, the applicability of the results is limited. The number of studies and infants included is small and none of the three included studies was of high quality. The protocols of two of the studies mandated the use of early exchange transfusion, limiting the generalizability of the results. Further well designed studies are needed before routine use of intravenous immunoglobulin can be recommended for the treatment of isoimmune haemolytic jaundice."
Anabrees J, AlFaleh K. Fluid restriction and prophylactic indomethacin versus prophylactic indomethacin alone for prevention of morbidity and mortality in extremely low birth weight infants. Cochrane Database of Systematic Reviews 2011, Issue 7.	Secondary outcomes pre-specified include: • Neurosensory impairment defined as rates of cerebral palsy, cognitive delay, deafness, blindness at 18 to 24 months' corrected age as per BSID score (Bayley 1993) • The composite of death or neurosensory impairment at 18 to 24 months' corrected age	No included trials "We found no randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis versus indomethacin prophylaxis alone in ELBW infants. A well-designed randomized trial is needed to address this question."
Austin N, Cleminson J, Darlow BA, McGuire W. Prophylactic	Primary outcomes pre-specified include:	"The finding of a reduction in risk of invasive fungal infection in very low birth weight infants treated with oral/topical non-

oral/topical non-absorbed antifungal agents to prevent invasive fungal infection in very low birth weight infants. Cochrane Database of Systematic Reviews 2015, Issue 10.	• Neurodevelopmental outcomes assessed beyond infancy (neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability, non-ambulant cerebral palsy, developmental delay); and cognitive and educational outcomes at 5 years or older (IQ and/or indices of educational achievement measured using a validated tool including school examination results)	absorbed antifungal prophylaxis should be interpreted cautiously because of methodological weaknesses in the included trials. Further large randomised controlled trials in current neonatal practice settings are needed to resolve this uncertainty. These trials might compare oral/topical non-absorbed antifungal agents with placebo, with each other, or with systemic antifungal agents and should include an assessment of effect on long-term neurodevelopmental outcomes."
Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2012, Issue 11.	Secondary outcomes pre-specified include: • Cerebral palsy • Neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, mental retardation (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" will be defined as having any 1 of the aforementioned deficits	"Early selective surfactant administration given to infants with RDS requiring assisted ventilation leads to a decreased risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality and chronic lung disease compared to delaying treatment of such infants until they develop worsening RDS."
Rivas-Fernandez M, Roqué i Figuls M, Diez-Izquierdo A, Escribano J, Balaguer A. Infant position in neonates receiving mechanical ventilation. Cochrane Database of Systematic Reviews 2016, Issue 11.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcomes at age 2 years: rates of cerebral palsy as assessed by physician, developmental delay (i.e. IQ < 2 SD) on validated assessment tools (e.g. the S-B Intelligence Scale or others), or sensory impairment	"This update of our last review in 2013 supports previous conclusions. Evidence of low to moderate quality favours the prone position for slightly improved oxygenation in neonates undergoing mechanical ventilation. However, we found no evidence to suggest that particular body positions during mechanical ventilation of the neonate are effective in producing sustained and clinically relevant improvement."
Balain M, Oddie SJ, McGuire W. Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants. Cochrane Database of Systematic Reviews 2015, Issue 9.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes assessed > 12 months' corrected age using validated tools: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of 1 or more of the following: non-ambulant cerebral palsy; DQ > 2 SD below the population mean; and blindness (VA < 6/60) or	"Although the data from one small trial indicates that antimicrobial-impregnated central venous catheters might prevent catheter-related bloodstream infection in newborn infants, the available evidence is insufficient to guide clinical practice. A large, simple and pragmatic randomised controlled trial is needed to resolve on-going uncertainty."

	deafness (any hearing impairment requiring or unimproved by amplification) • Death or neurological impairment assessed > 12 months' corrected age	
Bassler D, Kreutzer K, McNamara P, Kirpalani H. Milrinone for persistent pulmonary hypertension of the newborn. Cochrane Database of Systematic Reviews 2010, Issue 11.	Primary outcomes pre-specified include: • Neurodevelopment (assessed by the presence of cerebral palsy, cognitive delay, blindness or deafness, and the BSID-II) assessed > 18 months of life	"The efficacy and safety of milrinone in the treatment of PPHN are not known and its use should be restricted within the context of RCTs. Such studies should address a comparison of milrinone with placebo (in clinical situations where iNO is not available) or, in well resourced countries, should compare milrinone with iNO or as an adjunct to iNO compared with iNO alone."
Basuki F, Hadiati DR, Turner T, McDonald S, Hakimi M. Dilute versus full strength formula in exclusively formula-fed preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2013, Issue 11.	Secondary outcomes pre-specified include: • Neurodevelopment: o Death or severe neurodevelopmental disability defined as any 1 or a combination of the following: non-ambulant cerebral palsy; developmental delay (DQ < 70); auditory and visual impairment (each component will be analysed individually as well as part of the composite outcome) o Neurodevelopmental scores in survivors aged ≥ 12 months of age measured using validated assessment tools o Cognitive and educational outcomes in survivors aged > 5 years old	"There is evidence from three small, old trials at unclear risk of bias that use of dilute formula in preterm or low birth weight formula-fed infants leads to an important reduction in the time taken for these infants to attain an adequate energy intake. There was no evidence of important differences in feeding intolerance. The impact on serious gastrointestinal problems, including necrotising enterocolitis, was not reported. Further randomised trials are needed to confirm these results."
Beveridge CJE, Wilkinson AR. Sodium bicarbonate infusion during resuscitation of infants at birth. Cochrane Database of Systematic Reviews 2006, Issue 1.	Secondary outcomes pre-specified include: • Long-term severe neurodevelopmental disability reported at any time during follow-up. Defined as any of cerebral palsy, cognitive delay (score > 2 SD below mean for a recognised psychometric test e.g. BSID), blindness, and deafness	"There is insufficient evidence from randomised controlled trials to determine whether the infusion of sodium bicarbonate reduces mortality and morbidity in infants receiving resuscitation in the delivery room at birth."
Bhola K, Foster JP, Osborn DA. Chest shielding for prevention of a haemodynamically significant patent ductus arteriosus in preterm infants receiving phototherapy.	Secondary outcomes pre-specified include: • Neurodevelopmental disability (after at least 18 months' postnatal age) defined as neurological abnormality including cerebral palsy on clinical examination, developmental delay > 2 SD below population mean on a	"The available evidence is very low quality and insufficient to assess the safety or efficacy of chest shield during phototherapy for prevention of PDA in preterm infants. Further trials of chest shielding are warranted, particularly in settings where infants are

Cochrane Database of Systematic Reviews 2015, Issue 11.	standardised test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification at any time after term corrected age)	not receiving prophylactic or early echocardiographic targeted cyclo-oxygenase inhibitors for PDA."
Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Cochrane Database of Systematic Reviews 2004, Issue 3.	Primary outcomes pre-specified include: • Significant neurodevelopmental impairment (any 1 or combination of: cerebral palsy, developmental delay DQ > 2 SD, blindness) assessed at 1 to 2 years of age • Death or significant neurodevelopmental impairment (any 1 or combination of: cerebral palsy, developmental delay DQ > 2 SD, blindness) assessed at 1 to 2 years of age	"At present there is little evidence from randomised controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period. In the literature, there remains a body of opinion that seizures should be treated because of the concern that seizures in themselves may be harmful, although this is only supported by relatively low grade evidence (Levene 2002; Massingale 1993). Development of safe and effective treatment strategies relies on future studies of high quality (randomised controlled trials with methodology that assures validity) and of sufficient size to have the power to detect clinically important reductions in mortality and severe neurodevelopmental disability in addition to any short term reduction in seizure burden."
Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database of Systematic Reviews 2011, Issue 10.	Primary outcomes pre-specified include: • Neurodevelopmental impairment, defined as presence of 1 or more of the following: cerebral palsy, MDI or PDI < 70, blindness or deafness assessed between 18 and 24 months' postmenstrual age or with latest assessment up to 24 months' postmenstrual age	"Evidence from randomized trials in hyperglycemic VLBW neonates is insufficient to determine the effects of treatment on death or major morbidities. It remains uncertain whether the hyperglycemia per se is a cause of adverse clinical outcomes or how the hyperglycemia should be treated. Much larger randomized trials in hyperglycemic VLBW neonates that are powered on clinical outcomes are needed in order to determine whether, and how, the hyperglycemia should be treated."
Brion LP, Bell EF, Raghuveer TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 4.	Primary outcomes pre-specified include: • Mortality, combined outcome at 18 months including mortality (mortality, bronchopulmonary dysplasia, blindness, mental retardation, or cerebral palsy), and combined outcome at 18 months excluding mortality (bronchopulmonary dysplasia, blindness, mental retardation, or cerebral palsy)	"Vitamin E supplementation in preterm infants reduced the risk of intracranial hemorrhage but increased the risk of sepsis. In very low birth weight infants, vitamin E increased the risk of sepsis, and reduced the risk of severe retinopathy and blindness among those examined. Evidence does not support the routine use of vitamin E supplementation by intravenous route at high doses or aiming at serum tocopherol levels greater than 3.5 mg/dl."
Brown JVE, Embleton ND, Harding JE, McGuire W. Multi-nutrient	Primary outcomes pre-specified include:	"Limited available data do not provide strong evidence that feeding preterm infants with multi-nutrient fortified breast milk

fortification of human milk for preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 5.	• Neurodevelopmental outcomes assessed after 12 months post term: neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability. We defined neurodevelopmental impairment as the presence of 1 or more of the following: non-ambulant cerebral palsy, DQ > 2 SD below the population mean, and blindness (VA < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification)	compared with unfortified breast milk affects important outcomes, except that it leads to slightly increased in-hospital growth rates."
Brown JVE, Moe-Byrne T, McGuire W. Glutamine supplementation for young infants with severe gastrointestinal disease. Cochrane Database of Systematic Reviews 2014, Issue 12.	Primary outcomes pre-specified include: • Neurodevelopmental outcomes assessed beyond infancy (neurological evaluations, developmental scores, and classifications of disability including auditory and visual disability, non-ambulant cerebral palsy, and developmental delay) and cognitive and educational outcomes (IQ and/or indices of educational achievement measured using a validated tool, including school examination results)	"The available data from randomised controlled trials do not suggest that glutamine supplementation has any important benefits for young infants with severe gastrointestinal disease."
Bruschettini M, Romantsik O, Zappettini S, Banzi R, Ramenghi LA, Calevo MG. Antithrombin for the prevention of intraventricular hemorrhage in very preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 3.	Secondary outcomes pre-specified include: • Major neurodevelopmental disability assessed at age of 12 months or more (defined as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean), intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification)	"The administration of antithrombin seems not to reduce the incidence and severity of intraventricular hemorrhage in very preterm infants. Limited evidence is available on other clinically relevant outcomes. Given the imprecision of the estimate, the results of this systematic review are consistent with either a benefit or a detrimental effect of antithrombin and do not provide a definitive answer to the review question."
Bruschettini M, Zappettini S, Moja L, Calevo MG. Frequency of endotracheal suctioning for the prevention of respiratory morbidity in ventilated newborns. Cochrane Database of Systematic Reviews 2016, Issue 3.	Secondary outcomes pre-specified include: • Major neurodevelopmental disability (cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision less than 6/60 in both eyes), sensorineural deafness requiring amplification). We evaluated each component of major neurodevelopmental disability: o Cerebral palsy on physician assessment (yes/no) o Developmental delay or intellectual impairment: BSID or GMDS assessment > 2 SD below the mean	"There was insufficient evidence to identify the ideal frequency of ETT suctioning in ventilated neonates. Future research should focus on the effects in the very preterm newborns, that is, the most vulnerable population as concerns the risk of both lung and brain damage. Assessment should include the cases of prolonged ventilation, when more abundant, dense secretions are common. Clinical trials might include comparisons between 'as-scheduled' versus 'as-needed' endotracheal suctioning, that is, based on specific indications, as well frequent versus less frequent suctioning schedules."

	or intellectual impairment (IQ > 2 SD below mean); neuromotor development (BSID PDI) assessed in survivors; mental development (BSID MDI) assessed in survivors o Blindness vision (less than 6/60 in both eyes) o Sensorineural deafness requiring amplification	
Bruschettini M, Romantsik O, Zappettini S, Banzi R, Ramenghi LA, Calevo MG. Heparin for the prevention of intraventricular haemorrhage in preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 5.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (yes/no): cerebral palsy on physician assessment, developmental delay, i.e. IQ 2 SD below the mean on validated assessment tools, e.g. BSID MDI (Bayley 1993; Bayley 2006) • Major neurodevelopmental disability: cerebral palsy, developmental delay (BSID MDI (Bayley 1993; Bayley 2006) or GMDS assessment (Griffiths 1954) > 2 SD below the mean), intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We planned to evaluate each of these components as a separate outcome and to extract data on this long-term outcome from studies that evaluated children after 18 months of chronological age. Data on children aged 18 to 24 months and those aged 3 to 5 years were to be assessed separately	"There is very limited data on the effect of prophylactic administration of heparin on the incidence and severity of IVH in very preterm neonates. Both the identified trials used heparin in the context of maintaining umbilical line patency and not specifically as an agent to prevent germinal matrix-intraventricular haemorrhage. Given the imprecision of our estimates, the results of this systematic review are consistent with either a benefit or a detrimental effect of heparin and do not provide a definitive answer to the review question. Limited evidence is available on other clinically relevant outcomes."
Bruschettini M, Romantsik O, Zappettini S, Ramenghi LA, Calevo MG. Transcutaneous carbon dioxide monitoring for the prevention of neonatal morbidity and mortality. Cochrane Database of Systematic Reviews 2016, Issue 2.	Primary outcomes pre-specified include: • Major neurodevelopmental disability (cerebral palsy, developmental delay (BSID or GMDS > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification) (Jacobs 2013) Secondary outcomes pre-specified include: • Each component of major neurodevelopmental disability: (a) cerebral palsy on physician assessment (yes/no); (b) developmental delay or intellectual impairment: BSID or GMDS assessment > 2 SD below the mean or intellectual	No included trials "There was no evidence to recommend or refute the use of transcutaneous CO2 monitoring in neonates. Well-designed, adequately powered randomized controlled studies are necessary to address efficacy and safety of transcutaneous CO2 monitoring in neonates."

	impairment (IQ > 2 SD below mean); neuromotor development (BSID PDI) assessed in survivors; mental development (BSID MDI) assessed in survivors; (c) blindness vision (< 6/60 in both eyes); (d) sensorineural deafness requiring amplification. We will report these components of this long-term outcome for all trials that have evaluated children after 18 months' chronological age. We will perform separate analyses for children aged 18 months to 24 months and those aged 3 years to 5 years	
Cleminson J, McGuire W. Topical emollient for preventing infection in preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 1.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes assessed at > 12 months post term (measured using validated assessment tools) and classifications of disability, including auditory and visual disability. A composite outcome "severe neurodevelopmental disability" was defined as any 1 or combination of the following: non-ambulant cerebral palsy, severe developmental delay, auditory impairment, and visual impairment	"The available data do not provide evidence that the use of emollient therapy prevents invasive infection or death in preterm infants in high-, middle- or low-income settings. Some evidence of an effect of topical vegetable oils on neonatal growth exists but this should be interpreted with caution because lack of blinding may have introduced caregiver or assessment biases. Since these interventions are low cost, readily accessible, and generally acceptable, further randomised controlled trials, particularly in both community- and health care facility-based settings in low-income countries, may be justified."
Clerihew L, McGuire W. Antifungal therapy for newborn infants with invasive fungal infection. Cochrane Database of Systematic Reviews 2012, Issue 6.	Primary outcomes pre-specified include: • Neurodevelopmental outcomes assessed beyond infancy (neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability, non-ambulant cerebral palsy, developmental delay) and cognitive and educational outcomes (IQ and/or indices of educational achievement measured using a validated tool including school examination results)	"There are insufficient data to inform practice. Large randomised controlled trials are required to compare antifungal drugs, drug preparations or drug combinations for treating newborn infants with invasive fungal infection."
Cooke L, Steer PA, Woodgate PG. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 1.	Outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, developmental delay)	"This review demonstrates a significant decrease in the incidence of symptomatic PDA following treatment of an asymptomatic PDA with indomethacin. There is also a small but statistically significant decrease in the duration of requirement for supplemental oxygen. There are no reported long term outcomes in the included trials, and so it is not possible to comment on

		possible long term effects. Further studies are required to determine the long term benefits or harms of closing a PDA prior to the onset of symptoms."
Davies MW, Kimble RM, Woodgate PG. Ward reduction without general anaesthesia versus reduction and repair under general anaesthesia for gastroschisis in newborn infants. Cochrane Database of Systematic Reviews 2002, Issue 3.	Outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, and/or developmental delay)	No included trials "There is no evidence from RCTs to support or refute the practice of ward reduction for the immediate management of gastroschisis. There is an urgent need for RCTs to compare ward reduction versus reduction under general anaesthesia in infants with gastroschisis. Initial trials would best be limited to those infants with uncomplicated gastroschisis (using pre-defined selection criteria excluding infants that are unstable, have gut perforation, necrosis or atresia, have other organs requiring reduction besides bowel, or are considered to need a silo prior to any reduction). Trials should use adequate pain relief and specify a pre-defined time period after which manual reduction is abandoned."
Davies MW, Woodgate PG. Tracheal gas insufflation for the prevention of morbidity and mortality in mechanically ventilated newborn infants. Cochrane Database of Systematic Reviews 2002, Issue 2.	Outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, and/or developmental delay) at 1, 2, 3, 5, or 7 years	"There is evidence from a single RCT that TGI may reduce the duration of mechanical ventilation in preterm infants - although the data from this small study do not give sufficient evidence to support the introduction of TGI into clinical practice. The technical requirements for performing TGI (as performed in the single included study) are great. There is no statistically significant reduction in the total duration of respiratory support or hospital stay. TGI cannot be recommended for general use at this time."
De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database of Systematic Reviews 2008, Issue 1.	Secondary outcomes pre-specified include: • Long-term neurosensory outcomes at 2 years' corrected age or older as defined by the incidence of: o Cerebral palsy o Moderate to severe developmental delay o Blindness o Deafness	"Short binasal prong devices are more effective than single prongs in reducing the rate of re-intubation. Although the Infant Flow Driver appears more effective than Medicorp prongs the most effective short binasal prong device remains to be determined. The improvement in respiratory parameters with short binasal prongs suggests they are more effective than nasopharyngeal CPAP in the treatment of early RDS. Further studies incorporating longer-term outcomes are required. Studies

		are also needed to determine the optimal pressure source for the delivery of NCPAP."
Dimmick SJ, Badawi N, Randell T. Thyroid hormone supplementation for the prevention of morbidity and mortality in infants undergoing cardiac surgery. Cochrane Database of Systematic Reviews 2004, Issue 3.	Outcomes pre-specified include: • Development: neurological abnormality (cerebral palsy) or developmental delay on standardised tests in the first year	"At present, there is a lack of evidence concerning the effects of triiodothyronine supplementation in infants undergoing cardiac surgery. Further randomised controlled trials which include sufficiently large subject numbers in a variety of different age strata (neonates, infants and older children) need to be undertaken."
Foster JP, Psaila K, Patterson T. Non-nutritive sucking for increasing physiologic stability and nutrition in preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 10.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes at 12 months or more of age (corrected for preterm birth) measured using validated assessment tools such as BSID and classifications of disability, including auditory and visual disability. Severe neurodevelopmental disability will be defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient < 70), auditory and visual impairment	"Meta-analysis demonstrated a significant effect of NNS on the transition from gavage to full oral feeding, transition from start of oral feeding to full oral feeding, and length of hospital stay. None of the trials reported any adverse effects. Well-designed, adequately powered studies using reliable methods of randomisation, concealment of treatment allocation and blinding of the intervention and outcome assessors are needed. In order to facilitate meta-analysis of these data, future research should involve outcome measures consistent with those used in previous studies."
Görk AS, Ehrenkranz RA, Bracken MB. Continuous infusion versus intermittent bolus doses of indomethacin for patent ductus arteriosus closure in symptomatic preterm infants. Cochrane Database of Systematic Reviews 2008, Issue 1.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (sensorineural hearing loss, visual impairment, cerebral palsy, developmental delay at 24 months' corrected age assessed by a standardised and validated assessment tool and/or a child developmental specialist)	"The available data is insufficient to draw conclusions regarding the efficacy of continuous indomethacin infusion vs. bolus injections for the treatment of PDA. Although continuous indomethacin seems to cause less alterations in cerebral, renal and mesenteric circulations, the clinical meaning of this effect is unclear. Definitive recommendations about the preferred method of indomethacin administration in premature infants cannot be made based on the current findings of this review."
Henderson G, Anthony MY, McGuire W. Formula milk versus maternal breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2007, Issue 4.	Primary outcomes pre-specified include: • Development: ○ Neurodevelopmental outcomes at ≥ 12 months of age (corrected for preterm birth) measured using validated assessment tools	No included trials "There are no data from randomised trials of formula milk versus maternal breast milk for feeding preterm or low birth weight infants. This may relate to a perceived difficulty of allocating an alternative feed to an infant whose mother wishes to feed with her own breast milk. Maternal breast milk remains the default

	○ Severe neurodevelopmental disability defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70 or > 2 SD below the mean), severe auditory impairment (sensorineural deafness requiring (or too severe to (benefit from) hearing aids), or visual impairment (legal blindness). We plan to analyse each component individually as well as part of the composite outcome ○ Cognitive and educational outcomes at age > 5 years: IQ and/or indices of educational achievement measured using a validated assessment tool (including school examination results)	choice of enteral nutrition because observational studies, and meta-analyses of trials comparing feeding with formula milk versus donor breast milk, suggest that feeding with breast milk has major non-nutrient advantages for preterm or low birth weight infants."
Henderson G, Fahey T, McGuire W. Nutrient-enriched formula milk versus human breast milk for preterm infants following hospital discharge. Cochrane Database of Systematic Reviews 2007, Issue 4.	Primary outcomes pre-specified include: • Neurodevelopmental outcomes at ≥ 12 months of age (corrected for preterm birth) measured using validated assessment tools such as BSID and classifications of disability, including auditory and visual disability. Severe neurodevelopmental disability will be defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment	No included trials "There are no data from randomised controlled trials to determine whether feeding preterm infants following hospital discharge with nutrient-enriched formula milk versus human breast milk affects growth and development. Mothers who wish to breast feed, and their health care advisors, would require very clear evidence that feeding with a nutrient-enriched formula milk had major advantages for their infants before electing not to feed (or to reduce feeding) with maternal breast milk. If evidence from trials that compared feeding preterm infants following hospital discharge with nutrient-enriched versus standard formula milk demonstrated an effect on growth or development, then this might strengthen the case for undertaking trials of nutrient-enriched formula milk versus human breast milk."
Henderson-Smart DJ, Wilkinson AR, Raynes-Greenow CH. Mechanical ventilation for newborn infants with respiratory failure due to pulmonary disease. Cochrane	Secondary outcomes pre-specified include: • Neurodevelopmental abnormalities in childhood (developmental delay, cerebral palsy)	"When MV was introduced in the 1960s to treat infants with severe respiratory failure due to pulmonary disease, trials showed an overall reduction in mortality which was most marked in infants born with a birthweight of more than 2 kg. This review does not provide information to evaluate the relative benefits or harms of MV in the setting of modern perinatal care."

Database of Systematic Reviews 2002, Issue 4.		
Ho JJ, Henderson-Smart DJ, Davis PG. Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews 2002, Issue 2.	Secondary outcomes pre-specified include: • Long-term growth and neurodevelopmental outcome (cerebral palsy and abnormal mental development < 2 SD below the mean on a standardised score)	"Early application of CDP has a clinical benefit in the treatment of RDS in that it reduces subsequent use of IPPV and thus may be useful in preventing the adverse effects of this treatment. However, many of the trials were done in the 1970s and 1980s and re-evaluation of the strategy of early CDP in the era of antenatal steroid use and early surfactant administration is indicated focusing on administration methods."
Ho JJ, Rasa G. Magnesium sulfate for persistent pulmonary hypertension of the newborn. Cochrane Database of Systematic Reviews 2007, Issue 3.	Secondary outcomes pre-specified include: • Cerebral palsy on physician assessment	No included trials "On the basis of the current lack of evidence, the use of magnesium sulphate cannot be recommended in the treatment of PPHN. Randomised controlled trials are recommended."
Hunt R, Osborn DA. Dopamine for prevention of morbidity and mortality in term newborn infants with suspected perinatal asphyxia. Cochrane Database of Systematic Reviews 2002, Issue 3.	Primary outcomes pre-specified include: • Neurodevelopmental disability (neurological abnormality including cerebral palsy, developmental delay > 2 SD below population mean, or sensory impairment) *(Review reports on 'neurodevelopmental disability' for 1 RCT (14 infants), which did not include cerebral palsy)*	"There is currently insufficient evidence from randomised controlled trials that the use of dopamine in term infants with suspected perinatal asphyxia improves mortality or long-term neurodevelopmental outcome. The question of whether dopamine improves outcome for term infants with suspected perinatal asphyxia has not been answered. Further research is required to determine whether or not the use of dopamine improves mortality and long-term morbidity for these infants and if so, issues such as which infants, at what dose and with what co-interventions should be addressed."
Hunt R, Davis PG, Inder TE. Replacement of estrogens and progestins to prevent morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2004, Issue 4.	Primary outcomes pre-specified include: • Neurodevelopmental disability defined as neurological abnormality including cerebral palsy on clinical examination > 12 months' postnatal age, developmental delay > 2 SD below population mean on any standard test of development, blindness (VA < 6/60), or deafness (any hearing impairment requiring amplification) at any time after term corrected	"The one small randomised controlled trial demonstrated neither evidence of benefit or harm related to the replacement of estradiol and progesterone in preterm infants less than 30 weeks' gestation. A properly powered randomised controlled trial is required to determine whether or not administration of estradiol or progesterone, either alone or in combination, and at varying doses, confers any clinically significant benefits, or poses any risk, to the preterm infant."

Ibrahim H, Sinha IP, Subhedar NV. Corticosteroids for treating hypotension in preterm infants. Cochrane Database of Systematic Reviews 2011, Issue 12.	Primary outcomes pre-specified include: • Long-term neurodevelopmental outcome (cerebral palsy, developmental delay, sensorineural impairment, abnormal neurological examination)	"Hydrocortisone may be as effective as dopamine when used as a primary treatment for hypotension. But the long term safety data on the use of hydrocortisone in this manner is unknown. Steroids are effective in treatment of refractory hypotension in preterm infants without an increase in short term adverse consequences. However, long term safety or benefit data is lacking. With long term benefit or safety data lacking steroids cannot be recommended routinely for the treatment of hypotension in preterm infants."
Ibrahim MDH, Sinn JKH, McGuire W. Iodine supplementation for the prevention of mortality and adverse neurodevelopmental outcomes in preterm infants. Cochrane Database of Systematic Reviews 2006, Issue 2.	Primary outcomes pre-specified include: • Neurodevelopmental outcomes at ≥ 12 months of age (corrected for preterm birth) measured using validated assessment tools such as BSID • Severe neurodevelopmental disability defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment. We planned to analyse each component individually as well as part of the composite outcome	"There are insufficient data at present to determine whether providing preterm infants with supplemental iodine (to match fetal accretion rates) prevents morbidity and mortality in preterm infants. Future randomised controlled trials of iodine supplementation should focus on extremely preterm and extremely low birth weight infants, the group at greatest risk of transient hypothyroxinaemia. These trials should aim to assess the effect of iodine supplementation on clinically important outcomes including respiratory morbidity and longer term neurodevelopment."
Inglis GDT, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters. Cochrane Database of Systematic Reviews 2005, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment and/or developmental delay will be considered as separate components - at 1 year, 18 months, 2 years, or 5 years)	"There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when UVCs are inserted in newborn infants. There is no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with UVCs."
Inglis GDT, Jardine LA, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in ventilated newborn infants. Cochrane Database of Systematic Reviews 2007, Issue 3.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment and/or developmental delay at 1 year, 18 months, 2 years, or 5 years)	"There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when starting mechanical ventilation in newborn infants, or to support or refute continuing antibiotics once initial cultures have ruled out infection in mechanically ventilated newborn infants."
Inglis GDT, Jardine LA, Davies MW. Prophylactic antibiotics to	Secondary outcomes pre-specified include:	"There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when umbilical artery

reduce morbidity and mortality in neonates with umbilical artery catheters. Cochrane Database of Systematic Reviews 2007, Issue 4.	• Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment and/or developmental delay - at 1 year, 18 months, 2 years, or 5 years)	catheters are inserted in newborn infants, and no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical artery catheters."
Jardine LA, Inglis GDT, Davies MW. Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters. Cochrane Database of Systematic Reviews 2008, Issue 1.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, and/or developmental delay - at 1 year, 18 months, 2 years, or 5 years)	"Prophylactic systemic antibiotics in neonates with a central venous catheter reduces the rate of proven or suspected septicaemia. However, this may not be clinically important in the face of no significant difference in overall mortality and the lack of data on long-term neurodevelopmental outcome. Furthermore, there is a lack of data pertaining to the potentially significant disadvantages of this approach such as the selection of resistant organisms. The routine use of prophylactic antibiotics in infants with central venous catheters in neonatal units cannot currently be recommended."
Jardine LA, Inglis GDT, Davies MW. Strategies for the withdrawal of nasal continuous positive airway pressure (NCPAP) in preterm infants. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD006979. DOI: 10.1002/14651858.CD006979.pub2.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, and/or developmental delay - at 1 year, 18 months, 2 years, or 5 years)	"Infants who have their NCPAP pressure weaned to a predefined level and then stop NCPAP completely have less total time on NCPAP and shorter durations of oxygen therapy and hospital stay compared with those that have NCPAP removed for a predetermined number of hours each day. Future trials of withdrawing NCPAP should compare proposed strategies with weaning NCPAP pressure to a predefined level and then stopping NCPAP completely. Clear criteria need to be established for the definition of stability prior to attempting to withdraw NCPAP."
Kaushal A, McDonnell CG, Davies MW. Partial liquid ventilation for the prevention of mortality and morbidity in paediatric acute lung injury and acute respiratory distress syndrome. Cochrane Database of Systematic Reviews 2013, Issue 2.	Secondary outcomes pre-specified include: • Long-term neurodevelopment (cerebral palsy, sensorineural hearing loss, visual impairment, developmental delay) • Long-term disability	"There is no evidence from RCTs to support or refute the use of partial liquid ventilation in children with acute lung injury or acute respiratory distress syndrome. Adequately powered, high quality RCTs are still needed to assess its efficacy. Clinically relevant outcome measures should be assessed (mortality at discharge and later, duration of both respiratory support and hospital stay, and long-term neurodevelopmental outcomes). The studies should be published in full."
Kecskes Z, Healy G, Jensen A. Fluid restriction for term infants	Primary outcomes pre-specified include:	No included trials

with hypoxic-ischaemic encephalopathy following perinatal asphyxia. Cochrane Database of Systematic Reviews 2005, Issue 3.	• Severe neurodevelopmental disability at or equal to 12 months of age or more. Severe neurodevelopmental disability was defined as cerebral palsy, developmental delay (DQ < 70) or blindness (VA < 6/60 in both eyes), or any combination of these disabilities	"Given that fluid restriction for the treatment of hypoxic ischaemic encephalopathy following perinatal asphyxia is recommended in standard textbooks, there is a need for randomised, controlled trials to establish if this practice affects mortality and morbidity. As it may not be ethical to include neonates with acute renal failure in a randomised trial, these babies will have to be excluded from the trial. These studies should investigate the effects of fluid management on outcomes such as mortality, seizure activity, evidence of cerebral damage on histology, and effects on renal function and electrolytes."
Keir AK, Wilkinson D, Andersen C, Stark MJ. Washed versus unwashed red blood cells for transfusion for the prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 1.	Primary outcomes pre-specified include: • Cerebral palsy by physician assessment Secondary outcomes pre-specified include: • Composite outcome of mortality or severe adverse neurosensory outcome (or its complement, survival without serious adverse neurosensory outcome) at a defined period of follow-up at age 18 to 24 months' adjusted gestational age or older, where adverse neurosensory outcome is defined as: o Cerebral palsy by physician assessment o DQ (> 2 SD below the mean on validated assessment tool of cognitive function (e.g. BSID)) o Blindness (VA < 20/200 in best eye) o Deafness (hearing loss requiring amplification or cochlear implantation)	"We identified a single small study. The results from this study show a high level of uncertainty, as the confidence intervals are consistent with both a large improvement or a serious harm caused by the intervention. Consequently, there is insufficient evidence to support or refute the use of washed RBCs to prevent the development of significant neonatal morbidities or mortality. Further clinical trials are required to assess the potential effects of pre-transfusion washing of RBCs for preterm or very low birth weight infants, or both, on short- and long-term outcomes."
Kylat RI, Ohlsson A. Recombinant human activated protein C for severe sepsis in neonates. Cochrane Database of Systematic Reviews 2012, Issue 4.	Secondary outcomes pre-specified include: • Severe disability, defined as any of blindness, deafness, cerebral palsy or cognitive delay (score > 2 SD below the mean for a recognised psychometric test for neurodevelopmental outcome assessed by a validated test, e.g. BSID), or adverse neurological outcome, at 18 months of age or later. These outcomes will be reported both as a composite outcome and individually • Cerebral palsy	"Despite the scientific rationale for its use, there is insufficient data to use rhAPC for the management of severe sepsis in newborn infants. Due to the results among adults with lack of efficacy, an increase in bleeding and resulting withdrawal of rhAPC from the market, neonates should not be treated with rhAPC and further trials should not be conducted."

Lai NM, Foong SC, Foong WC, Tan K. Co-bedding in neonatal nursery for promoting growth and neurodevelopment in stable preterm twins. Cochrane Database of Systematic Reviews 2016, Issue 4.	Secondary outcomes pre-specified include: • Long-term neurodevelopment, measured by validated scales such as BSID (Washington 1998), whereby average scores between twin pairs would be taken if data were available. Clinically diagnosed non-ambulatory cerebral palsy or significant auditory and visual impairment would be accepted if data were available	"Evidence on the benefits and harms of co-bedding for stable preterm twins was insufficient to permit recommendations for practice. Future studies must be adequately powered to detect clinically important differences in growth and neurodevelopment. Researchers should assess harms such as infection, along with medication errors and caregiver satisfaction."
Lai NM, Rajadurai SV, Tan K. Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease. Cochrane Database of Systematic Reviews 2006, Issue 3.	Secondary outcomes pre-specified include: • Neurodevelopmental disabilities at or after 12 months' corrected age, assessed using validated tools like BSID, including diagnosed cerebral palsy, blindness, or deafness • Mortality or neurodevelopmental disabilities	No included trials "To date, no randomised controlled trials are available that examine the effects of increased versus standard energy intake for preterm infants with (or developing) CLD/BPD. Research should be directed at evaluating the effects of various levels of energy intake on this group of infants on clinically important outcomes like mortality, respiratory status, growth and neurodevelopment. The benefits and harms of various ways of increasing energy intake, including higher energy density of milk feed and/or fluid volume (clinically realistic target volume should be set), parenteral nutrition, and the use of various constituents of energy like carbohydrate, protein and fat for this purpose also need to be assessed."
Lai NM, Taylor JE, Tan K, Choo YM, Ahmad Kamar A, Muhamad NA. Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters. Cochrane Database of Systematic Reviews 2016, Issue 3.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcomes, measured using validated scales such as the BSID (Washington 1998) at 12, 18, or 24 months of age. Data on clinically diagnosed non-ambulatory cerebral palsy or significant auditory and visual impairment would be accepted if available	"Based on moderate-quality evidence, chlorhexidine dressing/alcohol skin cleansing reduced catheter colonisation, but made no significant difference in major outcomes like sepsis and CRBSI compared to polyurethane dressing/povidone-iodine cleansing. Chlorhexidine dressing/alcohol cleansing posed a substantial risk of contact dermatitis in preterm infants, although it was unclear whether this was contributed mainly by the dressing material or the cleansing agent. While silver-alginate patch appeared safe, evidence is still insufficient for a recommendation in practice. Future research that evaluates antimicrobial dressing should ensure blinding of caregivers and outcome assessors and ensure that all participants receive the same co-interventions, such as the skin cleansing agent. Major

		outcomes like sepsis, CRBSI and mortality should be assessed in infants of different gestation and birth weight."
Lai M, Inglis GDT, Hose K, Jardine LA, Davies MW. Methods for securing endotracheal tubes in newborn infants. Cochrane Database of Systematic Reviews 2014, Issue 7.	Secondary outcomes pre-specified include: • Incidence of an adverse neurodevelopmental outcome (e.g. cerebral palsy, sensorineural hearing loss, visual impairment, developmental delay) whenever measured in the primary studies	"This review highlighted the need for further well designed and completed studies to be conducted for this common neonatal procedure. Evidence is lacking to determine the most effective and safe method to stabilise the endotracheal tube in the ventilated neonate."
Lawn CJ, Weir FJ, McGuire W. Base administration or fluid bolus for preventing morbidity and mortality in preterm infants with metabolic acidosis. Cochrane Database of Systematic Reviews 2005, Issue 2.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes at ≥ 12 months of age (corrected for preterm birth) measured using validated assessment tools such as BSID and classifications of disability, including (a) auditory and (b) visual disability. The composite outcome of "severe neurodevelopmental disability" is defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment	"There is insufficient evidence from randomised controlled trials to determine whether infusion of base or fluid bolus reduces morbidity and mortality in preterm infants with metabolic acidosis. Further large randomised trials are needed."
Malwade US, Jardine LA. Home-versus hospital-based phototherapy for the treatment of non-haemolytic jaundice in infants at more than 37 weeks' gestation. Cochrane Database of Systematic Reviews 2014, Issue 6.	Primary outcomes pre-specified include: • Incidence (percentage) of chronic bilirubin encephalopathy or kernicterus, defined by a tetrad of choreoathetoid cerebral palsy, high-frequency sensorineural hearing loss, palsy of vertical gaze, and dental enamel hypoplasia	No included trials "No high-quality evidence is currently available to support or refute the practice of home-based phototherapy for non-haemolytic jaundice in infants at more than 37 weeks' gestation."
McGuire W, Fowlie PW, Evans DJ. Naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia. Cochrane Database of Systematic Reviews 2004, Issue 1.	Primary outcomes pre-specified include: • Severe neurodevelopmental disability assessed at ≥ 12 months of age. Severe neurodevelopmental disability will be defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment. Development should have been assessed by means of a previously validated tool, such as BSID PDI and MDI	"There are insufficient data available to evaluate the safety and effectiveness of the routine use of naloxone for newborn infants of greater than 34 weeks' gestation with suspected perinatal asphyxia. A further randomised controlled trial is needed to determine if naloxone benefits newborn infants with suspected perinatal asphyxia. Such a trial should assess clinically important outcomes such as mortality, and adverse short and long term neurological outcomes."

Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane Database of Systematic Reviews 2013, Issue 3.	Secondary outcomes pre-specified include: • Neurodevelopment: death or severe neurodevelopmental disability defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment. Each component will be analysed individually as well as part of the composite outcome	"The available trial data do not provide evidence of important beneficial or harmful effects of early trophic feeding for very preterm or very low birth weight infants. The applicability of these findings to extremely preterm, extremely low birth weight or growth restricted infants is limited. Further randomised controlled trials would be needed to determine how trophic feeding compared with enteral fasting affects important outcomes in this population."
Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database of Systematic Reviews 2015, Issue 10.	Secondary outcomes pre-specified include: • Neurodevelopment: o Death or severe neurodevelopmental disability defined as any 1 or a combination of the following: non-ambulatory cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment. Each component was to be analysed individually as well as part of the composite outcome o Neurodevelopmental scores in survivors aged 12 months or greater measured using validated assessment tools o Cognitive and educational outcomes in survivors aged > 5 years	"The available trial data suggest that advancing enteral feed volumes at daily increments of 30 to 40 mL/kg (compared to 15 to 24 mL/kg) does not increase the risk of NEC or death in VLBW infants. Advancing the volume of enteral feeds at slow rates results in several days of delay in establishing full enteral feeds and increases the risk of invasive infection. The applicability of these findings to extremely preterm, extremely low birth weight, or growth-restricted infants is limited. Further randomised controlled trials in these populations may be warranted to resolve this uncertainty."
Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database of Systematic Reviews 2014, Issue 12.	Secondary outcomes pre-specified include: • Neurodevelopment: o Death or severe neurodevelopmental disability defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment. Each component was analysed individually as well as part of the composite outcome o Neurodevelopmental scores in survivors aged 12 months or greater measured using validated assessment tools	"The evidence available from randomised controlled trials suggested that delaying the introduction of progressive enteral feeds beyond four days after birth did not reduce the risk of developing NEC in very preterm or VLBW infants, including growth-restricted infants. Delaying the introduction of progressive enteral feeds resulted in a few days' delay in establishing full enteral feeds but the clinical importance of this effect was unclear. The applicability of these findings to extremely preterm or extremely low birth weight was uncertain. Further randomised controlled trials in this population may be warranted."

	○ Cognitive and educational outcomes in survivors aged > 5 years	
Mosalli R, AlFaleh K. Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants. Cochrane Database of Systematic Reviews 2008, Issue 1.	Secondary outcomes pre-specified include: • Neurodevelopmental impairment (i.e. rates of cerebral palsy, cognitive delay defined as a MDI score < 70 (2 SD below the mean of 100) on the BSID II (Bayley 1993), deafness, blindness, or composite reported at 18 months' corrected age or later)	"Prophylactic surgical ligation of the PDA did not decrease mortality or BPD in ELBW infants. A significant reduction of stage II or III NEC was noted. Based on the current evidence, the high rate of spontaneous closure, availability of effective safe medical therapies, and the potential short and long-term complications of surgical ligation, the use such prophylactic surgical therapy is not indicated in the management of the preterm infants."
O'Donnell CPF, Bruschettini M, Davis PG, Morley CJ, Moja L, Calevo MG, Zappettini S. Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes. Cochrane Database of Systematic Reviews 2015, Issue 7.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment, developmental delay, i.e. IQ 2 SD < mean on validated assessment tools, e.g. BSID MDI)	"At present there is insufficient evidence from clinical trials to determine the efficacy and safety of initial sustained lung inflation for newborn infants resuscitated with PPV. RCTs comparing PPV with and without sustained inflations at neonatal resuscitation are warranted."
Ogunlesi TA, Odigwe CC, Oladapo OT. Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis. Cochrane Database of Systematic Reviews 2015, Issue 11.	Secondary outcomes pre-specified include: • Presence of severe neurological deficits or developmental delay between 1 and 2 years of age (a neurological deficit was defined as a functional abnormality of a body area that is observed as the result of an abnormality in function of the brain, spinal cord, muscles, or nerves; developmental delay was defined as any significant lag in a child's physical or motor, cognitive, behavioural, emotional, or social development, in comparison with other children of the same age and sex within similar environments; formal evaluation tools were used to assess neurological deficits and developmental delay). Examples of neurological deficits include mental retardation, cerebral palsy, epilepsy, blindness, and behavioural disorders. We considered evaluation tools such as BSID or GMDS (for	"Very low-quality data from two randomised controlled trials suggest that some reduction in death and hearing loss may result from use of adjunctive steroids alongside standard antibiotic therapy for treatment of patients with neonatal meningitis. Benefit is not yet seen with regards to reduction in neurological sequelae. Researchers who wish to clarify these findings must conduct more robustly designed trials with greater numbers of participants, evaluating more relevant outcomes and providing adequate follow-up."

	neurodevelopmental deficits), the GMFCS or the Movement ABC (for cerebral palsy), the Sonken-Silver VA test (for blindness), distraction tests (for behavioural disorders), and electroencephalography (for epilepsy) - all applied between 1 and 2 years of age. We also accepted other measures used by individual trialists to evaluate and document neurological deficits in their respective trials	
Onland W, Offringa M, van Kaam A. Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. Cochrane Database of Systematic Reviews 2012, Issue 4.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental sequelae, assessed after at least 1 year CGA and before a CGA of 4 years including cerebral palsy and BSID (MDI)	"Based on the results of the currently available evidence, inhalation corticosteroids initiated at ≥ 7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time. More and larger randomised, placebo-controlled trials are needed to establish the efficacy and safety of inhalation corticosteroids."
Osborn DA, Evans NJ. Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants. Cochrane Database of Systematic Reviews 2001, Issue 2.	Primary outcomes pre-specified include: • Neurodevelopmental disability (neurological abnormality including cerebral palsy, developmental delay, or sensory impairment)	"Dopamine was more successful than albumin at correcting low BP in hypotensive preterm infants, many of whom had already received volume. Neither intervention has been shown to be superior at improving blood flow or in improving mortality and morbidity in preterm infants. The trials do not allow any firm conclusions to be made as to whether or when volume or dopamine should be used in preterm infants."
Osborn DA, Hunt R. Postnatal thyroid hormones for preterm infants with transient hypothyroxinaemia. Cochrane Database of Systematic Reviews 2007, Issue 1.	Primary outcomes pre-specified include: • Neurodevelopmental status at follow-up. Neurodevelopmental outcome was categorised as: o Abnormal mental developmental > 12 months' corrected age (a development or IQ > 2 SD below the mean of a standardised test) o Abnormal neurological outcome (infants with abnormal mental development or definite cerebral palsy) o Motor deficits o Sensorineural impairments including hearing deficit requiring aids; VA < 6/60	"There is insufficient evidence to determine whether use of thyroid hormones for treatment of preterm infants with transient hypothyroxinaemia results in changes in neonatal morbidity and mortality, or reductions in neurodevelopmental impairments. Further research is required."

Osborn DA, Hunt R. Postnatal thyroid hormones for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews 2007, Issue 1.	Primary outcomes pre-specified include: • Abnormal neurodevelopmental outcome: o Abnormal mental development > 12 months' corrected age (a validated development or IQ > 2 SD below the mean of a standardised test) o Abnormal neurological outcome (infants with abnormal mental development or definite cerebral palsy) o Motor deficits o Sensorineural impairments (hearing deficit requiring aids or VA < 6/60)	"There is no evidence from controlled clinical trials that postnatal thyroid hormone treatment reduces the severity of respiratory distress syndrome, neonatal morbidity or mortality in preterm infants with respiratory distress syndrome."
Özek E, Soll R, Schimmel MS. Partial exchange transfusion to prevent neurodevelopmental disability in infants with polycythemia. Cochrane Database of Systematic Reviews 2010, Issue 1.	Primary outcomes pre-specified include: • Neurodevelopmental status at 2 years of age, neurodevelopmental status at school age. This will include both combined and separate analyses of the components of severe neurodevelopmental delay defined as an MDI < 70, cerebral palsy, vision loss, and hearing loss	"There are no proven clinically significant short or long-term benefits of PET in polycythemic newborn infants who are clinically well or who have minor symptoms related to hyperviscosity. PET may lead to an increase in the risk of NEC. The data regarding developmental follow-up are extremely imprecise due to the large number of surviving infants who were not assessed and, therefore, the true risks and benefits of PET are unclear."
Paradisis M, Osborn DA. Adrenaline for prevention of morbidity and mortality in preterm infants with cardiovascular compromise. Cochrane Database of Systematic Reviews 2004, Issue 1.	Primary outcomes pre-specified include: • Long-term neurodevelopmental outcome: cerebral palsy and standardised assessment of developmental delay or sensorineural impairment	"There are insufficient data on the use of adrenaline infusions in preterm infants with cardiovascular compromise to make recommendations for practice. There is a need for larger trials to determine whether adrenaline is effective in reducing morbidity and mortality in preterm infants with cardiovascular compromise."
Pfister RH, Soll R, Wiswell TE. Protein-containing synthetic surfactant versus protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. Cochrane Database of Systematic Reviews 2009, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, mental delay (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" was defined as having any 1 of the aforementioned deficits	"In the one trial comparing protein containing synthetic surfactants compared to protein free synthetic surfactant for the prevention of RDS, no statistically different clinical differences in death and chronic lung disease were noted. Clinical outcomes between the two groups were generally similar although the group receiving protein containing synthetic surfactants did have decreased incidence of respiratory distress syndrome. Further well designed studies comparing protein containing synthetic

		surfactant to the more widely used animal derived surfactant extracts are indicated."
Pfister RH, Soll R, Wiswell TE. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. Cochrane Database of Systematic Reviews 2007, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome at approximately 2 years' corrected age (range 18 months to 28 months) including cerebral palsy, mental retardation (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" was defined as having any 1 of the aforementioned deficits	"In two trials of protein containing synthetic surfactants compared to animal derived surfactant extract, no statistically different clinical differences in death and chronic lung disease were noted. In general, clinical outcomes between the two groups were similar. Further well designed studies of adequate size and power will help confirm and refine these findings."
Pilley E, McGuire W. Pre-discharge "car seat challenge" for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2006, Issue 1.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes at > 12 months post term measured using validated assessment tools such as BSID and classifications of disability, including auditory and visual disability. The composite outcome "severe neurodevelopmental disability" will be defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment	No included trials "It is unclear whether undertaking a pre-discharge car seat challenge is beneficial or harmful to preterm infants. Further studies are needed to determine whether the car seat challenge accurately predicts the risk of clinically significant adverse events in preterm infants travelling in car seats. If this is shown to be the case then a large randomised controlled trial is needed to provide an unbiased assessment of its utility in pre-discharge assessment."
Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2014, Issue 4.	Primary outcomes pre-specified include: • Death or severe neurodevelopmental disability defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment. We analysed each component individually as well as part of the composite outcome	"In preterm and low birth weight infants, feeding with formula compared with donor breast milk results in a higher rate of short-term growth but also a higher risk of developing necrotising enterocolitis. Limited data on the comparison of feeding with formula versus nutrient-fortified donor breast milk are available. This limits the applicability of the findings of this review as nutrient fortification of breast milk is now a common practice in neonatal care. Future trials may compare growth, development and adverse outcomes in infants who receive formula milk versus nutrient-fortified donor breast milk given as a supplement to maternal expressed breast milk or as a sole diet."
Qureshi MJ, Kumar M. D-Penicillamine for preventing retinopathy of prematurity in	Secondary outcomes pre-specified include:	"Administration of prophylactic D-penicillamine in preterm infants does not prevent acute or severe ROP, death or neurodevelopmental delay. D-penicillamine cannot be

preterm infants. Cochrane Database of Systematic Reviews 2013, Issue 9.	• Abnormal neurodevelopment defined as abnormal neurological examination, epilepsy, cerebral palsy, or DQ < 70 diagnosed at 1 year of corrected age or older	recommended for the prevention of ROP based on the available evidence."
Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2012, Issue 3.	Secondary outcomes pre-specified include: • Cerebral palsy • Neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, significant mental developmental delay (BSID < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" was defined as having any one of the aforementioned deficits *(Review notes that 2 RCTs have reported on cerebral palsy, but not in the 'acceptable range' pre-specified; therefore no results were reported:* *"Neurodevelopmental outcome: For this outcome, we considered any trial reporting at approximately 2 years' corrected age (acceptable range 18 months to 28 months) any of the following entities cerebral palsy, intellectual disability or developmental delay (Bayley Scales of Infant Development Mental Developmental Index < 70), legal blindness (< 20/200 visual acuity), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" would be defined as having any one of the aforementioned deficits. Two trials Sinkin 1998; Vaucher 1993 performed a follow-up study including infants recruited in the Kendig 1991 and Merritt 1991 trials respectively. Sinkin 1998 reported cerebral palsy but in 148 children at school age, no data were available from ages between 18 and 28 months. Vaucher 1993 reported on cerebral palsy and developmental delay in 145 survivors at 12 months' corrected age. No one study reporting neurodevelopmental outcomes at 24 months' corrected age was found")*	"Although the early trials of prophylactic surfactant administration to infants judged to be at risk of developing RDS compared with selective use of surfactant in infants with established RDS demonstrated a decreased risk of air leak and mortality, recent large trials that reflect current practice (including greater utilization of maternal steroids and routine post delivery stabilization on CPAP) do not support these differences and demonstrate less risk of chronic lung disease or death when using early stabilization on CPAP with selective surfactant administration to infants requiring intubation."

Rojas-Reyes MX, Orrego-Rojas PA. Rescue high-frequency jet ventilation versus conventional ventilation for severe pulmonary dysfunction in preterm infants. Cochrane Database of Systematic Reviews 2015, Issue 10.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (measured at approximately 2 years' corrected age; acceptable range 18 months to 28 months) including cerebral palsy, delayed neurodevelopment (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing); impairment defined as including any of the aforementioned deficits	"Study authors reported no significant differences in overall mortality between rescue high-frequency jet ventilation and conventional ventilation and presented highly imprecise results for important adverse effects such as intraventricular haemorrhage, new air leaks, airway obstruction and necrotising tracheobronchitis. The overall quality of evidence is affected by limitations in trial design and by imprecision due to the small number of infants in the included study. Existing evidence does not support the use of high-frequency jet ventilation as rescue therapy in preterm infants. Studies that target populations at greatest risk and that have sufficient power to assess important outcomes are needed. These trials should incorporate long-term pulmonary and neurodevelopmental outcomes."
Romantsik O, Bruschettini M, Zappettini S, Ramenghi LA, Calevo MG. Heparin for the treatment of thrombosis in neonates. Cochrane Database of Systematic Reviews 2016, Issue 11.	Secondary outcomes pre-specified include: • Major neurodevelopmental disability, that is, (1) cerebral palsy on physician assessment (yes/no); (2) developmental delay or intellectual impairment: BSID or GMDS assessment > 2 SD below the mean, or intellectual impairment (IQ > 2 SD below the mean); neuromotor development (BSID PDI) assessed in survivors; mental development (BSID MDI) assessed in survivors; (3) blindness vision (< 6/60 in both eyes); or (4) sensorineural deafness requiring amplification. We will report these components of this long-term outcome for all trials that have assessed children after 18 months' chronological age. We will perform separate analyses for children aged 18 to 24 months and for those aged 3 to 5 years	"We found no studies that met our inclusion criteria and no evidence from randomized controlled trials to recommend or refute the use of heparin for treatment of neonates with thrombosis."
Sankar MJ, Sankar J, Mehta M, Bhat V, Srinivasan R. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. Cochrane Database of Systematic Reviews 2016, Issue 2.	Secondary outcomes pre-specified include: • Adverse neurodevelopmental outcomes at 18 months to 24 months' corrected age: o Cerebral palsy and/or o Moderate to severe developmental delay as assessed on performance in formal neurodevelopmental testing such as the BSID scale	"Implications for practice: Intravitreal bevacizumab reduces the risk of refractive errors during childhood when used as monotherapy while intravitreal pegaptanib reduces the risk of retinal detachment when used in conjunction with laser therapy in infants with type 1 ROP. Quality of evidence was, however, low for both the outcomes because of the risk of detection and other biases. Effect on other critical outcomes and, more importantly,

		the long-term systemic adverse effects of the drugs are not known. The insufficient data precludes strong conclusions favouring routine use of intravitreal anti-VEGF agents in preterm infants with type 1 ROP. Implications for research: Further studies are needed to evaluate the effect of anti-VEGF agents on structural and functional outcomes in childhood and delayed systemic adverse effects such as myocardial dysfunction and adverse neurodevelopmental outcomes."
Schulzke SM, Kaempfen S, Trachsel D, Patole SK. Physical activity programs for promoting bone mineralization and growth in preterm infants. Cochrane Database of Systematic Reviews 2014, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental abnormalities at 18 to 24 months' corrected age or later: o Cerebral palsy o Developmental delay (assessed by standardised and validated test, e.g. GMDS or BSID test, with abnormality defined as > 2 SD below the mean) o Intellectual impairment (IQ > 2 SD below the mean as assessed by a standardised and validated test) o Blindness (vision < 6/60 in both eyes) o Sensorineural deafness requiring amplification	"Some evidence suggests that physical activity programs might promote short-term weight gain and bone mineralization in preterm infants. Data are inadequate to allow assessment of harm or long-term effects. Current evidence does not support the routine use of physical activity programs in preterm infants. Further trials incorporating infants with a high baseline risk of osteopenia are required. These trials should address adverse events, long-term outcomes, and the effects of nutritional intake (calories, protein, calcium, phosphorus)."
Shah PS, Ohlsson A. Alpha-1 proteinase inhibitor (a1PI) for preventing chronic lung disease in preterm infants. Cochrane Database of Systematic Reviews 2001, Issue 3.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (frequency of cerebral palsy and/or mental retardation, legal blindness, and /or deafness) *(Review reports on 'Developmental delay amongst infants assessed' for 1 RCT (83 infants); however it was not clear whether this included cerebral palsy (in review or RCT (published as abstract only))*	"Prophylactic administration of a1PI did not reduce the risk of CLD at 36 weeks or long term adverse developmental outcomes in preterm neonates."
Shah PS, Kaufman DA. Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. Cochrane Database of Systematic Reviews 2009, Issue 2.	Secondary outcomes pre-specified include: • Neurodevelopmental disability at 18 to 24 months (including cerebral palsy, cognitive impairment, deafness, and blindness)	"Antistaphylococcal immunoglobulins (INH A-21 and Altastaph) are not recommended for prevention of staphylococcal infections in preterm or VLBW neonates. Further research to investigate the efficacy of other products such as Pagibaximab is needed."

Shah SS, Ohlsson A, Halliday HL, Shah VS. Inhaled versus systemic corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. Cochrane Database of Systematic Reviews 2012, Issue 5.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome: Neurodevelopmental impairment was defined as presence of cerebral palsy and/or mental retardation (BSID MDI < 70) and/or legal blindness (< 20/200 VA) and/or deafness (aided or < 60 dB on audiometric testing) assessed at 18 to 24 months	"This review found no evidence that early inhaled steroids confer important advantages over systemic steroids in the management of ventilator dependent preterm infants. Neither inhaled steroids nor systemic steroids can be recommended as a part of standard practice for ventilated preterm infants. Because they might have fewer adverse effects than systemic steroids, further randomised controlled trials of inhaled steroids are needed that address risk/benefit ratio of different delivery techniques, dosing schedules and long-term effects, with particular attention to neurodevelopmental outcome."
Shah SS, Ohlsson A, Halliday HL, Shah VS. Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants. Cochrane Database of Systematic Reviews 2012, Issue 5.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome: Neurodevelopmental impairment is defined as presence of cerebral palsy and/or mental retardation (BSID MDI < 70) and/or legal blindness (< 20/200 VA) and/or deafness (aided or < 60 dB on audiometric testing) assessed at 18 to 24 months	"This review found no evidence that inhaled corticosteroids confer net advantages over systemic corticosteroids in the management of ventilator dependent preterm infants. Neither inhaled steroids nor systemic steroids can be recommended as standard treatment for ventilated preterm infants. There was no evidence of difference in effectiveness or side-effect profiles for inhaled versus systemic steroids. A better delivery system guaranteeing selective delivery of inhaled steroids to the alveoli might result in beneficial clinical effects without increasing side-effects. To resolve this issue, studies are needed to identify the risk/benefit ratio of different delivery techniques and dosing schedules for the administration of these medications. The long-term effects of inhaled steroids, with particular attention to neurodevelopmental outcome, should be addressed in future studies."
Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Cochrane Database of Systematic Reviews 2011, Issue 8.	Secondary outcomes pre-specified include: • Neurodevelopmental disability at 18 to 24 months (including cerebral palsy, cognitive impairment, deafness, and blindness)	"Sildenafil in the treatment of PPHN has significant potential especially in resource limited settings. However, a large scale randomised trial comparing sildenafil with the currently used vasodilator, inhaled nitric oxide, is needed to assess efficacy and safety."
Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low	Primary outcomes pre-specified include: • Neurodevelopmental impairment defined as presence of 1 or more of the following: cerebral palsy, MDI or PDI < 70,	"Glucose infusion rate: There is insufficient evidence from trials comparing lower with higher glucose infusion rates to inform clinical practice. Large randomized trials are needed, powered on

birth weight infants. Cochrane Database of Systematic Reviews 2011, Issue 10.	blindness or deafness assessed between 18 and 24 months' post-menstrual age or at latest assessment up to 24 months' corrected age	clinical outcomes including death, major morbidities and adverse neurodevelopment. Insulin infusion: The evidence reviewed does not support the routine use of insulin infusions to prevent hyperglycemia in VLBW neonates. Further randomized trials of insulin infusion may be justified. They should enrol extremely low birth weight neonates at very high risk for hyperglycemia and neonatal death. They might use real time glucose monitors if these are validated for clinical use. Refinement of algorithms to guide insulin infusion is needed to enable tight control of glucose concentrations within the target range."
Singh N, Halliday HL, Stevens TP, Suresh G, Soll R, Rojas-Reyes MX. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews 2015, Issue 12.	Secondary outcomes pre-specified include: • Cerebral palsy at approximately 2 years' corrected age (as defined by the study authors) • Neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, delayed neurodevelopment (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome 'neurodevelopmental impairment' was defined as having any 1 of the aforementioned deficits	"Significant differences in clinical outcome were noted in the comparison trials of modified minced lung surfactant extract (beractant) compared with porcine minced lung surfactant extract (poractant alfa) including a significant increase in the risk of mortality prior to discharge, death or oxygen requirement at 36 weeks' postmenstrual age, PDA requiring treatment and "receiving > 1 dose of surfactant" in infants treated with modified bovine minced lung surfactant extract compared with porcine minced lung surfactant extract. The difference in these outcomes was limited to studies using a higher initial dose of porcine minced lung surfactant extract. It is uncertain whether the observed differences are from differences in dose or from source of extraction (porcine vs. bovine) because of the lack of dose-equivalent comparison groups with appropriate sample size. No differences in clinical outcomes were observed in comparative trials between bovine lung lavage surfactant and modified bovine minced lung surfactants."
Soll R, Özek E. Prophylactic animal derived surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 1997, Issue 4.	Secondary outcomes pre-specified include: • Cerebral palsy • Neurodevelopmental outcome at approximately 2 years' corrected age (acceptable range 18 months to 28 months) including cerebral palsy, mental retardation (BSID MDI < 70), legal blindness (< 20/200 VA), and hearing deficit (aided	"Prophylactic intratracheal administration of animal derived surfactant extract to infants judged to be at risk of developing respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who receive prophylactic animal derived surfactant extract have a decreased risk of pneumothorax,

	or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" will be defined as having any 1 of the aforementioned deficits	a decreased risk of PIE, a decreased risk of mortality, and a decreased risk of BPD or death."
Stevens TP, Blennow M, Myers EH, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database of Systematic Reviews 2007, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome at hospital discharge and at a later time point (> 1 year post-conceptional age). Neurodevelopmental impairment is defined as the presence of cerebral palsy and/or mental retardation (BSID MDI < 70) and/or legal blindness (< 20/200 VA) and/or deafness (aided or < 60 dB on audiometric testing)	"Early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. A lower treatment threshold (FIO2 < 0.45) confers greater advantage in reducing the incidences of airleak syndromes and BPD; moreover a higher treatment threshold (FIO2 at study > 0.45) was associated with increased risk of PDA. These data suggest that treatment with surfactant by transient intubation using a low treatment threshold (FIO2 < 0.45) is preferable to later, selective surfactant therapy by transient intubation using a higher threshold for study entry (FIO2 > 0.45) or at the time of respiratory failure and initiation of mechanical ventilation."
Stewart A, Inglis GDT, Jardine LA, Koorts P, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in newborn infants with intercostal catheters. Cochrane Database of Systematic Reviews 2012, Issue 4.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, or developmental delay) at 1 year, 18 months, 2 years, or 5 years	No included trials "There are no data from randomised trials to either support or refute the use of antibiotic prophylaxis for intercostal catheter insertion in neonates. Any randomised controlled trials of antibiotic prophylaxis would need to account for the fact that neonates who require insertion of an intercostal catheter may already be receiving antibiotics for other indications."
Subramaniam P, Ho JJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 6.	Secondary outcomes pre-specified include: • Neurodevelopmental status at follow-up: neurodevelopment measured on a validated scale that measures cognitive, motor, behavioural function, or blindness, deafness, or cerebral palsy at about 2 years of age	"There is insufficient evidence to evaluate prophylactic CPAP compared to oxygen therapy and other supportive care. However when compared to mechanical ventilation prophylactic nasal CPAP in very preterm infants reduces the need for mechanical ventilation and surfactant and also reduces the incidence of BPD and death or BPD."

Tan K, Lai NM, Sharma A. Surfactant for bacterial pneumonia in late preterm and term infants. Cochrane Database of Systematic Reviews 2012, Issue 2.	Secondary outcomes pre-specified include: • Long-term neurological outcomes (cerebral palsy, development measured by BSID or GMDS, intellectual function measured by IQ score, and presence of visual or hearing impairments) at 18 months of age or greater	No included trials "There is no evidence from randomised controlled trials (RCTs) to support or refute the efficacy of surfactant in near-term and term infants with proven or suspected bacterial pneumonia. RCTs are still required to answer this question."
Thayyil S, Milligan D. Single versus double volume exchange transfusion in jaundiced newborn infants. Cochrane Database of Systematic Reviews 2006, Issue 4.	Primary outcomes pre-specified include: • Neurological deficits consistent with kernicterus at 2 years of age including athetoid cerebral palsy, impaired upward gaze and deafness, AN/AD, and subtle BIND (Shapiro 2005) Secondary outcomes pre-specified include: • Neurological deficits or neurodisability defined as any of deafness, cerebral palsy, or cognitive delay (score > 2 SD below the mean for any recognised test for neurodevelopment, e.g. BSID)	"There was insufficient evidence to support or refute the use of single volume exchange transfusion as opposed to double volume exchange transfusion in jaundiced newborns. A change from the current practice of double volume exchange transfusions for severe jaundice in newborns infant, cannot be recommended on current evidence."
Vasudevan C, Oddie SJ, McGuire W. Early removal versus expectant management of central venous catheters in neonates with bloodstream infection. Cochrane Database of Systematic Reviews 2016, Issue 4.	Primary outcomes pre-specified include: • Neurodevelopmental outcomes assessed after 12 months' post-menstrual age using validated tools: neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of 1 or more of the following: non-ambulant cerebral palsy, developmental delay (DQ > 2 SD below population mean), blindness (VA < 6/60), or deafness (any hearing impairment requiring or unimproved by amplification)	No included trials "There are no trial data to guide practice regarding early removal versus expectant management of central venous catheters in newborn infants with bloodstream infections. A simple and pragmatic randomised controlled trial is needed to resolve the uncertainty about optimal management in this common and important clinical scenario."

Verner AM, McGuire W, Craig JS. Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2007, Issue 4.	Secondary outcomes pre-specified include:
	• Development
	  ○ Neurodevelopmental outcomes at ≥ 12 months of age (corrected for preterm birth) measured using validated assessment tools
	  ○ Severe neurodevelopmental disability defined as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment
		"Despite that lack of evidence of benefit from randomised controlled trials, it is likely that taurine will continue to be added to formula milks and parenteral nutrition solutions used for feeding preterm and low birth weight infants given the putative association of taurine deficiency with various adverse outcomes. Further randomised controlled trials of taurine supplementation versus no supplementation in preterm or low birth weight infants are unlikely to be viewed as a research priority, but there may be

	○ Cognitive and educational outcomes at > 5 years old: IQ and/or indices of educational achievement measured using a validated assessment tool (including school examination results)	issues related to dose or duration of supplementation in specific subgroups of infants that merit further research."
Watson J, McGuire W. Responsive versus scheduled feeding for preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 8.	Secondary outcomes pre-specified include: • Neurodevelopmental outcomes at > 12 months' corrected age measured using validated assessment tools such as BSID and classifications of disability including auditory and visual disability. We defined the composite outcome 'severe neurodevelopmental disability' as any 1 or combination of the following: non-ambulant cerebral palsy, developmental delay (DQ < 70), auditory and visual impairment	"Overall, the data do not provide strong or consistent evidence that responsive feeding affects important outcomes for preterm infants or their families. Some (low quality) evidence exists that preterm infants fed in response to feeding and satiation cues achieve full oral feeding earlier than infants fed prescribed volumes at scheduled intervals. This finding should be interpreted cautiously because of methodological weaknesses in the included trials. A large RCT would be needed to confirm this finding and to determine if responsive feeding of preterm infants affects other important outcomes."
Wilkinson D, Andersen C, O'Donnell CPF, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database of Systematic Reviews 2016, Issue 2.	Secondary outcomes pre-specified include: • Long-term neurodevelopmental outcome (rates of cerebral palsy on physician assessment, developmental delay, i.e. IQ 2 SD < mean on validated assessment tools such as BSID MDI), blindness, hearing impairment requiring amplification	"HFNC has similar rates of efficacy to other forms of non-invasive respiratory support in preterm infants for preventing treatment failure, death and CLD. Most evidence is available for the use of HFNC as post-extubation support. Following extubation, HFNC is associated with less nasal trauma, and may be associated with reduced pneumothorax compared with nasal CPAP. Further adequately powered randomised controlled trials should be undertaken in preterm infants comparing HFNC with other forms of primary non-invasive support after birth and for weaning from non-invasive support. Further evidence is also required for evaluating the safety and efficacy of HFNC in extremely preterm and mildly preterm subgroups, and for comparing different HFNC devices."
Wong V, Cheuk DKL, Chu V. Acupuncture for hypoxic ischemic encephalopathy in neonates. Cochrane Database of Systematic Reviews 2013, Issue 1.	Primary outcomes pre-specified include: • Long-term (> 12 months) major neurodevelopmental disability such as cerebral palsy, developmental delay (BSID or GMDS assessment > 2 SD below the mean) or intellectual impairment (IQ > 2 SD below mean), blindness (vision <	No included trials "The rationale for acupuncture in neonates with HIE is unclear and the evidence from randomized controlled trial is lacking. Therefore, we do not recommend acupuncture for the treatment of HIE in neonates. High quality randomized controlled trials on acupuncture for HIE in neonates are needed."

	6/60 in both eyes), sensorineural deafness requiring amplification, or any combination of these disabilities	
Woodgate PG, Flenady V, Steer PA. Intramuscular penicillin for the prevention of early onset group B streptococcal infection in newborn infants. Cochrane Database of Systematic Reviews 2004, Issue 2.	Secondary outcomes pre-specified include: • Neurodevelopmental outcome (cerebral palsy, sensorineural hearing loss, visual impairment, developmental delay)	"This review does not support the routine use of intramuscular penicillin to prevent EOGBSD in newborn infants. There is a discrepancy between this finding and the results of a number of larger non-randomised trials. Explanations for this are proposed. There is a need for this intervention to be tested as a component of the existing prevention strategies in widespread use."
Young L, Embleton ND, McCormick FM, McGuire W. Multinutrient fortification of human breast milk for preterm infants following hospital discharge. Cochrane Database of Systematic Reviews 2013, Issue 2.	Primary outcomes pre-specified include: • Development: o Neurodevelopmental outcomes assessed using validated tools at > 12 months' corrected age and classifications of disability, including non-ambulant cerebral palsy, developmental delay, auditory and visual impairment o Cognitive and educational outcomes at > 5 years: IQ and/or indices of educational achievement measured using a validated tool (including school examination results)	"The limited available data do not provide convincing evidence that feeding preterm infants with multinutrient fortified breast milk compared with unfortified breast milk following hospital discharge affects important outcomes including growth rates during infancy. There are no data on long-term growth. Since fortifying breast milk for infants fed directly from the breast is logistically difficult and has the potential to interfere with breast feeding, it is important to determine if mothers would support further trials of this intervention."
Young L, Morgan J, McCormick FM, McGuire W. Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge. Cochrane Database of Systematic Reviews 2012, Issue 3.	Primary outcomes pre-specified include: • Development: o Neurodevelopmental outcomes assessed using validated tools at > 12 months' corrected age and classifications of disability, including non-ambulant cerebral palsy, developmental delay, auditory and visual impairment o Cognitive and educational outcomes at > 5 years: IQ and/or indices of educational achievement measured using a validated tool (including school examination results)	"Current recommendations to prescribe "post-discharge formula" for preterm infants following hospital discharge are not supported by the available evidence. Some limited evidence exists that feeding preterm infants following hospital discharge with "preterm formula" (which is generally only available for in-hospital use) may increase growth rates up to 18 months corrected age."
Ziino AJA, Davies MW, Davis PG. Epinephrine for the resuscitation of apparently stillborn or extremely	Primary outcomes pre-specified include: • Severe disability at follow-up at 12 months, 24 months, and 5 years on, defined as any of blindness, deafness, cerebral	No included trials "No randomised, controlled trials evaluating the administration of epinephrine to the apparently stillborn or extremely bradycardic

bradycardic newborn infants. Cochrane Database of Systematic Reviews 2002, Issue 3.	palsy, or cognitive delay (score > 2 SD below the mean for a recognised psychometric test, e.g. BSID) Secondary outcomes pre-specified include: • Cerebral palsy at 12 and 24 months, and at 5 years	newborn infant were found. Similarly, no randomised, controlled trials that addressed the issues of optimum dosage and route of administration of epinephrine were found. Current recommendations for the use of epinephrine in newborn infants are based only on evidence derived from animal models and the human adult literature. Randomised trials in neonates are urgently required to determine the role of epinephrine in this population."

Abbreviations: AN/AD: Auditory Neuropathy/Auditory Dyssynchrony; anti-VEGF: anti-vascular endothelial growth factor; BIND: bilirubin-induced neurological dysfunction; BP: blood pressure; BPD: bronchopulmonary dysplasia; BSID: Bayley Scales of Infant Development; CDP: continuous distending pressure; CGA: corrected gestational age; CLD: chronic lung disease; CO2: carbon dioxide; CPAP: continuous positive airway pressure; CRBSI: catheter-related bloodstream infection; DQ: developmental quotient; ELBW: extremely low birthweight; EOGBSD: early-onset group B streptococcus disease; ETT: endotracheal tube; FIO2: fraction of inspired oxygen; GMDS: Griffith Mental Development Scales; GMFCS: Gross Motor Function Classification System; HFNC: high-flow nasal cannula; HIE: hypoxic-ischaemic encephalopathy; iNO: inhaled nitric oxide; IPPV: intermittent positive-pressure ventilation; IQ; intelligence quotient; IVH: intraventricular haemorrhage; LMA: laryngeal mask airway; MDI: Mental Development Index; Movement ABC: Movement Assessment Battery for Children; MV mechanical ventilation; NCPAP: nasal continuous positive airway pressure; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; PDI: Psychomotor Development Index; PET: partial exchange transfusion; PIE: pulmonary interstitial emphysema; PPHN: persistent pulmonary hypertension of the newborn; PPV: positive-pressure ventilation; RBCs: red blood cells; RCT: randomised controlled trial; RDS: respiratory distress syndrome; rhAPC: recombinant human activated protein C; ROP: retinopathy of prematurity; S-B: Stanford–Binet; SD: standard deviation; TGI: tracheal gas insufflation; UVCs: umbilical venous catheters; VA: visual acuity; VLBW: very low birthweight.

Appendix 4: Supporting information for Chapter 4 publication

Table S1: Birth state/territory cerebral palsy (CP) register status and 2-year outcomes for children with a CP diagnosis in the ACTOMgSO$_4$ at 2 years

Characteristic	Included on ACPR (*n*=35)	Not included on ACPR (*n*=29)	OR (95% CI)	*p*
Birth state/territory CP register status				
Recently established	14	20	1	—
Long-standing	21	9	3.33 (1.17–9.49)	0.02
2-year paediatric assessment				
CP assessment				
Probably yes	5	11	1	—
Definitely yes	30	18	3.67 (1.12–12.01)	0.03
CP severity				
Mild	15	19	1	0.13[a]
Moderate	14	9	1.97 (0.68–5.69)	0.21
Severe	6	1	7.60 (0.82–70.16)	0.07
CP type				
Monoplegia	1	2	1	0.44[a]
Hemiplegia	10	4	5.00 (0.35–71.90)	0.24
Diplegia	12	12	2.00 (0.16–25.38)	0.59
Quadriplegia	8	3	5.33 (0.34–82.83)	0.23
Ataxic	2	4	1.00 (0.05–18.92)	1.00
Dystonic	1	1	2.00 (0.05–78.25)	0.71
Mixed	1	3	0.67 (0.03–18.06)	0.81
Walking freely				
Yes	13	18	1	—
No	22	11	2.77 (1.02–7.55)	0.047
Decreased limb tone				
No	31	23	1	
Yes	3	5	0.45 (0.10–2.06)	0.30
Increased limb tone				
No	4	5	1	—
Yes	30	23	1.63 (0.39–6.78)	0.50
Ankle clonus, more than five beats				
No	27	26	1	—
Yes	8	2	3.85 (0.74–19.93)	0.11
Positive Babinski response				
No	12	13	1	—
Yes	23	15	1.66 (0.60–4.64)	0.33
Dorsiflexion of ankle limited				
No	10	14	1	—
Yes	24	14	2.40 (0.84–6.87)	0.10
Hip abduction limited				
No	19	20	1	—
Yes	16	7	2.41 (0.82–7.06)	0.11
Hip extension limited				
No	24	20	1	—
Yes	11	7	1.31 (0.43–4.03)	0.64
2-year psychological assessment				
Mean BSID-II PDI corrected score (SD)	*n*=27[b] 63.6 (16.9)	*n*=24[c] 69.4 (21.1)	0.98 (0.96–1.01)[d]	0.28

2-year parental questionnaire				
Received care from physiotherapist				
No	4	7	1	—
Yes	28	22	2.23 (0.58–8.62)	0.25
Received care from occupational therapist				
No	13	13	1	—
Yes	20	16	1.25 (0.45–3.51)	0.67
Difficulty walking				
No	7	11	1	—
Yes	27	18	2.36 (0.78–7.09)	0.13
Difficulty sitting				
No	19	23	1	—
Yes	15	6	3.03 (0.97–9.41)	0.06
Difficulty using hands				
No	14	22	1	—
Yes	20	7	4.49 (1.48–13.61)	0.008
Difficulty with head control				
No	28	28	1	—
Yes	5	1	5.00 (0.55–45.68)	0.15

Odds ratios (ORs) calculated as the odds of a diagnosis of cerebral palsy (CP) on the Australian Cerebral Palsy Register (ACPR) for the given level of the characteristic over odds of CP diagnosis on the ACPR in the reference level. [a]Global *p*-value against the null hypothesis that the odds of being detected on the ACPR is the same across all levels of the characteristic. [b]Missing data for the Bayley Scales of Infant Development (2nd edition) Psychomotor Developmental Index (BSID-II PDI) because child considered untestable owing to severe disability (*n*=3) or behavioural problem (*n*=1), distance/unavailability of assessment (*n*=1), and parental refusal (*n*=3). [c]Missing data for BSID-II PDI because child considered untestable owing to severe disability (*n*=3) and distance/unavailability of assessment (*n*=2). [d]Corresponds to the relative change in odds associated with a one-unit increase in the PDI corrected score. ACTOMgSO_4, Australasian Collaborative Trial of Magnesium Sulphate; 95% CI, 95% confidence interval; SD, standard deviation.

Table S2: Birth state/territory cerebral palsy (CP) register status and 2-year outcomes for children without a CP diagnosis in the ACTOMgSO$_4$ at 2 years

Characteristic	Included on ACPR (*n*=20)	Not included on ACPR (*n*=829)	OR (95% CI)	*p*
Birth state/territory CP register status				
Recently established	4	426	1	—
Long-standing	16	403	4.23 (1.41–12.73)	0.01
2-year paediatric assessment				
CP assessment				
Probably no	7	69	1	—
Definitely no	13	759	0.17 (0.07–0.44)	<0.001
Walking freely				
Yes	17	817	1	—
No	3	12	12.02 (3.05–47.38)	<0.001
Decreased limb tone				
No	15	786	1	
Yes	5	34	7.71 (2.63–22.55)	<0.001
Increased limb tone				
No	18	792	1	—
Yes	2	28	3.14 (0.69–14.28)	0.14
Ankle clonus, more than five beats				
No	20	817	—	—
Yes	0	0	—	—
Positive Babinski response				
No	20	807	1	—
Yes	0	11	—	1.00[a]
Dorsiflexion of ankle limited				
No	17	803	1	—
Yes	3	15	9.45 (2.47–36.11)	0.001
Hip abduction limited				
No	19	808	1	—
Yes	1	8	5.32 (0.63–44.63)	0.12
Hip extension limited				
No	20	815	1	—
Yes	0	1	—	1.00[a]
2-year psychological assessment				
BSID-II PDI, corrected score, mean (SD)	*n*=19[b] 78.0 (20.4)	*n*=754[c] 91.4 (16.9)	0.96 (0.93–0.99)[d]	0.003
2-year parental questionnaire				
Received care from physiotherapist				
No	10	635	1	—
Yes	8	158	3.22 (1.25–8.27)	0.015
Received care from occupational therapist				
No	14	733	1	—
Yes	4	64	3.27 (1.04–10.25)	0.04
Difficulty walking				
No	14	782	1	—
Yes	4	30	7.45 (2.31–24.03)	0.001
Difficulty sitting				
No	19	808	1	—
Yes	0	4	—	1.00[a]
Difficulty using hands				

No	17	806	1	—
Yes	2	6	15.80 (2.98–83.87)	0.001
Difficulty with head control				
No	19	809	1	—
Yes	0	1		1.00[a]

Odds ratios (ORs) calculated as odds of CP diagnosis on the Australian Cerebral Palsy Register (ACPR)for the given level of the characteristic over odds of CP diagnosis on ACPR in the reference level. [a]*p*-value from Fisher's exact test. [b]Missing data for for the Bayley Scales of Infant Development (2nd edition) Psychomotor Developmental Index (BSID-II PDI) owing to distance/unavailability of assessment (*n*=1). [c]Missing data for BSID-II PDI because child considered untestable owing to severe disability (*n*=3) or behavioural problem (*n*=26), distance/unavailability of assessment (*n*=39), and parental refusal (*n*=7). [d]Corresponds to the relative change in odds associated with a one-unit increase in the PDI corrected score. ACTOMgSO_4, Australasian Collaborative Trial of Magnesium Sulphate; SD, standard deviation.

Appendix 5: Supporting information for Chapter 5 publication

S1 Appendix. Forest plots and funnel plots for comparisons 1-8

Forest plots from randomised controlled trials

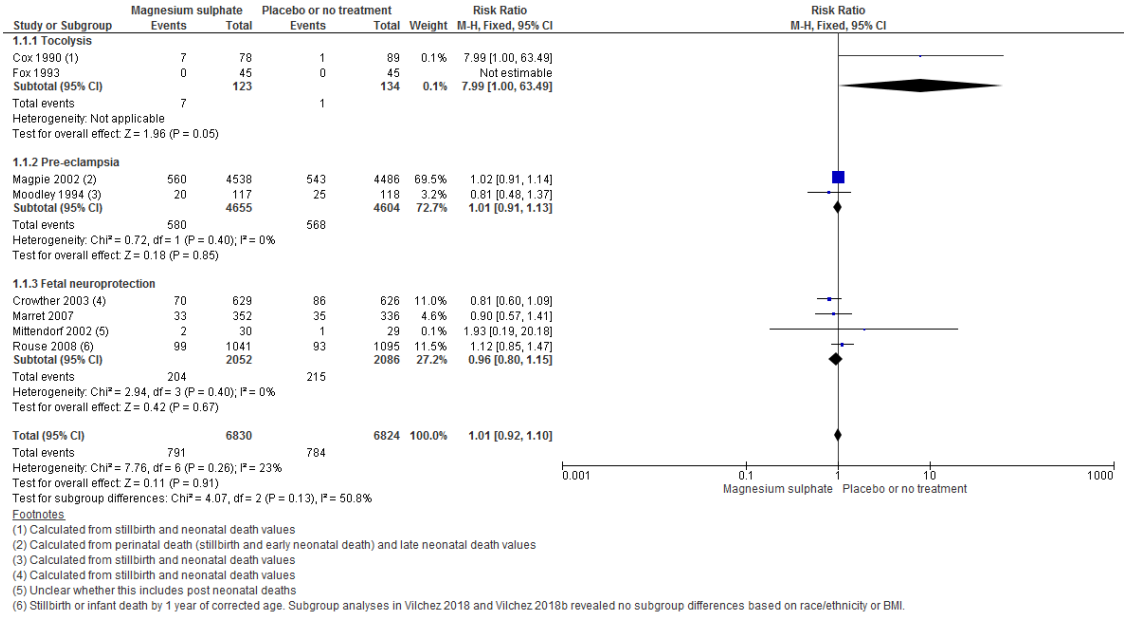


Figure 1. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.1 Perinatal death

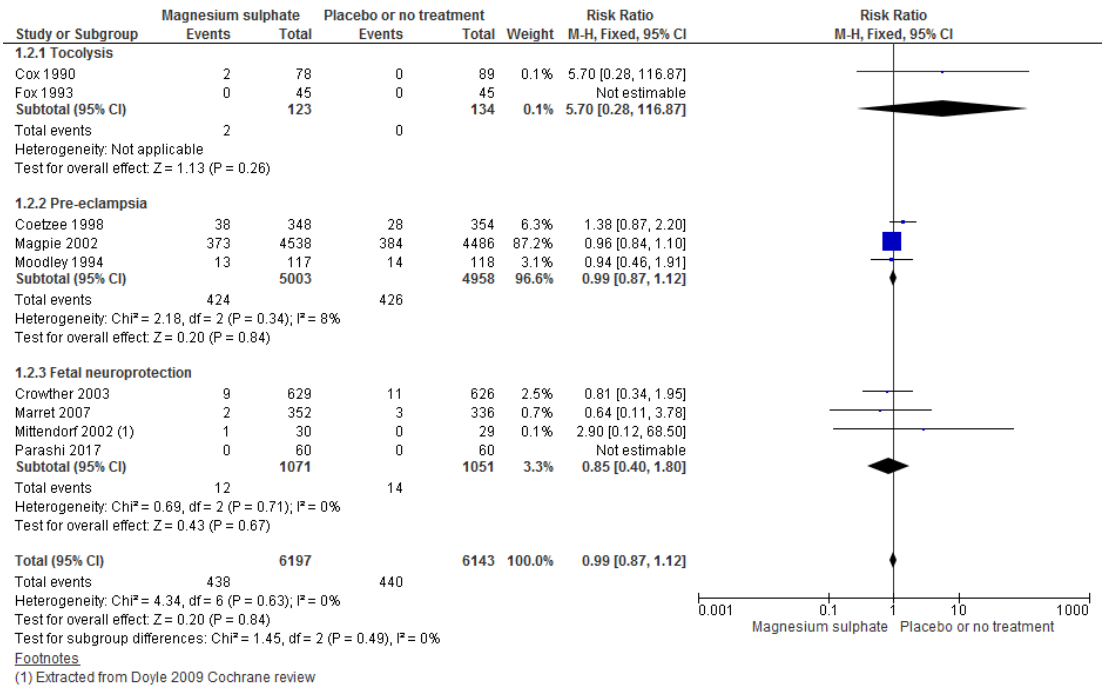


Figure 2. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.2 Stillbirth

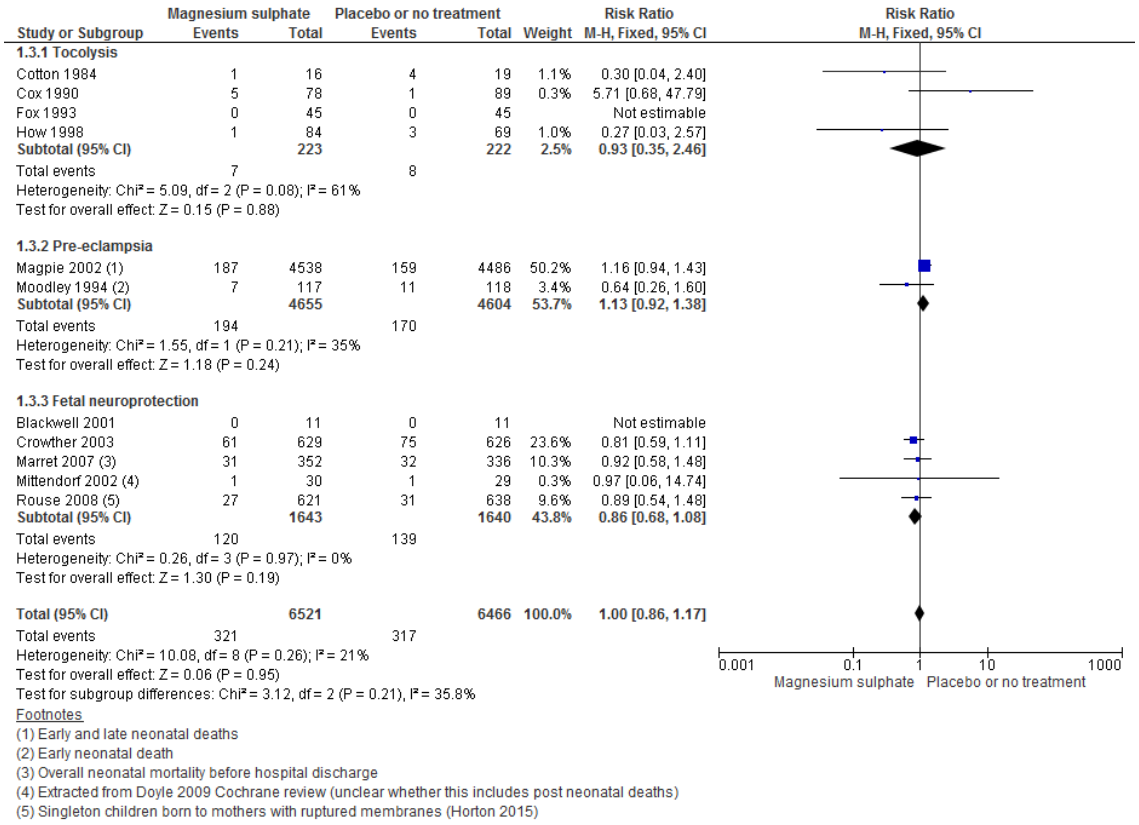


Figure 3.1. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.3 Neonatal death

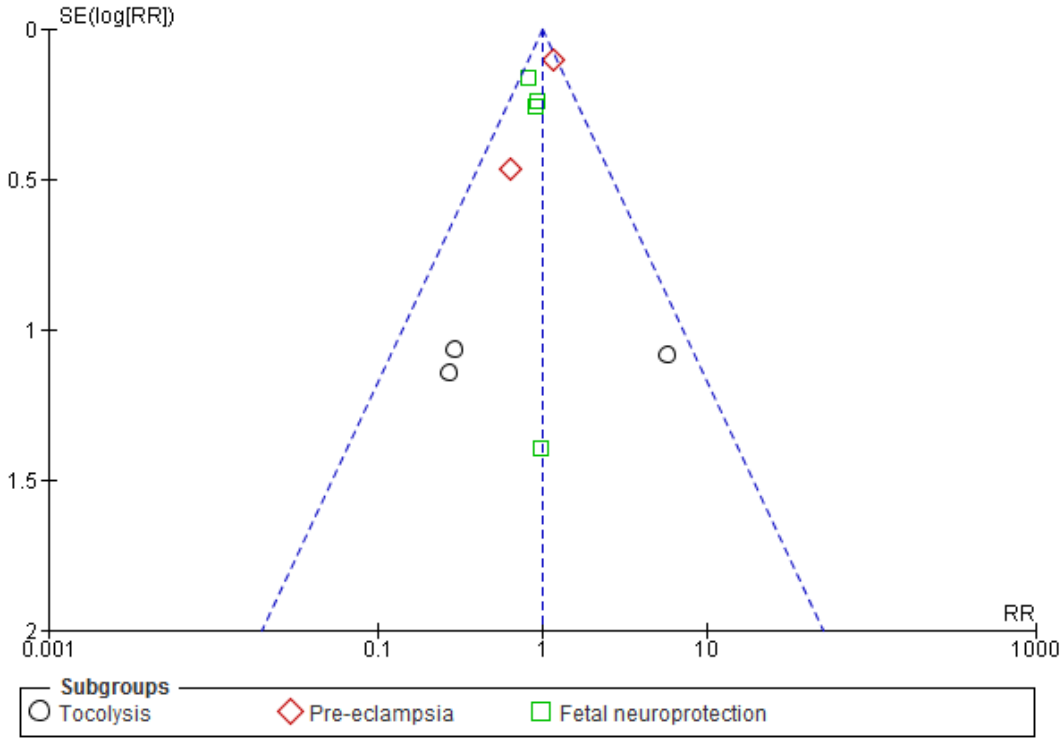


Figure 3.2. Funnel plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.3 Neonatal death

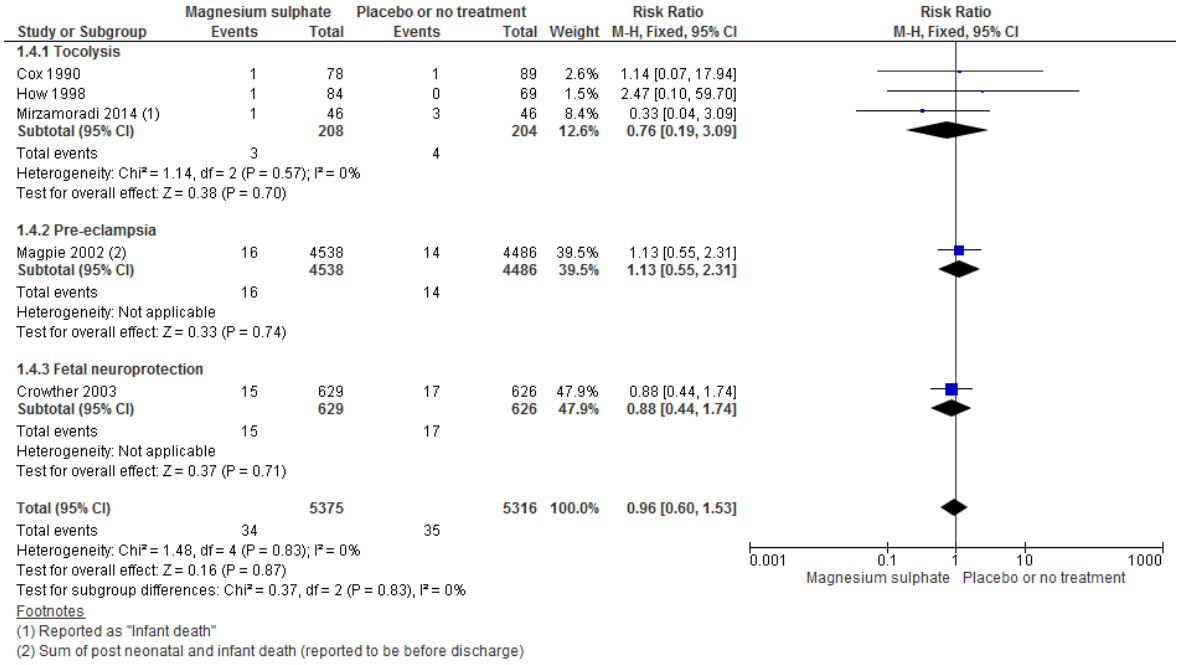


Figure 4. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.4 Death > 28 days, before discharge

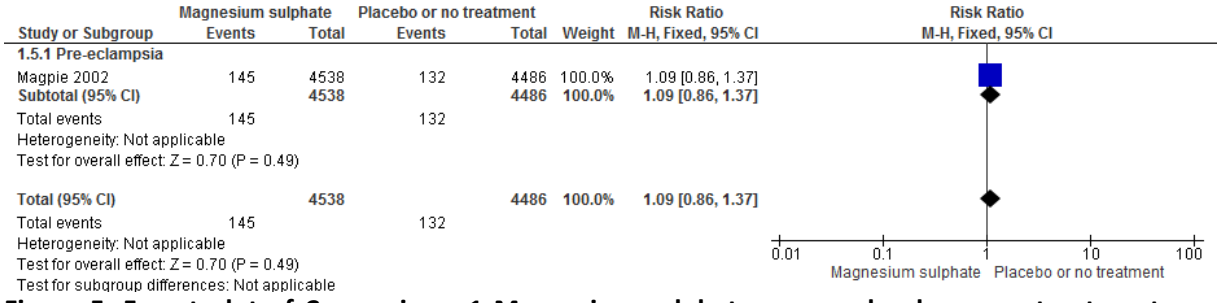


Figure 5. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.5 Early neonatal death

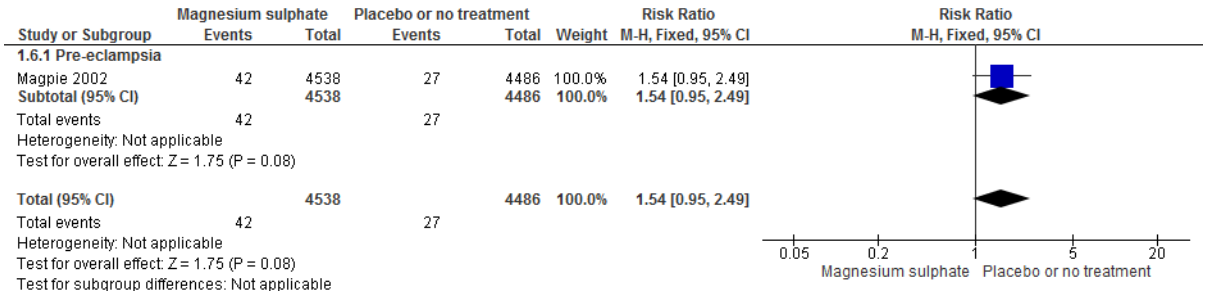


Figure 6. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.6 Late neonatal death

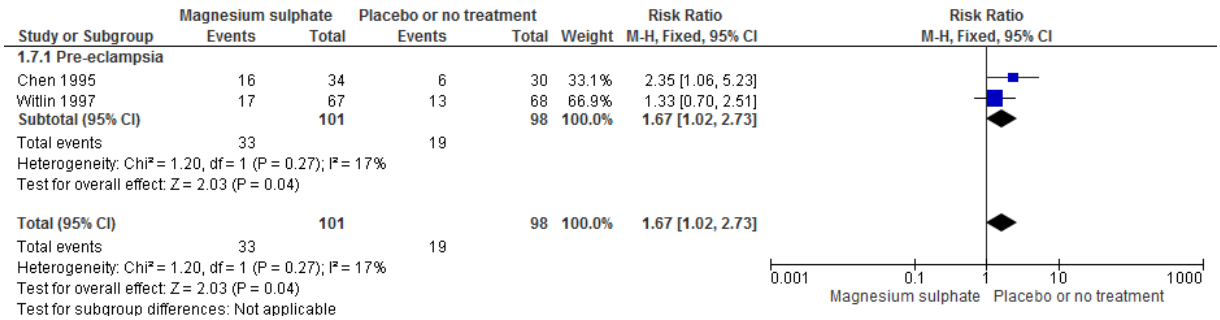


Figure 7. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.7 Apgar score < 7 at 1 minute

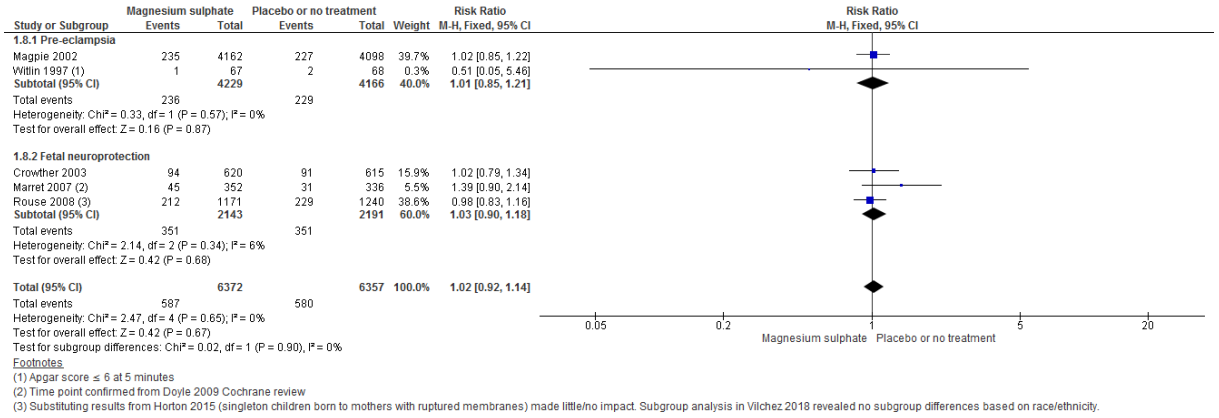


Figure 8. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.8 Apgar score < 7 at 5 minutes

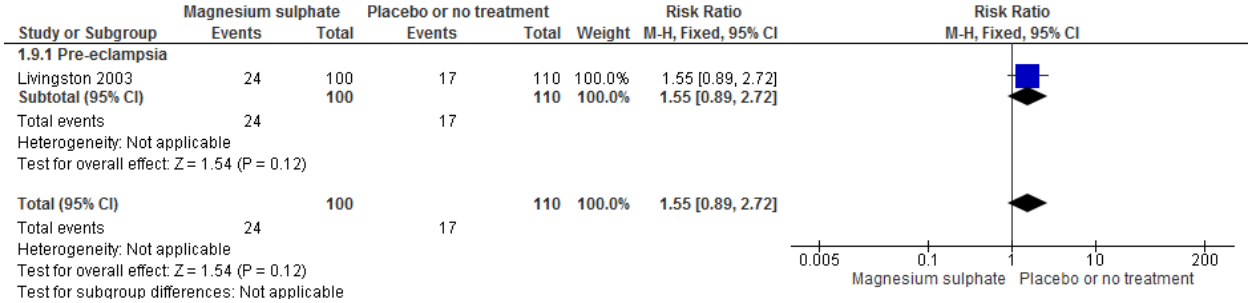


Figure 9. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.9 Meconium at delivery

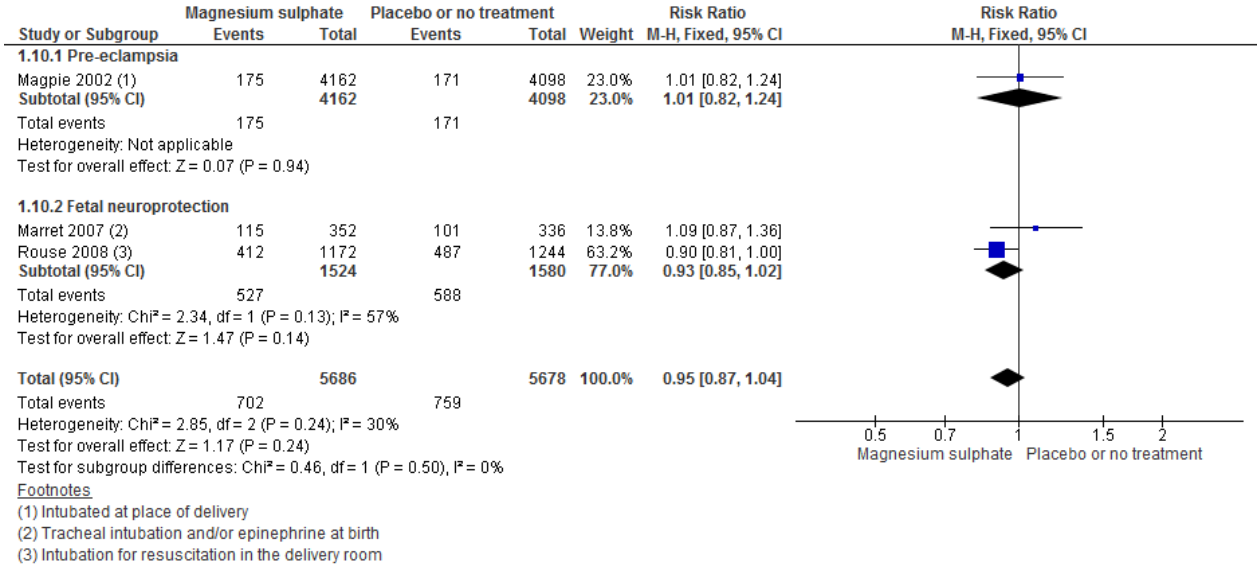


Figure 10. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.10 Intubated at birth

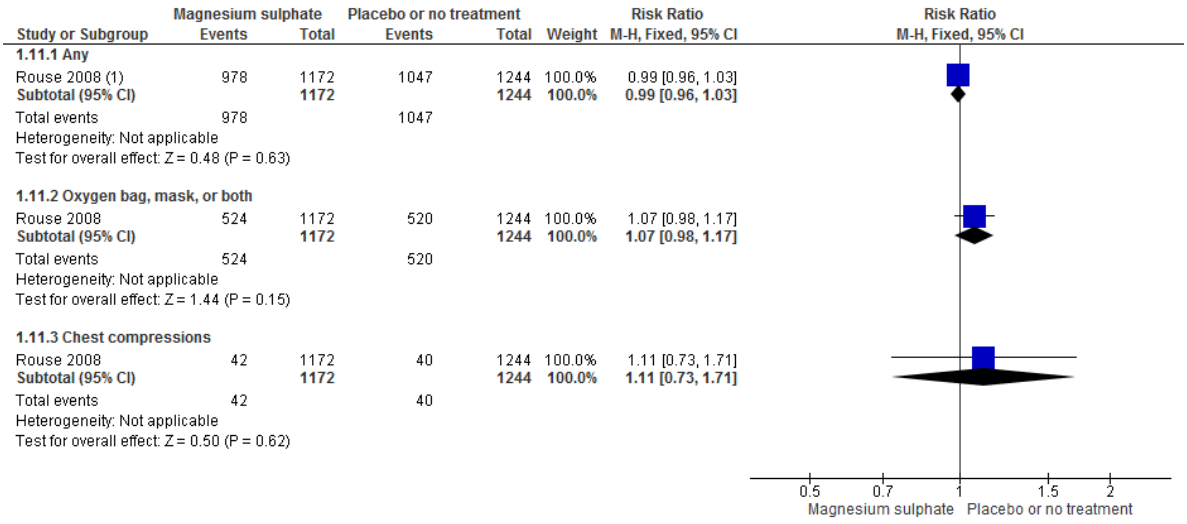


Figure 11. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.11 Resuscitation in the delivery room

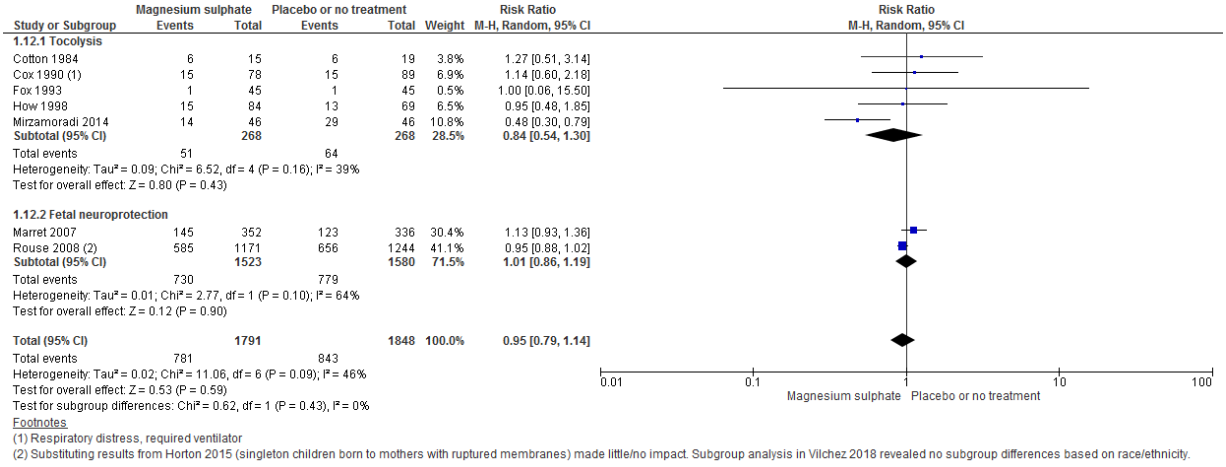


Figure 12. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.12 Respiratory distress syndrome

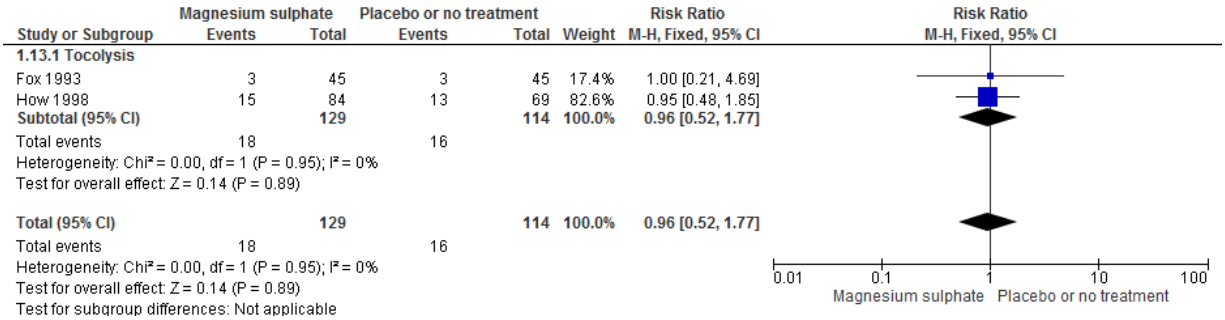


Figure 13. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.13 Transient tachypnoea of the newborn

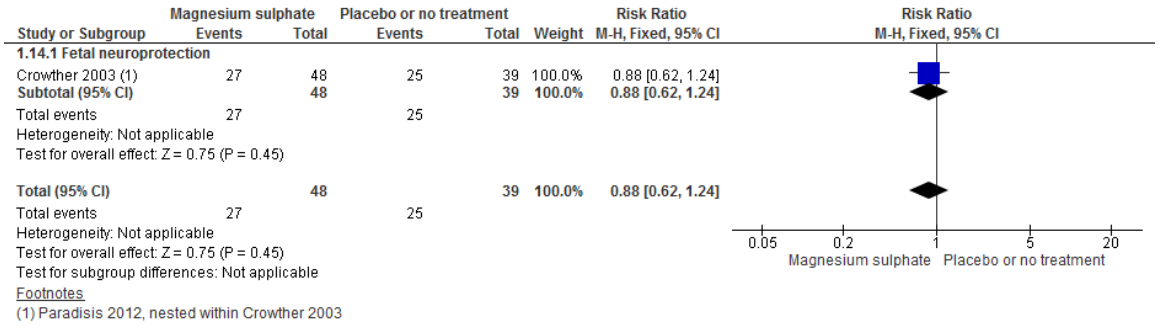


Figure 14. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.14 Surfactant

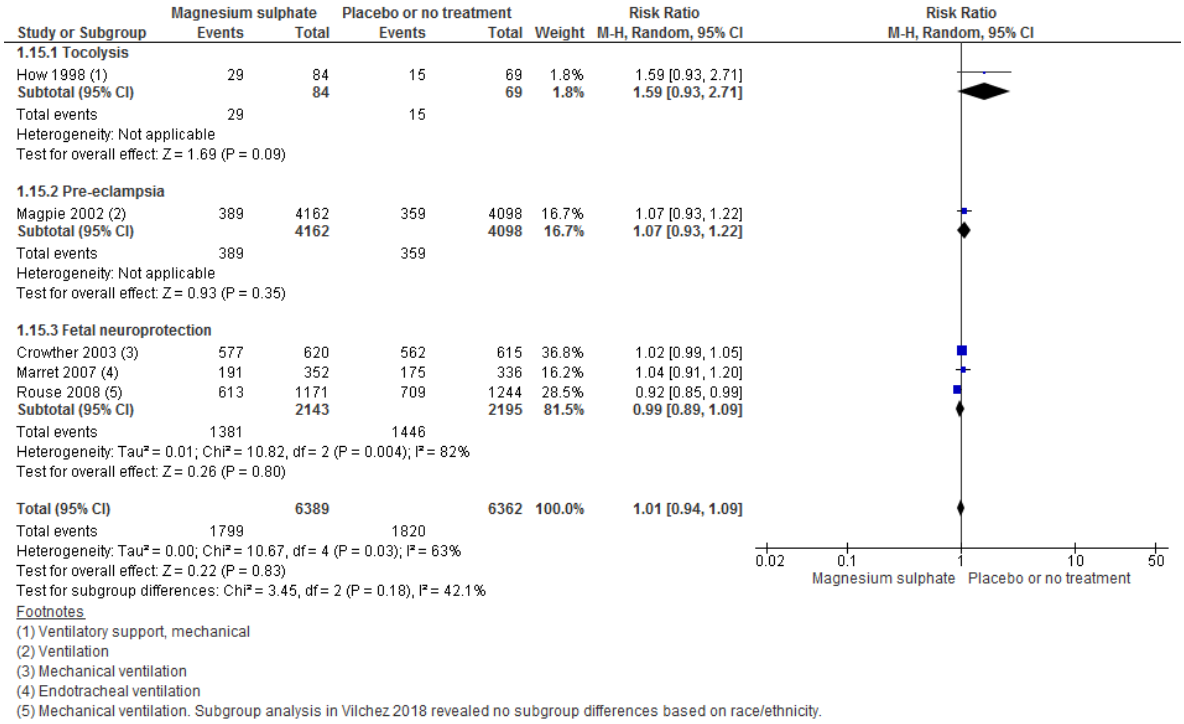


Figure 15. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.15 Mechanical ventilation

**Additional data reported by How 1998: ventilatory support (magnesium sulphate group (84 babies) median: 2.5 days (interquartile range: 11; range: 0.04 to 81) versus no treatment group (69 babies) median: 5 days (interquartile range: 7; range 0.5 to 383; "P = not significant"). A further trial reported that "The average number of days with the use of the ventilator… were similar in the two groups" (Fox 1993), however did not provide data suitable for inclusion in a meta-analysis.*

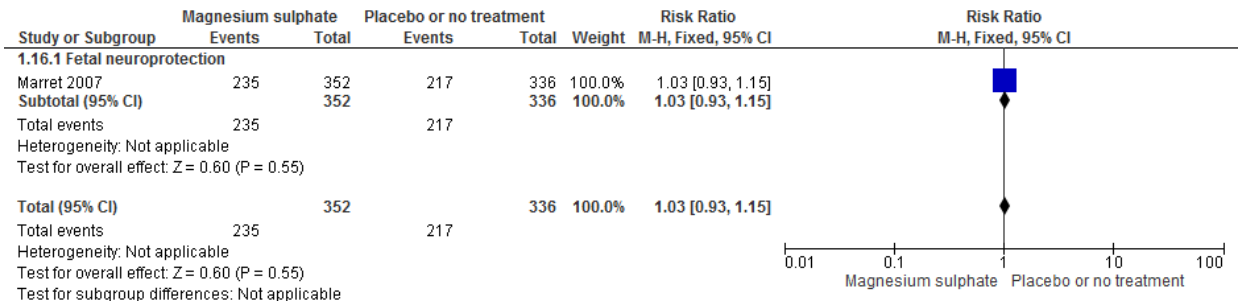


Figure 16. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.16 Non-invasive ventilation

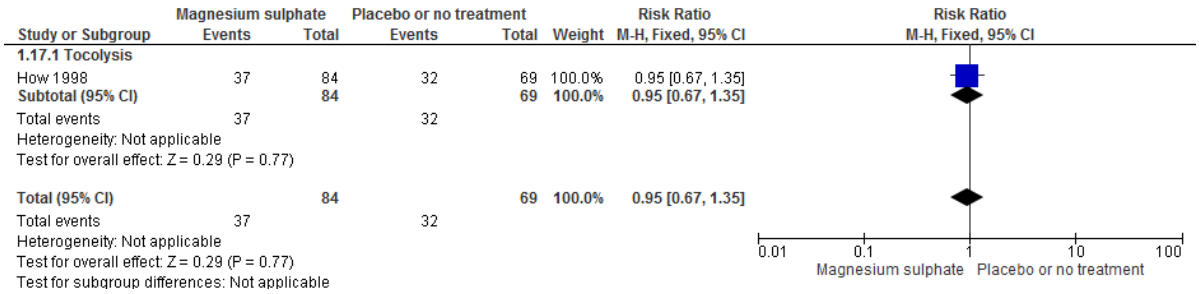


Figure 17. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.17 Oxygen required*

**Additional data reported by How 1998: oxygen required (magnesium sulphate group (84 babies) median: 4 days (interquartile range: 27; range: 0.04 to 95) versus no treatment group (69 babies) median: 5.5 days (interquartile range: 15.8; range 0.2 to 383; "P = not significant")*

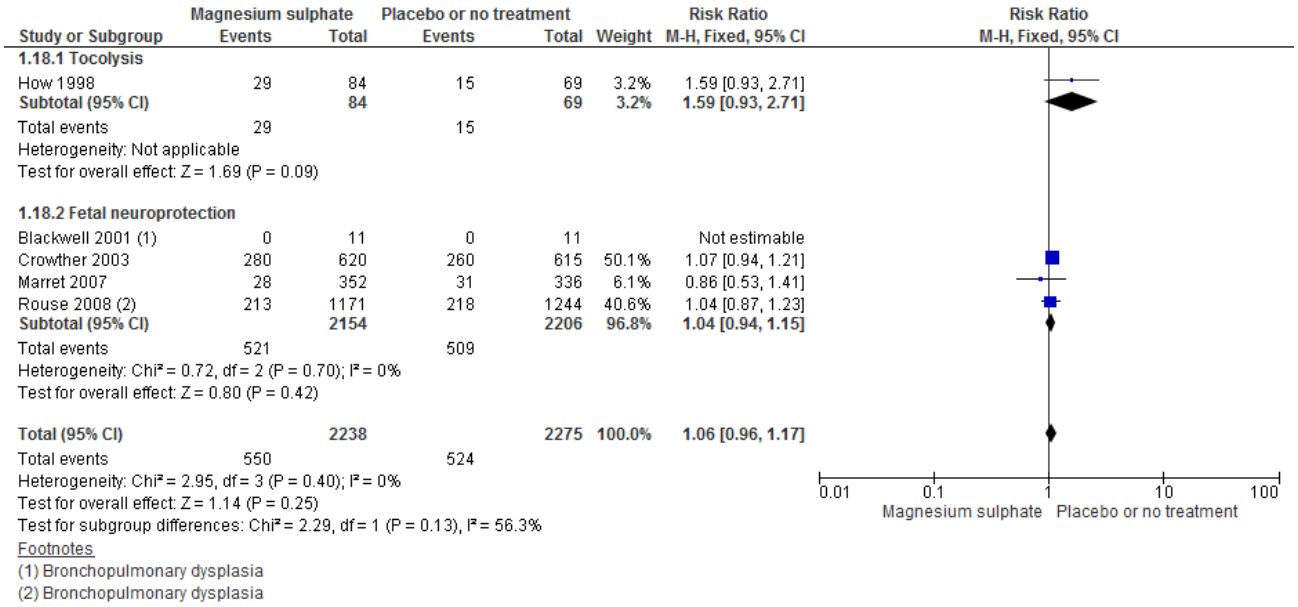


Figure 18. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.18 Chronic lung disease

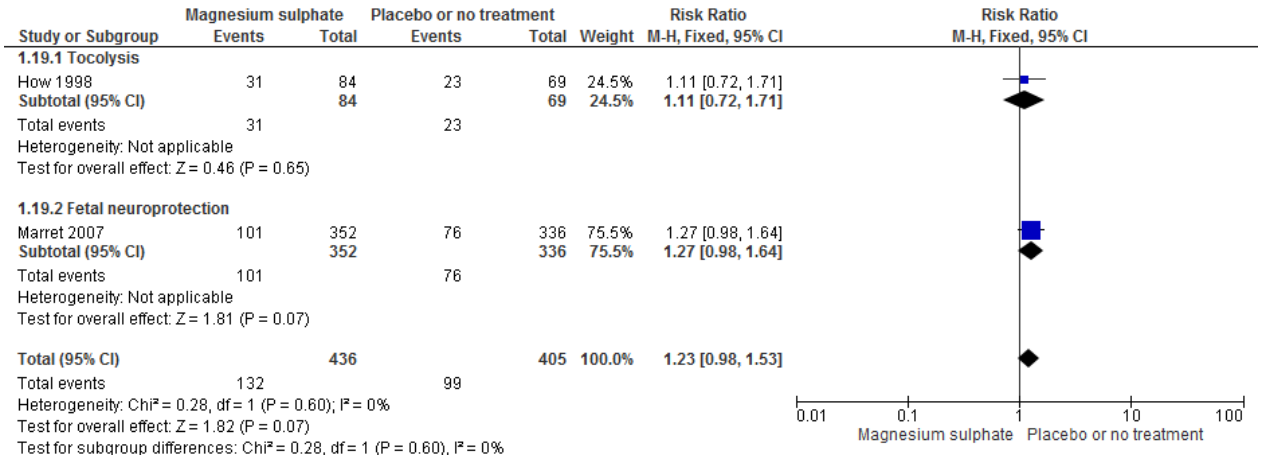


Figure 19. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.19 Apnoea and bradycardia

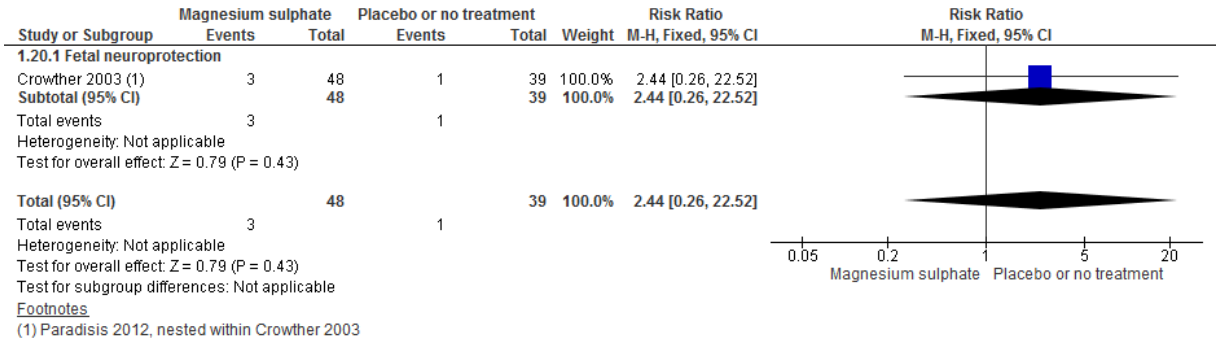


Figure 20. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.20 Pneumothorax

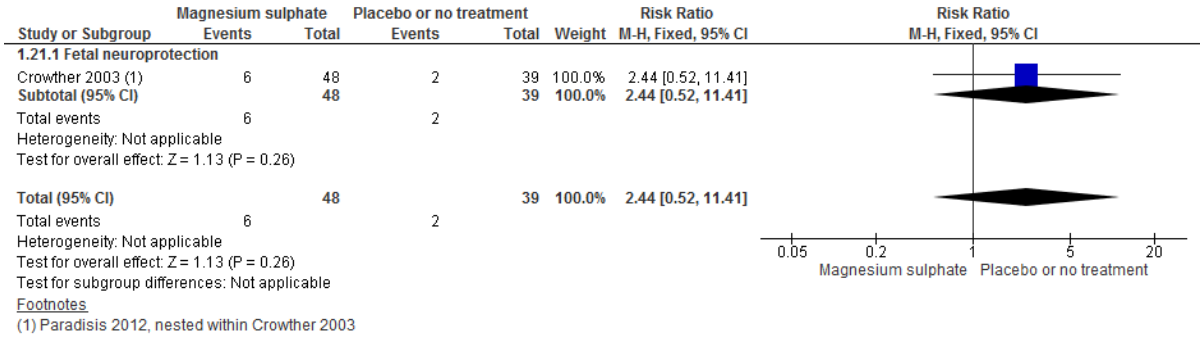


Figure 21. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.21 Pulmonary haemorrhage

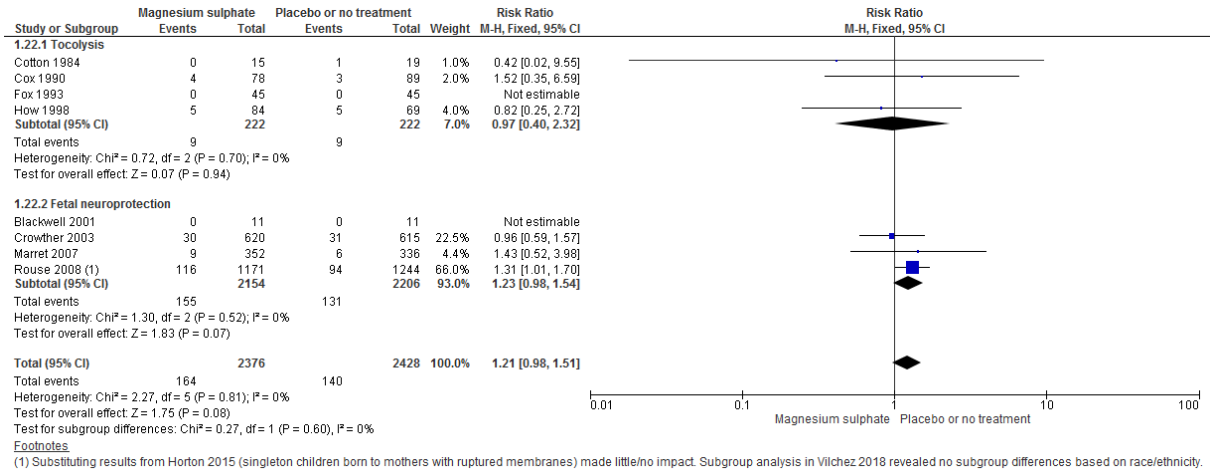


Figure 22. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.22 Necrotising enterocolitis

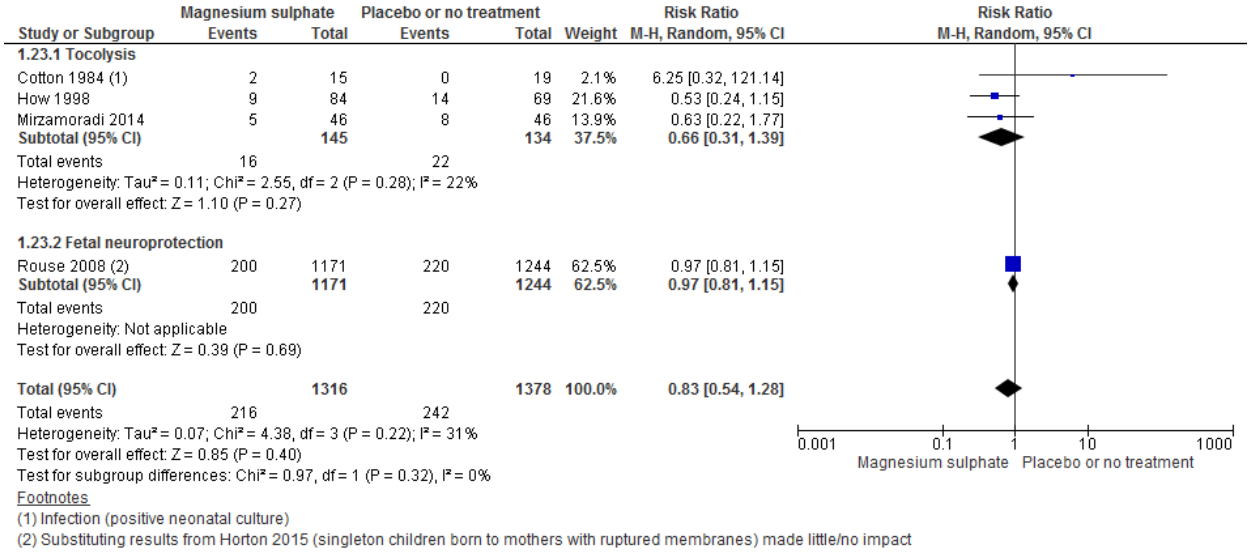


Figure 23. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.23 Sepsis

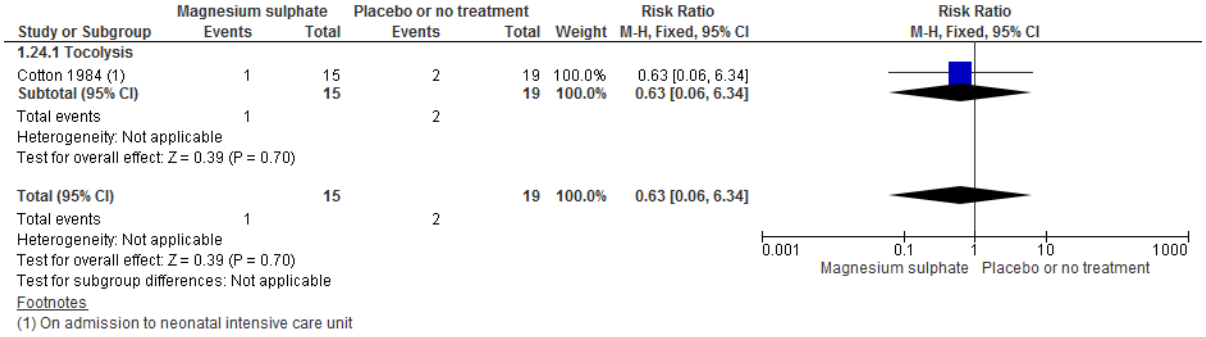


Figure 24. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.24 Hypoglycaemia on neonatal intensive care unit admission

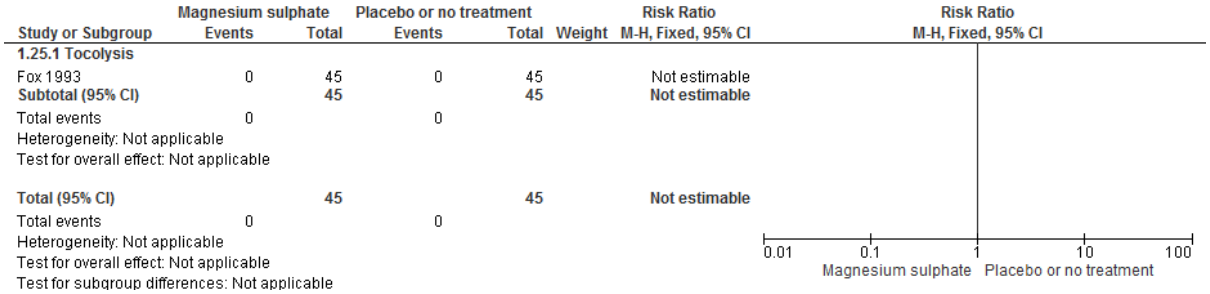


Figure 25. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.25 Poor feeding

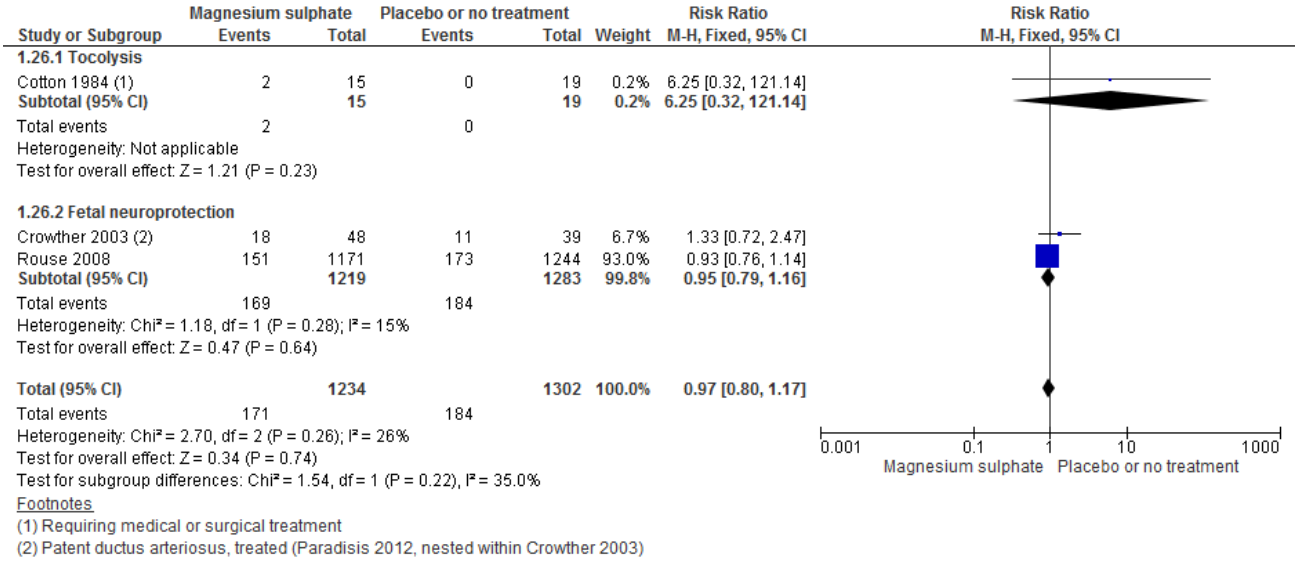


Figure 26. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.26 Patent ductus arteriosus

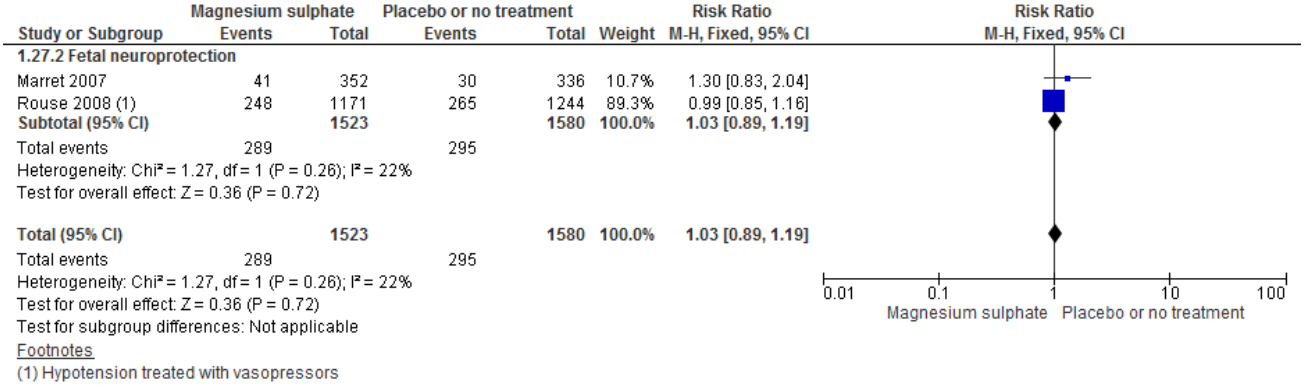


Figure 27. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.27 Hypotension

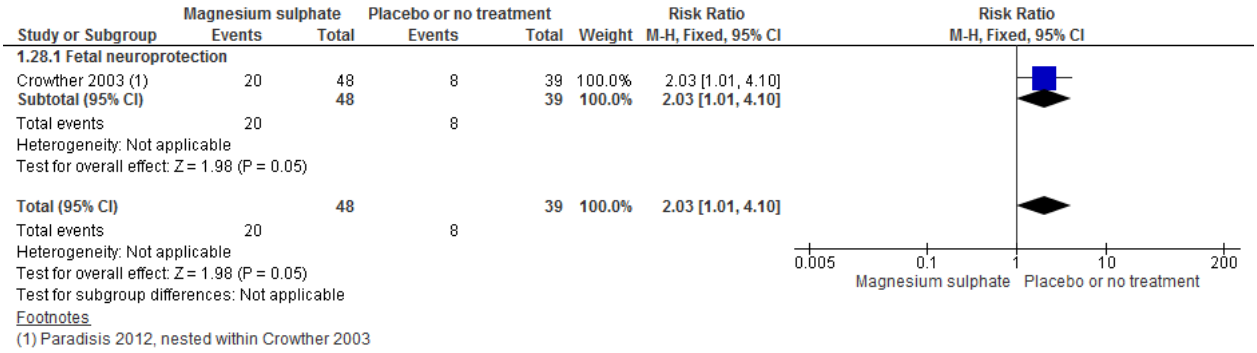


Figure 28. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.28 Volume expansion

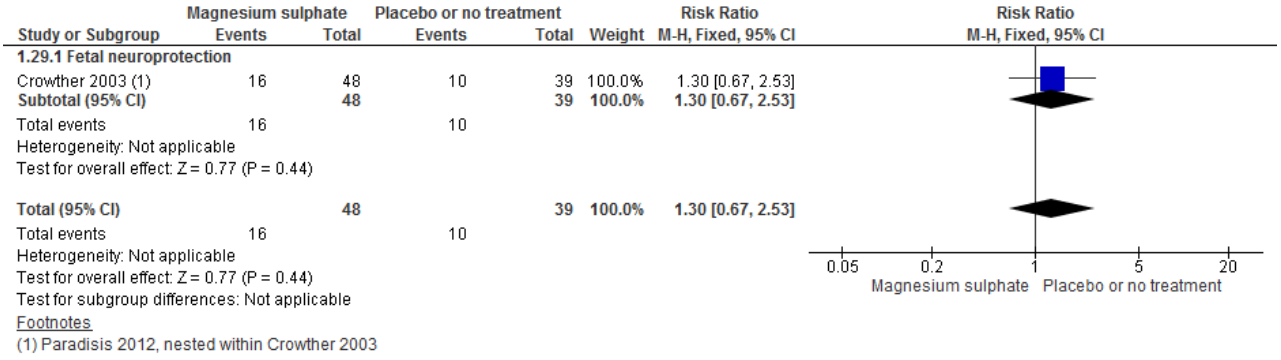


Figure 29. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.29 Mean blood pressure < 10th centile in first 24 hours

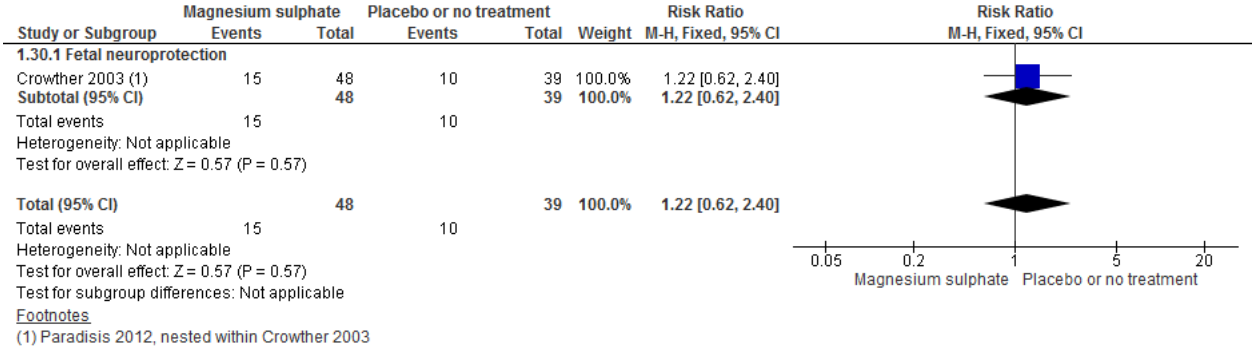


Figure 30. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.30 Superior vena cava flow (< 41 mL/kg/min) in first 24 hours

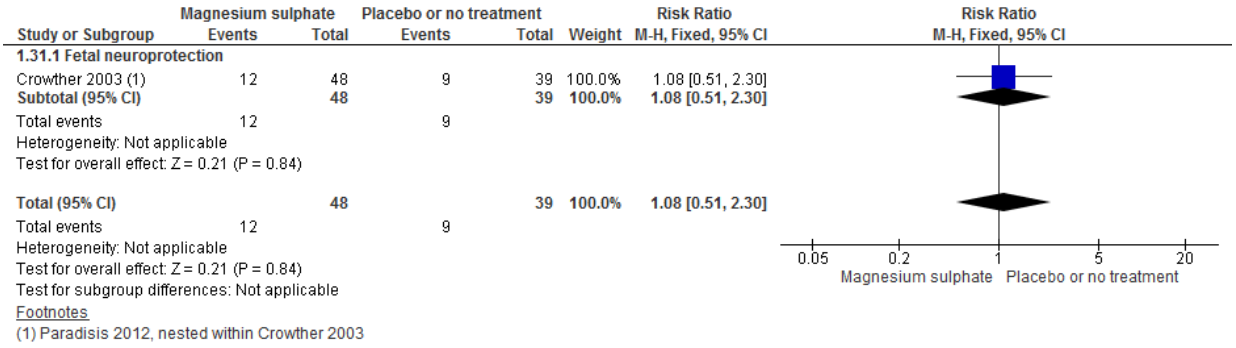


Figure 31 Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.31 Right ventricular output (< 120 mL/kg/min) in first 24 hours

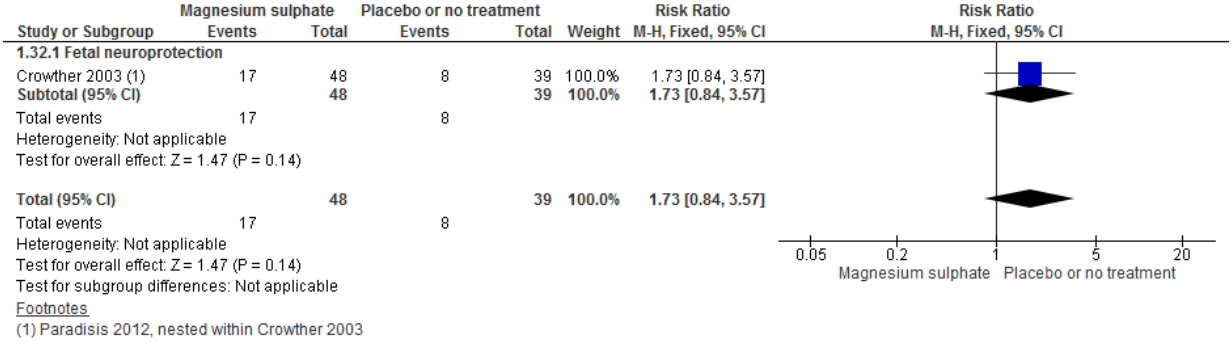


Figure 32 Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.32 Dobutamine

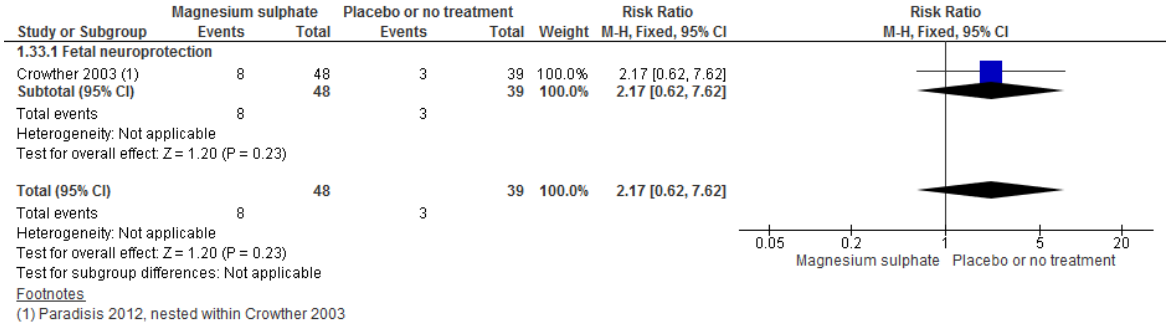


Figure 33 Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.33 Dopamine

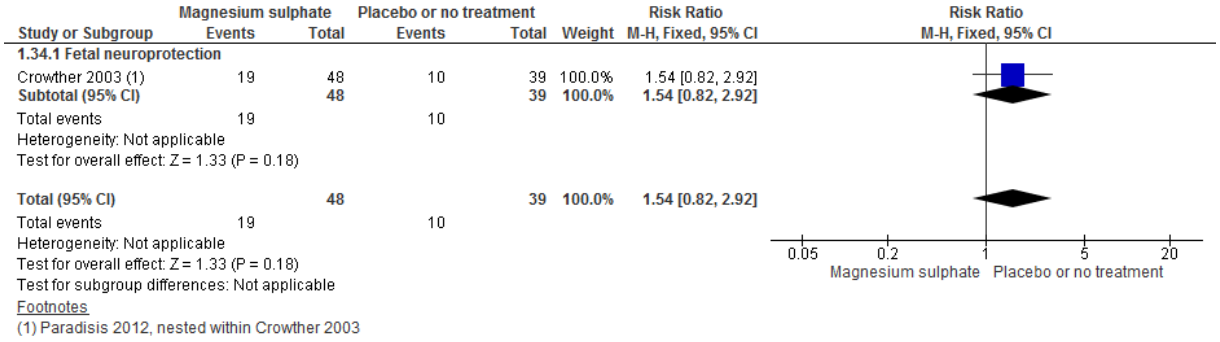


Figure 34 Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.34 Any inotrope

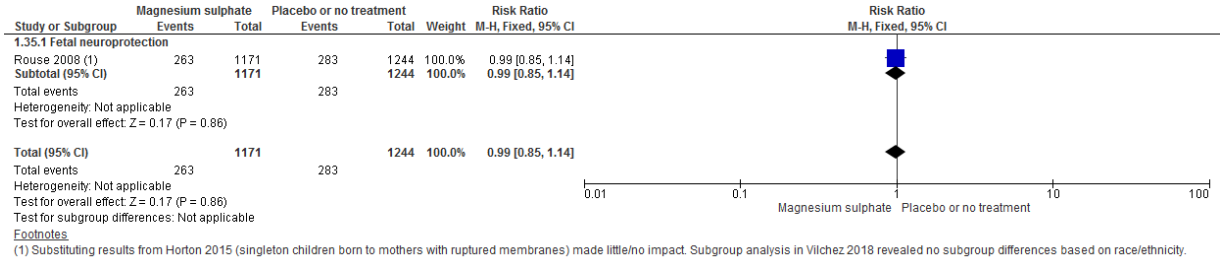


Figure 35 Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.35 Retinopathy of prematurity

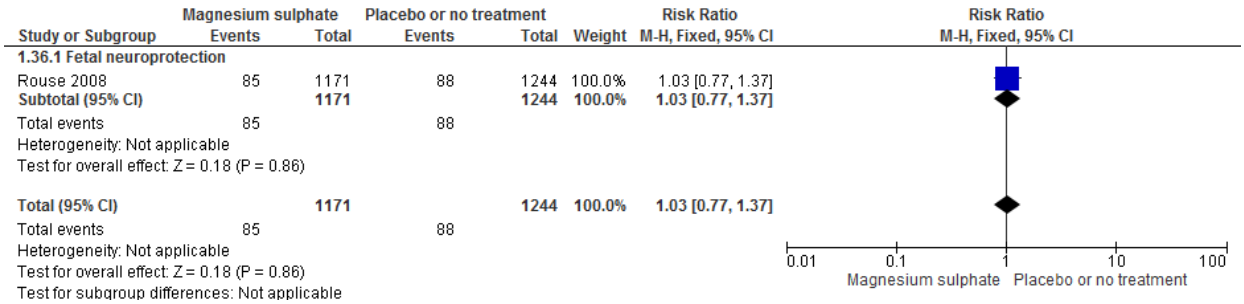


Figure 36 Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.36 Generalised hypotonicity

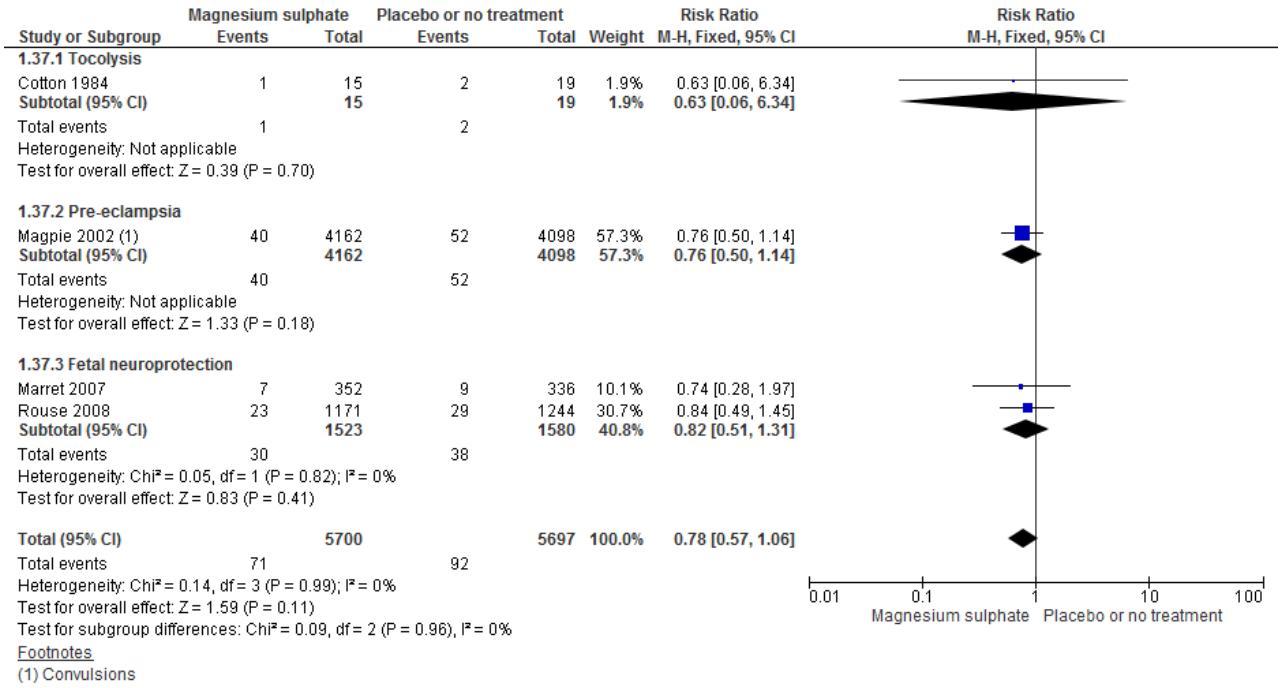


Figure 37. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.37 Seizures

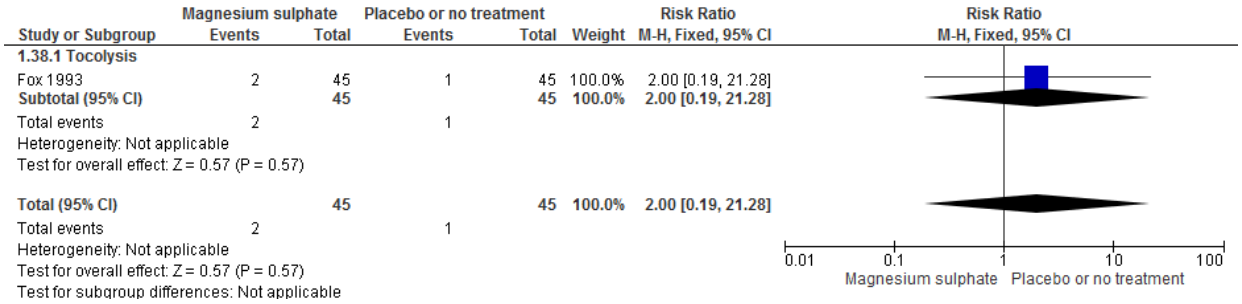


Figure 38. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.38 Hyperbilirubinaemia

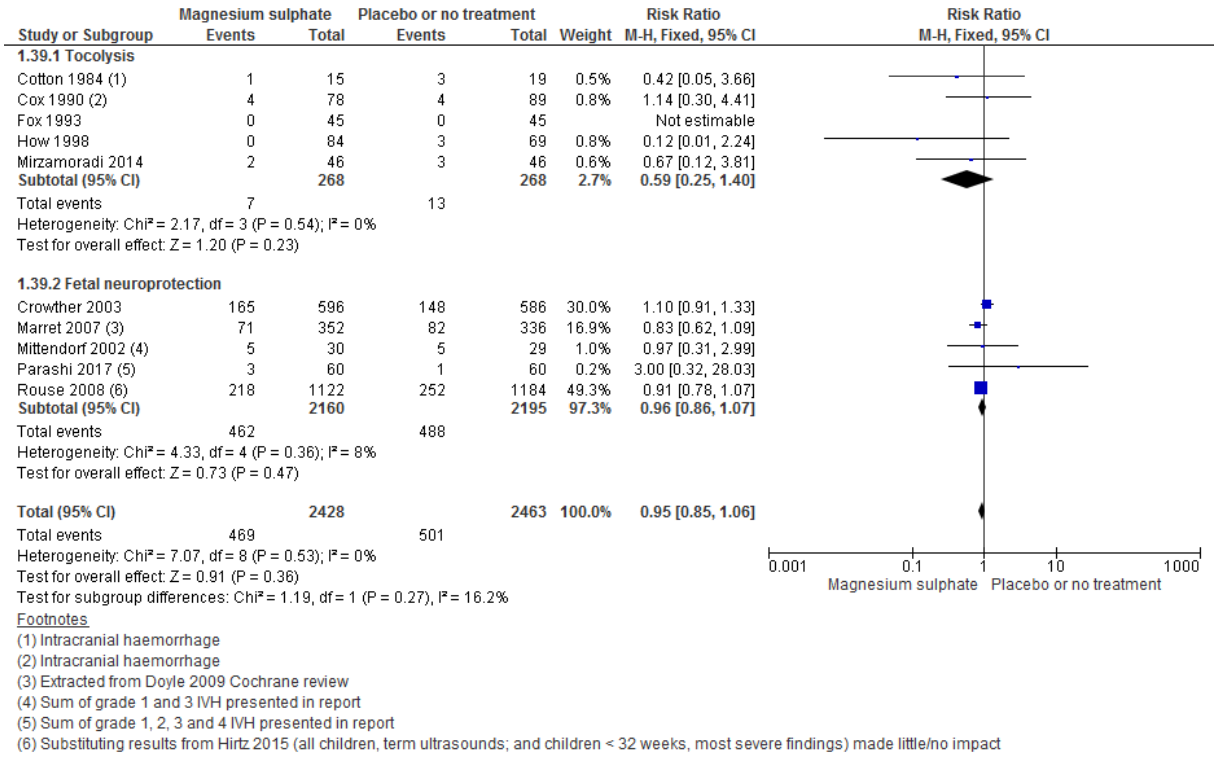


Figure 39.1. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.39 Intraventricular haemorrhage

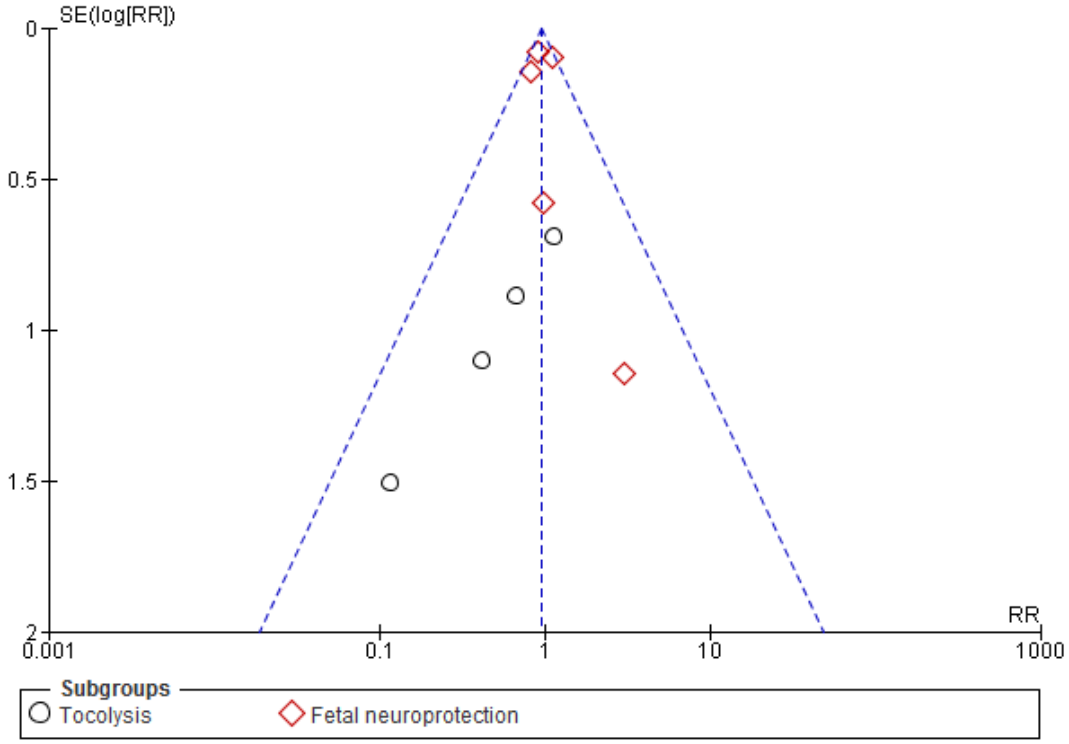


Figure 39.2. Funnel plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.39 Intraventricular haemorrhage

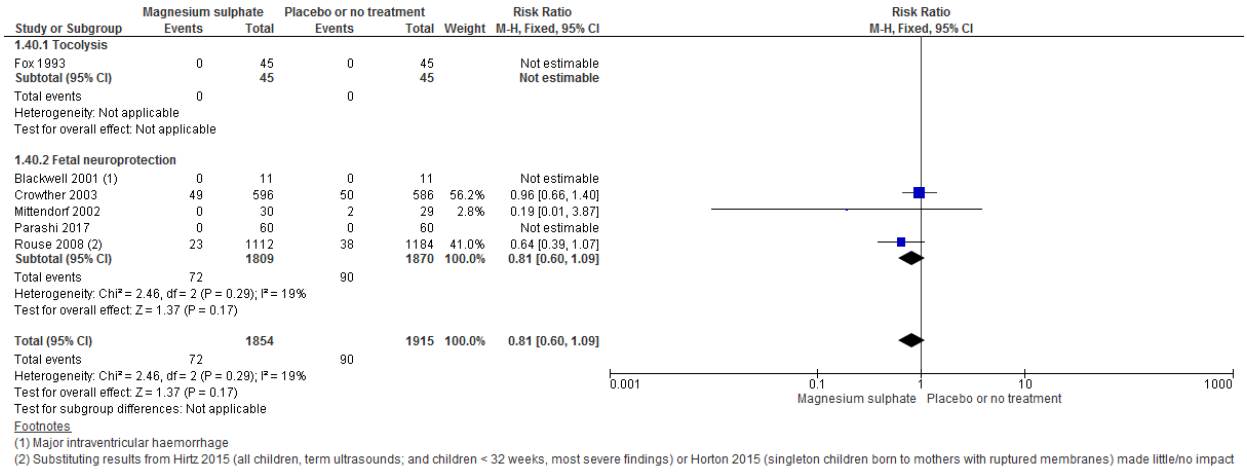


Figure 40. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.40 Intraventricular haemorrhage, grade III/IV

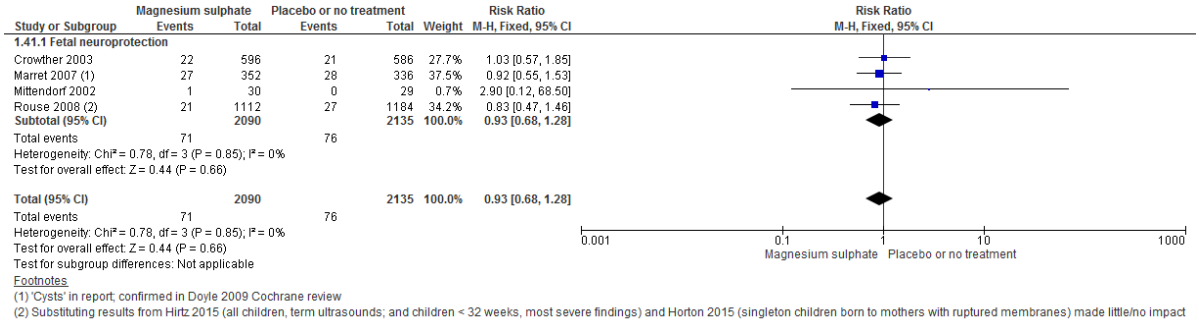


Figure 41. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.41 Periventricular leucomalacia

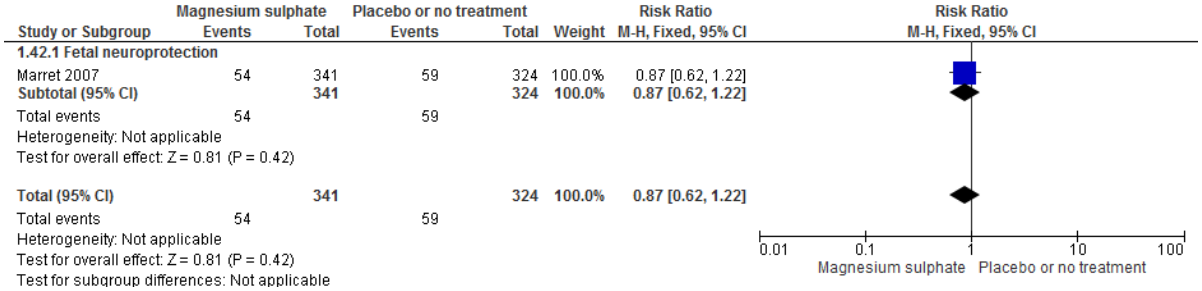


Figure 42. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.42 Any white matter injury

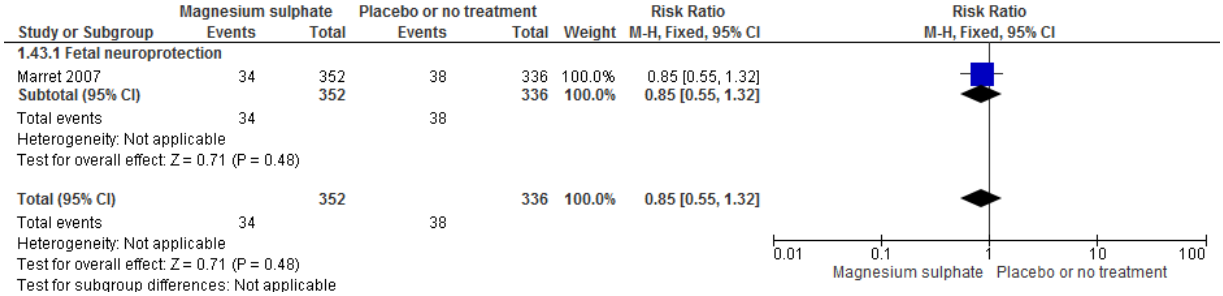


Figure 43. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.43 Severe white matter injury

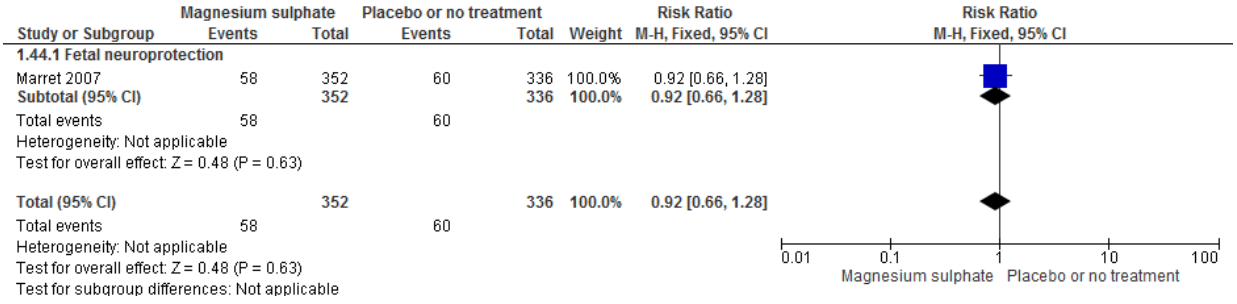


Figure 44. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.44 Severe white matter injury or death

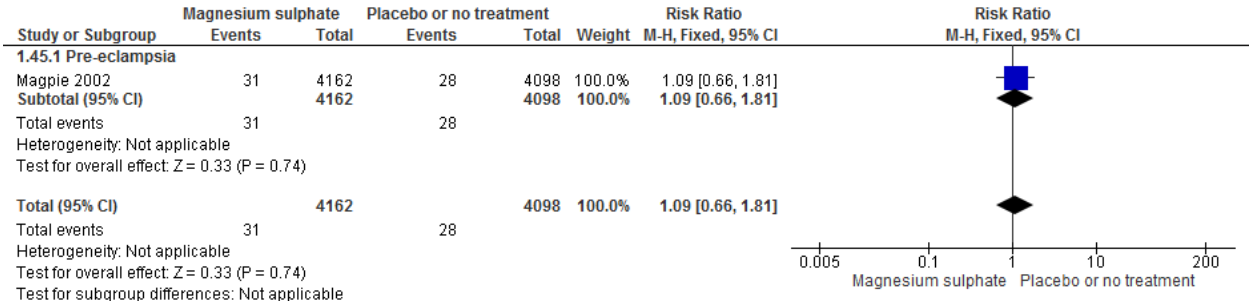


Figure 45. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.45 Persistent parenchymal echogenicity

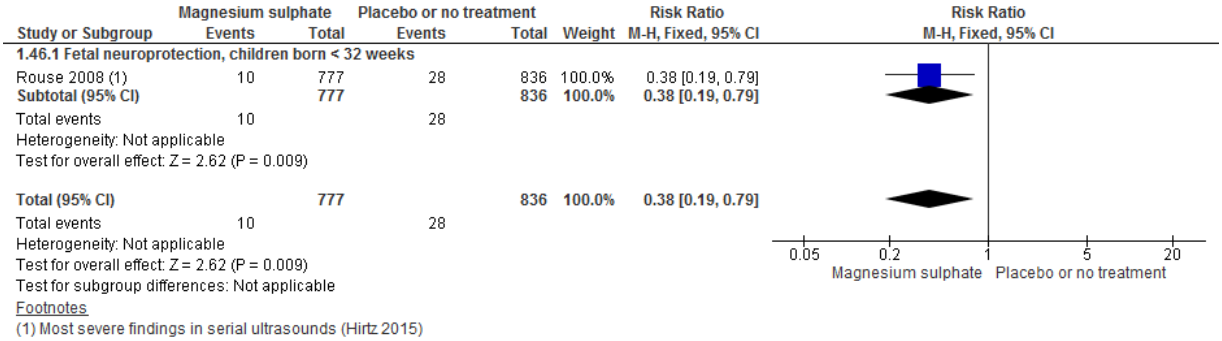


Figure 46. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.46 Echodensity

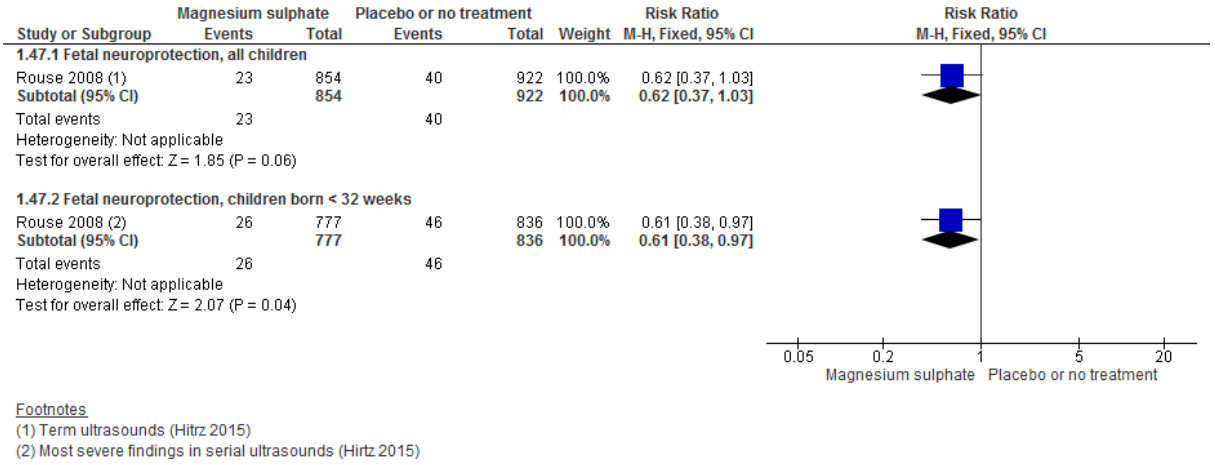


Figure 47. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.47 Echolucency

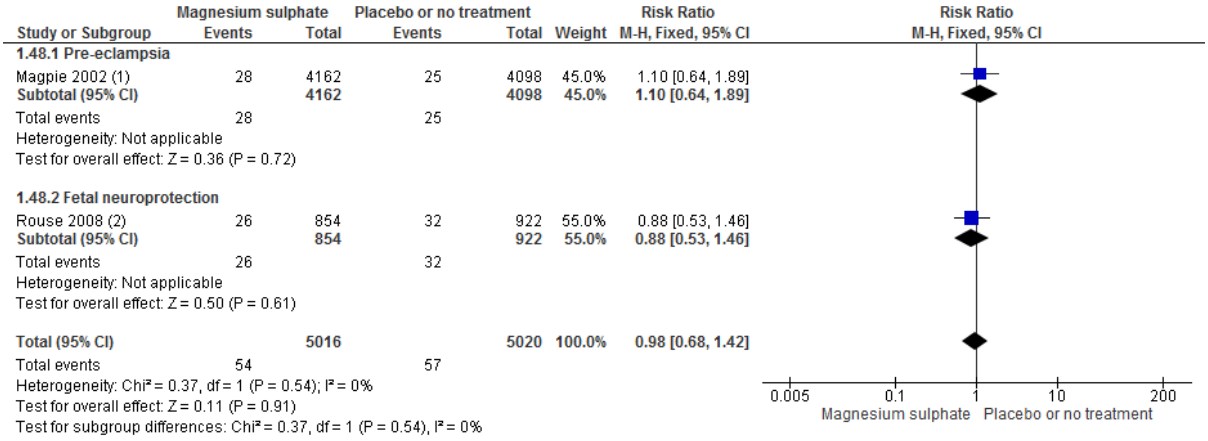


Figure 48. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.48 Ventriculomegaly

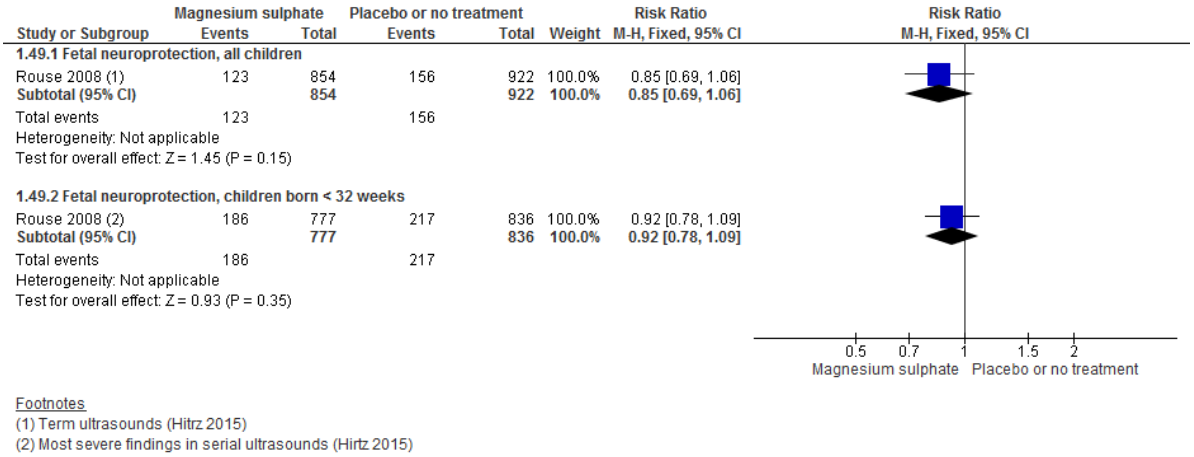


Figure 49. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.49 Any of echodensity, echolucency, intraventricular haemorrhage, periventricular haemorrhage, ventriculomegaly

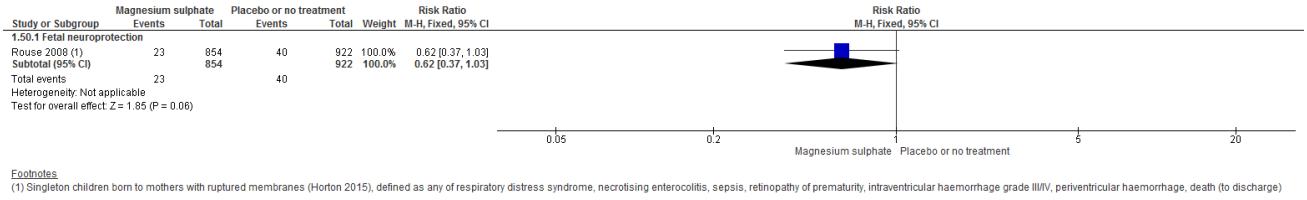


Figure 50. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.50 Composite adverse outcome

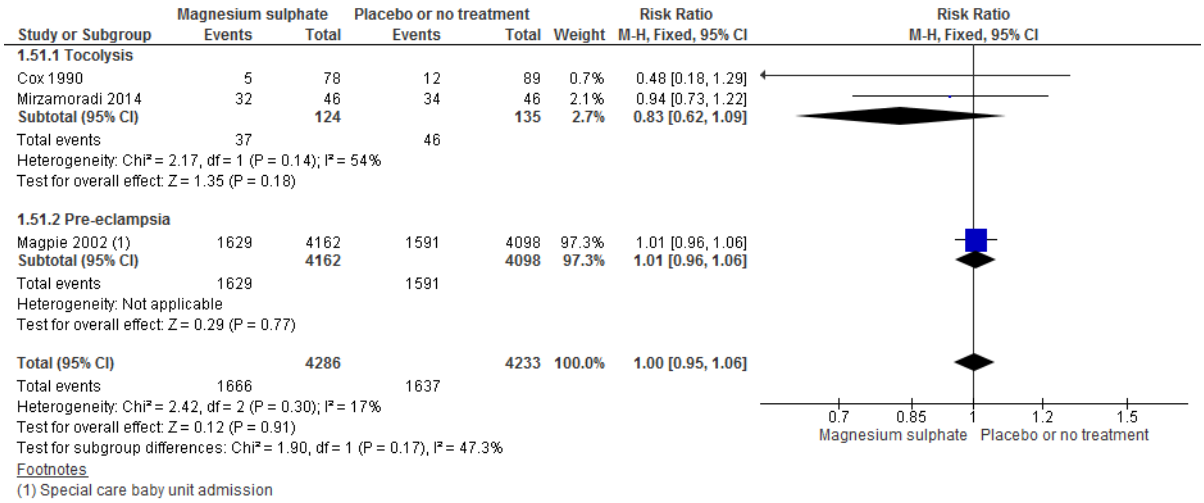


Figure 51. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.51 Neonatal intensive care unit admission*

****Two trials reported that "There were no differences between groups in… admissions to the NICU," (Colon 2015) and "The average… newborn intensive care time for infants who did have complications were similar in the two groups" (Fox 1993), however did not provide data suitable for inclusion in a meta-analysis.***

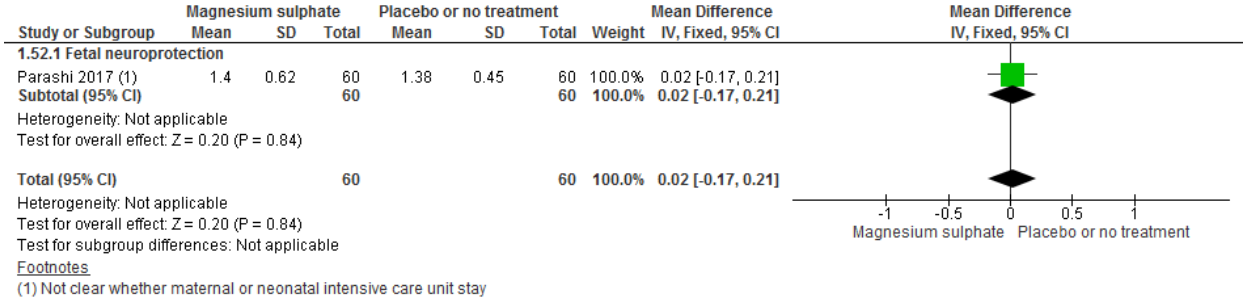


Figure 52. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.52 Intensive care unit stay (days)*

**Two trials reported the data in a format not suitable for meta-analysis, and similarly, did not see a clear difference between groups (magnesium sulphate group (620 babies): median: 76 days (range: 61 to 94) versus placebo group (615 babies) median: 74 days (range: 59 to 95); P = 0.66 (Crowther 2003); (magnesium sulphate group (84 babies) median: 29 days (interquartile range: 28; range: 2 to 204) versus no treatment group (69 babies) median: 28 days (interquartile range: 22; range 2 to 383; "P = not significant") (How 1998).*

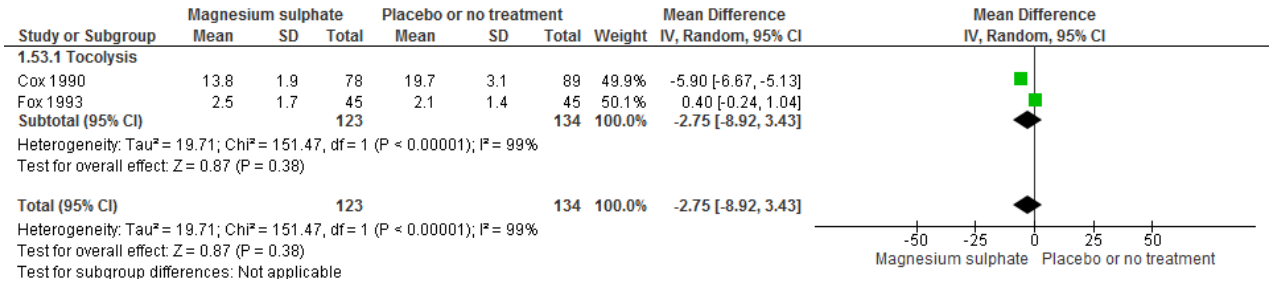


Figure 53. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.53 Hospital stay (days)

Figure 54. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.54 Special care baby unit admission > 7 days or death

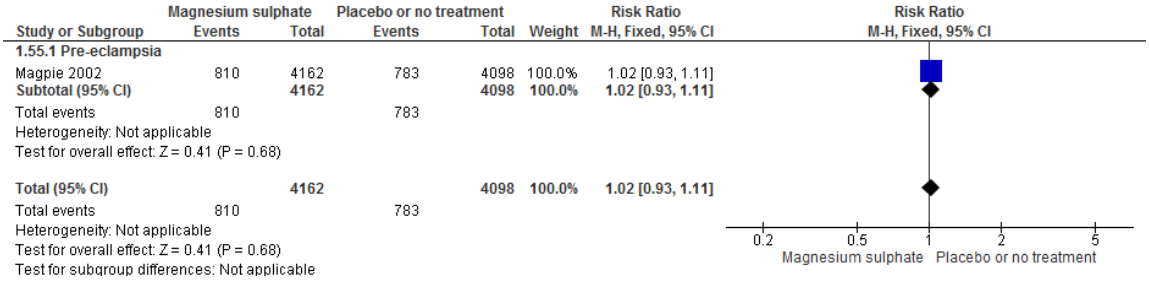


Figure 55. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.55 Special care baby unit admission > 7 days

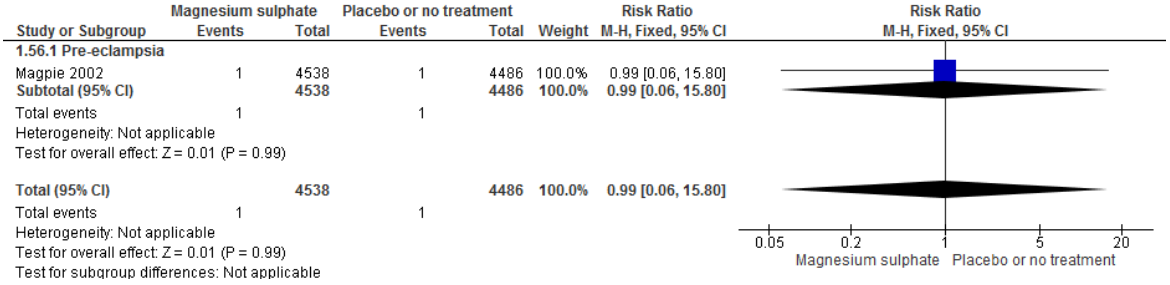


Figure 56. Forest plot of Comparison: 1 Magnesium sulphate versus placebo or no treatment, outcome: 1.56 Still in hospital at 6 weeks

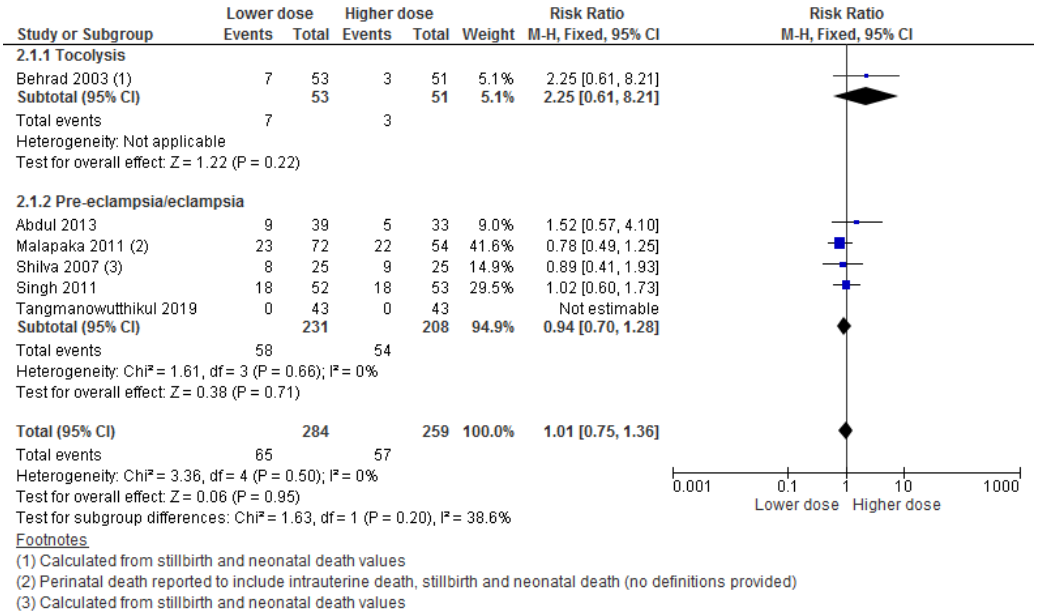


Figure 57. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.1 Perinatal death*

** One trial reported that "The neonatal outcome was similar in both the groups (p=0.911)" (Agrawal 2015); however did not provide data for inclusion in a meta-analysis.*

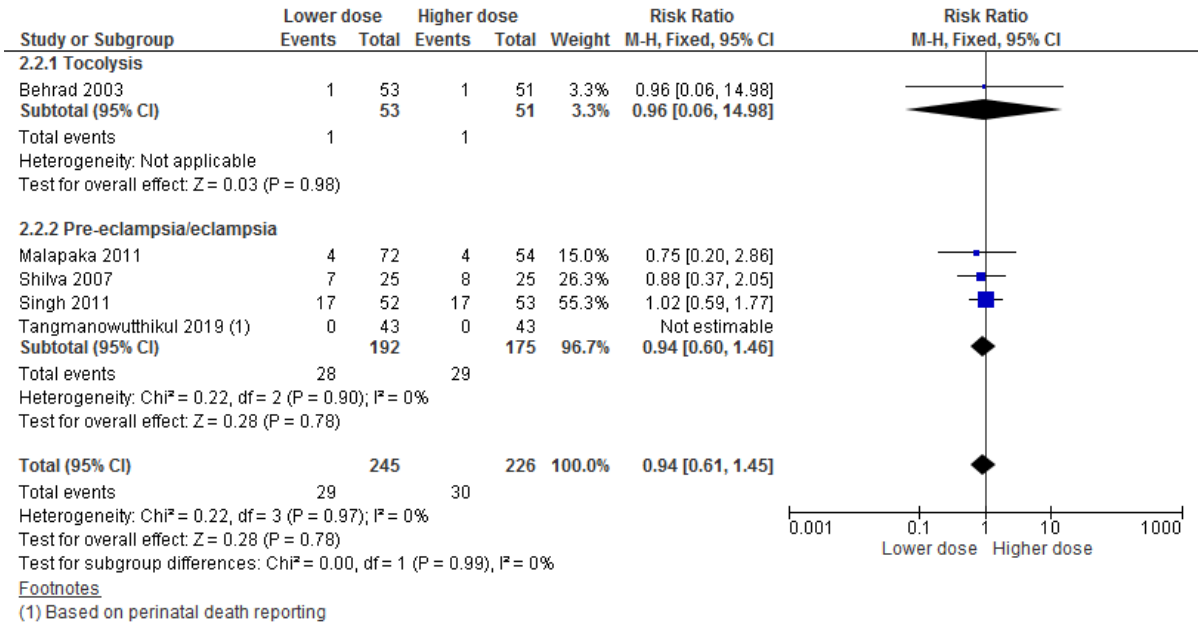


Figure 58. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.2 Stillbirth

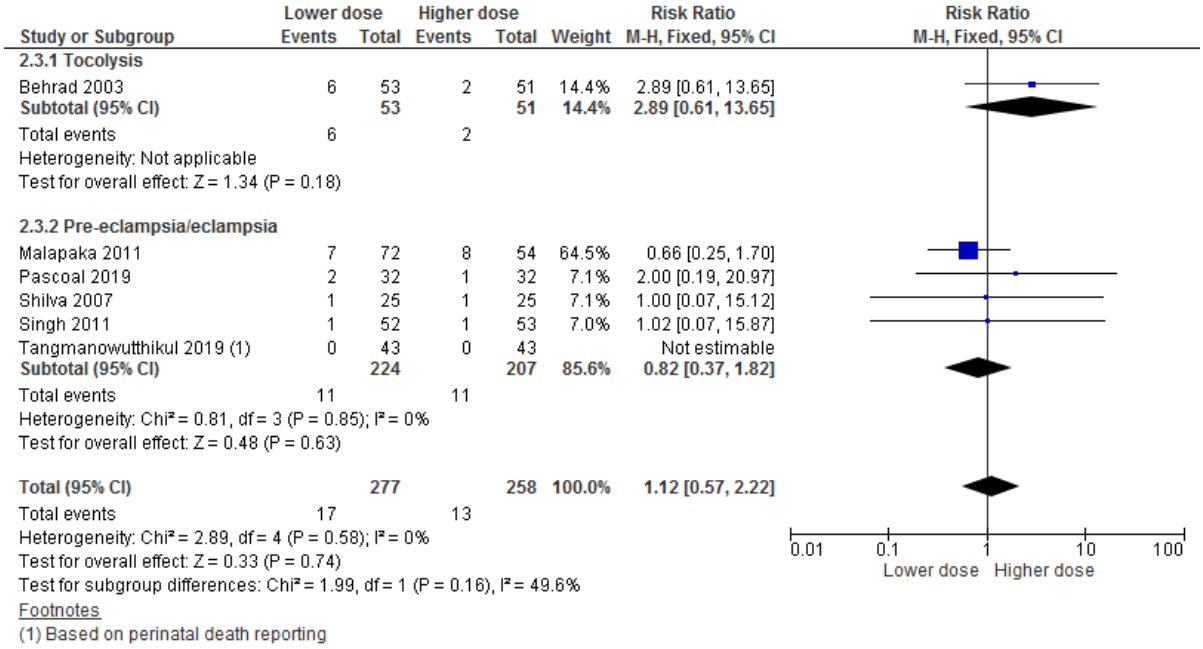


Figure 59. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.3 Neonatal death

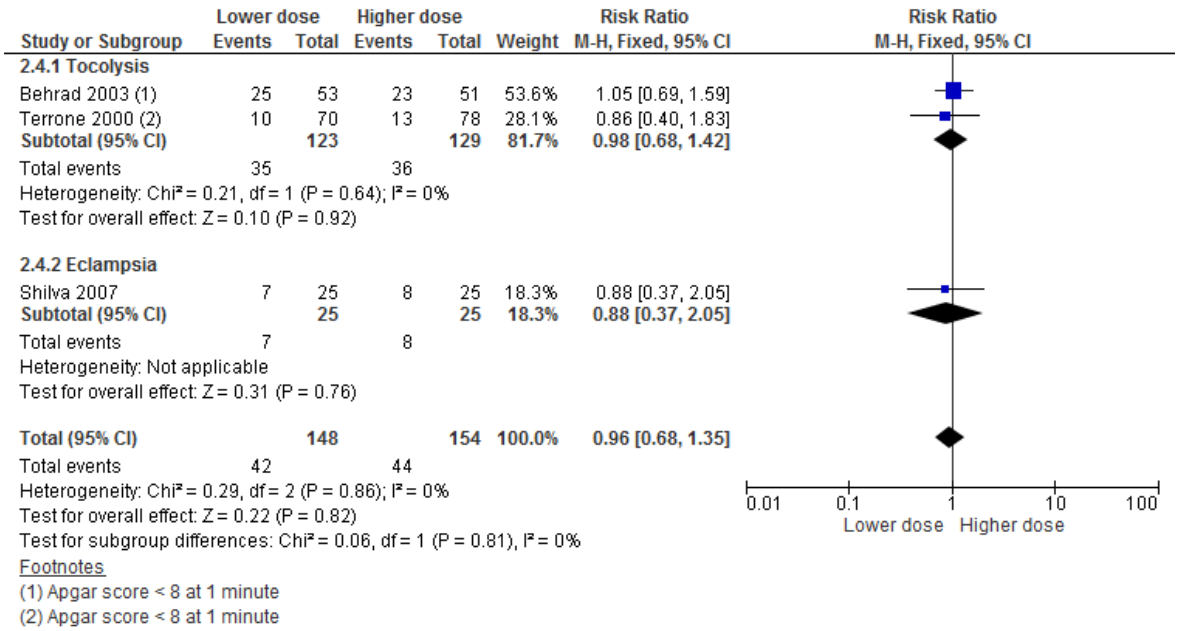


Figure 60. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.4 Apgar score < 7 at 1 minute

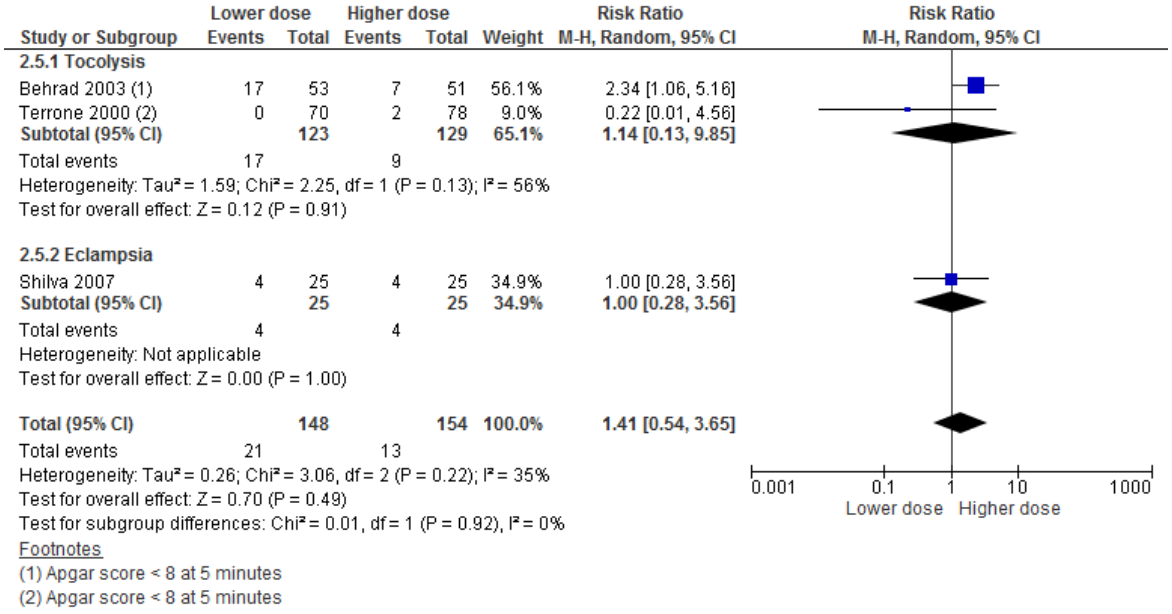


Figure 61. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.5 Apgar score < 7 at 5 minutes

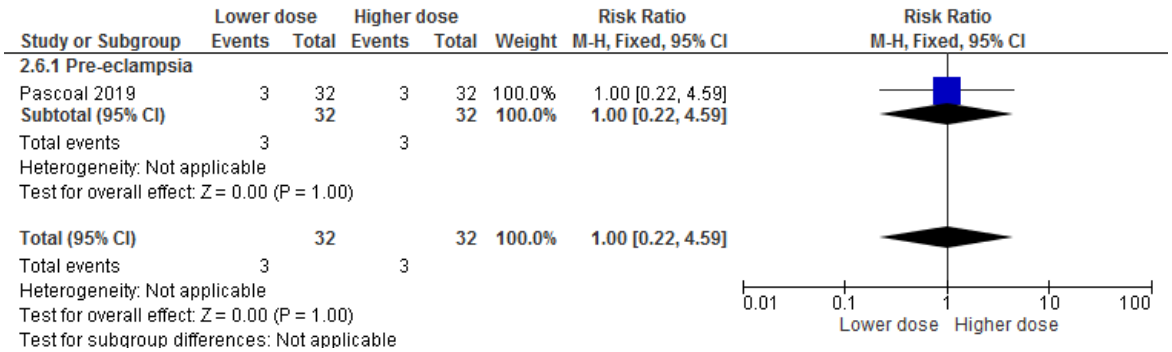


Figure 62. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.6 Resuscitation

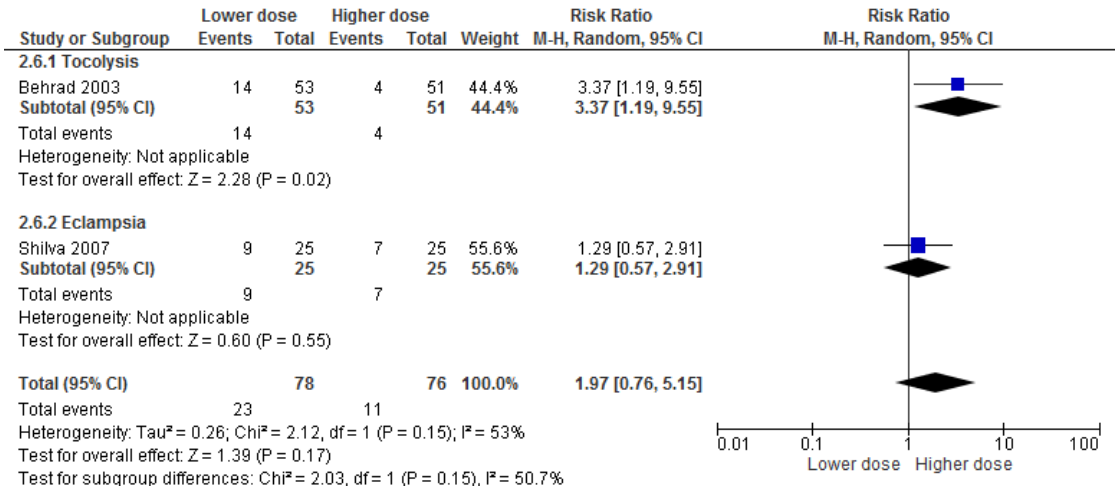


Figure 63. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.7 Respiratory distress syndrome

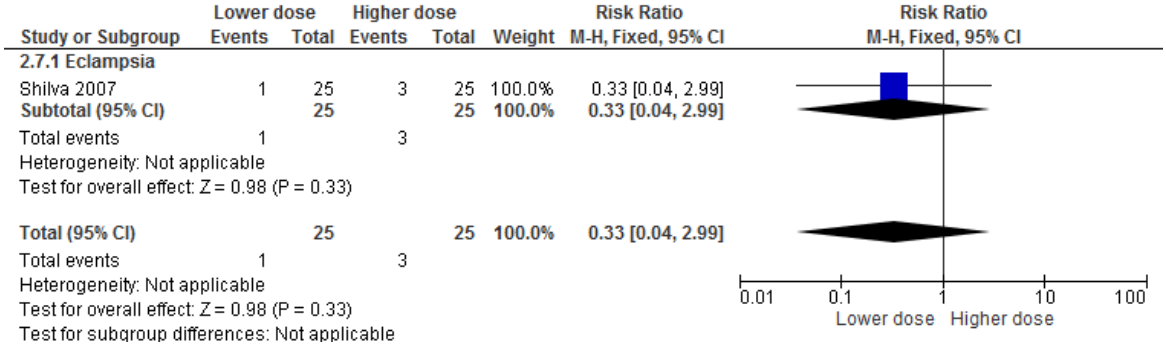


Figure 64. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.8 Respiratory depression

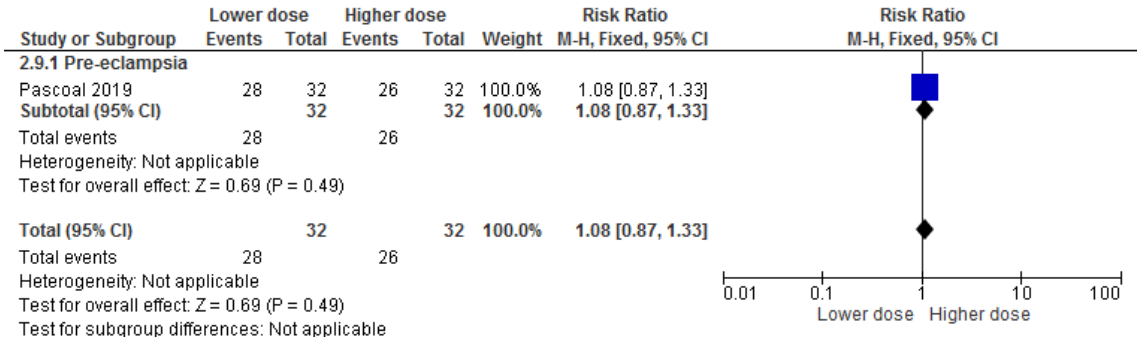


Figure 65. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.9 Respiratory disorders

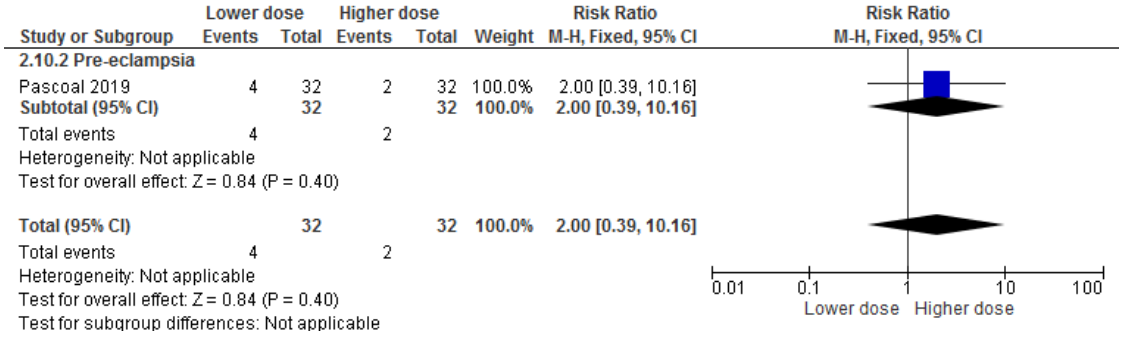


Figure 66. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.10 Mechanical ventilation

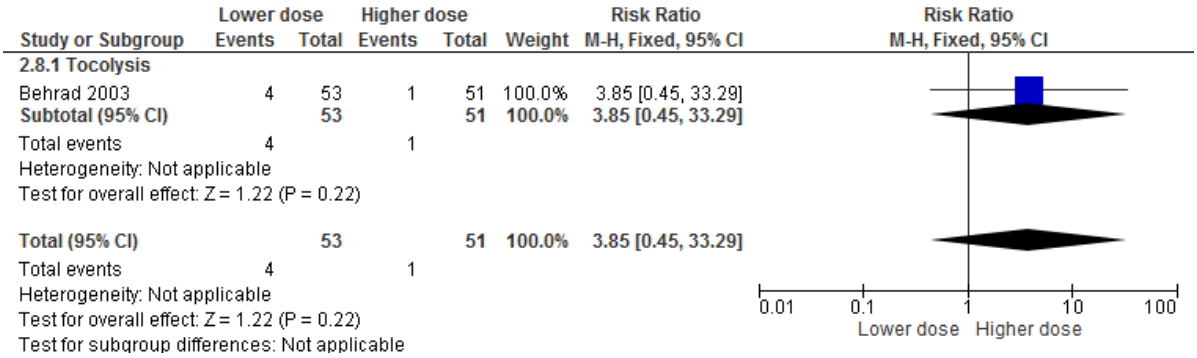


Figure 67. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.11 Bradycardia

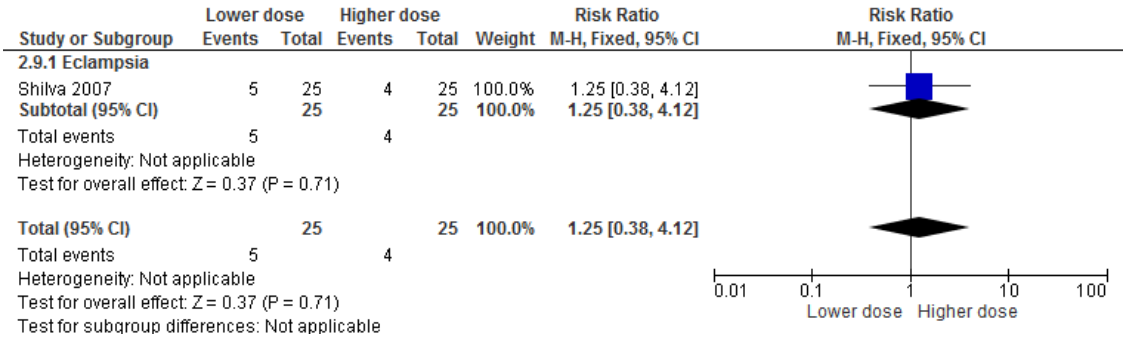


Figure 68. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.12 Jaundice

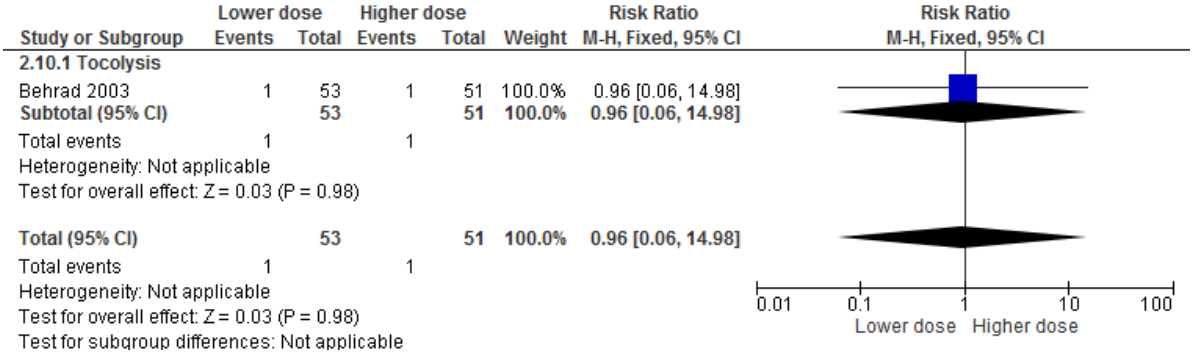


Figure 69. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.13 Hypoglycaemia

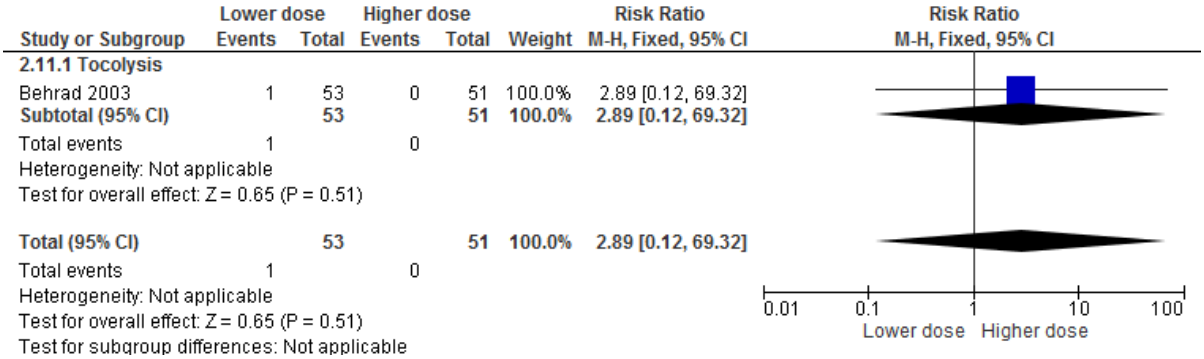


Figure 70. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.14 Hypocalcaemia

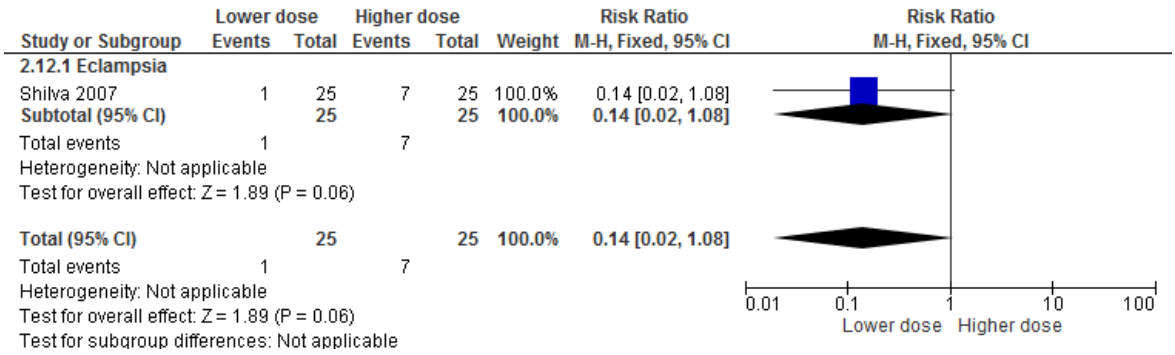


Figure 71. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.15 Hypotonia

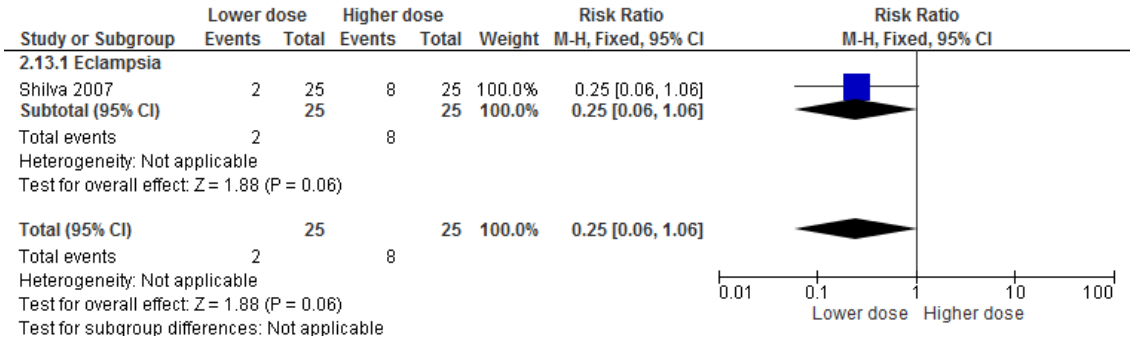


Figure 72. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.16 Requirement for calcium gluconate

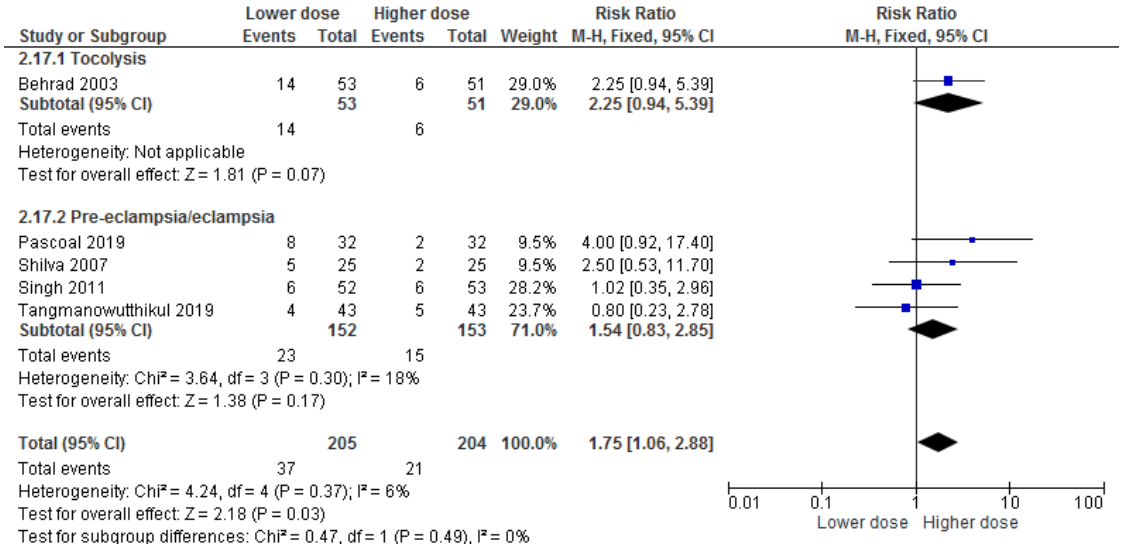


Figure 73. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.17 Neonatal intensive care unit admission

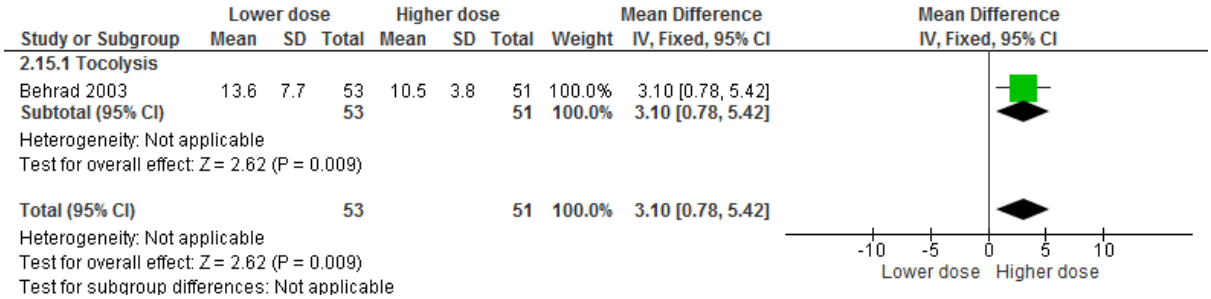
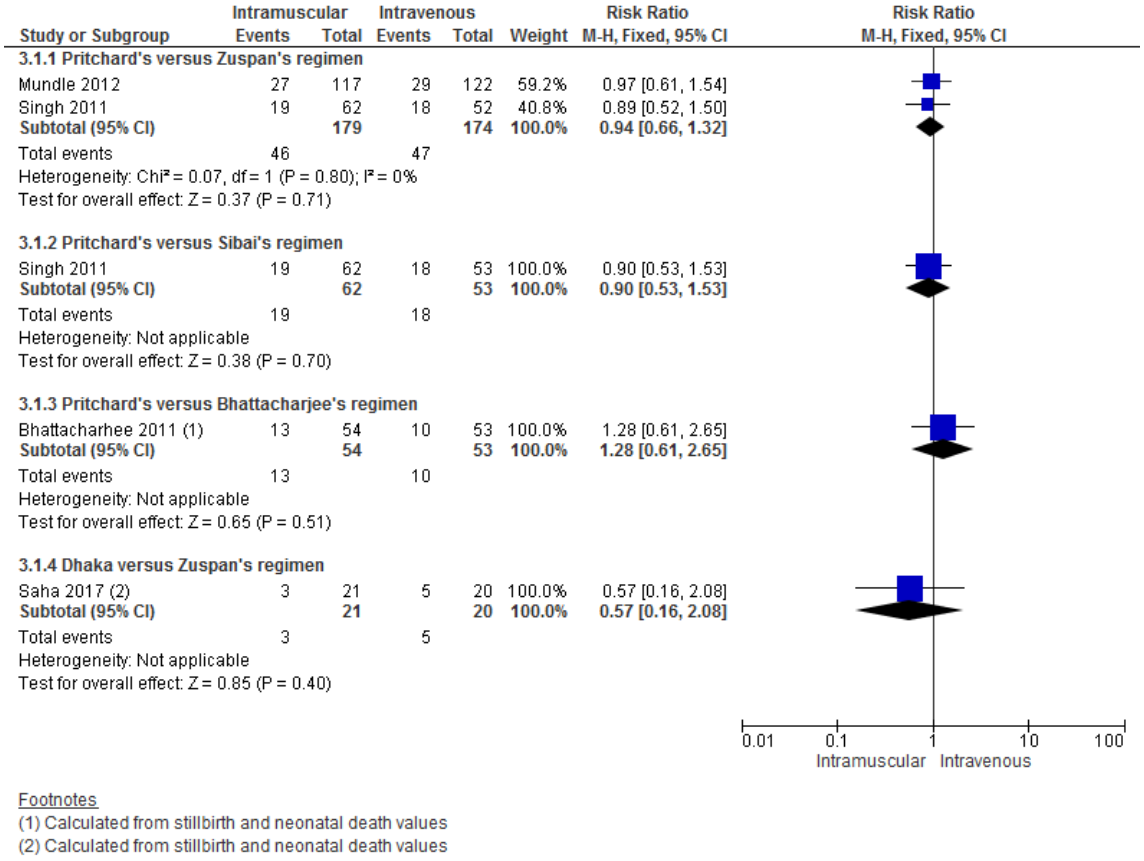


Figure 74. Forest plot of Comparison: 2 Lower versus higher dose regimens of magnesium sulphate, outcome: 2.18 Neonatal intensive care unit stay (days)



Footnotes
(1) Calculated from stillbirth and neonatal death values
(2) Calculated from stillbirth and neonatal death values

Figure 75. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.1 Perinatal death

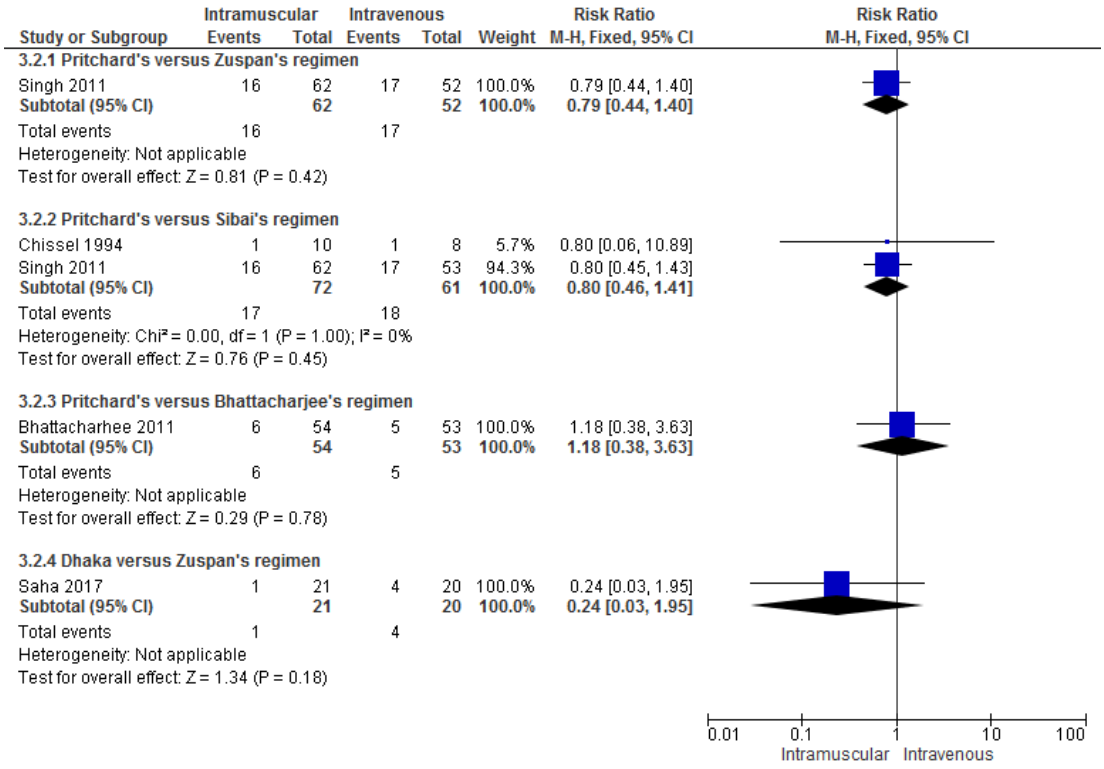


Figure 76. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.2 Stillbirth

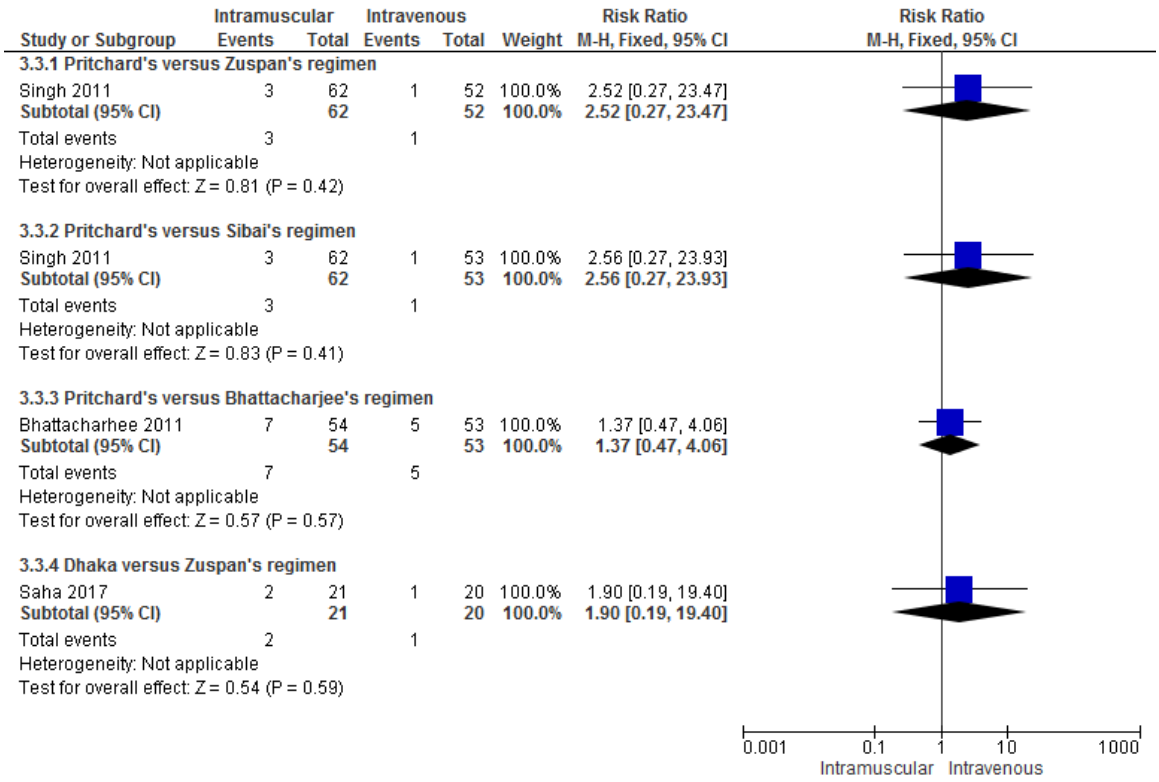


Figure 77. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.3 Neonatal death

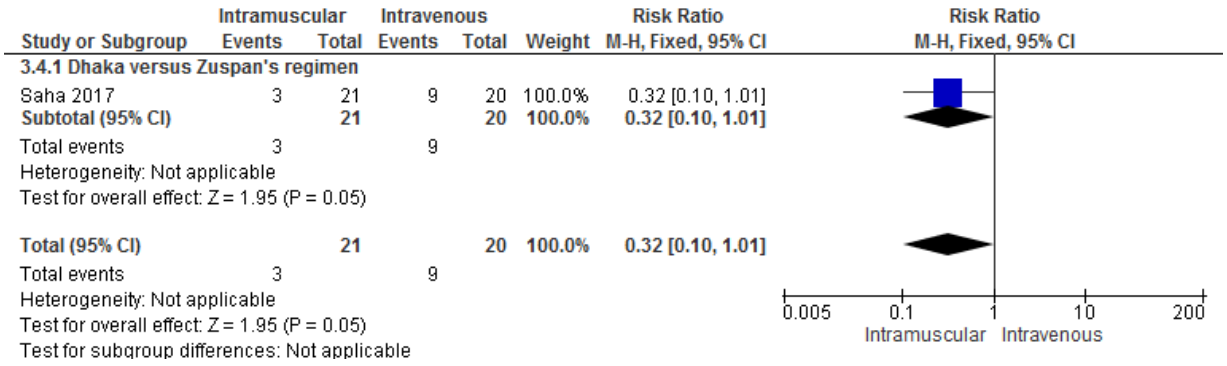


Figure 78. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.4 Apgar score < 7 at 1 minute

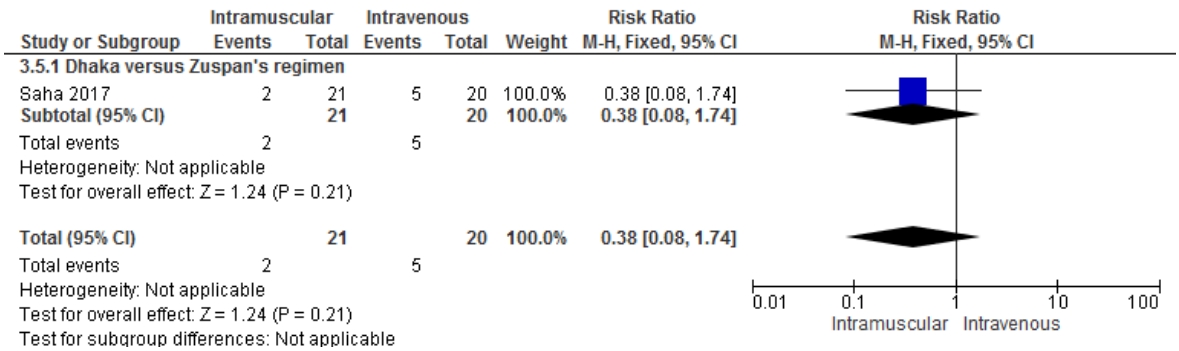


Figure 79. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.5 Apgar score < 7 at 5 minutes

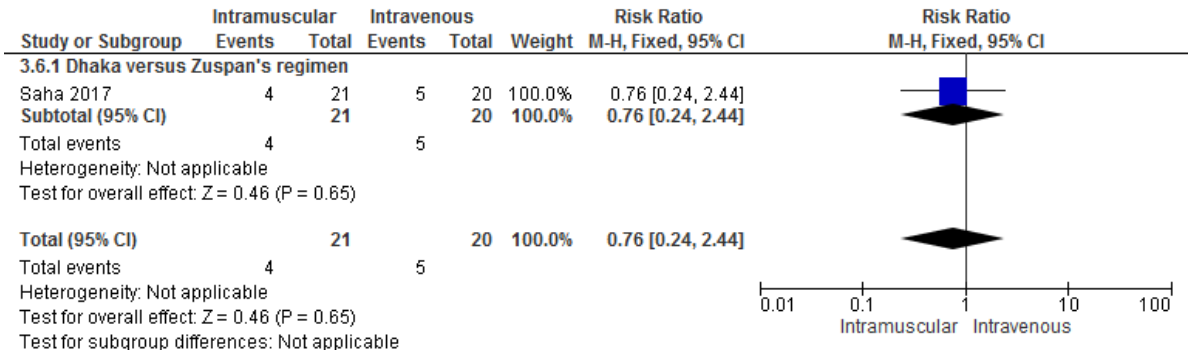


Figure 80. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.6 Respiratory distress syndrome

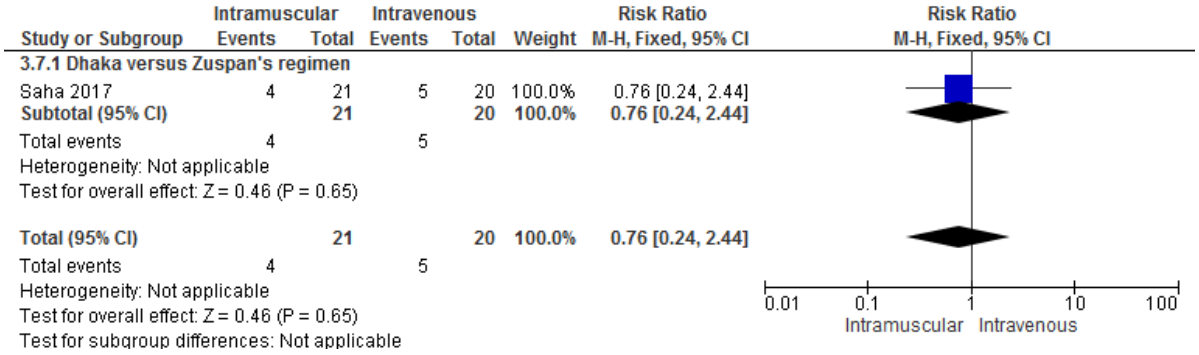


Figure 81. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.7 Jaundice

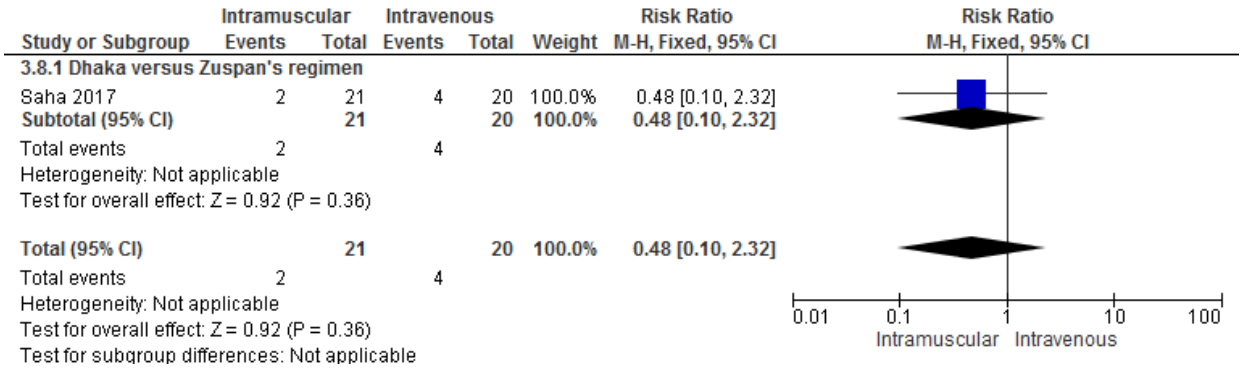


Figure 82. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.8 Hypotonia

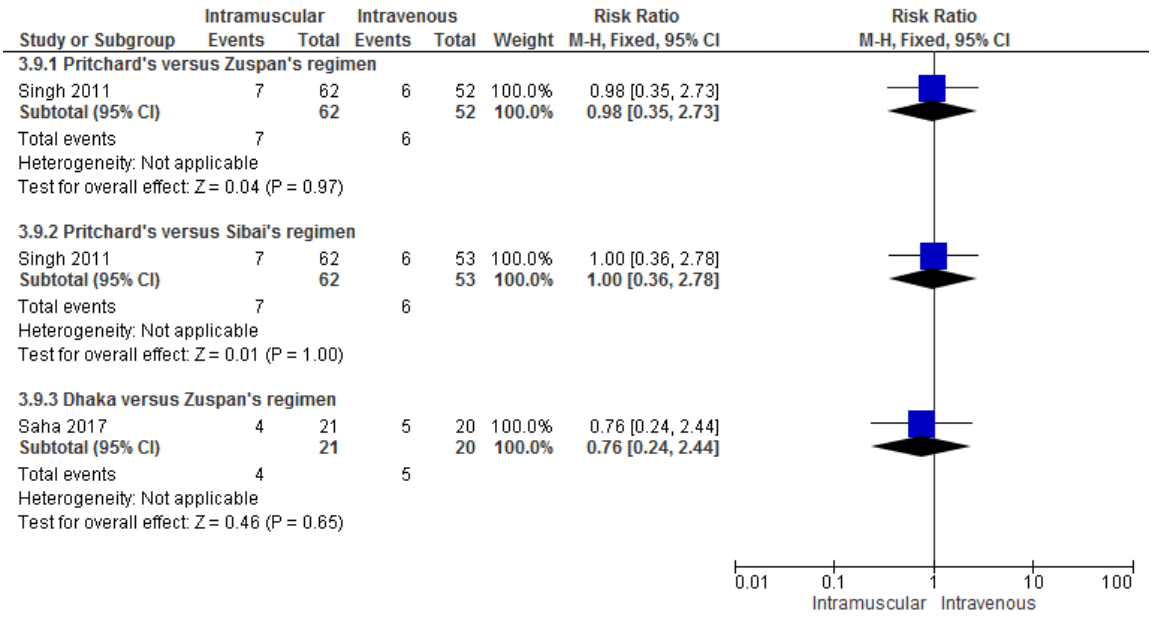
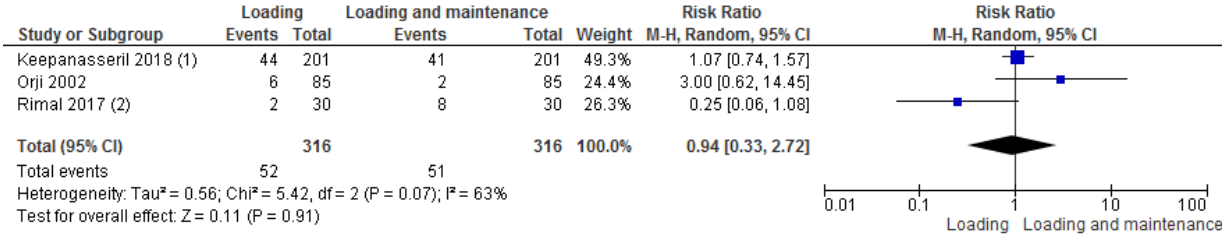
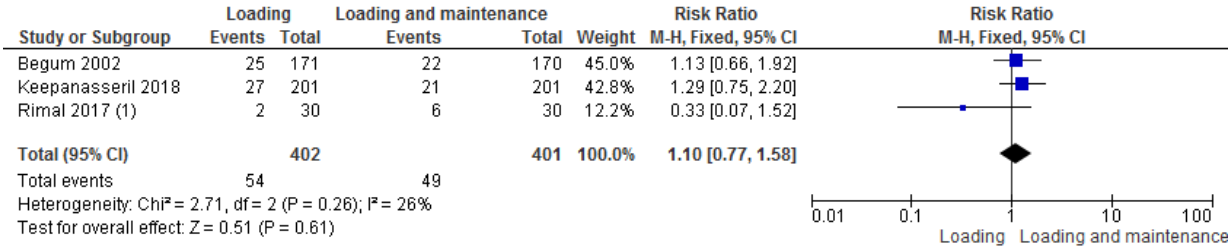


Figure 83. Forest plot of Comparison: 3 Intramuscular versus intravenous maintenance dose of magnesium sulphate, outcome: 3.9 Neonatal intensive care unit admission



Footnotes
(1) Calculated from stillbirth and neonatal death values
(2) Calculated from stillbirth and neonatal death values

Figure 84. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.1 Perinatal death



Footnotes
(1) Intrauterine fetal death and fresh stillbirth

Figure 85. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.2 Stillbirth

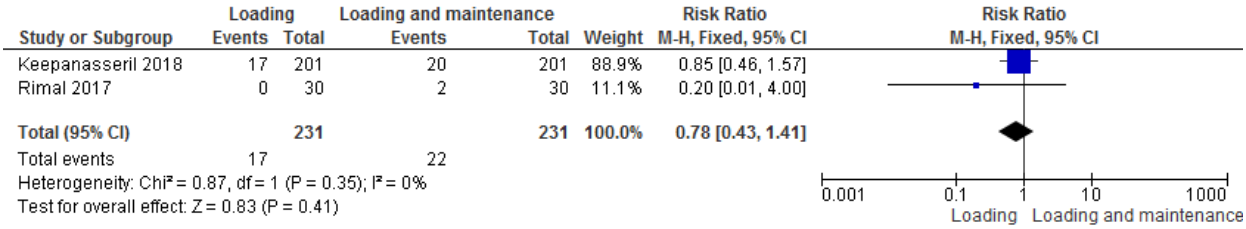


Figure 86. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.3 Neonatal death

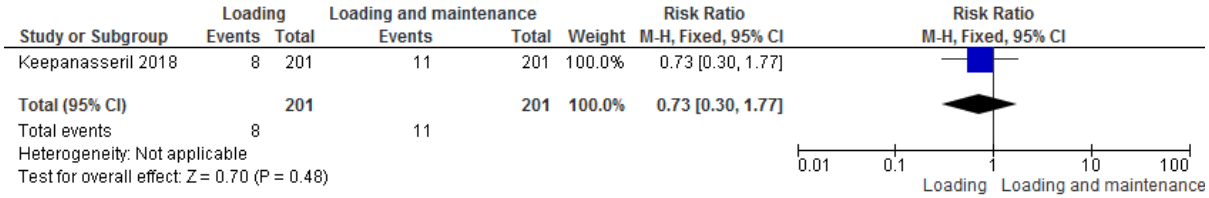


Figure 87. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.4 Neonatal death < 7 days

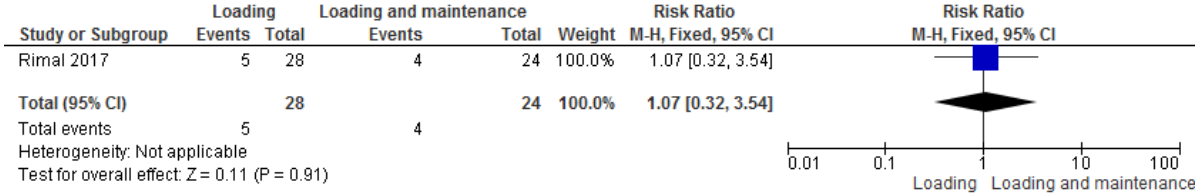


Figure 88. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.5 Apgar score < 7 at 0 minutes

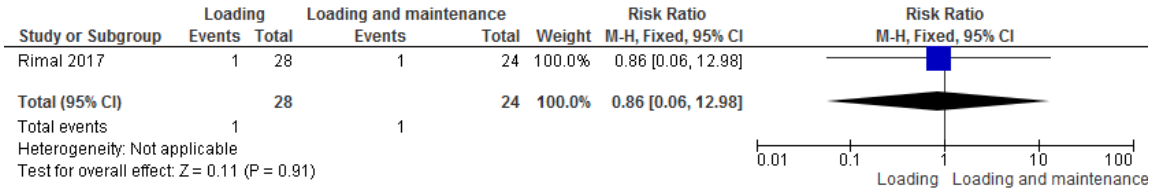


Figure 89. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.6 Apgar score < 7 at 1 minute

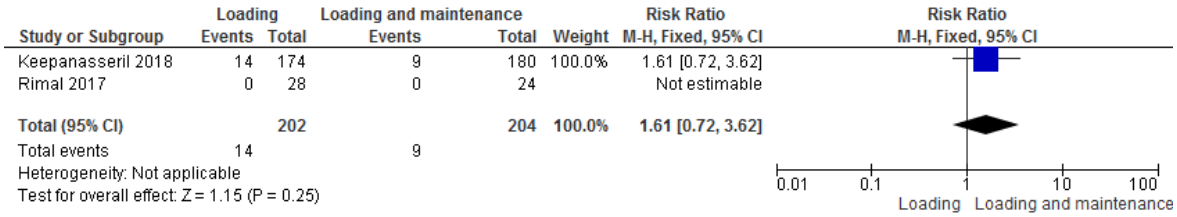


Figure 90. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.7 Apgar score < 7 at 5 minutes

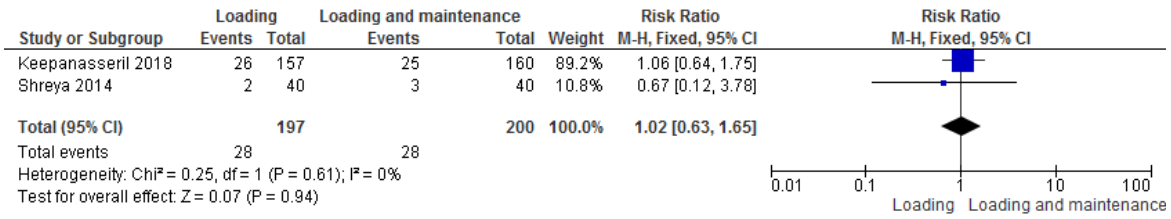


Figure 91. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.8 Neonatal intensive care unit admission for respiratory distress

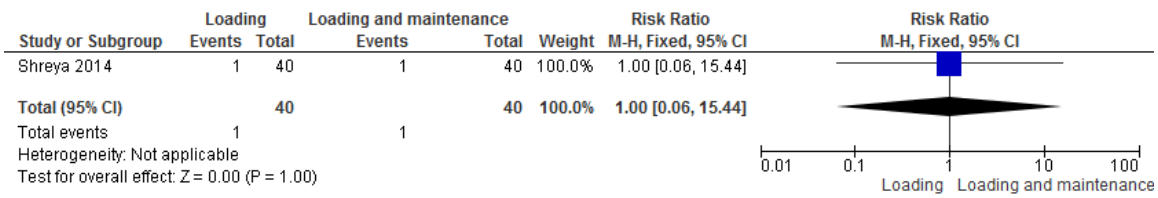


Figure 92. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.9 Neonatal intensive care unit admission for early onset sepsis

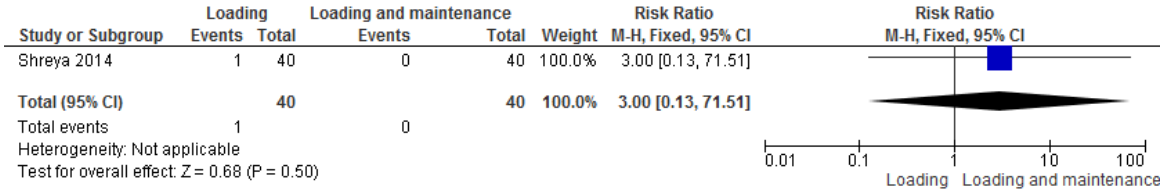


Figure 93. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.10 Neonatal intensive care unit admission for late onset sepsis

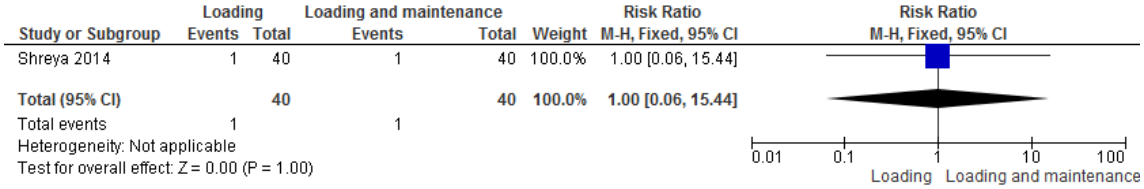


Figure 94. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.11 Neonatal intensive care unit admission for meconium aspiration syndrome

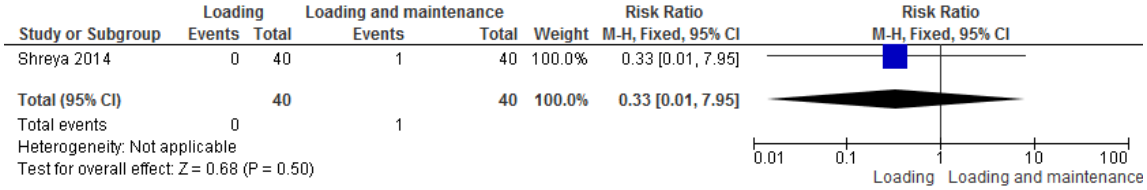


Figure 95. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.12 Neonatal intensive care unit admission for birth asphyxia

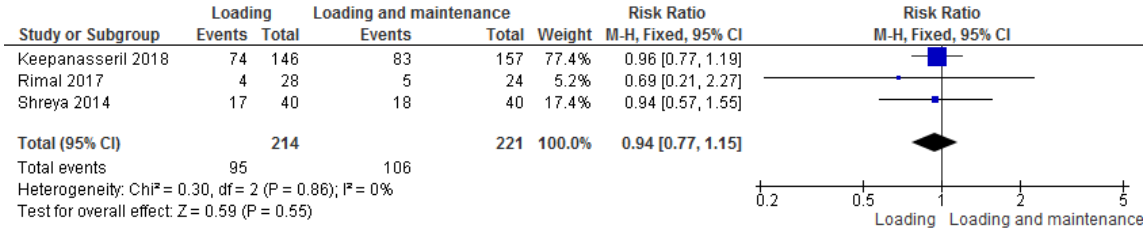
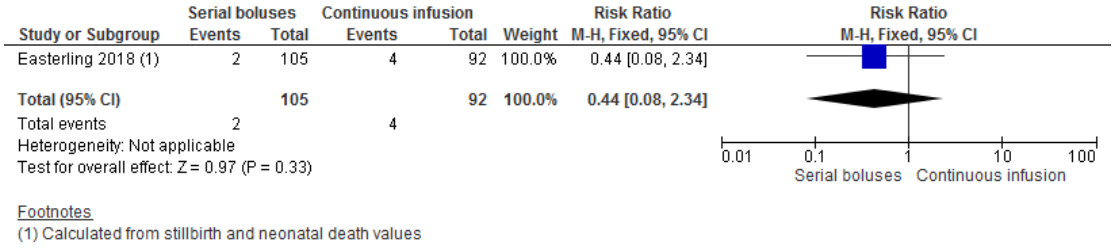


Figure 96. Forest plot of Comparison: 4 Loading dose versus loading and maintenance doses of magnesium sulphate, outcome: 4.13 Neonatal intensive care unit admission



Footnotes
(1) Calculated from stillbirth and neonatal death values

Figure 97. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.1 Perinatal death

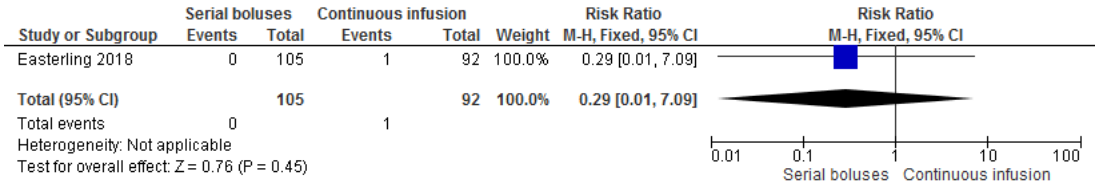


Figure 98. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.2 Stillbirth

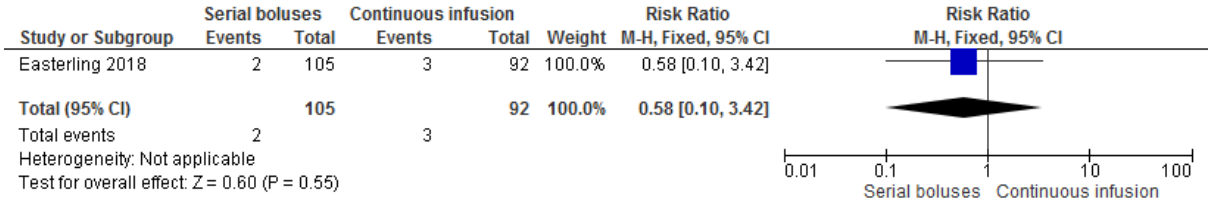


Figure 99. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.3 Neonatal death

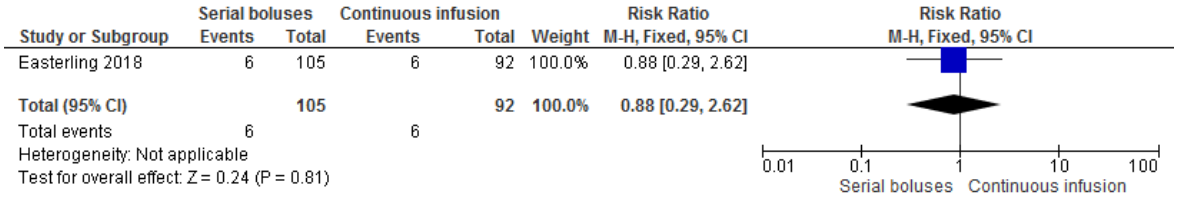


Figure 100. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.4 Intubated at birth

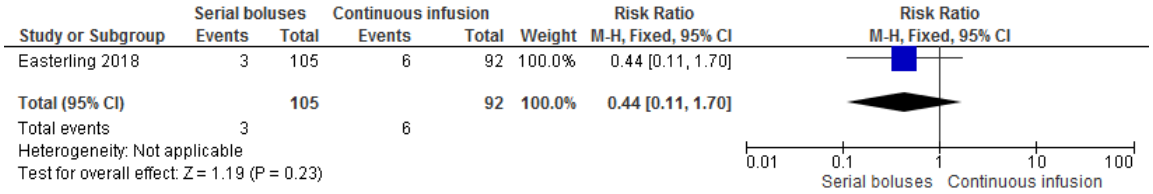


Figure 101. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.5 Mechanical ventilation

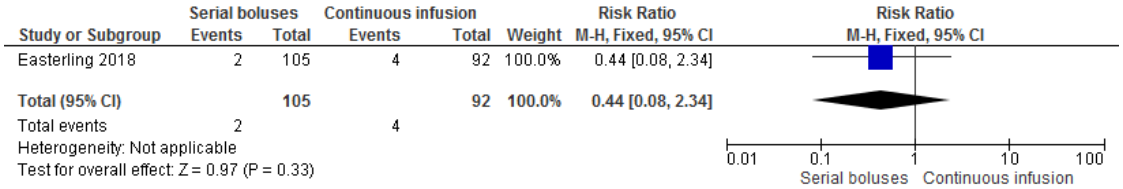


Figure 102. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.6 Bradycardia (< 110 beats per minute)

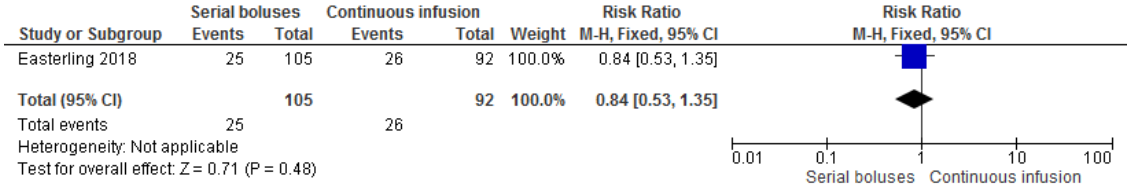


Figure 103. Forest plot of Comparison: 5 Serial intravenous boluses versus continuous maintenance infusion of magnesium sulphate, outcome: 5.7 Special care baby unit admission

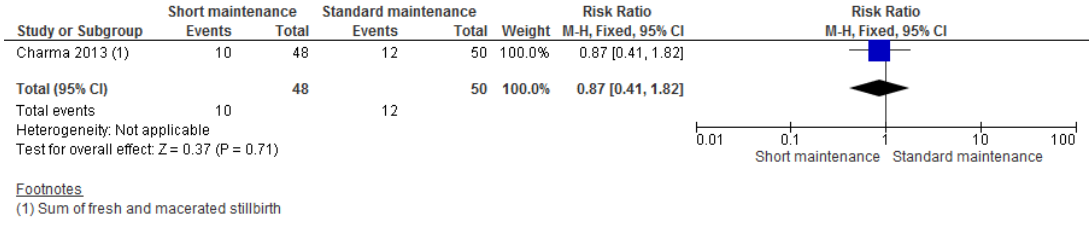


Figure 104. Forest plot of Comparison: 6 Short versus standard maintenance course of magnesium sulphate, outcome: 6.1 Stillbirth

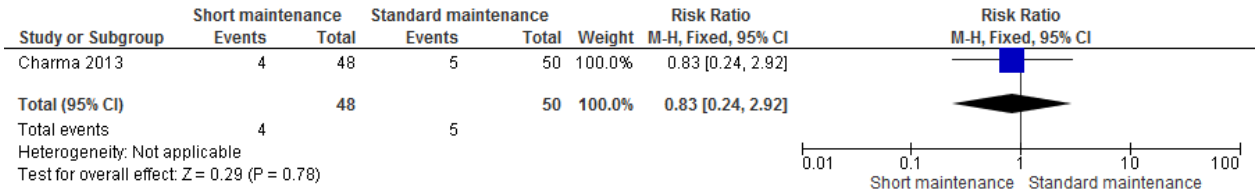


Figure 105. Forest plot of Comparison: 6 Short versus standard maintenance course of magnesium sulphate, outcome: 6.2 Birth asphyxia

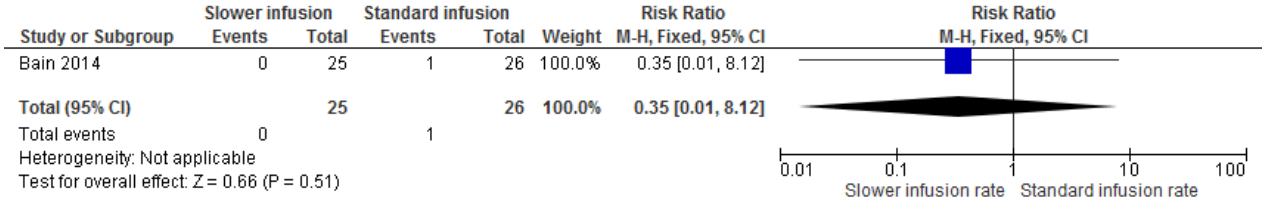
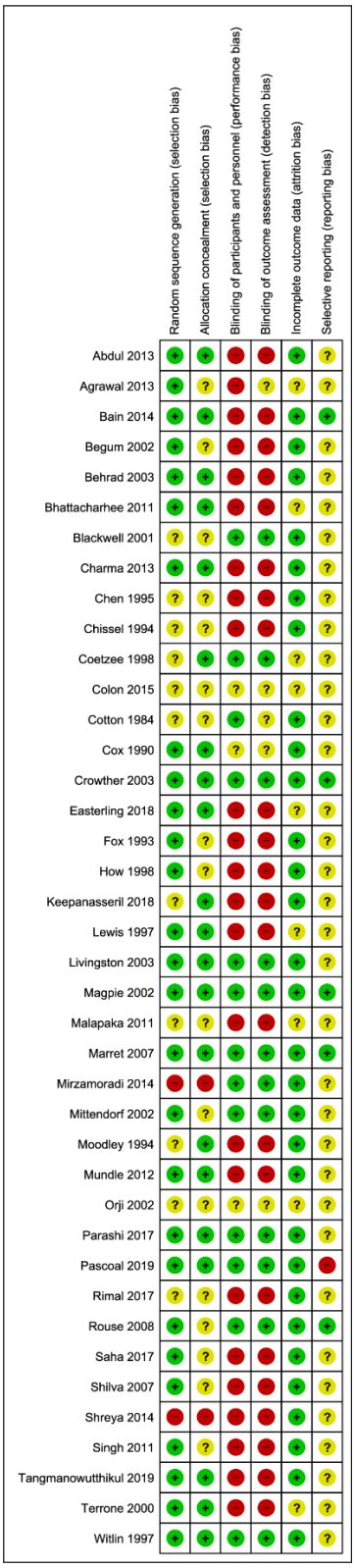


Figure 106. Forest plot of Comparison: 7 Slower versus standard rate of loading dose of magnesium sulphate, outcome: 7.1 Stillbirth

Figure 107. Forest plot of Comparison: 8 Weaning versus no weaning of magnesium sulphate, outcome: 8.1 Apgar score < 7 at 5 minutes

S1 Fig. Risk of bias for randomised controlled trials

Risk of bias summary showing judgements about each risk of bias item for the 40 included randomised trials. Green represents ‘low risk of bias’; yellow, ‘unclear risk of bias’; red, ‘high risk of bias.’



S1 PRISMA Checklist

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **Quote:** "Antenatal magnesium sulphate and adverse neonatal outcomes: a systematic review and meta-analysis"	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **Quote:** "Background. There is widespread, increasing use of magnesium sulphate in obstetric practice for pre-eclampsia, eclampsia, and preterm fetal neuroprotection; benefit for preventing preterm labour and birth (tocolysis) is unproven. We conducted a systematic review and meta-analysis to assess whether antenatal magnesium sulphate is associated with unintended adverse neonatal outcomes. Methods and findings. CINAHL, Cochrane Library, LILACS, MEDLINE, Embase, TOXLINE, and Web of Science, were searched (inceptions to 3 September 2019)…"	Abstract, paragraphs 1-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **Quote:** "Introduction. Antenatal magnesium sulphate is commonly used in obstetric practice. Systematic reviews and clinical practice guidelines support its use when given for maternal neuroprotection in pre-eclampsia or eclampsia [1-3], and for neuroprotection of the fetus in women at risk of preterm birth (for cerebral palsy prevention) [4-7]…"	Introduction, paragraphs 1-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **Quote:** "The aim of our study, therefore, was to conduct a comprehensive systematic review to assess whether antenatal magnesium sulphate is associated with including perinatal death and other unintended adverse neonatal outcomes."	Introduction, paragraph 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **Quote:** "We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline; the relevant checklist is provided in S1 PRISMA Checklist. Prior to conduct, this systematic review was registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42013004451) [18]. The Australian Cerebral Palsy Alliance Research Foundation-funded review protocol is available in S1 Text."	Methods, paragraph 1; and S1 Text

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. **Quote:** "Inclusion criteria. We included randomised and quasi-randomised controlled trials as well as non-randomised controlled studies (non-randomised trials, cohort studies, and case-control studies), and case reports. We excluded cross-sectional studies and case series. We included studies available as abstracts only, along with full-text publications…"	Methods, paragraphs 3-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **Quote:** "Search strategy. Comprehensive searches of the bibliographic databases CINAHL, Cochrane Library, LILACS, MEDLINE, Embase, TOXLINE, and Web of Science, were undertaken from their respective inceptions to 3 September 2019, using combinations of MeSH and free text terms. The search strategies are available in S2 Text."	Methods, paragraph 2; and S2 Text
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2 Text
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **Quote:** "Study selection. After screening all titles and abstracts, we obtained full-text articles for studies that appeared to meet the inclusion criteria. All full-text articles were assessed for inclusion. Each stage was carried out by 2 reviewers, and we resolved any discrepancies through discussion, or, if required, we consulted a third reviewer…"	Methods, paragraph 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **Quote:** "Data extraction and management. For included studies, data were extracted using a standardised form, including information regarding design, participants, the magnesium sulphate regimen(s), the control/comparison if applicable, neonatal adverse outcomes reported, results relevant to the review and the risk of bias…"	Methods, paragraph 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, paragraph 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **Quote:** "Assessment of risk of bias. Quality appraisal of intervention studies was undertaken utilising established guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions [19]. The quality assessment of observational studies was guided by the RTI Item Bank [20]."	Methods, paragraph 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **Quote:** "Data synthesis and analysis. Data analyses were undertaken by study design. Statistical analyses for randomised trials were performed using Review Manager, version 5.3 [21]. We presented quantitative data from individual studies as risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, with 95% confidence intervals (CIs)..."	Methods, paragraph 9

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **Quote:** "For all outcomes, we carried out analyses as far as possible on an intention-to-treat basis. Pooled estimates were calculated using fixed-effect meta-analysis (Mantel-Haenszel method) where there was a sufficient quantity of data, with clinical homogeneity…"	Methods, paragraphs 9-11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, paragraph 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **Quote:** "For our primary review outcome (perinatal death) and other mortality outcomes, we conducted subgroup analyses based on indication for use, and characteristics of the magnesium sulphate loading and maintenance dose regimens, as these factors were considered likely to influence outcomes…"	Methods, paragraph 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **Quote:** "Results. Study selection. The results of the search strategy, including the sources of the studies, their assessment and final inclusion are shown in Fig 1. The database searching identified 5,890 records, and other searching identified a further 11 records. Review of the titles and abstracts and exclusion of irrelevant and duplicate records yielded 777. Of these, we excluded 572 for the documented reasons (see S3 Text for list of records excluded due to absence of an English translation). We included a total of 205 articles, relating to 197 studies. See S4 Text for references for all included studies."	Results, paragraph 1; and Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **Quote:** "Evidence from randomised controlled trials. Forty randomised trials were included, the characteristics of which are detailed in S1 Table, and the risk of bias assessments summarised in Fig 2, S1 Fig, and S2 Table [22-61]…" **Quote:** "Evidence from non-randomised comparative studies. One hundred and thirty-eight non-randomised studies were included: 5 non-randomised trials, 35 prospective cohort studies (7 with nested case-control analyses), 82 retrospective cohort studies (16 with nested case-control analyses), 8 non-concurrent cohort studies, and 8 case-control studies [62-199]. The characteristics of the studies, and risk of bias assessments are detailed in S1 and S2 Tables…" **Quote:** "Evidence from case reports. Nineteen reports describing a total of 134 babies exposed to antenatal magnesium sulphate with adverse outcomes were included [200-218] (see Table 9; the detailed characteristics of cases are presented in S4 Table)."	Results paragraphs 2, 27-28 and 36; S4 Text, S1 Table and S4 Table
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **Quote:** "Forty randomised trials were included, the characteristics of which are detailed in S1 Table, and the risk of bias assessments summarised in Fig 2, S1 Fig, and S2 Table [22-61]…" **Quote:** "One hundred and thirty-eight non-randomised studies were included… The characteristics of the studies, and risk of bias assessments are detailed in S1 and S2 Tables…"	Results paragraph 2-3, 27-28; Fig 2, S1 Fig and S2 Table

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1, 4 and 6; S1 Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 1, 4, 6; S1 Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results paragraph 2-3 and 27-28; Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **Quote:** "When considering indication for use, the tocolysis subgroup showed an increase in perinatal death (RR 7.99; 95% CI 1.00 to 63.49; 2 trials, 257 babies; analysis 1.1.1) which was not observed in the pre-eclampsia or fetal neuroprotection subgroups..."	Results, paragraphs 5 and 9; Tables 2, 3, and 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **Quote:** "Discussion. Overall, no clear difference in our primary review outcome, perinatal death, was shown..."	Discussion, paragraphs 1-6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **Quote:** "Strengths and limitations. The main limitations of our review relate to missing data for important outcomes across most studies, the inclusion of published data only, and the heterogeneity of included studies, …"	Discussion, paragraphs 7-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **Quote:** "In conclusion, our findings do not support any clear associations between perinatal death or other adverse neonatal outcomes and antenatal magnesium sulphate exposure when given for the beneficial indications of maternal neuroprotection in pre-eclampsia/eclampsia, and fetal neuroprotection in cerebral palsy prevention…"	Discussion, paragraph 12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **Quote:** "This work was carried out with funding from the Cerebral Palsy Alliance Research Foundation, Australia (https://research.cerebralpalsy.org.au/), grant PG2015 (ES, PM, MM, CC). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."	Funding

S1 Table. Characteristics of included studies

Randomised controlled trials

Study; design	Setting	Participants	MgSO4 indication	Relevant comparison groups	Outcome measure(s)	Funding and conflicts
Abdul 2013; RCT	Nigeria 2008	N = 72 women and their babies Inclusions: women with antepartum, intrapartum or postpartum E including imminent E Exclusions: women with E in critical conditions, with hypotension and low RR	E	Lower dose regimen: modified 'Dhaka regimen': 4 g IV LD and 5 g IM LD; 2.5 g/4 hours IM MD for 24 hours post birth or last convulsion, N = 39 women and their babies Higher dose regimen: 'Pritchard's regimen'': 4 g IV LD and 10 g IM LD; 5 g IM/4 hours MD for 24 hours post birth or convulsion, N = 33 women and their babies All women: 2 g IV given for breakthrough convulsions	Perinatal death	Funding: NR Conflicts: none
Agrawal 2013; RCT Abstract	India 1 year	N = 75 women and their babies Inclusions: women with E Exclusions: NR	E	Lower dose regimen: 4 g IV LD and 6 g IM LD; 3 g/4 hour IM MD until 24 hours after birth, N = 36 women and their babies Higher dose regimen: "standard dose… Pritchard regimen", N = 39 women and their babies	Not in meta-analysis: "neonatal outcome"	NR
Bain 2014; RCT	Australia Time period NR	N = 51 women and their babies Inclusions: women with a single or twin pregnancy at < 30 weeks GA, if birth was planned or expected within 24 hours	FN	Slower rate of LD: 4 g IV LD over 60 minutes, N = 25 women and their babies	Stillbirth	Funding: 1 author supported by The University of Adelaide Conflicts: 2 authors report none; 2 authors were also authors on a relevant

		Exclusions: women in the 2nd stage of labour, who had already received MgSO4, or had any of the following contraindications (absent patellar reflexes, hypocalcaemia, RR < 16 breaths/minute, renal failure, urine output < 100 mL during last 4 hours)		Standard rate of LD: 4 g IV LD over 20 minutes, N = 26 women and their babies Both groups: 1 g/hour IV MD until birth or for up to 24 hours		Cochrane review; 1 author was the PI of the ACTOMgSO4 RCT; 2 authors were members of a guideline panel for relevant national guidelines
Begum 2002; RCT	Bangladesh 1999	N = 401 women and their babies Inclusions: women with E eligible for MgSO4 Exclusions: contraindications for MgSO4 therapy (e.g. oliguria, renal failure, absence tendon reflex), comatose patients, women who received MgSO4 from outside, women whose pregnancy was continued	E	LD only: 4 g IV LD over 15-20 minutes and 6 g IM LD, N = 202 women and their babies LD and MD: 4 g IV LD over 15-20 minutes and 6 g IM LD; 2.5 g/4 hours IM MD for 24 hours after birth or last convulsion, N = 199 women and their babies All women: for recurrent convulsion, women in LD only group received 2.5 g IV and MD was started for 24 hours; in women receiving MD already, a further 2.5 g IV given and MD continued	Stillbirth	NR
Behrad 2003; RCT	Iran 2000-2001	N = 100 women and their babies Inclusions: singleton or twin gestation between 24 and 35 weeks GA, spontaneous preterm labour (uterine contractions > 4 per 20 minutes along with 1 of the following observations: cervical dilatation of ≥ 1 cm but < 5 cm, cervical effacement ≥ 80% and/or progressive cervical	T	Lower dose regimen: 4 g IV LD over 20 minutes; 2 g/hour MD, N = 50 women and their babies Higher dose regimen: 6 g IV LD over 20 minutes; 2 g/hour IV MD, increased if required up to 4 g/hour, N = 50 women and their babies	Perinatal death, stillbirth, neonatal death, Apgar score < 8 at 1 minute, Apgar score < 8 at 5 minutes, RDS, bradycardia, hypoglycaemia, hypocalcaemia, NICU admission, NICU stay (mean ± SD) (days)	NR

		dilation and effacement), ability to provide informed consent Exclusions: higher order multiple gestations, ROM, non-reassuring fetal assessment (abnormalities of the fetal heart rate pattern), evidence of intrauterine infection (temperature of 38 or higher, leucocytosis, uterine tenderness, malodorous discharge), vaginal bleeding, patients with history of DM, myasthenia gravis or any other neuromuscular diseases, impaired renal function, hypotension, maternal bradycardia, atrioventricular block, and inability or refusal to provide informed consent		All women: successful T = < 4 contractions/hour with no further advancement in cervical dilation/effacement; failed T (and cessation of treatment) = dilation progressed to 6 cm and/or contractions persisted > 30 minutes at maximum dose		
Bhattacharhee 2011; RCT	India 2007-2009	N = 144 women and their babies Inclusions: women admitted with antepartum, intrapartum or postpartum E Exclusions: E with added complications (e.g. cerebrovascular accident, heart failure, renal failure, pulmonary oedema), referred cases who had already received initial dosage of MgSO4 at the referring centre	E	IM MD: 'Pritchard's regimen': 4 g IV slow bolus LD and 10 g IM LD; 5 g/4 hours IM MD, N = 72 women and their babies IV MD: 4 g IV slow bolus LD; 6 g/8 hours IV LD, N = 72 women and their babies All women: 2 g IV bolus if needed for recurrent convulsions	Perinatal death, stillbirth, neonatal death	Funding: NR Conflicts: none
Blackwell 2001; RCT	Author from USA Time period NR	N = 22 women and their babies Inclusions: women with singleton pregnancies at > 32	FN	MgSO4: 6 g IV LD over 20-30 minutes; 2 g/hour IV MD until birth, N = 11 women and their babies	Neonatal death, CLD (BPD), NEC, IVH grade 3/4 ('major')	NR

		weeks GA complicated by PPROM (< 37 weeks GA), PROM > 18 hours (GA > 18 weeks), or clinical chorioamnionitis Exclusions: any indication for MgSO4 therapy (seizure prophylaxis or T), known maternal hypersensitivity to MgSO4, fetal structural defects, FGR (birthweight < 10th percentile for GA), systemic maternal infection (e.g. pneumonia or pyelonephritis), advanced cervical dilation (≥ 8 cm) or imminent delivery, women with medical disorders such as any renal, cardiac or pulmonary disease, pulmonary hypertension or myasthenia gravis		Placebo: matched volume of Ringer's lactate solution of 20-30 minutes as a LD; continuous infusion of matched volume Ringer's lactate solution as MD until birth N = 11 women and their babies		
Charma 2013; RCT	Nigeria 2011	N = 112 women and their babies Inclusions: women with E Exclusion criteria: women with E who had received any anticonvulsant elsewhere before referral; added complications like stroke, renal failure and heart failure	E	Short MD: 4 g IV slow bolus LD and 10 g IM LD; 5 g/4 hours IM MD, for 2 doses only, N = 56 women and their babies Standard MD: 'Prichard's regimen': 4 g IV slow bolus LD and 10 g IM LD; 5 g/4 hours IM MD for 24 hours after birth or last convulsion, N = 56 women and their babies All women: 2 g IV for recurrent convulsions	Stillbirth, birth asphyxia	Funding: NR Conflicts: none

Chen 1995; RCT	Taiwan 1989-1992	N = 64 women and their babies Inclusions: signs of severe hypertension (BP > 150/100 mmHg) with 1 or more features of severe PE (systolic BP 166 mmHg or higher; diastolic BP 110 mmHg or higher; proteinuria persistent 2+ or more; oliguria 500 mL or less in 24 hours; serum creatinine elevated; thrombocytopenia; hyperbilirubinemia; sGOT elevation marked; visual disturbance; headache; upper abdominal pain; pulmonary oedema or cyanosis; obvious FGR) Exclusions: IUD, chronic hypertension superimposed with PE, E at admission	PE	MgSO4: 4 g IV LD over 10 minutes; 1 g/hour IV MD until 1 day after birth, N = 34 women and their babies No treatment: no MgSO4, N = 30 women and their babies	Apgar score ≤ 6 at 1 minute	NR
Chissel 1994; RCT	South Africa Time period NR	N = 17 women and their babies Inclusions: women with severe PE and imminent E; proteinuria of at least 1+ assessed by a semi quantitative dipstick method, and diastolic BP of 120 mmHg or more which did not settle during a 4 hour observation period Exclusions: NR	PE	IM MD: 'Pritchard's regimen': 4 g IV LD over 15 minutes and 10 g IM LD; 5 g/4 hours IM MD for 24 hours, providing delivery had occurred, N = 9 women and their babies IV MD: 'Sibai's regimen': 6 g IV LD over 15 minutes; 2 g/hour IV MD for 24 hours, providing delivery had occurred N = 8 women and their babies	Stillbirth	Funding: support from South African Medical Research Council Conflicts: NR
Coetzee 1998; RCT	South Africa 1991	N = 822 women and their babies Inclusions: women with severe PE (2 or more of the following: diastolic BP ≥ 110 mmHg, significant proteinuria, and	PE	MgSO4: 4 g IV LD over 20 minutes; 1 g/hour IV MD until 24 hours after birth, N = 345 women and their babies (analysed)	Stillbirth	NR

		symptoms of imminent E) where a decision to terminate pregnancy had been made [note: twin pregnancies were included] Exclusions: women younger than 16 years, already receiving MgSO4 or other anticonvulsants		Placebo: saline placebo as above, N= 240 women and their babies (analysed)		
Colon 2015; RCT Abstract	Authors from USA Time period NR	N = 30 women and their babies Inclusions: women between 24-34 weeks GA presenting with vaginal bleeding and uterine contractions and diagnosed with non-severe placental abruption Exclusion criteria: NR	T	MgSO4: IV, N = 15 women and their babies Placebo: IV placebo, N = 15 women and their babies	Not in meta-analysis: NICU admission	NR
Cotton 1984; RCT	Authors from USA Time period NR	N = 54 women and their babies Inclusions: women between 26 and 34 weeks GA (and estimated fetal weight between 750-2000 g) in preterm labour (where, following hydration, persistent uterine contractions occurred ≥ 3 in 10 minutes, and cervical examination suggested active labour (any of the following: 1) evidence of progressive cervical dilatation overtime; 2) a dilatation of 2 cm or greater; 3) cervical effacement of ≥ 80%; or 4) spontaneous ROM)); with singleton or twin pregnancies Exclusions: women with a cervical dilatation > 4 cm; women with evidence of fetal	T	MgSO4: 4 g IV LD over 15 minutes; 2 g/hour IV MD – women with intact membranes, discontinued after 12 hours if no uterine activity; in women with ROM, continued for > 48 hours, N = 16 women and their babies Placebo: continuous IV infusion of dextrose in lactated Ringer's solution at 125 ml/hour, N = 19 women and their babies [19 women and their babies in terbutaline group not considered further]	Neonatal death, RDS, NEC, sepsis (positive culture), hypoglycaemia on NICU admission, PDA (requiring either medical or surgical treatment), seizures, IVH (ICH)	Funding: supported by NIH and the Ariel Kaare Rosholt Weathers-Lowin Medical Research Foundation Conflicts: NR

		pulmonary maturity or bacteria on Gram's stain				
Cox 1990; RCT	USA 1987-1989	N = 156 women and their babies Inclusions: preterm labour (defined by regular uterine contractions associated with cervical dilation ≥ 1 cm but < 5 cm); GA between 24-34 weeks; intact fetal membranes; no maternal or fetal complications necessitating delivery (singleton and twin pregnancies) Exclusions: NR	T	MgSO4: 4 g IV LD; 2 g/hour IV MD, increased to 3 g/hour if contractions persisted after 1 hour; continued for 24 hours (with re-treatment later if needed), N = 76 women and their babies Placebo: IV physiologic saline solution at 80 mL/hour for 24 hours. N = 80 women and their babies	Perinatal death, stillbirth, neonatal death, death > 28 days, before discharge, RDS (requiring ventilator) NEC, IVH (ICH), NICU admission, hospital stay (mean ± SD) (days)	NR
Crowther 2003; RCT	Australia and New Zealand 1996-2000	N = 1062 women and their babies Inclusions: women pregnant with single, twin, triplet or quadruplet foetuses < than 30 weeks GA, where birth was planned or expected within 24 hours Exclusions: women in the 2nd stage of labour, women who had received MgSO4 therapy in this pregnancy, or with contraindications to MgSO4 therapy (RR < 16/minute, absent patellar reflexes, urine output < 100 mL in the previous 4 hours, renal failure, hypocalcaemia)	FN	MgSO4: 4 g IV LD over 20 minutes; 1 g/hour IV MD until birth or for up to 24 hours, N = 535 women and their babies Placebo: 8 mL sodium chloride solution/20 minutes; 2 mL/hour until birth or for up to 24 hours, N = 527 women and their babies	Perinatal death, stillbirth, neonatal death, death > 28 days, before discharge, Apgar score < 7 at 5 minutes, MV, CLD, NEC, IVH, IVH grade 3/4, PVL Not in meta-analyses: length of hospital stay (median, range) (days) Additional outcomes from Paradisis 2012 (N = 87 babies), nested within Crowther: PDA treated, surfactant, volume expansion, dobutamine, dopamine, any inotrope, SVC flow < 41 mL/kg/min 1st 24 hours, RVO < 120 mL/kg/min 1st 24 hours, mean BP < 10th centile 1st 24 hours, pneumothorax, pulmonary haemorrhage	Funding: supported by NHMRC, Channel 7 Research Foundation of SA, Queen Victoria Hospital Research Foundation, and The University of Adelaide Conflicts: none

Easterling 2018; RCT	Egypt 2015-2016	N = 200 women and their babies Inclusions: women with severe PE, pregnant or ≤ 24 hours postpartum, deemed to benefit from treatment with MgSO4 Exclusions: women who had experienced an E seizure, who had received MgSO4 within 24 hours of enrolment, or who had a serum creatinine > 1.2 mg/dL at the time of enrolment	PE	Serial IV bolus regimen: 6 g IV LD over 30 minutes using Springfusor spring-loaded pump, through flow control tubing; 2 g IV bolus over 10 minutes every 2 hours as MD, N = 100 women and their babies Continuous infusion regimen: 4 g IV LD over 20 minutes; 1 g/hour IV MD by mini-drip, N = 100 women and their babies	Perinatal death, stillbirth, neonatal death, intubated at delivery, MV, bradycardia, SCBU admission	Funding: supported by Merck for Mothers Conflicts: none
Fox 1993; RCT	Authors from USA Time period NR	N = 90 women and their babies Inclusions: patients between 34 and 37 weeks GA, > 15 but < 45 years of age, in documented preterm labour with cervical change, capable of giving informed consent Exclusions: cervical dilatation ≥ 3 cm, unknown GA, ROM, or with medical or obstetric conditions necessitation delivery (such as PIH, cardiac disease, fetal distress, or haemorrhage); evidence of suspected anomalies and maternal allergy to MgSO4	T	MgSO4: 4 g IV bolus LD; 2-4 g/hour IV MD until uterine quiescence [oral magnesium gluconate used as further MD], N = 45 women and their babies No treatment: conservative management, with hydration, sedation and observation; labour was allowed to continue without intervention after admission to the labour suite, N = 45 women and their babies	Perinatal death, stillbirth, neonatal death, RDS, TTN, NEC, poor feeding, hyperbilirubinaemia, IVH, IVH grade 3/4, hospital stay (mean ± SD) (days) Not in meta-analyses: days with the use of the ventilator (mean), NICU time for infants who did have complications (mean)	Funding: supported by Vicksburg Hospital Medical Foundation Conflicts: NR
How 1998; RCT	USA 1992-1995	N = 145 women and their babies Inclusions: patients between 24-34 completed weeks GA with PPROM (documented by obvious vaginal pooling and/or confirmed by ferning and alkaline pH using nitrazine	T	MgSO4: in the presence of ≥ 6 contractions/hour: 6 g IV LD; 2 g/hour IV MD, increased up to 5 g/hour; maintained for 4 hours, gradually decreased by 1-2 g/hour, maintained for 6-8 hours before discontinuation (could be re-started), N = 78 women and their babies	Stillbirth, death > 28 days, before discharge, RDS (HMD), TTN, MV, oxygen required, CLD, apnoea and bradycardia, NEC, sepsis, IVH Not in meta-analyses: length of nursery stay (median, IQR, range) (days), ventilator support (median,	NR

		paper) (singleton and twin pregnancies) Exclusions: evidence of chorioamnionitis and/or fetal stress or advanced active labour (≥ 3 cm dilatation by sterile speculum exam) on admittance; patient's refusal; obstetrical indications for expedient delivery (PE/E, abruptio placenta, lethal anomalies, severe IUGR)		No treatment: expectant management, N = 67 women and their babies	IQR, range) (days), oxygen required (median, IQR, range) (days)	
Keepanasseril 2018; RCT	India 2011-2013	N = 402 women and their babies Inclusions: women with a singleton pregnancy complicated by severe PE Exclusions: women with plasma creatinine value ≥ 2 mg/dL, deranged coagulation profile, platelet count < 50,000/mm3, past diagnosis of myasthenia gravis, or seizure disorders, already on MgSO4 prophylaxis on admission	PE	LD only: 4 g IV LD over 10-15 minutes and 6 g IM LD, N = 201 women and their babies LD and MD: 'Dhaka regimen': 4 g IV LD over 10-15 minutes and 6 g IM LD; 2.5 g/4 hours IM MD, for 24 hours postpartum, N = 201 women and their babies All women: 2 g IV given for recurrence of convulsions, and 2.5 g/4 hours IM MD continued until 24 hours post birth or last convulsion	Perinatal death, stillbirth, neonatal death, neonatal death < 7 days, Apgar score < 7 at 5 minutes, NICU admission for RD, NICU admission	Funding: NR Conflicts: none
Lewis 1997; RCT	USA 1993-1996	N = 144 women and their babies Inclusions: women with intact membranes between 24-35 weeks GA who had undergone successful single-agent tocolysis with MgSO4; preterm labour: defined as regular uterine contractions with either documented cervical change or	T	Weaning: MgSO4 weaned by approximately 1 g every 4 hours; when the dose was < 1 g/hour it was discontinued, and women were monitored for 4 hours, N = 72 women and their babies analysed	Apgar score < 7 at 5 minutes	NR

		a cervix dilated ≥ 2 cm and 75% effaced; successful tocolysis: uterine quiescence for ≥ 12 hours with no further cervical change (requiring approximately 24 hours for completion) Exclusions: NR		No weaning: MgSO4 abruptly stopped and women observed for 4 hours, N = 69 women and their babies analysed All women had received: 6 g IV LD over 20 minutes; 2-3.5 g/hour IV MD		
Livingston 2003; RCT	USA 1996-2001	N = 222 women and their babies Inclusions: women at term or preterm, who developed mild PE (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg on 2 occasions ≥ 6 hours apart, in association with new onset proteinuria, defined as +1 or greater on dipstick on ≥ 2 occasions) before onset of labour; women admitted for planned caesarean birth and who developed mild PE during the postpartum period were also included (singleton and twin pregnancies) Exclusions: women with chronic hypertension or severe PE	PE	MgSO4: 6 g IV LD over 20 minutes; 2 g/hour IV MD, continued for 12 hours, or until 12 hours postpartum, N = 109 women and their babies Placebo: identical administration of indistinguishable IV saline, N = 113 women and their babies	Meconium at delivery	NR
Magpie 2002; RCT	33 counties (Africa, the Americas, Asia-Pacific region, Europe) 1998-2001	N = 10,141 women and their babies Inclusions: women with PE and there was uncertainty about whether to use MgSO4; irrespective of whether they had had an anticonvulsant at a referring hospital, or whether the pregnancy was singleton or multiple (the woman had not	PE	MgSO4: 4 g IV LD over 10-15 minutes; MD of either: 1 g /hour IV for 24 hours, or 5 g/4 hours IM (plus 10 g IM with LD) for 24 hours, N = 5071 women and their babies Placebo: as above, N = 5070 women and their babies	Perinatal death, stillbirth, neonatal death, death > 28 days, before discharge, early neonatal death, late neonatal death, Apgar score < 7 at 5 minutes, intubated at delivery, MV, seizures, persistent parenchymal echogenicity, abnormal ventriculomegaly, NICU admission, SCBU admission > 7	Funding: UK MRC, UK Department for International Development, the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction Conflicts: none

		given birth, or was 24 hours or less postpartum; BP was 90 mm Hg diastolic or 140 mm Hg systolic or more on ≥ 2 occasions; proteinuria was ≥ 1+; and there was clinical uncertainty about whether MgSO4 would be beneficial) Exclusions: hypersensitivity to MgSO4, hepatic coma with a risk of renal failure, or myasthenia gravis		All women: trial treatment could be continued > 24 hours if considered necessary by clinician; if woman had a convulsion, treatment stopped and MgSO4 used	days or death, SCBU admission > 7 days, still in hospital at 6 weeks	
Malapaka 2011; RCT	India 2007-2009	N = 126 women and their babies Inclusions: women with E or imminent E Exclusions: NR	E	Lower dose regimen: for women with E: 4 g IV LD over 15-20 minutes; 2 g IM or slow IV/3 hours until 24 hours after last convulsion or abortion/birth, whichever was later; if convulsions recurred 30 minutes after LD, an additional 2 g IV/IM given and MD continued; therapy was considered failed if convulsions continued after 2 additional doses; no LD for women with imminent E N = 72 women and their babies Higher dose regimen: 'Pritchard's regimen': 4 g IV LD and 5 g IM as LD; 5 g IM/4 hours MD until 24 hours after last convulsion or abortion/birth, N = 54 women and their babies	Perinatal death, stillbirth, neonatal death	Funding: NR Conflicts: none
Marret 2007; RCT	France 1997-2003	N = 573 women and their babies Inclusions: pregnant women with a singleton, twin or triplet very preterm fetus < 33 weeks	FN	MgSO4: 4 g IV LD over 30 minutes, N = 286 women and their babies analysed	Perinatal death, stillbirth, neonatal death, Apgar score < 7 at 5 minutes, intubated at delivery (tracheal intubation and/or epinephrine), RDS, MV	Funding: supported by the French Department of Health obtained in 1997 and a grant from Rouen University Hospital

		GA if birth was expected or planned within 24 hours Exclusions: women could not have received betamimetics, aminoglycosides or steroids for ≥1 hour; women with foetuses with severe malformations or chromosomal abnormalities, or if they met ≥ 1 of the following criteria: hypotension, cardiac rhythm abnormalities, hydroelectrolyte abnormalities, renal insufficiency, ingestion during last 24 hours of calcium channel blockers, digitalins or indomethacin, persistent signs of cardiovascular toxicity or tachycardia > 1 hour after cessation of tocolytic intake, myasthenia or indication for emergency caesarean; women with pregnancy-associated vascular disease (PE, FGR, haemolysis, elevated liver-function test results, low-platelet syndrome, retroplacental haematoma)		Placebo: 40 mL infusion of isotonic saline over 30 minutes, N = 278 women and their babies analysed	(endotracheal ventilation), non-invasive ventilation, CLD (oxygen dependency at 36 weeks), apnoea and bradycardia, NEC, hypotension, seizures, IVH, PVL, any WMI, severe WMI, severe WMI or death	Conflicts: NR
Mirzamoradi 2014; qRCT	Iran 2010-2012	N = 92 women and their babies Inclusions: pregnant women with GA < 34 weeks, hospitalised for PROM and labour complaints; the absence of concomitant disease such as chorioamnionitis or a history of drug sensitivity to MgSO4; no	T	MgSO4: 4 g IV LD over 20 minutes; 2 g/hour IV LD until 24 hours after complete cessation of uterine contractions, N = 46 women and their babies Placebo, N = 46 women and their babies	Death > 28 days, before discharge (infant death), RDS, sepsis, IVH, NICU admission	Funding: NR Conflicts: none

		previous use of ; to 'curb' labour complain in a recent pregnancy; the absence of twin or multiple pregnancy Exclusions: probable chorioamnionitis; progress of labour (4 cm cervical dilatation); allergy or medical complications in combination with MgSO4; fatal fetal anomalies; non-reassuring fetal status; severe FGR; severe PE/E; maternal haemorrhage with haemodynamic instability				
Mittendorf 2002; RCT	USA 1995-1997	N = 57 women and their babies – in neuroprotective arm of the RCT Inclusions: women in active preterm labour (cervical dilation > 4 cm), with or without PROM, at > 24 but < 34 completed weeks GA, with reassuring fetal assessment, and absence of clinical features that were suggestive initially of infection or PE Exclusions: mothers with triplet or higher order gestations; women with PE	FN	MgSO4: 4 g IV bolus LD, N = 29 women and their babies Placebo: saline control, N = 28 women and their babies	Perinatal death, stillbirth, neonatal death, IVH, IVH grade 3/4, PVL	Funding: the United Cerebral Palsy Research and Educational Foundation Conflicts; NR
Moodley 1994; RCT	South Africa Time period NR	N = 228 women and their babies Inclusions: women with severe proteinuric hypertension (PE) (diastolic BP 110 mm Hg or greater, not settled with bed rest and sedation within 4-6	PE	MgSO4: 'Pritchard's regimen': 4 g IV LD over 20 minutes and 10 g IM LD; 5 g/4 hours IM MD, with a maximum of 6 doses, n = 112 women and their babies	Perinatal death, stillbirth, neonatal death (early)	Funding: support from MRC of South Africa Conflicts: NR

		hours, with proteinuria of + or greater, detected by a semi-quantitative 'dipstick' method in either a clean-catch specimen or a catheter specimen of urine), or judged to have imminent E requiring delivery (severe hypertension and other symptoms such as severe persistent headache, nausea and omitting, visual disturbances, and epigastric pain or signs such as clonus and brisk reflexes) (including twins and singleton pregnancies) Exclusions: prior anticonvulsant therapy or antihypertensive drugs		No treatment, N = 116 women and their babies		
Mundle 2012; RCT	India 2008-2009	N = 300 women and their babies Inclusions: all pregnant women diagnosed with PE whose providers deemed would benefit from MgSO4 – systolic BP ≥ 140 mm Hg or a diastolic BP ≥ 100 mm Hg and proteinuria ≥ 1+; had not given birth or were 24 hours or less postpartum; exhibited urine output > 100 mL or more during the previous 4 hours or > 25 mL/hour; agreed to comply with the study procedures; 18 years or older. Exclusions: women with E or seizing at the time of enrolment;	PE	IM MD: 'Pritchard's regimen': 4 g IV LD and 10 g IM LD; 5 g/4 hours IM MD continued for 24 hours and stopped when clinically indicated, N = 153 women and their babies IV MD: 'Zuspan's regimen': 4 g IV LD; 1 g/hour IV MD (using Springfusor pump) continued for 24 hours and stopped when clinically indicated, N = 147 women and their babies	Perinatal death	Funding: support from the John D. and Catherine T. Macarthur Foundation, and Go Medical, Subiaco, Australia (provided pump and tubing at reduced rate) Conflicts: NR

		received MgSO4 therapy 24 hours prior to study enrolment				
Orji 2012; RCT Abstract	Africa 2011	N = 170 women and their babies Inclusions: severe PE Exclusions: NR	PE	LD only: 4 g IV LD over 15 minutes, and 10 g IM MD, N = 85 women and their babies LD and MD: 'Pritchard's regimen': 4 g IV LD over 15 minutes and 10 g IM LD; 5 g IM/4 hours MD 24 hours, N = 85 women and their babies	Perinatal death	NR
Parashi 2017; RCT	Iran Time period NR	N = 120 women and their babies Inclusions: pregnant women with PROM at 34 weeks GA Exclusions: hypertension, PE, trauma, gestational or aggravated DM, any type of metabolic disease affecting the pregnancy outcome, long-term drug use, gestational histories affecting the pregnancy outcomes	FN	MgSO4: 6 g IV LD over 20-30 minutes; 2 g/hour MD during 12 hours before labour, N = 60 women and their babies Placebo: "conventional treatment with normal saline infusion", N = 60 women and their babies	Stillbirth, IVH, IVH grade 3/4H, intensive care unit stay (mean ± SD) (days)	NR
Pascoal 2019; RCT	Brazil 2015-2016	N = 62 women and their babies Inclusions: women with severe PE (defined by ACOG criteria), prescribed MgSO4 Exclusions: E prior to initial MgSO4 LD, use of other medicines or illicit drugs that could interfere with maternal haemodynamics, contraindications to MgSO4 (known hypersensitivity to the drug, oliguria with urinary output below 25 mL per hour, or severe myasthenia), acute or	PE	Lower dose regimen: 6 g IV LD over 20 minutes, 1 g/hour IV MD, N = 31 women and their babies Higher dose regimen: 6 g IV LD over 30 minutes; 2 g/hour IV MD, N = 31 women and their babies	Neonatal death, need for resuscitation, 'respiratory disorders', MV, NICU admission	Funding: supported by IMIP Conflicts: none

		chronic kidney disease and a diminished level of consciousness				
Rimal 2017; RCT	Nepal 2014-2015	N = 60 women and their babies Inclusions: diagnosed cases of severe PE who were admitted to the ward, gave written informed consent, and were in labour or planned for termination of pregnancy Exclusions: women < 20 GA, and who had received MgSO4 before admission to the ward	PE	LD only: 4 g IV LD over 5 minutes and 10 g IM LD, N = 30 women and their babies LD and MD: 'Pritchard's regimen': 4 g IV LD over 5 minutes and 10 g IM LD; MD every 3 hours IM for 24 hours from time of birth or last convulsion, N = 30 women and their babies All women: for recurrent convulsions, 2 g IV given over 5 minutes; MD continued until 24 hours after birth/last dose	Perinatal death, stillbirth, neonatal death, Apgar score < 7 at 0 minutes, Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, NICU admission	Funding: NR Conflicts: none
Rouse 2008; RCT	USA 1997-2004	N = 2241 women and their babies Inclusions: women carrying singletons or twins at 24 through 31 weeks GA, at high risk for spontaneous delivery because of ROM at 22-31 weeks GA, or because of advanced preterm labour with dilatation of 4-8 cm and intact membranes; or if an indicated preterm delivery was anticipated within 2-24 hours (e.g. because of FGR) Exclusions: women where delivery was anticipated within < 2 hours or if cervical dilatation > 8 cm; with ROM < 22 weeks,	FN	MgSO4: 6 g IV LD over 20-30 minutes; 2 g/hour IV MD until birth or 12 hours, N = 1096 women and their babies Placebo: identical appearing placebo as above, N = 1145 women and their babies All women: if delivery had not occurred after 12 hours, the infusion was discontinued and resumed when delivery was imminent; if at least 6 hours had passed another LD was given	Perinatal death (fetal or infant death < 1 year), Apgar score < 7 at 5 minutes, intubated at delivery, resuscitation in delivery room (oxygen bag, mask or both; any; chest compressions), RDS, MV, CLD (BPD), NEC, sepsis (culture-proven), hypotension (treated with vasopressors), PDA, ROP, generalised hypotonicity, seizures, IVH, IVH grade 3/4, PVL Hirtz 2015 (presents data for all children, term ultrasounds, N = 1776 babies; children born < 32 weeks GA, most severe findings, N = 1613 babies): IVH, IVH grade 3/4, PVL, ventriculomegaly,	Funding; support from NICHD and the National Institute of Neurological Disorders and Stroke Conflicts: none

		with unwillingness of the obstetrician to intervene for the benefit of the fetus, major fetal anomalies or death, maternal hypertension or PE, maternal contraindications to MgSO4 (e.g. severe pulmonary disorders), and receipt of IV MgSO4 within the previous 12 hours			echodensity, echolucency, any of above Horton 2015 (presents data for singleton children born to mothers with PPROM only, N = 1259 babies): death (to hospital discharge), Apgar score < 7 at 5 minutes, RDS, NEC, sepsis (culture-proven), ROP, IVH grade 3/4, PVL, composite (any of RDS, NEC, sepsis, ROP, IVH grade 3/4, PVL, death) Vilchez 2018 (presents data for women with singleton pregnancies, with no documented congenital anomalies, that received MgSO4 or placebo, N = 1894 babies; and reports subgroup analyses based on race/ethnicity: African-America, N = 852; Caucasian, N = 686; Hispanic, N = 338; Asian, N = 18): stillbirth/death, low Apgar score, resuscitation, assisted ventilation, RD, TTN, surfactant use, NEC, ROP, NICU admission, composite outcome (≥ 1 complication) Vilchez 2018b (presents data for 2096 children born to women with BMI data; and reports subgroup analyses based on BMI): perinatal death (assumed to be as per Rouse 2008)	

Saha 2017; RCT	India Time period NR	N = 41 women and their babies Inclusions: patients with antepartum and intrapartum E; E was diagnosed if a patient with PE or hypertension experienced convulsions after 20 weeks GA Exclusions: patients with E who experienced complications such as coma, pulmonary oedema, oliguria, ICH, who had already received MgSO4, phenytoin and diazepam before attending the hospital	E	IM MD: 'Zuspan's regimen': 4 g IV LD; 1 g/hour IV MD for 24 hours after last convulsion or birth, N = 20 women and their babies IV MD: 'Dhaka regimen': 4 g IV LD and 6 g IM LD; 2.5 g/4 hour IM MD for 24 hours after last convulsion or birth, N = 21 women and their babies All women: in cases of convulsion recurrence, 2 g IV administered	Perinatal death, stillbirth, neonatal death, Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, RD, jaundice, hypotonia, NICU admission	Funding: Department of Science and Technology (DST Government Organisation), Chandigarh Administration, India Conflicts: none
Shilva 2007; RCT Brief communication	India Time period NR	N = 50 women and their babies Inclusions: women with antepartum E Exclusion: renal failure, pulmonary oedema, having received MgSO4 before coming into the hospital	E	Lower dose regimen: 'Dhaka regimen', N = 25 women and their babies Higher dose regimen, N = 25 women and their babies All women: in cases of convulsion recurrence, 2 g IV administered	Perinatal death, stillbirth, neonatal death, Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, RD, respiratory depression, jaundice, hypotension, hypotonia, requirement for calcium gluconate, NICU admission	NR
Shreya 2014; qRCT	India 2010-2012	N = 80 women and their babies Inclusions: all pregnant women with imminent E having one of the following: persistent headache, visual disturbances, epigastric pain; or pregnant women with E: convulsions in a pregnant woman that cannot be attributed to other causes Exclusions: not willing to participate; women receiving any anticonvulsant or MgSO4 prior to arrival at the hospital; contraindications for MgSO4	PE/E	LD only: 4 g IV LD over not less than 3 minutes, and 4 g IM LD, N = 40 women and their babies LD and MD: 'Pritchard's regimen': 4 g IV LD over not less than 3 minutes, followed by 10 g IM LD; 5 g IM/4 hours MD, for 24 hours following convulsion or birth, N = 40 women and their babies All women: 2 g IV over 2 minutes for convulsion recurrence after 30 minutes	NICU admission for RD, NICU admission for early onset sepsis, NICU admission for late onset sepsis, NICU admission for meconium aspiration syndrome, NICU admission for birth asphyxia, NICU admission	NR

		such as respiratory depression, renal failure, hypersensitivity, heart block, Addison's disease, severe hepatitis, myocardial damage, myasthenia gravis				
Singh 2011; RCT	India 2 year period	N = 158 women and their babies Inclusions: patients presenting with E Exclusions: women diagnosed with other causes of convulsions in pregnancy like cerebral malaria and epilepsy	E	IM: 'Pritchard's regimen': 4 g IV LD over 3-5 minutes and 10 g IM LD; 5 g/4 hours IM until 24 hours after delivery or last convulsion, N = 60 women and their babies IV: 'Zuspan's regimen': 4 g IV LD over 5-10 minutes; 1 g/hour IV MD until 24 hours after delivery or last convulsion, N = 49 women and their babies IV: 'Sibai's regimen': 6 g IV LD over 15-20 minutes; 2 g/hour IV until 24 hours after delivery or last convulsion, N = 49 women and their babies All women: if convulsions persisted 15 minutes post LD, 2 g IV given	Perinatal death, stillbirth, neonatal death, NICU admission	NR
Tangmanowutthikul 2019	Thailand 2018	N = 86 women and their babies Inclusions: women with PE with severe features (according to ACOG guideline), admitted with GA ≥ 24 weeks Exclusions: serum creatinine > 1.3 mg/dL, hypersensitivity to MgSO4, myocardial damage, diabetic coma, heart block and myasthenia gravis.	PE	Lower dose regimen: Weight-adjusted protocol: 4 g IV LD; IV MD: 1.2 g/hour for < 60 kg, 1.3 g/hour for 60-79.9 kg, 1.4 g/hour for 80-99.9 kg and 1.5 g/hour for ≥ 100 kg; continued until 24 hours after birth, N = 43 women and their babies	Perinatal death, stillbirth, neonatal death, NICU admission	Funding: support from Dr. Thammanoon Wisittanawat, director of Udonthani Hospital Conflicts: None

				Higher dose regimen: 4 g IV LD; 2 g/hour IV MD, N = 43 women and their babies Serum concentrations monitored at 2 and 4 hours, adjusted and continued until 24 hours after birth		
Terrone 2000; RCT	USA 1997-1998	N = 160 women and their babies Inclusions: singleton or twin gestation between 24-34 weeks GA, spontaneous preterm labour (advancement seen on cervical examination with uterine contractions while the patient was admitted to the triage unit or dilatation of 2 cm and effacement of 80% with ≥ 6 uterine contractions/hour), and ability to provide informed consent Exclusions: higher-order multiple gestations, ROM, non-reassuring fetal assessment, evidence of intrauterine infection, treatment with any tocolytic agent before maternal transport, and inability or refusal to provide informed consent, inability to tolerate high doses of MgSO4 (e.g. renal failure)	T	Lower dose regimen: 4 g IV LD over 20 minutes; 2 g/hour IV MD, N = 78 women and their babies Higher dose regimen: 4 g IV LD over 20 minutes; 5 g/hour IV MD, N = 82 women and their babies All women: if after 1st hour contractions/cervical dilation or effacement continued MD increased by 1 g/hour until successful T or treatment failure	Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes	Funding: supported by Vicksburg Hospital Medical Foundation Conflicts: NR
Witlin 1997; RCT	USA 1995-1996	N = 135 women and their babies Inclusions: women with a GA of at least 37 weeks, with recent-onset hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90	PE	MgSO4: 6 g IV LD over 15-20 minutes; 2 g/hour IV MD, continued until 12 hours postpartum, N = 67 women and their babies	Apgar score ≤ 6 at 1 minute, Apgar score ≤ 6 at 5 minutes	NR

		mm Hg) and proteinuria (≥ 300 mg/24 hours) Exclusions: women meeting criteria for severe PE; fetal malpresentation; congenital anomalies; non-reassuring fetal testing; contraindications to the use of MgSO4; contraindications to a trial of labour		Placebo: saline infusion identical in appearance, N = 68 women and their babies		

Abbreviations: ACOG: American College of Obstetrics and Gynecologists; BP: blood pressure; BPD: bronchopulmonary dysplasia; CLD: chronic lung disease; CP: cerebral palsy; dL: decilitre; DM: diabetes mellitus; DST: Defence Science and Technology; E: eclampsia; FGR: fetal growth restriction; g: grams; GA: gestational age; HMD: hyaline membrane disease; ICH: intracranial haemorrhage; IM: intramuscular; IMIP: Instituto de Medicina Integral Prof. Fernando Figueira; IQR: interquartile range; IUD: intrauterine death; IUGR: intrauterine growth restriction; IV: intravenous; IVH: intraventricular haemorrhage; kg: kilograms; LD: loading dose; MD: maintenance dose; mg: milligrams; MgSO4: magnesium sulphate; MRC: Medical Research Council; MV: mechanical ventilation; N: number; NEC: necrotising enterocolitis; NHMRC: National Health and Medical Research Council; NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development; NICU: neonatal intensive care unit; NIH: National Institutes of Health; NINDS: National Institute of Neurological Disorders and Stroke; NR: not reported; PDA: patent ductus arteriosus; PE; pre-eclampsia; PI: primary investigator; PIH: pregnancy-induced hypertension; PPROM: preterm premature rupture of membranes; PROM: premature rupture of membranes; PVL: periventricular leucomalacia; qRCT: quasi-randomised controlled trial; RCT: randomised controlled trial; RD: respiratory distress; RDS: respiratory distress syndrome; ROM: rupture of membranes; RR: respiratory rate; RVO: right ventricular output; SCBU: special care baby unit; SD: standard deviation; sGOT: serum glutamic-oxaloacetic transaminase; SVC: superior vena cava; TTN: transient tachypnoea of the newborn; UK: United Kingdom; UNDP/UNFPA/WHO: United National Development Programme/United National Population Fund/Word Health Organization; USA: United States of America; WMI: white matter injury

Non-randomised studies

Study; design	Setting	Participants	MgSO4 indication	Relevant comparison groups	Outcome measure(s)	Funding and conflicts
Adama-Hondegla 2013; unclear: results appear to be presented as RCS with CCS(N)	Togo 2007-2009	N = 170 women, 178 babies Inclusions: (singleton/twin) newborns > 28 weeks GA from women diagnosed with E before birth (definition provided) Exclusions: NR	E	1: Babies still living at the 7th day of life, N = 147 babies 2: Stillbirths and neonatal deaths in the 1st 7 days, N = 31 babies	MgSO4 exposure (10 g in 500 mL, IV 20 drops/minute)	NR
Alexander 2006; PCS	USA 2000-2004	N = from 72004 births, 87 women with E and their babies included in analyses Inclusions: women with and without GH (detailed definition provided) Exclusions: NR	GH/PE	1: No GH and no MgSO4 with E, N = 49 women and their babies 2: GH and IV MgSO4 with E, N = 11 and their babies 3: GH and no MgSO4 with E, N = 27 and their babies	Adverse outcome composite, perinatal death	NR
Alston 2016; NCCS	USA 2004-2009	N = 169 babies Inclusions: neonates born from singleton pregnancies between 24-34 weeks GA Exclusions: birth before 24 weeks GA or after 34 weeks GA, indication for preterm birth was something other than spontaneous preterm labour, or the infant chart could not be linked to the maternal chart	T	1: Period of MgSO4 use for T (2004-2006) (6 g IV LD; 2 g/hour IV MD), N = 102 (90 babies in analyses) 2: Period of no MgSO4 use for T (2007-2009), N = 67 (64 babies in analyses)	Hospital stay (days) (mean, no measure of variance), neonatal death, RDS, BPD, sepsis, NEC, IVH	NR
Ambadkar 2017; PCS	Authors from India 1 year period	N = 120 women and babies Inclusions: women admitted to labour ward ≥ 34 weeks GA with PE/E Exclusions: women who received different dosages of MgSO4, who required discontinuation of MgSO4 due to toxicity, who had chronic medical disorders or anomalous fetuses, APH, or any other co-existing major obstetric problem	PE/E	1: MgSO4 (Pritchard's regimen: 4 g IV over 10 minutes and 5 g IM LD; 5 g/4 hours IM MD), N = 60 babies 2: Matched patients with PE not requiring MgSO4 or any other anticonvulsant, N = 60 babies 1: MgSO4 and NICU admission, yes, N = 13 babies 2: MgSO4 and no NICU admission, N = 47 babies	Neonatal death, NICU admission, hypotonia, RD, meconium passage (< 6, 6-12, > 12 hours) NICU admission: MgSO4 dose (categories: LD, LD + 1, LD + 2, LD + 3, LD + 4, LD + 5, LD + 7 doses), duration of MgSO4 (< 6, 6-12, 12-18, ≥ 18 hours), time elapsed since last MgSO4 dose	Funding: NR Conflicts: none

					and birth (1-2, 2-3, 3-4, 4-5, > 5 hours)	
Bajaj 2018; RCS	USA 2012-2013	N = 7014 babies Inclusions: babies born at 29+0 to 33+6 weeks GA who were enrolled in the NRN MPT registry Exclusions: babies in whom a prenatal diagnosis caused a decision to withdraw or limit intensive care	NR	1: Routine care without resuscitation, N = 1684 babies 2: Oxygen or CPAP but not ventilation, intubation or CPR, N = 2279 babies 3: Bag and mask ventilation but not intubation or CPR, N = 1831 babies 4: ETT intubation but not CPR, N = 1034 babies 5: CPR, N = 186 babies	MgSO4 exposure	Funding: supported by NIH, NICHD, NCATS Conflicts: none
Basu 2012; RCS	USA 2006-2010	N = 475 babies Inclusions: preterm neonates born between 24-32 weeks GA admitted to the NICU Exclusions: neonates with major congenital malformations or chromosomal anomalies, and those born to women who received MgSO4 for PE/E	FN	1: MgSO4 (6 g IV LD over 30 minutes; 2 g/hour IV MD until birth), N = 289 babies 2: No MgSO4, N = 186 babies	Survival without IVH/PVL, resuscitation, intubation, BPD, IVH/PVL. ROP, PDA, LOS (days) (mean ± SD), death	NR
Belden 2017; unclear: results appear to be presented as RCS with CCS(N)	USA 2012-2013	N = 83 babies born to 72 women Inclusions: neonates born at 24 weeks GA or greater who were admitted to the NICU and whose mothers received MgSO4 infusions prior to birth Exclusions: neonates with independent factors that could lead to feeding intolerance, including congenital abnormalities, such as gastroschisis and neonatal abstinence syndrome	FN/PE	1: Enteral feeding intolerance, N = 49 babies 2: No feeding intolerance, N = 34 babies 1: MgSO4 > 80 g, N = NR 2: MgSO4 ≤ 80 g, N = NR	MgSO4 dose (g) (mean ± SD) Enteral feeding intolerance, parenteral nutrition (days) (measure NR)	Funding: NR Conflicts: none
Bertello Grecco 2019; PCS Abstract	Authors from Argentina Time period NR	N = 93 women and their babies Inclusions: women > 18 years with PE Exclusions: NR	PE	1: MgSO4 IV ≤ 24 hours, N = 51 women and their babies 2: MgSO4 IV > 24 hours, N = 42 women and their babies	Neonatal death, respiratory depression, hypotonia, NICU admission	NR

Black 2006; PCS	Authors from USA Time period NR	N = 134 babies Inclusions: preterm infants who received neonatal care, < 35 weeks GA at birth and considered high-risk for developmental and health problems because they either weighed < 1,500 g at birth or required MV Exclusions: infants with congenital diagnoses associated with developmental problems (such as Down syndrome, congenital hydrocephalus, or microcephaly) or symptomatic from substance exposure; infants with family situations such that obtaining consent would be impossible or intrusive	PE/PIH/HELLP/T	1: MgSO4 with (N = 45)/without (N = 5) steroids, N = 50 babies 2: No MgSO4 with (N = 38)/without steroids (N = 46), N = 84 babies	Ventilation (days) (mean ± SD), methylxanthines (days) (mean ± SD), NBRS (mean ± SD), IVH	Funding: NIH NINR Conflicts: none
Blackwell 2002; PCS	Authors from USA Time period NR	N = 39 babies Inclusions: term women (≥ 37 weeks GA) with PE (mild or severe) who received MgSO4, and controls who did not receive MgSO4 Exclusions: FGR (birthweight < 10th centile for GA), multiple gestations, fetal structural anomalies, clinical chorioamnionitis or prior exposure to MgSO4	PE	1: MgSO4 (6 g IV LD over 20-30 minutes; 2 g/hour IV MD until birth), N = 13 babies 2: No MgSO4, N = 26 babies	Troponin I ≥ 1.0 ng/mL	NR
Bonta 2000; PCS Abstract	USA 1995-1999	N = 379 women and babies Inclusions: women requiring IV MgSO4 who delivered while receiving treatment Exclusions: NR	T	1: MgSO4 IV < 72 hours, N = 199 babies 2: MgSO4 IV > 72 hours, N = 45 babies 3: No MgSO4, N = 135 babies	HsPDA treated with indomethacin	NR
Bozhurt 2016; RCS	Turkey 2010-2012	N = 387 babies Inclusions: preterm infants < 32 weeks GA born to women with PE, who survived to 2 years Exclusions: NR	PE	1: MgSO4 (6 g IV LD over 20 minutes; 2 g/hour IV MD for 24 hours), N = 59 babies 2: No MgSO4, N = 328 babies	RDS, BPD, hypoglycaemia, apnoea, PDA, IVH grade 3/4 and PVL, PVL only, culture proven sepsis, NEC grade ≥ II, ROP grade > 3	Funding: NR Conflicts: none

Boyle 2018; RCS Abstract	USA 2012-2015	N = 285 women and babies Inclusions: women who delivered non-anomalous singleton fetuses at term by primary caesarean with a category 2 or 3 FHR tracing as an indication for birth Exclusions: NR	NR	1: MgSO4, N = 16 babies 2: No MgSO4, N = 271 babies [note discrepancy between total N and group Ns reported]	Composite adverse neonatal outcome (defined as Apgar score < 7 at 5 minutes, arterial cord pH < 7.1 and/or base deficit ≥ 12, admission to the NICU, need for immediate neonatal resuscitation beyond bulb suction and stimulation, or hospitalisation ≥ 3 days)	NR
Brazy 1982; RCS	USA 1979	N = 56 babies Inclusions: infants born before 36th week GA to women with early and severe hypertension in pregnancy (resting diastolic BP ≥ 110 mmHg and proteinuria); for each infant of mother with hypertension, a control infant (born to a normotensive mother) was selected on the basis of GA and birth order Exclusions: no major congenital abnormalities, major disease (IDD, sickle cell anaemia, renal failure, heart disease), no known exposure to insulin or tocolytic agents; for control infants: no known exposure to sedatives, diuretics or drugs with antihypertensive properties	ESHP	1: Hypertensive women treated with IV MgSO4, N = 28 babies 2: Non-hypertensive women, with no MgSO4, N = 28 babies	Days hospitalised (mean ± SD), thrombocytopenia, leukopenia, neutropenia, DIC, severe respiratory disease, TTN, delayed adaptation, PDA, hypotension, delayed stooling (> 24 hours), ileus, hypotonia, other disease (CNS haemorrhage, air block, acute renal failure, NEC), neonatal death, death after 28 days of age, before hospital discharge, stillbirth	NR
Brookfield 2015; unclear: results appear to be presented PCS with CCS(N) Abstract	Authors from USA 2012-2014	N = 55 women and babies Inclusions: pregnant women prescribed MgSO4 for FN/PE < 32 weeks GA (4 g LD; 2 g/hour MD) Exclusions: NR	FN/PE	1: Resuscitation (oxygen, bag/mask, intubation, chest compressions), N = 27 babies 2: No resuscitation, N = 28 babies	MgSO4 dose (g) (mean ± SD)	NR
Brookfield 2016; RCS (secondary analysis of RCT) Abstract	NR (see Rouse 2008)	N = 1496 women and babies Inclusions: women who had received 1 course of antenatal steroids and had PPROM at < 32 weeks Exclusions: NR	FN	1: MgSO4, N = 735 babies 2: No MgSO4, N = 761 babies	RDS, ventilation	NR

Brown 2019; unclear, appears to be presented as CCS Abstract	Canada 2002-2016	N = 218 babies Inclusions: babies born < 31 weeks GA diagnosed with SH (SBP > 100 mmHg requiring treatment, before discharge from NICU, or on 3 consecutive occasions during outpatient follow-up), and controls matched for GA, sex and birthweight Exclusions: babies who died < 7 days of age	NR	1: SH, N = 109 babies 2: No SH, N = babies	MgSO4 exposure	NR
Canterino 1999; RCS	USA 1990-1996	N = 918 babies Inclusions: inborn neonates with GA from 23-34 weeks and birthweights from 500-1750 g Exclusions: major congenital anomalies, neonatal death by day 3, transfers before day 3	PE/T	1: MgSO4, N = 398 babies 2: No MgSO4, N = 520 babies 1: Abnormal cranial sonograms, N = 39 babies 2: Normal findings, N = 125 babies 1: Severe lesions, N = 27 babies 2: Normal findings, N = 127 babies	Apgar score < 7 at 5 minutes, RD, neonatal death, abnormal sonograms (any PVL or IVH), severe lesions (any PVL, PVL with IVH, or IVH grade 3/4)	NR
Cawyer 2019; RCS Abstract	USA 2008-2011	N = 2468 women and their babies Inclusions: women with PE without severe features at any time in pregnancy, who delivered > 32 weeks GA Exclusions: NR	PE	1: MgSO4 at any time during delivery hospitalisation, N = 1353 babies 2: No MgSO4, N = 1115 babies	Perinatal or neonatal death, NICU admission	NR
Cho 2014; RCS Abstract	NR	N = 570 women and babies Inclusions: pregnant women with preterm birth and their paired neonates Exclusions: NR	NR	1: MgSO4 IV, N = 101 babies 2: No MgSO4, N =469 babies	Hypocalcaemia	NR
Chowdhury 2009; unclear: PCS (or NRT)	India 2001-2015	N = 630 women (529 babies born to antepartum/intrapartum cases) Inclusions: consecutive women with clinical diagnosis of E regardless of when/where the convulsions occurred, whether pregnancy was single/multiple, and whether baby had been delivered Exclusions: women with convulsions due to epilepsy or other causes	E	1: MgSO4 by Pritchard's regimen (8 g IV over 2-3 minutes and 5 g IM in each buttock LD; 5 g/4 hours IM MD for at least 24 hours after birth/last convulsion), N = 480 women (406 babies born to antepartum/intrapartum cases) 2: MgSO4 by low-dose IV regimen (4 g IV LD over 2-3 minutes; 0.6	Stillbirth, early neonatal death due to birth asphyxia and prematurity (1st 7 days), perinatal death	NR

				g/hour IV MD for at least 24 hours after birth/last convulsion), N = 150 women (123 babies born to antepartum/intrapartum cases)		
Chun 2014; RCS English abstract; article in Korean	Authors from Korea 2003-2013	N = 209 women and babies Inclusions: women who delivered vaginally with the diagnosis of PE Exclusions: CD	PE	1: MgSO4, N = 119 babies 2: No MgSO4, N = 90 babies	Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, NICU admission	CD
Cuff 2018; RCS	Authors from USA 2014-2015	N = 224 women and their babies: 44 women and 54 babies exposed to MgSO4 within 12 hours of birth Inclusions: women who had a preterm birth < 32 weeks GA and had received MgSO4 prior to birth Exclusions: women with PE, known fetal anomalies, and/or stillbirth	FN	1: 2014 (dosing according to BEAM trial: 6 g IV LD; 2 g/hour IV MD for 12 hours), N = 18 babies exposed within 12 hours of birth 2: 2015 (dosing according to PREMAG trial: 4 g IV MD; no MD), N = 36 babies exposed within 12 hours of birth	Apgar score < 7 at 5 minutes, ROP grade 3/4, IVH grade 3/4	Funding: NR Conflicts: none
Das 2015; PCS	India 2011-2012	N = 100 women and their babies Inclusions: women with antepartum or intrapartum E (definition provided) > 20 weeks GA, presenting in obstetric, labour and/or wards, who have informed consent Exclusions: women with complications such as renal failure, severe pulmonary oedema with respiratory failure, cerebrovascular accident, and DIC, who received MgSO4 before coming to hospital, with known seizure disorders, with multiple pregnancies, with infants with congenital malformations or birthweights < 1000 g	E	1: 8 g MgSO4, N = 20 babies 2: > 8 g MgSO4, N = 80 babies MgSO4: low-dose regimen: 3 g IV over 15 minutes and 2.5 g IM in each buttock LD; 2.5 g/4 hours IM in alternate buttocks MD	Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, Apgar score ≤ 3 at 1 minute, Apgar score ≤ 3 at 5 minutes, respiratory depression, intubation in delivery room, bradycardia, hypotonia, hyporeflexia, NICU admission, significant respiratory support in NICU, time to 1st stool > 24 hours, time to 1st void > 48 hours, number of episodes of feeding intolerance ≥ 3, stillbirth, neonatal death due to complications of hypermagnesemia	Funding: Burdwan Medical College Conflicts: none

Deering 2005; RCS	USA 12 month period	N = 221 babies Inclusions: all preterm admissions Exclusions: congenital anomalies, admission > 24 hours of life, hydrops fetalis, no SNAP score calculated, transport back to the referring hospital before all information could be obtained	PE/T	1: MgSO4, N = 103 babies 2: No MgSO4, N = 118 babies	SNAP score (mean ± SD), SNAP score > 10	Funding: no funding Conflicts: NR
De Jesus 2015; RCS	USA 2011-2012	N = 1544 babies Inclusions: infants born between 23+0-28+6 weeks GA and enrolled in the generic database Exclusions: NR	FN/PIH/T	1: MgSO4, N = 1091 babies 2: No MgSO4, N = 453 babies	Delivery room resuscitation (PPV via bag and mask, any CPAP devices, intubation, chest compression and epinephrine), delivery room intubation, day 1 MV, day 1 ET MV, day 3 MV, day 3 ET MV, hypotension, PDA treated (medical or surgical), RDS, pulmonary haemorrhage, traditional BPD, late onset sepsis/meningitis, NEC stage II or greater, ROP any stage, IVH or parenchymal haemorrhage, cPVL, death, cumulative days on MV (median, Q1, Q3), cumulative days on oxygen support (median, Q1, Q3), LOS (median, Q1, Q3)	Funding: NIH and NICHD Conflicts: none
del Moral 2007; RCS	USA 1995-2004	N = 954 babies included, 941 babies analysed Inclusions: neonates with birthweights between 500-1000 g admitted to NICU Exclusions: NR	PE/T	1: MgSO4 (4-6 g IV bolus LD; 2 g/hour IV MD), N = 546 babies 2: No MgSO4, N = 395 babies	PDA, death, IVH grade 3/4, PVL	Funding: Supported by University of Miami, Project Newborn Conflicts: NR
delValle 1998; unclear: PCS Abstract	NR (“single regional perinatal center”)	N = 110 babies Inclusions: all VLBW Exclusions: NR	NR	1: MgSO4, N = 34 babies 2. No MgSO4, N = 76 babies	Surfactant treatment, indomethacin treatment, PDA, NEC, IVH, PVL	NR

	1994					
Derks 2016; NCCS Abstract	Netherlands 2011-2015	N = 207 babies Inclusions: extremely preterm infants born 24-28 weeks GA Exclusions: NR	FN	1: 2 years post MgSO4 implementation, N = 99 babies 2: 2 years pre MgSO4 implementation, N = 108 babies	PWML at 30 and 40 weeks MRI, early intubation for respiratory insufficiency, hypotension	NR
De Silva 2018; RCS (within report of ITS)	Canada 2011-2015	N = 14108 babies Inclusions: babies born at 24+0-31+6 weeks GA and collected information about use of MgSO4 for FN as well as pregnancy characteristics Exclusions: babies with congenital anomalies were excluded, as in prior CNN analyses	FN	1: MgSO4 for FN, N = 5314 babies 2: No MgSO4, N = 7238 babies 3: MgSO4 for another indication, N = 1556 babies	Intensive resuscitation (either chest compressions or intubation and ventilation or epinephrine administration in the delivery room)	Funding: CIHR Conflicts: none
de Veciana 1995; RCS	USA 1985-1991	N = 73 women, 80 babies Inclusions: women with diagnosis of advanced preterm labour (occurrence of painful, palpable uterine contractions ≥ 2 times in 10 minutes for > 1 hour); cervical dilation ≥ 3.5 cm on admission; estimated GA < 36 weeks; available information of labour course and pregnancy outcome Exclusions: documented ROM, amniocentesis documenting pulmonary maturity; history consistent with incompetent cervix ± cerclage in place; clinical evidence of amnionitis; vaginal bleeding on admission	T	1: MgSO4 IV (4-6 g IV LD; 2-4 g/hour IV MD for at least 48 hours and no longer than 7 days), N = 44 women, 48 babies 2: No MgSO4 tocolysis, N = 29 women, 32 babies	Days in hospital (mean ± SD), days intubated (mean ± SD), RDS (mild to severe), RDS severe, IVH grade I-IV, NEC, neonatal death, Apgar score < 7 at 5 minutes	NR
Downey 2017; RCS	USA 2007-2013	N = 28035 babies Inclusions: ELBW (≤ 1000 g) infants discharged during study period Exclusions: outborn infants, and infants with severe congenital anomalies	FN/PE/T	1: MgSO4, N = 11789 1: No MgSO4, N = 16246	SIP, neonatal death in 1st 21 days of life, surgical NEC, medical NEC, death, NEC or SIP, IVH grade 3/4	Funding: some authors receive support from NIH, USA government, NICHD, NHLBI, FDA, Cempra Pharmaceuticals, and 'industry'; others report no

						conflicts. Sponsors had no involvement in design, collection, analysis, interpretation, writing and submission.
Drassinower 2015; RCS (secondary analysis of RCT) Abstract	NR (see Rouse 2008)	N = 1047 women and babies Inclusions: non-anomalous, singleton pregnancies receiving MgSO4 or placebo, exposed for > 3 hours at time of birth Exclusions: women exposed for < 3 hours or if drug was discontinued prior to birth	FN	1: MgSO4, N = 461 babies 2: Placebo, N = 586 babies	Composite of immediate outcomes (Apgar score < 7 at 5 minutes, oxygen administration in delivery room, intubation, chest compressions, hypotension, hypotonicity), Apgar score < 7 at 5 minutes, oxygen bag, mask or both, intubation, chest compressions, hypotension treated with vasopressors, generalised hypotonicity, RDS, MV, seizures, IVH, death	NR
Duffy 2012; RCS	USA 4 year period	N = 5387 women and babies Inclusions: women who reached the second stage of labour, born ≥ 37 weeks GA, and had ≥ 10 minutes of EFM tracing in 30 minutes before birth and an available umbilical arterial cord blood gas, with singleton pregnancies, cephalic presentation and no known fetal anomalies Exclusions: women who delivered by caesarean before labour or before complete dilatation	Severe PE	1: MgSO4 (6 g IV LD; 2 g/hour IV MD), N = 248 babies 2: No MgSO4, N = 5139 babies	Composite adverse outcome (fetal acidemia, base excess ≤ -12.00, SCBU or NICU admission)	Funding: 1 author supported by Robert Wood Johnson Foundation Conflicts: none
Edwards 2018; RCS (secondary	USA 1997-2004	N = 1944 women and babies	FN	Chorioamnionitis, N = 228 mother and babies	MgSO4 exposure	Funding: NR Conflicts: none

analysis of RCT), also presents CC(N) analysis		Inclusions: women considered at high risk of preterm birth between 24-31 weeks GA (risk based on presentation with ROM between 22-31 weeks GA, spontaneous labour with cervical dilation of 4-8 cm, or providers anticipated an indicated preterm birth within 2-24 hours) Exclusions: multiple gestation, chromosomal abnormalities, stillbirth, congenital anomalies, or missing information regarding the presence or absence of clinical chorioamnionitis		1: MgSO4, N = 109 babies 2: No MgSO4, N = 119 babies No chorioamnionitis, N = 1716 women and babies 1: MgSO4, N = 839 babies 2: No MgSO4, N = 877 babies MgSO4: 6 g IV LD over 20-30 minutes; 2 g/hour IV MD until birth or 12 hours; re-treatment permitted	IVH, NEC, BPD	
Elimian 2002; RCS	USA 1998-2001	N = 401 babies Inclusions: premature neonates born between 23-34 weeks GA following preterm labour with intact membranes or PPROM Exclusions: neonates exposed to MgSO4 for seizure prophylaxis	T	1: MgSO4 (4 g IV LD; 2-3 g/hour IV MD), N = 190 babies 2: No to MgSO4 with/without other tocolytics, N = 211 babies 1: MgSO4 for > 24 hours, N = 79 babies 2. MgSO4 for ≤ 24 hours, N = 111 babies	Apgar score < 7 at 5 minutes, RDS, surfactant, antibiotics, PDA, IVH/PVL, NEC, sepsis, neonatal death (1st 28 days)	NR
Elliot 2003; RCS Abstract	Authors from USA 1997-2003	N = 14092 babies N = 9782 babies in groups of interest (excluded terbutaline and combination T groups) Inclusions: 24-32 weeks GA at birth, no major congenital anomalies, no PE, birthweight > 400 g Exclusions: NR	T	1: MgSO4, N = 6186 babies 2: No MgSO4, N = 3596 babies	Neonatal death, IVH, NEC, ROP	NR
Farkouh 2001; RCS	USA 1997-2000	N = 12876 babies Inclusions: non-anomalous live born babies admitted to the NICU between 23-34 completed weeks GA	PE/T	1: MgSO4, N = 4612 babies 2: No MgSO4, N = 8264 babies	Neonatal death (in NICU < 28 days)	Funding: supported by Pediatrix Medical Group Conflicts: NR

		Exclusions: newborns transferred to/from an outside facility < 28 days, or whose discharge status was unknown				
FineSmith 1997; CCS	USA 1992-1994	N = 54 babies (from sample of 492) Inclusions: birthweight < 1750 g, survival for > 7 days, ≥ 1 CUS > 7 days, with all information on infant's chart/labour and birth record: GA, history of maternal complications and reason for prematurity, length of ROM, antenatal steroid exposure, MgSO4 exposure, other tocolytic agent exposure, mode of birth, evidence of PE, Apgar score, days intubation Additional inclusions for cases: cPVL Additional inclusions for controls: selected from pool infants with normal CUS or IVH grade 1; control pool infants with birthweight outside of range in cPVL group were removed; 2 controls selected per case Exclusions: NR	PE/T	1: cPVL, N = 18 babies 2: No cPVL, N = 36 babies	MgSO4 exposure	NR
Gano 2016; unclear: results appear to be presented as PCS with CCS(N)	USA 2011-2015	N = 73 babies Inclusions: premature newborns < 33 weeks GA admitted to NICU Exclusions: clinical evidence of a congenital malformation or syndrome, congenital infection or status too unstable for transport to MRI	FN/PE/T	1: MgSO4, N = 49 babies 2: No MgSO4, N = 24 babies 1: Cerebellar haemorrhage, N = 27 babies 2: No cerebellar haemorrhage, N = 46 babies	Cerebellar haemorrhage (and size), WMI, IVH MgSO4 exposure	Funding: supported by NIH; 1 author supported by University of California (funded Mark and Lynne Benioff and Bill and Melinda Gates Foundation) Conflicts: none
Garcia Alonso 2018; PCS	Spain 2012-2015	N = 118 babies Inclusions: infants born before 32 weeks GA whose mothers received MgS04 as a	FN	1: MgSO4 (4 g IV LD over 30 minutes; 1 g/hour IV MD until birth	Resuscitation, IMV, surfactant, BPD, PDA, death, IVH, NEC, PVL, ROP	Funding: NR Conflicts: none

		neuroprotective agent and who were admitted to the NICU, and infants with same GA, who were born in the same time period Exclusions: infants with other risk factors that contributed to an immediate poor development: a polymalformed patient and another patient who passed away during the 1st hour of life after a placental abruption		or 24 hours; re-treatment permitted), N = 62 babies 2: No MgSO4, N = 56 babies		
Gasparyan 2017; unclear: PCS English abstract; article in Russian	CD	N = 62 women and babies Inclusions: neonates of recurrent delivering women born between 27-28 weeks GA Exclusions: CD	FN	1: MgSO4, N = 37 babies 2: No MgSO4, N = 25 babies	IVH, IVH grade 3/4	CD
Ghidini 2001; CCS	USA 1995-1996	N = 69 babies Inclusions for cases: consecutive infants diagnoses with NEC Inclusions for controls: each case matched with 2 controls: next infants admitted to NICU with similar GA and gender, but no NEC Exclusions: infants with structural or chromosomal anomalies	PE/T (4 g IV bolus LD; 2 g/hour IV MD)	1: NEC, N = 23 babies 2: No NEC, N = 46 babies	MgSO4 exposure	NR
Gibbins 2013; RCS	USA 2007-2011	N = 373 women and their babies (313 born < 32 weeks in analyses for relevant outcomes) Inclusions: selected pregnant women with threatened or planned birth < 32 weeks GA Women eligible for MgSO4 for FN protocol: admitted with viable fetus < 32 weeks with either 1) preterm labour, 2) PPROM, or 3) obstetric/medical indication for birth (e.g. severe PE/FGR) Exclusions: NR	Predominately FN (unclear whether also given for PE/T)	1: MgSO4 (6 g IV bolus LD; 2 g/hour IV MD until birth or when birth no longer considered imminent; repeat dosing permitted), N = 247 women (223 babies born < 32 weeks analysed) 2: No MgSO4, N = 126 (90 babies born < 32 weeks analysed)	Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, resuscitation (none, oxygen bag and mask, intubation, chest compressions), discharged alive, NICU admission, LOS (days) (median, range), individual morbidities, hypotonia	Funding: NR Conflicts: none
Girsen 2015; RCS	USA 1999-2002	N = 2166 women and babies Inclusions: singleton pregnancies from the Cesarean Registry that were coded for maternal PE and > 37 weeks GA at birth	PE	1: MgSO4, N = 1747 babies 2: No MgSO4, N = 419 babies	NICU admission, NICU admission within 2 hours of birth, NICU LOS (days) (median, range), LOS (days) (median, range), Apgar score < 7 at 1	Funding: assistance of NICHD, the MFMU Network and the Protocol

		Exclusions: cases with uterine rupture, chorioamnionitis and major congenital malformations, cases with absence of available data on each variable			minute, Apgar score < 7 at 5 minutes, Apgar score < 7 at 10 minutes, RDS, ventilation support within 24 hours of birth, prolonged hypotonicity within 72 hours of birth, seizures, sepsis, HIE, neonatal death, prolonged NICU LOS (≥ 8 days)	Subcommittee recognised Conflicts: none
Gonzalez-Quintero 2001; PCS Abstract	USA 1992-1999	N = 851 babies Inclusions: neonates with birthweights 500-1000 g Exclusions: NR	NR	1: MgSO4, N = 438 babies 2: No MgSO4, N = 413 babies	Overall survival, early survival (alive at 7 days), severe RDS, IVH, PDA, early PDA (< 7 days)	NR
Greenberg 2011; RCS with CCS(N)	USA 2006-2008	N = 252 babies (note: discrepancies in text and tables) Inclusions: singleton newborn infants who were born at ≥ 35 weeks GA to mothers who received MgSO4 before birth for PE Exclusions: multiple gestations, neonates who met any antenatal criteria for automatic NICU admission (maternal clinical chorioamnionitis before birth and major fetal anomalies requiring immediate evaluation)	PE	1: NICU admission, N = 52 babies 2: Well baby nursery admission, N = 200 babies MgSO4: 4 g IV LD over 20-30 minutes; 1-2 g/hour IV MD	Duration of MgSO4 (hours) (mean ± SD), MgSO4 dose (g) (mean ± SD), > 12 hours MgSO4 exposure, > 30 g MgSO4 exposure	Funding: none Conflicts: NR
Greenberg 2013; RCS	USA 2006-2008	N = 264 babies Inclusions: singleton newborns ≥ 37 weeks GA born to women with a diagnosis of PE Exclusions: multiple gestations, neonates who met any antenatal criteria for automatic NICU admission including a clinical diagnosis of maternal chorioamnionitis and major fetal anomalies requiring immediate evaluation	PE	1: MgSO4, N = 190 babies 2: No MgSO4, N = 74 babies 1: < 12 hours MgSO4 (< 30 g), N = 132 babies 2: ≥ 12 hours (≥ 30 g), N = 58 babies MgSO4: 4 g IV LD over 20-30 minutes; 2 g/hour IV MD	Meconium stained AF, NICU admission, initial admission (NICU vs. well baby nursery), primary admit diagnosis (RDS, rule out sepsis, hypotonia, hypothermia, LBW, hyperbilirubinaemia, hypermagnesemia, other), NICU LOS (days) (median, IQR), treatments needed (respiratory, fluids/nutritional	Funding: Oscar G and Elsa S Mayer Family Foundation Conflicts: none

					support, antibiotics, phototherapy)	
Grether 1998; CCS	USA 1983-1985	N = 168 babies (128 analysed) Inclusions for cases: infants who weighed < 1500 g at birth and died in 1st 28 days Exclusions for cases: death from congenital anomalies, in the context of home birth or birth in a military facility, birthweight < 500 g or GA < 22 weeks, birthweight > 1500 g, multiple congenital anomalies Inclusions for controls: singletons born weighing < 1500 g from the same birth years and counties as the neonatal deaths, who survived to age 3 years and did not have disabling CP	T	1: Neonatal death, N = 85 babies (53 analysed) 2: Survival to 3 years with no disabling CP, N = 85 babies (75 analysed) 1: Neonatal death no maternal PE, N = 21 babies 2: Survival to 3 years with no disabling CP no maternal PE, N = 35 babies	MgSO4 exposure, MgSO4 exposure for PE, MgSO4 exposure for T	Funding: supported by authors institutions Conflicts: NR
Grimbly 2015; unclear: results appear to be presented as RCS with CCS(N) Abstract	Authors from USA 2013-2014	N = 175 babies Inclusions: neonates < 33 weeks GA at birth Exclusions: congenital anomalies or conditions that may adversely affect breathing or ventilation	NR	1: Hypoglycaemia within 1st hour of birth, N = 69 babies 2: No hypoglycaemia, N = 106 babies	MgSO4 exposure	NR
Gulcan 2006; PCS	Turkey 2003-2004	N = 200 babies Inclusions: consecutive preterm newborns < 37 weeks GA admitted to the NICU Exclusions: congenital anomaly, birth at another hospital and admission after 24 hours of age with no information on stool passage, death before stool passage, and development of NEC before stool passage	T	1: MgSO4 (4 g IV LD; 2-3 g/hour IV MD), N = 35 babies 2: No MgSO4, N = 165 babies	RDS	NR
Gursoy 2015; PCS	Turkey 2011-2013	N = 50 babies Inclusions: AGA neonates born 26-34 weeks GA, whose mothers were exposed to MgSO4 (cases); birthweight and GA matched neonates whose mothers did not received MgSO4 (controls)	PE/T	1: MgSO4 (6 g IV LD over 30 minutes; 0.8 g/hour IV MD until birth), N = 25 babies 2: No MgSO4, N = 25 babies	Hypotension, hypertension, NEC, RDS, PDA, ICH stage I-II, feeding intolerance	Funding: NR Conflicts: none

		Exclusions: neonates with absence of antenatal Doppler examination or presence of absent/reversed end diastolic velocity in umbilical artery, congenital malformation, perinatal asphyxia, and chorioamnionitis				
Havranek 2011; RCS	Authors from USA Time period: NR	N = 56 babies Inclusions: GA < 37 weeks, and birthweight < 2500 g and AGA Exclusions: presence of major congenital anomalies, the administration of vasoactive drugs other than caffeine, or a diagnosis of anaemia or polycythaemia	PE/T	1: MgSO4 in 24 hours prior to birth (4-6 g IV bolus LD; 2-3 g/hour IV MD prior to birth), N = 27 babies 2: No MgSO4, N = 29 babies	Caffeine treatment, ventilator support, phototherapy, umbilical artery catheter, enteral feedings day 1, death during hospitalisation, NEC	NR
Hechtman 2002; unclear: RCS with CCS(N) Abstract	Authors from USA 1997-2000	N = 85 babies Inclusions: singleton pregnancies ≥ 23 weeks GA, with birthweights between 500-1000 g Exclusions: women with PE, PROM or fetal structural or chromosomal abnormalities	T	1: Neonatal deaths at < 28 days or prior to hospital discharge, N = 19 babies 2: Survivors, N = 66 babies	MgSO4 exposure, MgSO4 dose (g) (median, range), exposure to > 48 g total MgSO4	NR
Holcomb 1991; unclear: NCCS	USA Time period: NR	N = 23 women, 33 babies Inclusions for exposed: infants born to women who received IV MgSO4 for T for > 7 days Inclusions for non-exposed: 2 infants selected for each exposed infant (having no more than 3 days exposure to MgSO4), matched for single/multiple pregnancies and for GA at birth ± 2 weeks Exclusions: women with pregnancies complicated by IDD, metabolic bone disease, thyroid disease, renal disease, infection with syphilis, toxoplasma, rubella, cytomegalovirus; neonates without chest radiograph in 1st 48 hours	T	1: MgSO4 > 7 days IV, N = 11 babies 2: No MgSO4, or MgSO4 for < 3 days, N = 22 babies	Definitely abnormal chest radiograph (proximal humeri, radiographic abnormalities: transverse radiolucent and/or sclerotic bands)	NR

Hom 2018; RCS Abstract	Authors from USA 2013-2016	N = 52 women and babies Inclusions: women with PPROM up to 34 weeks GA Exclusions: NR	FN	1: MgSO4, N = 26 women and babies 2: No MgSO4, N = 26 women and babies	IVH	Funding: NR Conflicts: none
Hong 2019; RCS Abstract	Authors from Korea 2012-2016	N = 598 babies Inclusions: babies born 24+0 to 31+6 weeks GA Exclusions: NR	NR (includes FN)	1: January 2012-December 2013: MgSO4 for FN not adopted (16.2% exposure), N = 270 babies 2: January 2014-March 2016: MgSO4 for FN used routinely (60.6% exposure), N = 264 babies 3: April 2016-December 2016: MgSO4 abandoned (potential NEC risk) (14.0% exposure), N = 64 babies 1: MgSO4, N = 213 babies 2: No MgSO4, N = 385 babies	Neonatal death, neonatal death due to NEC, NEC, severe NEC (grade ≥ 2), "other neonatal outcomes"	NR
Igarashi 1995; unclear: RCS (or NCCS) English abstract; article in Japanese	CD	N = 42 babies Inclusions: hypermagnesemic preterm infants born to women treated with MgSO4 for T, and preterm infants born to normal women Exclusions: CD	T	1: Hypermagnesemic infants exposed to MgSO4, N = 27 babies (with (N = 15) and without (N = 12) complications) 2: Infants born to "normal mothers", N = 15 babies	Respiratory and cardiovascular symptoms (respiratory depression, hypotonia, hypotension, requirement for prolonged dopamine and calcium gluconate)	CD
Imamoglu 2014; PCS	Turkey 2011-2012	N = 53 babies Inclusions: neonates between 26-34 weeks GA Exclusions: neonates without antenatal Doppler examination and with absent/reversed end diastolic velocity in umbilical artery; neonates with clinical conditions such as congenital malformation, chromosomal anomaly, perinatal asphyxia, sepsis, PROM, chorioamnionitis, polycythaemia, anaemia and whose mothers had multiple pregnancies; neonates with	PE/T	1: MgSO4 (6 g IV LD over 30 minutes; 0.8 g/hour IV MD until birth), N = 20 babies 2: No MgSO4, N = 33 babies	RDS, PDA, IVH, caffeine treatment, ibuprofen, inotrope use, phototherapy	Funding: NR Conflicts: none

		uncertain GA; women having ritodrine for tocolysis; neonates who suffered from hypotension, exposed to drug therapies that could change CBF velocity or arterial blood pressure and any metabolic pathology				
James 2015; PCS	Ireland 2013-2014	N = 38 babies Inclusions: preterm infants < 29 weeks GA exposed to MgSO4; infants not exposed to MgSO4 matched for birthweight, GA, mode of birth Exclusions: NR	FN	1: MgSO4 within 4 hours of birth (4 g IV LD over 20 minutes; no subsequent infusion), N = 19 babies 2: No MgSO4, N = 19 babies	IVH grade 3/4, inotropes (1st week), pulmonary haemorrhage, NEC, CLD, death before discharge, early onset sepsis, invasive ventilation days 1 and 2, PDA days 1 and 2	Funding: support from the EU and Friends of the Rotunda Conflicts: none
Jazayeri 2003; RCS	Authors from USA 1998-2001	N = 72 women and babies Inclusions: women who delivered after PPROM < 34 weeks GA who received corticosteroids and antibiotics (cases: received MgSO4; controls matched for GA within a week) Exclusions: women with clear indication for birth (chorioamnionitis, abnormal fetal surveillance, maternal haemorrhage)	T	1: MgSO4, N = 36 babies 2: No MgSO4, N = 36 babies	NICU LOS (days) (mean ± SE), meconium, RDS, IVH, NEC, sepsis, neonatal death	NR
Jeanneteau 2014; RCS Abstract	Authors in France 2011-2012	N = 119 women and their babies Inclusions: women with fetuses < 33 weeks GA whose birth was planned or expected within 24 hours Exclusions: NR	FN	1: MgSO4 (4 g IV LD; 1 g/hour IV MD until birth or for 12 hours), N = 81 women 2: No MgSO4, N = 38 women	Apgar score < 7 at 5 minutes, closed cardiac massage, adrenaline, “neonatal morbi-mortality”	NR
Jones 2018; RCS Abstract	Authors in USA 2012-2014	N = 120 babies Inclusions: infants born between 32+0-33+6 weeks GA Exclusions: NR	PE/T	1: MgSO4, N = NR 2: No MgSO4, N = NR	Adverse bowel events	Funding: NR Conflicts: none
Jung 2018; RCS	South Korea 2005-2013	N = 184 women and their babies Inclusions: singleton pregnancies complicated by PPROM at 23+0-31+6 weeks GA who were hospitalised and received MgSO4 for T (MgSO4 group) or did not receive T (MgSO4,	T	1: MgSO4 (6 g IV LD over 30 minutes; 1 g/hour IV MD until uterine quiescence), N = 143 women and babies 2: No MgSO4, N = 41 women and babies	Stillbirth, neonatal death, early neonatal death, perinatal death, Apgar score < 7 at 5 minutes, pulmonary hypoplasia, RDS, BPD, NEC, early onset sepsis, ROP, ROP	Funding: no support Conflicts: none

		beta-adrenergic receptor agonists, or calcium-channel blockers) (no MgSO4 group) Exclusions: patients who were not candidates for expectant management of pregnancy at admission, such as those with intrauterine infection, significant vaginal bleeding, placental abruption, cord prolapse, non-reassuring fetal status, or advanced labour, patients with multifetal gestations, pregnancy associated hypertension, fetal anomalies, and IUGR			grade 2/3, hearing impairment, NICU LOS (days) (mean ± SD), IVH, IVH grade 3/4, PVL, bone abnormalities	
Kamilya 2005; NCCS	India 1995-1997 and 2002-2004	2002-2004: N = 26752 births, 769 women with E, 474 women with antepartum/intrapartum E, 481 babies 1995-1997: N = 31352 births, 877 women with E, 731 women with antepartum/intrapartum E, 724 babies Inclusions: all births; antepartum and intrapartum E included for assessment of perinatal death Exclusions: NR	E	1: 2002-2004 (almost universal MgSO4 use), N = 481 babies 2: 1995-1997 (no MgSO4 use), N = 724 babies	Perinatal death	NR
Kamyar 2015a; RCS Abstract	Authors in USA 2003-2013	N = 271 babies Inclusions, non-anomalous singleton infants weighing ≤ 1000 g Exclusions: NR	FN/PE/T	1: MgSO4, N = 133 babies 2: No MgSO4, N = 138 babies	Composite morbidity (IVH, PVL, BPD, NEC, RDS, ROP and/or death), neonatal death, individual morbidities	NR
Kamyar 2015b; RCS Abstract	USA 2003-2013	N = 1246 babies Inclusions: infants born 23+0 to 31+6 weeks GA Exclusions: multiple gestations, fetal anomalies, aneuploidy	FN/PE/T	1: MgSO4, N = 457 babies 2: No MgSO4, N = 789 babies	Composite morbidity (IVH, BPD, NEC, and/or death prior to hospital discharge), neonatal death	NR
Kamyar 2015c; RCS (secondary analysis of RCT) Abstract	NR (see Rouse 2008)	N = 2431 babies Inclusions: women with non-anomalous singleton and twin gestations born ≥ 24 weeks GA Exclusions: NR	FN	Males, N = 1147 babies 1: MgSO4, N = 643 babies 2: No MgSO4, N = 504 babies Females, N = 1284 babies	Composite severe morbidity (IVH grade 3/4, PVL, BPD, NEC, and/or death)	NR

				1: MgSO4, N = 536 babies 2: No MgSO4, N = 748 babies		
Kamyar 2016a; RCS (secondary analysis of RCT)	See Rouse 2008	N = 396 babies Inclusions: women diagnosed with intrapartum clinical chorioamnionitis (clinical diagnosis of chorioamnionitis with ≥ 1 of: maternal temperature of > 37.8°C or antibiotic administration for the documented indication of chorioamnionitis; chorioamnionitis noted on placental pathology alone was not considered sufficient for a diagnosis of chorioamnionitis) Exclusions: no chorioamnionitis, twins, loss to follow up before birth	FN	1: MgSO4 (6 g IV LD over 20-30 minutes; 2 g/hour IV MD), N = 192 babies 2: Placebo, N = 204 babies	Stillbirth or death by age 1, severe composite morbidity (1 or more of: sepsis, severe IVH, PVL, NEC stage 2/3, BPD), sepsis, severe IVH, PVL, NEC stage 2/3, BPD, death before hospital discharge	Funding: support from The University of Utah and National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH Conflicts: none
Kamyar 2016b; RCS with CCS(N) (secondary analysis of RCT)	USA 1997-2004	N = 697 babies Inclusions: singleton and twin infants admitted, randomised, and born between 23.0-27.9 weeks GA Exclusions: infants with chromosomal abnormalities, major congenital malformations, and/or with incomplete outcomes	FN	1: MgSO4, N = 332 babies 2: No MgSO4, N = 365 babies 1: MgSO4, N = 148 babies born < 26 weeks GA 2: No MgSO4, N = 145 babies born < 26 weeks GA MgSO4 exposed babies 1: NICU death and/or NEC stage 2/3, N = 73 babies 2: Survival without NEC stage 2/3, N = 259 babies	Death and/or NEC stage 2/3 MgSO4 infusing at birth, total amount of MgSO4 received (g) (mean ± SD)	Funding: supported by NIHCD Conflicts: NR
Katayama 2011; RCS	Japan 2004-2008	N = 160 babies Inclusions: extremely preterm neonates (GA < 28 weeks), all who received prophylactic indomethacin within 6 hours of birth Exclusions: infants with chromosomal abnormalities	T (1 woman for PE)	1: MgSO4 (no LD; 0.5-1 g/hour IV MD), N = 41 babies 2: No MgSO4, N = 119 babies MgSO4 1: Low dose (< 50 g), N = 19 babies 2: High dose (≥ 50 g), N = 22 babies	Early closure of DA, symptomatic PDA, successful response to indomethacin of PDA, successful response to surgical treatment of PDA, failure of early closure of DA	Funding: NR Conflicts: none

Kelly 1992; PCS Abstract	NR	N = 10 women and babies Inclusions: women treated with continuous MgSO4 infusion for preterm labour, and controls (30-35 weeks GA) Exclusions NR	T	1: MgSO4 IV, N = 5 babies 2: No MgSO4, N = 5 babies	Morbidity	NR
Khodapanahandeh 2008; CCS	Iran 2004-2005	N = 121 babies Inclusions: VLBW (< 1500 g) infants admitted (cases: IVH grade 3/4) Exclusions: deaths during the 1st 48 hours of life	T	1: IVH grade 3/4, N = 39 babies 2: No IVH grade 3/4, N = 82 babies	MgSO4 exposure	NR
Kimberlin 1998; RCS	USA 1992-1992	N = 308 babies (363 in death analyses) Inclusions: singleton infants ≤ 1000 g with a GA ≥ 20 weeks who were not the product of an induced abortion or antepartum stillbirth, who survived > 2 days after birth, who were born without major anomalies, who were deemed potentially viable by the obstetricians, and would have undergone a caesarean birth for fetal indications Exclusions: infants born to women diagnosed with PE	T	1: MgSO4, N = 124 babies (138 for death analyses) 2: No MgSO4, N = 184 babies (225 for death analyses)	Death ≤ 2 days, death 3-120 days, intact survival (survival to hospital discharge or 120 days without any serious morbidities), death at ≥ 2 days and < 120 days, IVH grade 3/4, ROP grade 3/4, abnormal neurological evaluation, seizure activity, NEC requiring surgery, oxygen dependence at discharge, duration of ventilation (days) (median, measure of variance NR), NICU LOS (days) (mean ± SD)	NR
Koksal 2002; unclear: results appear to be presented as PCS with CCS(N)	Turkey Year NR	N = 120 babies Inclusions: live born infants with birthweights 750-1500 g Exclusions: NR	T	1: Infants with IVH; with severe abnormalities, grade 3/4 GMH-IVH or PVL, N = 18 babies 2: Infants with minimal, grade 1/2 GMH-IVH or no abnormalities, N = 102 babies	MgSO4 exposure	NR
Kuban 1992; PCS	USA 1984-1987	N = 449 babies Inclusions: weighed 1500 g or less, and had a CUS performed within the 1st 15 days after birth Exclusions: NR	PE/T	1: MgSO4, N = 90 babies 2: No MgSO4, N = 359 babies	GMH-IVH	Funding: The Joint Program of Neonatology Conflicts: NR

Lai 2017; RCS Abstract	Authors from Taiwan 12 year study	N = NR Inclusions: women diagnosed with PE who delivered ≥ 37 weeks GA Exclusions: NR	PE	1: MgSO4, N = NR 2: No MgSO4, N = NR	Muscle tone scores (units NR), SCBU admission, NICU admission, delayed adaptation	NR
Lee 2013; RCS English abstract; article in Korean	Korea 2005-2012	N = 81 babies Inclusions: VLBW infants born to women with PE who had been admitted to the NICU Exclusions: NR	PE	1: MgSO4, N = 20 babies 2: No MgSO4, N = 61 babies 1: MgSO4 and sPDA, N = 15 babies 2: MgSO4 and no sPDA, N = 5 babies	RDS, ventilation, sPDA, operated PDA, ROP, NEC, IVH grade ≥ 1, PVL, death	CD
Lee 2015; RCS Abstract	Korea 2007-2013	N = 570 women and babies Inclusions: pregnant women with preterm birth, and their neonates Exclusions: NR	T	1: MgSO4 IV, N = 101 babies 2: No MgSO4, N = 469 babies	Hypocalcaemia	NR
Leung 2016; unclear: results appear to be presented as PCS with CCS(N)	USA 1999-2003	N = 289 babies Inclusions: neonates born < 33 weeks GA with birthweight < 1501 g who were enrolled in a prospective study of the relationship of inflammatory markers and invasive ureaplasma with respiratory and CUS outcomes; with documented hearing screen Exclusions: congenital brain/neural tube defects, confirmed congenital infections and no available cord blood or venous sample within 12 hours of birth	PE/E/T	1: Passed hearing screen, N = 244 babies 2: Failed hearing screen, N = 45 babies	MgSO4 exposure, MgSO4 and betamethasone exposure	Funding: supported by the University of Maryland and NIH Conflicts: none
Leviton 1997; PCS	Authors from USA 1991-1993	N = 1331 women and 1518 babies Inclusions: infants weighing 500 to 1500 g when born Exclusions: death before CUS, or unavailability of CUS and information about receipt of MgSO4 and potential confounders	Unclear (PE/PIH/T)	1: MgSO4, N = 678 babies 2: No MgSO4, N = 840 babies	IVH, PEA: early, late, any, hypoechoic image, late hypoechoic image, ventriculomegaly	Funding: National Institute of Neurological Disorders and Stroke Conflicts: NR
Lipsitz 1971; unclear: PCS (or NRT)	Authors from USA Time period NR	N = 37 babies Inclusions: newborn infants (all between 33-42 weeks GA) born to toxaemic women who received MgSO4 as per regimens to the right	PE/E	1: MgSO4 IV LD and MD (2-4 g IV LD; 1 g/hour IV MD - Zuspan's regimen), N = 29 babies	Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, clinical score of 3, clinical score > 0 (the higher the score, with a	NR

		Exclusions: NR		2: MgSO4 IV LD, IM MD (2-3 g IV LD; IM MD), N = 8 babies	maximum of 3, the greater the apparent toxicity of excess Mg: 1 point for flaccidity and hyporeflexia, 1 for resuscitation or assisted ventilation, 1 for week or absent cry unrelated to tracheal intubation), death, resuscitation, assisted ventilation	
Lloreda-Garcia 2016; NCCS English abstract; article in Spanish	CD	N = 107 babies Inclusions: preterm infants < 32 week exposed to MgSO4 for FN, and a historic group immediately prior to this treatment Exclusions: infants that had not reached lung maturity with corticosteroids	FN	1: MgSO4, N = 56 babies 2: No MgSO4, N =51 babies	Resuscitation, Apgar score ≤ 5 at 1 minute, Apgar ≤ 5 at 5 minutes, CPAP/nasal IMV, CMV, HFOV, surfactant treatment, PDA treated, vasoactive drugs, blood products, sepsis confirmed, pathological brain ultrasound, no stools at 48 hours, no bowel movements at 72 hours , NEC, death, CRIB (median, range), meconium evacuation delay, parenteral nutrition	CD
Martin 1998; RCS	Authors from USA 1992-1994	N = 193 women and babies Inclusions = pregnancies complicated by severe PE (according to the ACOG criteria) between 26-32 weeks GA, and (for comparison), pregnancies delivered due to preterm labour during the same period between 26-32 weeks GA Exclusions: diagnosis of PPROM	PE/T	1: MgSO4, N = 118 babies 2: No MgSO4, N = 75 babies	IVH	NR
Matsuda 1997; RCS with CCS(N)	Japan 1992-1994	N = 139 babies born to 114 women; and a further 51 control babies Inclusions: neonates born to all pregnant women who received IV MgSO4 (cases);	PE/T	1: MgSO4 (according to Zuspan's regimen: 4 g IV LD over 30 minutes; 1-2 g/hour IV MD), N = 114 women and 139 babies 2: No MgSO4, N = 51 babies	Bone abnormalities GA at start of MgSO4 (weeks) (mean ± SD), duration of	NR

		neonates born to pregnant women given no MgSO4 in the same period (controls) Exclusions: pregnancies complicated by metabolic bone disease, thyroid disease, renal disease, congenital infections (syphilis, toxoplasmosis, cytomegalovirus)		1: MgSO4 and bone abnormalities, N = 13 babies 2: MgSO4 and no bone abnormalities, N = 101 babies	MgSO4 (days) (mean ± SD), MgSO4 dose (g) (mean ± SD)	
McGuiness 1980; NRT	Authors from USA 1977-1978	N = 37 women and their babies Inclusions: consecutive women with PE, thought clinically to be at term with appropriately grown infants (study group); normotensive women at term with appropriately grown infants (control group) Exclusions: NR	PE	1: MgSO4 (4 g IV LD over 30 minutes; 1-2 g/hour IV MD), N = 23 women and their babies 2: Dextrose-water or dextrose-saline, N = 14 women and their babies	Significant birth asphyxia, hypocalcaemia	NR
McPherson 2014; RCS (secondary analysis of RCT)	USA 1997-2004	N = 933 women and their babies Inclusions: women at high risk for preterm delivery between 24-31 weeks GA because of ROM (between 22-31 weeks GA), spontaneous labour with cervical dilation of 4-8 cm, or anticipated indicated preterm delivery within 2-24 hours, with singleton, non-anomalous fetuses (diagnosed before or after birth) randomised to MgSO4 who received the study drug Exclusions: NR	FN	1: MgSO4 < 12 hours cumulative, N = 356 women and babies 2: MgSO4 12-18 hours cumulative, N = 341 women and babies 3: MgSO4 > 18 hours cumulative, N = 236 women and babies MgSO4: 6 g IV LD over 20-30 minutes; 2 g/hour IV MD until birth or for 12 hours; re-treatment permitted	Apgar score < 7 at 5 minutes, resuscitation in delivery room (oxygen blow-by, oxygen bag, mask or both, intubation, chest compressions), NEC, ROP, RDS, MV, BPD, seizures, any IVH, IVH grade 3/4, NICU admission	Funding: NR Conflicts: none
Mikhael 2019; RCS	USA 2010-2016	N = 302 babies Inclusions: babies with a birthweight ≤ 1000 g and/or GA ≤ 28 weeks with no congenital gastrointestinal anomalies Exclusions: NR	NR (includes FN)	1: MgSO4 ≤ 7 days prior to birth, N = 210 babies 2: No MgSO4 ≤ 3 days prior to birth, N =192 babies 1: MgSO4 ≤ 3 days prior to birth, N = 179 babies 2: No MgSO4 ≤ 3 or ≤ 7 days prior to birth, N = 123 babies	Death, early death, postnatal steroids, NEC, early NEC, SIP, early SIP, SIP or NEC or death, early SIP or NEC or death, late onset-sepsis, postnatal NSAIDs for PDA, IVH ≥ grade 3 Early defined as: 1st 2 weeks of life	Funding: NIH Conflicts: none

				1: MgSO4 ≤ 3 days prior to birth, N = 179 babies 2: No MgSO4 ≤ 3 days prior to birth, N = 31 babies 1: Pre MgSO4 protocol implementation, N = 112 babies 2: Post MgSO4 protocol implementation, N = 190 babies 4 g IV LD over 30 minutes; 2 g/hour IV MD for 12 hours or until birth; repeated if birth not within 12 hours (repeat LD if > 6 hours has passed since discontinuation)		
Mitani 2011; RCS with CCS(N)	Japan 2006-2007	N = 425 babies Inclusions: single, spontaneous preterm births born between 22-31 weeks GA Exclusions: chromosomal abnormalities and/or anomalous births	T	1: MgSO4 (4 g IV LD over 30 minutes; 1-2 g/hour IV MD), N = 236 babies 2: No MgSO4, N = 189 babies 1: Adverse outcome (IVH, PVL, CP, infantile death), N = 80 babies 2: Good outcome, N = 315 babies 1: < 2 days MgSO4, N = 49 babies 2: > 2 days MgSO4, N = 174 babies 1: MgSO4 and adverse outcome, N = 49 babies 2: MgSO4 and good outcome, N = 174 babies	Fetal and neonatal death, Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, RDS, IVH, PVL MgSO4 exposure Combined adverse outcome (death, IVH, PVL, CP), IVH, PVL Duration of MgSO4 (hours) (median, range)	NR
Mittendorf 2005; RCS (secondary analysis of RCT) Abstract	NR (see Mittendorf 2002)	N = 146 babies Inclusions: surviving neonates with data on antenatal MgSO4 exposure and neuropathogenesis (IVH grade 2 and/or LSV)	FN/T	1: MgSO4 0 to 4 g, N = 90 babies 2: MgSO4 5 to 49 g, N = 23 babies 3: MgSO4 ≥ 50 g, N = 33 babies	IVH grade 3 and/or LSV	NR

		Exclusions: NR				
Mittendorf 2009; RCS (secondary analysis of RCT) Abstract	NR (see Mittendorf 2002)	N = 140 babies Inclusions: babies with HUS data linked to MgSO4 exposure Exclusions: NR	FN/T	1: No MgSO4, N = 64 babies (note: women received other tocolytic) 2: MgSO4 > 0 to < 10 g, N = 27 babies 3: MgSO4 10 to < 30 g, N = 8 babies 4: 30 to < 50 g, N = 11 babies 5: ≥ 50 g, N = 30 babies	TSV	NR
Morag 2015; RCS	Israel 2015	N = 645 women and 705 babies Inclusions for 'study group': infants born 34+0-35+6 weeks GA, born alive Inclusions for matched term infants: infants born 37+0-41+6 weeks GA within 2 weeks of index case, matched for gender and mode of birth Exclusions: infants born at 36 weeks GA, diagnosed with genetic syndromes or major malformations	PE	1: Preterm infants, N = 235 babies 2: Term infants, N = 470 babies 1: Preterm infants with MgSO4, N = 10 women 2: Preterm infants with no MgSO4, N = 168 women	Respiratory disease (including RDS, TTN and disorders of air leak such as pneumothorax and pneumomediastinum)	Funding: NR Conflicts: none
Morag 2016; RCS	Authors from Israel 2012-2013	N = 190 babies Inclusions: infants admitted to a tertiary care NICU, born < 32 weeks GA without congenital anomalies or known genetic disorders Exclusions: NR	FN/PE	1: MgSO4 (5 g IV LD over 30 minutes; 2 g/hour IV MD), N = 145 babies 2: No MgSO4, N = 45 babies	Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, IV (days) (mean ± SD), treated early hypotension, intubation, oxygen at 28 days, oxygen at 36 weeks, proven NEC, sepsis, IVH grade 3/4/PVL, discharge (week) (mean ± SD), death	Funding: NR Conflicts: none
Moschos 2001; CCS Abstract	2 year period	N = 75 babies Inclusions: NEC cases, and controls matched for GA Exclusions: infants with structural or chromosomal anomalies	NR	1: NEC, N = 25 babies 2: No NEC, N = 50 babies	MgSO4 exposure	NR
Murata 2005; unclear: results appear to be	Japan 1992-1997	N = 201 babies Inclusions: all appropriate for date babies born at 24 to 33 weeks GA (maternal transports with predominant indications for	T	1: cPVL, N = 35 babies 2: No cPVL, N = 166 babies	MgSO4 exposure	NR

presented as RCS with CCS(N)		maternal transfers and then all inborn neonates) Exclusions: babies with major anomalies, with IVH grade 3/4, or who died within 2 weeks after birth		MgSO4: 1-4 g/hour IV LD; 0.5-2 g/hour IV MD		
Nakamura 1991; unclear: results appear to be presented as RCS with CCS(N) Abstract	NR	N = 58 women and their babies Inclusions: premature or PE women treated with MgSO4 and their newborns (4 g IV LD over 30 minutes, 1-2.5 g/hour IV MD) Exclusions: NR	PE	1: Ileus, N = NR 2: No ileus, N = NR	MgSO4 dose (g) (mean ± SD)	NR
Narasimhulu 2017; RCS	USA 2013-2014	N = 304 women and babies Inclusions: neonates born at 24-33+6 weeks GA admitted to the NICU Exclusions: neonates with major congenital malformations or chromosomal anomalies, neonates transferred from outside facilities	FN/PE	1: MgSO4 (4 g IV LD for PE, 6 g IV LD for FN; 2 g/hour IV MD), N = 237 women and babies 2: No MgSO4, N = 67 women and babies	Apgar score ≤ 5 at 1 minute, Apgar score ≤ 5 at 5 minutes, delivery room resuscitation, hypotension, hypocalcaemia, IVH grade 3/4, BPD, ROP grade 3+, PVL, intubation, NEC, PDA, death, composite outcome (death, IVH grade 3/4, BPD, ROP grade 3+, PVL, NEC), NICU LOS (days) (median, Q1-Q3)	Funding: NR Conflicts: none
Nassar 2006; RCS	Lebanon 1995-2003	N = 155 women Inclusions: all women admitted for IV MgSO4 T at ≥ 25 weeks GA Exclusions: women who required a combination of other tocolytics and those with an underlying maternal disease like pre-existing hypertension or renal disease	T	1: MgSO4 > 48 hours, N = 78 women, 112 babies 2: MgSO4 ≤ 48 hours, N = 77 women, 86 babies MgSO4: 4 g IV LD over 20 minutes; 2 g/hour, increased up to 4 g/hour IV MD	Apgar score < 4 at 1 minute, Apgar score < 7 at 5 minutes, hypotonia, IVH, neonatal deaths (per 1,000), abnormal bone mineralisation	NR
Nelson 1995; CCS	USA 1983-1985	N = 117 babies Inclusions for cases: singletons who weighed < 1500 g at birth, survived to age 3 years (residents in California to that age), with moderate or severe congenital CP	PE/T	1: CP, N = 42 babies 2: No CP, N = 75 babies For review outcomes: 1: No CP, MgSO4, N = 27 babies [discrepancy in text/table]	Apgar score < 6 at 5 minutes, ICH/IVH	Funding: supported by Center for Environmental Health and Injury Control, CDC,

		Exclusions: children with mild CP, with abnormalities of tone/reflexes but no functional impairment, and those with isolated hypotonia or disability acquired after 1st 28 days of life, or non-accidental head trauma in 1st month of life Inclusions for controls: randomly selected, approximately 2 per case, from the population of infants < 1500 g at birth, born in same counties and birth years, who survived to age 3 years		2: No CP, no MgSO4, N = 48 babies		ATSDR, US Public Health Service, and US DHHS Maternal and Child Health Bureau Conflicts: NR
Nunes 2018; RCS	Brazil 2009-2014	N = 75 women, 99 babies (94 available for analyses) Inclusions: patients with premature newborn deliveries between 24-32 weeks GA Exclusions: NR	FN	1: MgSO4 (4 g IV LD over 30 minutes; no MD), N = 26 babies 2: No MgSO4, N = 68 babies	Abnormal heart rate, abnormal respiratory rate (tachypnoea), abnormal temperature (hypothermia, hyperthermia), oxygen saturation < 95%, Hemoglucotest abnormal (hypoglycaemia, hyperglycaemia), anaemia (haemoglobin < 16.4 g/dL), ventilation: non-invasive, ventilation: ET	Funding: NR Conflicts: none
Okusanya 2012; NRT	Nigeria 2008-2009	N = 103 women and their babies Inclusions: severe PE or E at the antenatal and labour ward (detailed definitions provided) Exclusions: women who had diazepam prior to arrival and those with history of chronic seizure disorder	PE/E	1: MgSO4 10 g IM LD; 5 g/4 hours IM MD until 24 hours after birth or last convulsion, N = 54 women and their babies 2: MgSO4 4 g IV and 10 g IM LD; 5 g/4 hours IM MD until 24 hours after birth or last convulsion, N = 49 women and their babies	Apgar score < 7 at 5 minutes, perinatal death	NR
Ozlu 2019; RCS	Turkey 2011-2016	N = 280 babies Inclusions: babies hospitalised in the NICU ≤ 32 weeks GA with completed antenatal steroid doses	FN	1: 2014-2016 (post MgSO4 implementation; unclear uptake), N = 108 babies 2: 2011-2012 (pre MgSO4 implementation), N = 172 babies	Death, resuscitation at birth, RDS, ventilator support, ventilation (days) (mean ± SD, and median, minimum and maximum), BPD, oxygen use	Funding: none Conflicts: none

		Exclusions: babies who did not receive complete antenatal steroid doses, who had congenital anomalies, who were exposed to MgSO4 for PE, or who were sent to another hospital		MgSO4 implemented in 2013: 6 g IV LD over 30 minutes, 2 g/hour IV MD until birth or 24 hours	(days) (mean ± SD, and median, minimum and maximum), NEC, early neonatal sepsis, feeding intolerance, could not get full enteral feeding, could not start any enteral feeding, starting day of enteral feeding (day) (mean ± SD, and median, minimum and maximum), time of full enteral feeding (day) (mean ± SD, and median, minimum and maximum), PDA, ROP, IVH, IVH grade 3/4, duration of hospital stay (days) (mean ± SD, and median, minimum and maximum)	
O Reilly 2016; RCS Abstract	Ireland 2012	N = 100 babies Inclusions: preterm infants born 24-32 weeks GA whose mothers did/did not receive MgSO4 IV Exclusions: NR	FN	1: MgSO4 IV, N = 55 babies 2: No MgSO4, N = 45 babies	Duration of intubation (hours) (median, variance measure NR)	NR
Palatnik 2019; CCS	USA 2011-2015	N = 779 babies Inclusions: babies born from singleton/twin pregnancies at 23+1 to 31+6 weeks GA Cases: babies diagnosed with early onset neonatal sepsis on blood or CSF culture in 1st 72 hours of life, or who died in the 1st week of life Controls: eligible babies who did not meet criteria for cases Exclusions: babies transferred from outside institutions, born following pregnancies complicated by major fetal anomaly or with no intent for resuscitation	NR	1: Cases (early onset neonatal sepsis or death in 1st week of life), N = 73 babies 2: Controls, N = 706 babies	MgSO4 exposure	Funding: none Conflicts: none

Paneth 1991; PCS	USA 1984-1987	N = 1037 babies Inclusions: geographically representative sample of infants weighing 2000 g or less born or cared for in 3 NICUs Exclusions: infants with insufficient information about details of labour and birth to permit satisfactory classification of maternal exposure	PE/PEH/T	1: MgSO4, N = 362 babies 2: No MgSO4, N = 675 babies	GM/IVH, PEL/VE, neonatal death	Funding: NINDS Conflicts: NR
Perlman 1995; RCS Abstract	Authors from USA 1988-1992	N = 1025 babies Inclusions: singleton preterm infants < 1500 g Exclusions: NR	PIH	1: MgSO4, N = 192 babies 2: No MgSO4, N = 833 babies	PV-IVH, IVH grade 3/4	NR
Petrov 2013; NRT Abstracts (2)	Authors from Moldova	N = 140 women and babies Inclusions: pregnant women with monofetal pregnancies, from 26-33+6 weeks GA, who delivered to 34 weeks GA Exclusions NR	FN	1: MgSO4 (IV LD over 15 minutes; 1g/hour IV MD), N = 80 babies 2: Placebo, N = 60 babies	Neurological complications, haemodynamic complications	NR
Petrova 2012; RCS with CCS(N)	USA 2004-2008	N = 178 babies Inclusions: GA 23-31 weeks, no congenital malformations or reports of maternal hypertension or PE, HUS done during 1st 14 days postpartum Inclusions for controls: double-match approach used, matched by exact GA in completed weeks and by same/similar birthweight (± 100 g); due to non-availability or > 1 control for ELBW infants, the authors selected 1 control; where several controls available, 1 randomly selected Exclusion criteria: NR	T	1: IVH, N = 89 babies 2: No IVH, N = 89 babies MgSO4: 4-6 g IV LD over 30 minutes; 1-3 g/hour IV MD until 12-24 hours uterine quiescence	MgSO4 exposure	Funding: Memorial Research Fund Conflicts: none
Qasim 2017; unclear: results appear to be presented as PCS with CCS(N) Abstract	Authors from USA	N = 105 babies Inclusions: premature infants < 32 weeks GA and < 1500 g Exclusions: NR	NR	1: MgSO4, N = 95 babies 2: No MgSO4, N = 10 babies	HsPDA	NR

Rantonen 2001; PCS	Finland 1996-1998	N = 55 babies (19 were in a ritodrine exposure group and not further considered) Inclusions: preterm infants consecutively born at < 33 weeks GA, with no major congenital malformations, and written informed consent Exclusions: no exclusions	PE/T	1: MgSO4 (5 g IV LD over 20 minutes; 1-2 g/hour IV MD), N = 19 babies 2: No MgSO4 (born immediately after exposed infants, with no T or anticonvulsants), N = 19 babies	Dexamethasone, dopamine, dobutamine, surfactant, PDA, PV-IVH grade 1-4, PV-IVH grade 3/4, HIE/increased echodensity, RDS and MV, NICU admission, death, blood-culture confirmed septicaemia	Funding: supported by Research Foundation of the Orion Corporation, T Turku University Foundation, and the Sigrid Juselius Foundation, Finland Conflicts: NR
Rasch 1982; PCS	USA Time period NR	N = 79 babies Inclusions: infants of mothers with PE treated with MgSO4, infants of women with PE not treated with MgSO4, and infants of normal women (definition for PE provided) Exclusions: Infants born to women with pre-existing hypertension or other chronic diseases, preterm infants and infants with complicating factors such as tight nuchal cord, documented late decelerations, signs of sepsis, or asphyxia, infants whose mothers had received general anaesthesia or doses of sedative drugs within 2.5 hours of birth	PE	1: Born to PE women treated with MgSO4 (4 g IV and 10 g IM LD; 0.3 g/hour IV MD until birth), N = 36 babies 2: Born to PE women with no MgSO4, N = 18 babies 3: Born to normal women, N = 25 babies	Poor sucking and cry response, cyanosis during feedings, requirement for IV fluid treatment, neurologic section of the Dubowitz examination at birth, over 24 hours after birth, individual measures of Dubowitz examination	NR
Rattray 2014; NCCS	USA 2009-2010, 2011	N = 155 babies Inclusion: singleton and twin gestation ELBW (< 1000 g) inborn and admitted to NICU Exclusions: infants born with major congenital malformations or chromosomal anomalies	FN	1: Pre-MgSO4 FN protocol (January 2009 – July 2010; 50.6% MgSO4), N = 81 babies 2: During MgSO4 FN protocol (July – November 2010; 78.3% MgSO4), N = 23 babies 3: After MgSO4 FN protocol (January – October 2011; 60.8% MgSO4), N = 51 babies	Postnatal hydrocortisone, postnatal NSAIDs, SIP or death, SIP, death	Funding: NR Conflicts: none

				MgSO4: 6 g IV LD; 2 g/hour IV MD until birth or 12 hours; re-treatment permitted		
Rauf 2017; RCS	Turkey 2011-2016	N = 107 women and babies Inclusions: maternal age between 18-39 years, with singleton pregnancies born before 32nd week of pregnancy Exclusions: pregnant women who were treated with MgSO4 for T or E prophylaxis, multiple pregnancies, fetal death, associated fatal congenital anomalies or chromosomal abnormalities, women with contraindications for MgSO4 use	FN	1: MgSO4 (6 g IV LD over 30 minutes; 2 g/hour IV MD until birth or up to 12 hours), N = 46 babies 2: No MgSO4, N = 61 babies	Active resuscitation at birth (respiratory support with ET intubation), NICU LOS (days) (mean ± SD), respiratory support, MV, nasal CPAP, nasal SMIV, oxygen hood, IVH and grade 1-4, PVL, convulsion, hypotonia, encephalopathy, ROP, neonatal death	NR
Rhee 2012; PCS	USA 2001	N = 23 women and 22 babies (with usable specimens) Inclusions for exposed: women exposed to MgSO4 for PE/T at the time of birth Inclusions for unexposed: women who presented in labour with no evidence of PE or preterm labour and did not require MgSO4 Exclusions: women with multiple gestations and women unable to give consent	PE/T	1: MgSO4 ('standard protocol'), N = 11 women, 10 babies 2: No MgSO4, N = 12 women, 12 babies	NICU admission, Apgar score < 7 at 5 minutes	Funding: NR Conflicts: none
Riaz 1998; PCS with CCS(N)	USA 1995-1996	N = 52 babies Inclusions: infants whose GA was ≥ 34 weeks and whose mothers received a minimum of 12 hours of MgSO4 (study group), and the next infant of similar GA born after enrolment of study infant (control group) Exclusions: infants with severe congenital anomalies, neuromuscular disorders, significant parenchymal lung disease, and adverse intrapartum event	PIH/T	1: MgSO4 (1-3 g/hour IV), N = 26 babies 2: No MgSO4, N = 26 babies 1: MgSO4 and NICU admission, N = 12 babies 2: MgSO4 and no NICU admission, N = 14 babies	Hypotonia, delivery room support (bag and mask ventilation), NICU admission, delayed adaptation, presumed or ruled-out sepsis, delayed feeding (1st feeding ≥ 8 hours after birth), feeding intolerance, hospital stay (days) (mean ± SD), apnoea density (mean ± SD), apnoea ≥ 15 seconds (associated with bradycardia) (mean ± SD),	NR

					apnoea ≥ 10 seconds (mean ± SD), pathologic apnoea (≥ 15 seconds associated with bradycardia) MgSO4 dose (g) (mean ± SD), duration of MgSO4 (hours) (mean ± SD)	
Rizzolo 2019; RCS Abstract	Canada 2013-2017	N = 3788 babies Inclusions: babies born 23+0-28+6 weeks GA admitted to NICUs participating in the Canadian Neonatal Network Exclusions: NR	FN	1: MgSO4, N = NR 2: No MgSO4, N = NR	Death or SNI (grade ≥ 3 IVH and/or PVL)	NR
Sahin 2001; PCS	Turkey 1995-1996	N = 40 babies Inclusions for 'cases': newborns from women with PE or E who had been treated with MgSO4 Inclusions for 'controls': newborn from normal pregnant women, who did not receive any drug that could affect the contractility of smooth muscles Exclusions: NR	PE/E	1: MgSO4 (4 g IV and 10 g IM LD, 5 g in each buttock; 5 g/4 hours IM MD until 24 hours after birth), N = 20 babies 2: No MgSO4, N = 20 babies	Not voiding in 1st 24 hours, residual urine after 1st micturition (> 5 mL), urinary tract abnormality, neurologic pathology	NR
Sakae 2017; NCCS	Japan 2008-2015	N = 45 women, 48 babies Inclusions: all women who had been diagnosed with early-onset severe PE and were treated (diagnosis made according to Japanese criteria (detail provided) Exclusions: NR	PE	1: Post-protocol: April 2013 onwards (100% MgSO4 use), N = 17 women, 19 babies 2: Pre-protocol: prior to April 2013 (36% MgSO4 use), N = 28 women, 29 babies 1: > 48 hours MgSO4, N = 17 women, 19 babies 2: ≤ 48 hours MgSO4, N = 10 women, 10 babies 3: No MgSO4, N = 18 women, 19 babies	Composite of serious complications (1 or more of: neonatal death, assisted ventilation with ETT > 24 hours, RDS, PPH, PDA, BPD, cPVL, IVH grade ≥ 3, NEC and sepsis)	Funding: NR Conflicts: none

				MgSO4: 4 g IV LD; 1 g/hour IV MD until 24 hours after birth		
Salafia 1995; unclear: results appear to be presented as RCS with CCS(N	USA 1988-1993	N = 406 women and their babies Inclusions: all women delivering with GA < 32 weeks Exclusions: stillbirth, fetal congenital anomalies, multiple gestation, maternal diabetes mellitus, chronic hypertension, hydrops fetalis, placenta previa, and elective birth for IUGR	T (4 g IV LD over 20 minutes; 2 g/hour IV MD)	1: Early GM-IVH (≤ 72 hours), N = 44 babies 2: Late GM-IVH (> 72 hours), N = 21 babies 3: No GM-IVH, N = 341 babies	MgSO4 exposure	NR
Sarkar 2009; unclear: results appear to be presented as RCS with CCS(N)	USA 2001-2007	N = 59 babies Inclusions: infants with birthweight < 1500 g admitted to the NICU, with severe IVH (grade 3/4) determined by routine cranial sonography (during 1st 7-10 days of life) Exclusions: NR	NR	1: IVH grade 3, N = 28 babies 2: IVH grade 4, N = 31 babies	MgSO4 exposure	NR
Schanler 1997; PCS	Authors from USA Time period NR	N = 41 babies Inclusions: infants born pregnant women between 24-32 weeks GA; 1) preterm labour treated for > 1 week with strict bed rest and IV MgSO4; 2) similar women in whom strict bed rest was ordered for the obstetrical indications of either placenta praevia or preterm labour Exclusions: systemic illness (diabetes mellitus, chorioamnionitis, medications known to affect calcium metabolism)	T	1: MgSO4 (6 g IV LD over 30 minutes; 2 g/hour (1.5-3.5 g/hour) IV MD, discontinued in second stage of labour/at caesarean); N = 16 women, 22 babies 2: No MgSO4, N = 15 women, 19 babies	Apgar score < 7 at 5 minutes, LOS (days) (mean ± SD), HMD, PDA, IVH, NEC, birth depression, oxygen treatment, oxygen treatment > 1 month, MV, MV > 1 week, methylxanthine treatment for apnoea	Funding: support from General Clinical Research Center, Baylor College of Medicine/Texas Children's Hospital Clinical Research Center, NIH; and USDA/ARS. Conflicts: NR
Scudiero 2000; RCS with CCS(N)	USA 1986-1999	N = 127 babies Inclusions: infants with birthweights 700-1249 g, born following preterm labour treated with MgSO4 for T Exclusions: infants born to women with PE or PE superimposed on chronic hypertension,	T	1: Fetal or neonatal deaths, N = 18 babies 2: Survivors, N = 109 babies 1: MgSO4 ≤ 24 g, N = 43 babies	MgSO4 for T > 48 g, and ≤ 48 g vs > 48 g Death	Funding: supported by University of Chicago Conflicts: NR

		infants with birthweights < 700 g and > 1249 g, fetuses and neonates with major congenital anomalies		2: MgSO4 > 24 but ≤ 48 g, N = 25 babies 3: MgSO4 > 48 g, N = 59 babies		
Shalabi 2017; RCS	Canada 2011-2014	N = 4355 babies Inclusions: infants born between 22-27 weeks GA and admitted to any of the 29 tertiary level neonatal units participating in the CNN Exclusion criteria: infants with a major congenital anomaly or who were moribund on admission, those who had missing data regarding MgSO4 administration	Any	1: MgSO4 IV, N = 2055 babies 2: No MgSO4, N = 2300 babies	Apgar score < 7 at 5 minutes, SNAP-II score > 20, MV day 1, prophylactic indomethacin, PDA treated with indomethacin, postnatal steroids for hypotension, postnatal steroid for BPD, PDA treated (indomethacin or ibuprofen), postnatal steroids or PDA treatment, NEC stage II or higher, SIP, NEC or SIP, death prior to discharge, NEC or SIP associated death, IVH grade 3/4 or PVL, ROP stage 3 or above or ROP treated, BPD, nosocomial infection	Funding: no specific funding, CNN coordinating centre supported by CIHR Conflicts: none
Shamsuddin 2005; NRT	Pakistan 2001	N = 265 women and their babies (207 antepartum/intrapartum PE/E cases) Inclusions: women with E or severe PE; pregnancy > 28 weeks GA, blood pressure > 140/100 mmHg, urine output > 30 mL/hour and respiratory rate > 16/minute Exclusions: urine output < 30 mL/hour, absent patellar reflex, respiratory rate < 16/minute	PE/E	1: MgSO4 LD at home before referral to hospital (4 g IV over 20 minutes and 3 g IM LD in each buttock), N = 102 women and babies 2: No MgSO4 before referral to hospital, N = 105 women and babies	Asphyxia, stillbirth	Funding: WHO Conflicts: NR
Shokry 2010; PCS	Saudi Arabia 2007-2008	N = 48 women and their babies Inclusions: singleton pregnancies with risk of preterm labour, intact fetal membranes, no major fetal congenital anomalies and no maternal or fetal complications necessitating immediate delivery, 30-34 weeks GA	T	1: MgSO4 (4 g IV LD over 20 minutes; 1-2 g/hour IV MD), N = 28 women and their babies 2: No MgSO4, N = 20 women and their babies	RDS, PV-IVH, seizures, MV, surfactant use, inotropic drug use, PDA, neonatal death	Funding: NR Conflicts: none

		Inclusions for 'controls': infants born immediately after reaching the hospital, where the mother had a contraindication for tocolysis/MgSO4 but fulfilled other inclusions Exclusions: women with any significant complications during pregnancy or birth such as PE and those with multiple pregnancies, all infants with perinatal asphyxia, infection, anaemia and polycythaemia				
Stetson 2019; NCCS Research Letter	USA 2002-2014	N = 110 babies Inclusions: children who received a CP diagnosis, delivered before 32 weeks GA Exclusions: NR	FN/PE	1: 2002-2008 (pre-BEAM trial, 36% uptake MgSO4), N = 42 babies 2: 2009-2014 (post-BEAM trial, 62% uptake MgSO4), N = 68 babies	BPD, IVH	Funding: supported by NICHD, Cerebral Palsy Foundation, March of Dimes Prematurity Research Center Conflicts: none
Stockley 2018; RCS	Canada 2010-2011	N = 336 babies (defined according to fetal standards: estimated fetal weight < 10th centile); or 177 babies (defined according to neonatal standards: actual birthweight < 10th centile) Inclusions: growth-restricted babies < 28 weeks GA admitted to 1 of the tertiary NICUs participating in the CNN, who were assessed in neurodevelopmental follow up clinics at 18-36 months CA Exclusions: babies with major congenital or chromosomal anomalies, planned palliative care prior to birth, or with missing data	NR	Growth restriction (fetal standards) 1: Intrapartum MgSO4 exposure, N = 112 babies 2: No MgSO4, N = 224 babies Growth restriction (neonatal standards) 1: Intrapartum MgSO4 exposure, N = 61 babies 2: No MgSO4, N = 116 babies	Death in NICU and post-discharge, Apgar score < 7 at 5 minutes, chest compression or epinephrine, SNAP-II score > 20, BPD, NEC, late-onset sepsis, ROP stage 3/4/5 or treated, IVH grade 1/2, IVH grade 3/4,	Funding: none (specific for this study) Conflicts: none

Suh 2015; RCS English abstract; article in Korean	Authors from Korea 2009-2013	N = 586 babies N = 150 babies of relevance (excluded normotensive controls) Inclusions: term infants who were delivered from normotensive and antihypertensive drug ± MgSO4 treated women Exclusions: CD	HD	1: Antihypertensive drugs and MgSO4, N = 40 babies 2: Antihypertensive drugs only, N = 110 babies	LOS (days) (mean ± SD), duration of ventilation (days) (mean ± SD), duration of oxygen (days) (mean ± SD), RDS, BPD, moderate to severe, BPD, PDA treated (medication ± operation), ROP treated with laser, NEC, IVH grade ≥ 2, PVL, death	CD
Teng 2006; unclear: results appear to be presented as RCS with CCS(N)	Authors from USA 2002-2003	N = 184 babies Inclusions: all viable singleton premature infants without lethal anomalies, born between 23-30 weeks GA and were admitted to the NICU Exclusions: NR	PE/T	1: Early hypotension, N = 75 babies 2: No early hypotension, N = 109 babies	MgSO4 exposure	NR
Verma 2006; unclear: results appear to be presented as RCS with CCS(N)	USA 2000-2001	N = 45 babies Inclusions: all ELBW < 1000 g at birth infants admitted consecutively to the NICU Exclusions: infants suffering chromosomal anomalies, major congenital malformation or any organ system or hydrops fetalis	PE/T	1: PIE on chest radiograph, N = 11 babies 2: no PIE on chest radiograph, N = 34 babies	MgSO4 dose (g) (mean ± SD), MgSO4 dose ≥ 10 g	Funding: General Clinical Research Grant Conflicts: NR
Weintraub 2001; RCS	Israel 1995-1998	N = 2794 babies (have not considered the 263 babies and 177 infants exposed to ritodrine and indomethacin) Inclusions: VLBW newborn infants (birthweight < 1500 g), at GA 24-32 weeks, with a CUS examination during the 1st 24 days of life Exclusions: death in delivery room, < 24 weeks or > 32 weeks GA, born to mother with PIH, no CUS examination, receipt of combination of tocolytic drugs	T	1: MgSO4 (≥ 12 hours before birth), N = 341 babies 2: No tocolysis (for ≥12 hours before birth), N = 2013 babies	PVH/IVH grade 3/4	NR

Weisz 2015; RCS	Canada 2011-2012	N = 6015 babies Inclusions: infants born 23+0 to 31+6 weeks GA Exclusions: infants with major congenital anomalies and those who were moribund on admission (i.e. a physician, in consultation with the parents, had made an explicit decision not to provide life support at the time of birth); infants whose MgSO4 exposure status was missing	FN/PE/T/UK	1: MgSO4 for FN, N = 1387 babies 2: No MgSO4, N = 3868 babies 23-28 weeks GA 1: MgSO4 for FN, N = 731 babies 2: No MgSO4, N = 1813 babies 29-31 weeks GA 1: MgSO4 for FN, N = 656 babies 2: No MgSO4, N = 2055 babies 1: MgSO4 for FN, N = 1387 babies 2: MgSO4 for PE/T = 214 babies 3: MgSO4 for UK = 546 babies 1: MgSO4 for any indication, N = 2147 babies 2: No MgSO4, N = 3868 babies	Any resuscitation (mask CPAP or PPV, ETT intubation and ventilation, chest compressions or epinephrine) , CPAP only, bag/mask or neopuff ventilation, intubation and ventilation, chest compressions, epinephrine (ETT or IV), Apgar score < 7 at 5 minutes, surfactant use, SNAP-II score > 20, intensive resuscitation (intubation and ventilation, or chest compressions or epinephrine administration in delivery room), death, BPD, NEC stage ≥ II, IVH grade 3/4 or PVL, ROP stage ≥ II, sepsis, composite outcome (morality or any major morbidity)	Funding: supported by CIHR and Ontario Ministry of Health and Long-term Care, individual participating hospitals Conflicts: 1 author supported by CIHR
Whitsel 2004; RCS Abstract	Authors from USA 1997-2002	N = 118 babies Inclusions: non-anomalous infants ≤ 1000 g and/or < 28 weeks GA Exclusions: NR	NR	1: MgSO4, N = NR 2: No MgSO4, N = NR	Death, late bacterial sepsis	NR
Whitten 2015; unclear: results appear to be presented as RCS with CCS(N) Abstract	USA 2013	N = 6791 babies Inclusions: term (> 37 weeks GA) singleton neonates Exclusions: NR	NR	1: LOS ≤ 3 days, N = 6472 babies 2: LOS ≥ 4 days, N = 319 babies	MgSO4 exposure	NR
Wiswell 1996; PCS Abstracts (2)	Authors from USA 1991-1994	N = 137 babies Inclusions: ventilated preterm infants > 33 weeks GA Exclusions: NR	PIH/T	1: MgSO4, N = 61 babies 2: No MgSO4, N = 76 babies	NEC, ICH grade 3/4, cPVL in survivors ≥ 21 days, ICH grade 3/4 or cPVL	Funding: Supported in part by NIH 5RO1 HD21453-06 Conflicts: NR

Wutthigate 2017; unclear: results appear to be presented as PCS with CCS(N)	Thailand 2015	N = 57 women, 63 babies Inclusions: pregnant women who received intrapartum MgSO4 Exclusions: women with known fetal conditions affecting infant neurological ability, including congenital anomalies and major chromosomal abnormalities, women under general anaesthesia (risk of respiratory depression)	PIH/T (4 g IV LD; 2 g/hour IV MD)	1: Apnoeic episodes, N = 8 babies 2: No apnoeic episodes, N = 55 babies	MgSO4 dose (reported as mg/dL) (mean ± SD)	Funding: Faculty of Medicine Siriraj Hospital, Mahidol University Conflicts: none
Yokoyama 2010; RCS	Japan 2005-2007	N = 117 babies Inclusions for 'cases': newborns whose mothers had received IV MgSO4 for > 5 days for T Inclusions for 'cases': newborns whose mothers did not received MgSO4 in same period; matched for GA, birthweight and number of multiple gestations Exclusions: NR	T	1: MgSO4 (4 g IV LD over 1 hour; 1-2 g/hour IV MD), N = 58 babies 2: No MgSO4, N = 59 babies	RDS, IVH, PDA, ROP, death, NEC, bone change (osteopenic radiolucent bands at metaphyses of long bones)	NR
Young 1977; NRT	USA 1974-1975	N = 144 women and their babies Inclusions: women with PE or E based on criteria of the American Committee on Maternal Welfare Exclusions: NR	PE/E	1: MgSO4 'push' IV (10 g IM LD and 2 g IV LD over 10 minutes; MD of 2 g IV slow push over 10 minutes every 1-2 hours), N = 97 women and babies 2: MgSO4 continuous IV (10 g IM LD; 1 g/hour IV MD), N = 47 women and babies	Perinatal death	NR

Abbreviations: ACOG: American College of Obstetricians and Gynecologists; AF: amniotic fluid; AGA: appropriately grown for age; APH: antepartum haemorrhage; ATSDR: Agency for Toxic Substances and Disease Registry; BP: blood pressure; BPD: bronchopulmonary dysplasia; CA: corrected age; CBF: cerebral blood flow; CCS: case-control study; CCS(N): case-control study (nested); CD: cannot determine; CPR: cardiopulmonary resuscitation; CSF: cerebrospinal fluid; DC: Center for Disease Control and Prevention; CIHR: Canadian Institutes of Health Research; CLD: chronic lung disease; CMV: continuous mandatory *ventilation*; CNN: Canadian Neonatal Network; CNS: central nervous system; CP: cerebral palsy; CPAP: *continuous positive airway pressure*; cPVL: cystic periventricular leucomalacia; CRIB: clinical risk *index* for babies; CUS: cranial ultrasound; DA: ductus arteriosus; DHHS: Department of Health & Human Service; DIS: disseminated intravascular coagulation; E: eclampsia; EFM: electronic fetal monitoring; ELBW: extremely low birthweight; ESHP: early and severe hypertension in pregnancy; ET: endotracheal; ETT: endotracheal tube; EU: European Union; FDA: Food and Drug Administration; FGR: fetal growth restriction; FHR: fetal heart rate; FN: fetal neuroprotection; g: grams; GA: gestational age; GH: gestational hypertension; GM-IVH: germinal matrix intraventricular haemorrhage; HD: hypertensive disorders of pregnancy; HFOV: high frequency oscillatory ventilation; HMD: hyaline membrane disease; HsPDA: haemodynamically significant patent ductus arteriosus;

HUS: head ultrasound; ICH: intracranial haemorrhage; IDD: insulin-dependent diabetes; IM: intramuscular; IMV: intermittent mandatory ventilation; IQR: interquartile range; IV: intravenous; ITS: interrupted time series; IUGR: intrauterine growth restriction; IVH: intraventricular haemorrhage; LD: loading dose; LOS: length of stage; LSV: lenticulostriate vasculopathy; MD: maintenance dose; MFMU: Maternal Fetal Medicines Unit; Mg: magnesium; MgSO4: magnesium sulphate; mL: millilitres; MPT: moderately preterm; MRI: magnetic resonance imaging; MV: mechanical ventilation; N: number; NBRS: Neurobiologic Risk Scale; NCATS: National Center for Advancing Translational Sciences; NCCS: non-concurrent cohort study; NEC: necrotising enterocolitis; NHLBI: National Heart, Lung, and Blood Institute; NICHD: National Institute of Child Health and Human Development; NICU: neonatal intensive care unit; NINDS: National Institute of Neurological Disorders and Stroke; NINR: National Institute of Nursing Research; NIH: National Institutes of Health; NR: not reported; NRN: Neonatal Research Network; NRT: non-randomised trial; NS: not significant; NSAIDs: non-steroidal anti-inflammatory drugs; PCS: prospective cohort study; PDA: patent ductus arteriosus; PE: pre-eclampsia; PEA: parenchymal echo abnormality; PIE: pulmonary interstitial emphysema; PIH: pregnancy-induced hypertension; PPH: persistent pulmonary hypertension; PPROM: preterm premature rupture of membranes; PROM: premature rupture of membranes; PPV: positive pressure ventilation; PROM: premature rupture of membranes; PV-IVH: periventricular intraventricular haemorrhage; PVL: periventricular leucomalacia; PWML: punctate white matter lesions; RCS: retrospective cohort study; RCT: randomised controlled trial; RD: respiratory distress; RDS: respiratory distress syndrome; ROM: rupture of membranes; ROP: retinopathy of prematurity; SCBU: special care baby unit; SD: standard deviation; SE: standard error; SH: systemic hypertension; SIP: spontaneous intestinal perforation; SMIV: synchronized intermittent mandatory *ventilation*; SNAP: Score For *Neonatal* Acute Physiology; SNI: severe neurological injury; sPDA: significant PDA; T: tocolysis; TSV: thalamostriate or mineralising vasculopathy; TTN: transient tachypnoea of the newborn; UK; unknown; USA: United States of America; USDA/ARS: Unites States Department of Agriculture, Agricultural Research Service; VLBW: very low birthweight; WHO: World Health Organization; WMI: white matter injury

S2 Table. Risk of bias of included studies

Randomised controlled trials

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Abdul 2013	Low risk: Quote: "computer-generated numbers."	Low risk: Quote: "delivered by sealed opaque envelope."	High risk: Quote: "our trial was not blinded."	High risk: Quote: "our trial was not blinded."	Low risk: No apparent missing outcome data.	Unclear risk: The study protocol is not available. Unclear whether the published report includes all pre-specified outcomes. Limited pre-specification of outcomes in methods of report.
Agrawal 2013 Abstract	Low risk: Quote: "using a computer generated random table."	Unclear risk: No detail provided (abstract only).	High risk: No blinding (assumed due to nature of intervention and control).	Unclear risk: No detail provided (abstract only).	Unclear risk: No detail provided (abstract only).	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Abstract only.
Bain 2014	Low risk: Quote: "The randomisation sequence was computer generated."	Low risk: Quote: "treatment allocated by the telephone randomisation service at the University of Adelaide."	High risk: Quote: "The midwives, who could not be blinded to the treatment group allocation…. Midwives and obstetricians were asked not to discuss treatment group allocation with the women."	High risk: No blinding reported.	Low risk: No apparent missing data.	Low risk: Trial registration (ACTRN12605000765628) available, and outcomes reported as pre-specified.
Begum 2002	Low risk: Quote: "patients were randomly assigned by lottery… we randomly selected a piece of paper from a box to determine if the patient was to receive only loading or both loading and	Unclear risk: No detail provided.	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. No clear pre-specification of outcomes in methods of report.

	the maintenance schedule."					
Behrad 2003	Low risk: Quote: "Patients were randomly assigned by computer-generated random number allocation."	Low risk: Quote: "with consecutively numbered opaque envelopes."	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Limited pre-specification of outcomes in methods of report.
Bhattacharhee 2011	Low risk: Quote: "computer-generated randomisation protocol."	Low risk: Quote: "the allocation was concealed in sealed, sequentially numbered, brown envelopes, which had been prepared by the statistician at each centre."	High risk: Quote: "Because of the nature of the drug administration, the patients and the doctors responsible for drug administration were not blinded to the randomisation allocation."	High risk: No blinding reported.	Unclear risk: Reason(s) for missing neonatal outcome data not reported (53/67 and 54/70 babies included in analyses).	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Secondary outcomes included "maternal and perinatal outcomes."
Blackwell 2001	Unclear risk: Quote: "Randomization was conducted through the hospital pharmacy."	Unclear risk: As above.	Low risk: Quote: "Patients received the study medication in unlabeled intravenous bags, and all clinicians, labor and delivery personnel, and research nurses were blinded to which medication each patient received."	Low risk: As above, and "Placental examination was performed by pathologists blinded to patient study group."	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Unclear pre-specification of outcomes in methods of report.
Charma 2013	Low risk: Quote: "using a computer generated randomization protocol."	Low risk: Quote: "The allocation was concealed in sealed sequentially numbered brown envelops."	High risk: Quote: "Because of the nature of drug administration, the doctors and nurses responsible for drug administration were not blinded to the randomization allocation."	High risk: No blinding reported.	Low risk: Relatively low proportion of missing data (6/56 and 8/56), balanced between groups.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. "Both maternal and perinatal outcomes were recorded."
Chen 1995	Unclear risk: Quote: "were all randomized."	Unclear risk: As above.	High risk: No blinding (no placebo used).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report

						includes all pre-specified outcomes. "The clinical data, and fetal and maternal complications, and outcome of both groups were analysed."
Chissel 1994	Unclear risk: Quote: "patients were randomly allocated."	Unclear risk: As above.	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. "Clinical outcome... were recorded for both groups."
Coetzee 1998	Unclear risk: Quote: "women were randomised."	Low risk: Quote: "women were allocated using sealed opaque envelopes containing a card instructing the use of solution A or solution B. These cards (but not the envelopes) were consecutively numbered. Envelopes were distributed in mixed batches of 20 and these always had equal numbers of A and B."	Low risk: Placebo used. Quote: "The sterile solutions were prepared by the hospital pharmacy… The identity of the solutions marked A or B were changed periodically by pharmacy without the knowledge of the investigators. The identity of the solutions was revealed only on completion of the study."	Low risk: As above.	Unclear risk: On completion of the study 123/822 random envelopes and data sheets could not be retrieved from patient records, and it was not possible to determine who had been randomised to the treatment and placebo groups – these women were excluded from there study.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Only the primary outcome detailed in the methods of the report.
Colon 2015 Abstract	Unclear risk: Quote: "were randomized."	Unclear risk: No detail provided (abstract only).	Unclear risk: Saline placebo used (limited detail provided; abstract only).	Unclear risk: No detail provided (abstract only).	Unclear risk: No detail provided (abstract only).	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Abstract only.

Cotton 1984	Unclear risk: Quote: "patients were randomized."	Unclear risk: As above.	Low risk: Placebo used.	Unclear risk: No detailed provided.	Low risk: 1 women in the treatment group was lost to follow up and excluded from analyses.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes.
Cox 1990	Low risk: Quote: "Patients were assigned to treatment or control groups by means of a random number table."	Low risk: Quote: "group allocation predetermined and placed in consecutively numbers and sealed envelopes."	Unclear risk: Saline used in control group; serial magnesium serum level determinations in the treatment group indicate that blinding may not have been achieved.	Unclear risk: No detail provided.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Outcomes not clearly pre-specified in methods of report.
Crowther 2003	Low risk: Quote: "The study randomization numbers were generated by computer."	Low risk: Quote: "managed by nonclinical staff at the University of Adelaide's Maternal Perinatal Clinical Trials Unit… Each study number was placed on a masked treatment pack… Eligible women… were enrolled by taking the next treatment pack."	Low risk: Placebo used. Quote: "All perinatal staff were blinded to treatment group allocation."	Low risk: As above. Quote: "Surviving children were assessed at a corrected age of 2 years by developmental paediatricians and psychologists blinded to treatment group allocation."	Low risk: Outcome data up to discharge available for all 1062 women and 1255 infants alive at randomisation; 2 year corrected age outcomes available for 1047 children (99% of survivors); 14 children (9 in the magnesium group and 5 in the placebo group) did not have 2 year cerebral palsy assessment and were excluded from analyses.	Low risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes, however methods of report list detailed outcomes which are subsequently reported in the results.
Easterling 2018	Low risk: Quote: "randomisation code based on a computerised	Low risk: Quote: "sequentially numbered, sealed, opaque envelope."	High risk: Quote: "open-label."	High risk: No blinding reported.	Unclear risk: 99.1% (105/106) neonates from serial IV bolus group analysed (1	Unclear risk: The study protocol is not available. Unclear whether the published report includes all pre-specified outcomes. No pre-

	pseudo-random number generator.”				had missing data); 90.2% (92/102) neonates from continuous infusion group analysed (2 born to mothers enrolled postpartum, 6 discharged prior to birth, 2 had missing data); small imbalance in exclusions between groups	specification of outcomes in trial registration (NCT02091401).
Fox 1993	Low risk: Quote: "in which the group selection was generated from a table of random numbers."	Unclear risk: Insufficient detail provided. Quote: "The randomization was performed by using the sealed-envelope method… A disinterested third party (the pharmacy) was in charge of selection of the envelope for each patient."	High risk: Quote: "The treating physicians did not have access to the randomization envelopes but were not blinded to group assignment." No placebo used.	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Methods of report indicate other neonatal outcomes of interest which are not subsequently reported in results.
How 1998	Low risk: Quote: "generated from a table of random numbers."	Unclear risk: Insufficient detail provided. Quote: "sealed envelope."	High risk: No blinding (no placebo used).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Outcomes not clearly pre-specified in methods of report.

Keepanasseril 2018	Unclear risk: Insufficient detail provided. Quote: "Randomisation was done by a predetermined schedule that used a block approach… Randomisations schedule and the allocation concealment was done by a person unrelated to the study."	Low risk: Quote: "Resident doctor on duty opened the randomisation schedule placed in sequential opaque envelopes."	High risk: No blinding (due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes.
Lewis 1997	Low risk: Quote: "Randomization was accomplished by use of a random number table."	Low risk: Quote: "The randomization cards were placed in an opaque envelope that remained sealed until informed consent was obtained after successful tocolysis. The randomization cards were stored in an area away from clinical care."	High risk: No blinding (due to nature of intervention and control).	High risk: No blinding reported.	Unclear risk: 144 women were included in the study, 3 delivered elsewhere and were not included in analyses (not reported from which groups these women were excluded from). Neonatal outcome data does not appear to take into account the 18 sets of twins.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Only primary outcome pre-specified in methods of report.
Livingston 2003	Low risk: Quote: "Computer-generated group assignment was	Low risk: Quote: "Study group assignment was by sealed, consecutively	Low risk: Placebo used. Quote: "All medication was mixed in the pharmacy and labelled “study	Low risk: Quote: "data were collected from chart abstraction… Investigators remained	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified

	devised by simple randomization sequence."	numbered, opaque envelopes."	drug" to maintain allocation concealment."	blinded during data collection."		outcomes. Outcomes not clearly pre-specified in methods of report.
Magpie 2002	Low risk: Quote: "with an allocation sequence based on a block size of eight, also generated by the Clinical Trial Service Unit."	Low risk: Quote: "Hospitals with reliable access to telephones used a central telephone randomisation service at the Clinical Trial Service Unit, in Oxford... Hospitals without reliable access to telephones used a local pack system."	Low risk: Placebo used. Quote: "The magnesium sulphate and placebo ampoules were identical, and the solutions looked the same."	Low risk: As above.	Low risk: 5 women excluded (2 in each group due to no data; 1 in magnesium sulphate group due to wrong trial); follow up data available for 99.7% women randomised before delivery and 98.6% of babies.	Low risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes, however methods of report list detailed outcomes which are subsequently reported in the results.
Malapaka 2011	Unclear risk: Quote: "The women were randomly assigned to the groups."	Unclear risk: As above.	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Unclear risk: Insufficient detail provided; group numbers (N=72 and N=54) unbalanced.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes.
Marret 2007	Low risk: Quote: "Randomisation numbers were generated by computer."	Low risk: Quote: "Central telephone randomisation was managed by staff of the NICU."	Low risk: Quote: "The two solutions looked identical so that the women were unaware of whether they received a MgSO4 or placebo solution. Treatment assignment was single blind."	Low risk: As above. Quote: "For all surviving infants, CUS was conducted by a senior neonatologist or radiologist in each centre separately and in a blind manner relative to treatment allocation."	Low risk: 573 women were randomised, 9 women were excluded from the 3 centres that included < 5 women; 564 women were analysed; all fetuses alive at randomisation (magnesium: 352, placebo: 336) included in mortality analyses.	Low risk: Quote: "This study is registered as an International Standard Randomised Controlled Trial, number 00120588." Not able to locate registration, however methods of report list detailed outcomes which are subsequently reported in the results.

Mirzamoradi 2014	High risk: Quasi-randomised. Quote: "those who had an odd code were allocated to the intervention group and others to the control group."	High risk: Quote: "For random allocation, treatment diets (intervention and control groups) were packed in separate packages and coded from 1 to 92 by an expert midwife. When an eligible patient was accepted into the study, another expert interviewed her and a code from 1 or 92 was assigned to questionnaires regardless of medicinal packages coding."	Low risk: Placebo used. Quotes: "None of the research staff were aware of the treatment allocation of patients in order for blinding purposes;" "All steps were considered blinding principles in the control group too."	Low risk: As above.	Low risk: No apparent missing data.	Unclear risk: While the trial registration (IRCT2012091810876N1) is available, this registration was retrospective. Outcomes not well pre-specified in methods of report, e.g. "fetal and maternal complications."
Mittendorf 2002	Low risk: Quote: "a computerized program… was used."	Unclear risk: No detail provided.	Low risk: Placebo used. Quote: "doubly masked."	Low risk: Quote: "The technicians and researchers who processed all biologic specimens were masked to previous and subsequent health outcomes."; "The developmentalist was masked to the antenatal exposure variables."	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes.
Moodley 1994	Unclear risk: Insufficient detail provided. Quote: "Patients were	Low risk: Quote: "randomly distributed… using the next of a set of consecutively	High risk: No blinding (no placebo used).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Outcomes not well

	randomly distributed."	numbered, sealed, opaque envelopes."				pre-specified in the methods of report: "Main Outcome Measure: The onset of convulsions and both maternal and fetal complications between the groups."
Mundle 2012	Low risk: Quote: "a randomization sequence generated by computer with blocks of 10."	Low risk: Quote: "consecutive opaque envelopes."	High risk: Quote: "However, it was not possible to blind women and providers to the treatment."	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes; methods of report details additional neonatal outcomes which are not subsequently reported in the results.
Orji 2012 Abstract	Unclear risk: Insufficient data provided. Quote: "randomized."	Unclear risk: No detail provided (abstract only).	Unclear risk: Quote: "single blind." Unclear who was blinded.	Unclear risk: As above.	Unclear risk: No detail provided (abstract only).	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Abstract only.
Parashi 2017	Low risk: Quote: "by means of a computer-generated randomization list."	Low risk: Quote: "by using sealed opaque medication packets that numbers and used consecutively."	Low risk: Placebo used.	Low risk: Quotes: "double-blind"; "they all were assessed with ultrasonography by an experienced radiologist who was blind about the groups."	Low risk: No apparent losses.	Unclear risk: While the trial registration (IRCT2016080729223N1) is available, this registration was retrospective, and no clear pre-specification of outcomes in methods of report.
Pascoal 2019	Low risk: Quote: “randomization list was prepared using the Random Allocation software program, version 1.0.”	Low risk: Quote: “The numbered envelopes were sent to the high-risk unit and to the intensive care unit where the women were consecutively assigned to one of the	Low risk: Quotes: “The pharmacist received the randomization list of numbers… defining whether the patient would be in the 1-gram/hour or 2-grams/hour group. The pharmacist then prepared ampoules with distilled water for the 1-gram/hour group, and	Low risk: Quote: “Throughout the entire study, the investigators, the attending physicians, and the patients remained unaware of the group to which the	Low risk: No apparent missing data.	High risk: Trial was terminated early due to poor recruitment; outcomes not reported as pre-specified in original registration (NCT02396030).

		maintenance regimens. The numbered envelope containing the ampoules was only opened at the time of preparation of the maintenance dose of magnesium sulfate."	ampoules with a total of 6 grams of magnesium sulfate for the 2-grams/hour group. Both sets of ampoules were identical in color and size. Only the pharmacist was aware of the contents of the ampoules;" and "Throughout the entire study, the investigators, the attending physicians, and the patients remained unaware of the group to which the patient had been allocated."	patient had been allocated."		
Rimal 2017	Unclear risk: Quote: "The participants were randomized."	Unclear risk: No detail provided.	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. No clear pre-specification of outcomes in methods of report.
Rouse 2008	Low risk: Quote: "Group assignment was made according to a computer-generated random sequence."	Unclear risk: No detail provided.	Low risk: Placebo used.	Low risk: As above. Quote: "double-blind."	Low risk: 9/1096 and 4/1145 women in the magnesium and placebo groups were lost to follow up before delivery; thus 1087/1096 and 1141/1145 women were included in maternal analyses; all live born infants included in neonatal analyses; 1133/1188 and 1203/1256 fetuses/children included in primary	Low risk: While the trial registration (NCT00014989) is available, this registration was retrospective, however methods of report list detailed outcomes which are subsequently reported in the results.

					outcome in the magnesium and placebo groups.	
Saha 2017	Low risk: Quote: "according to computer generation."	Unclear risk: No detail provided.	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: While the trial registration (CTRI/ 2009 000339, 05–08-2009) is available, this registration appears to have been retrospective; need for calcium gluconate detailed in methods and trial registration as an outcome of interest but not subsequently reported.
Shilva 2007	Low risk: Quote: "the patients were randomized using a Tippet table."	Unclear risk: No detail provided (short report).	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Outcomes not clearly pre-specified in short report: "compared for maternal and neonatal outcome."
Shreya 2014	High risk: Quote: "Randomisation was done by giving above regimen alternatively."	High risk: As above.	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Unclear risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Outcomes not clearly pre-specified in short report: "Maternal and fetal complications."
Singh 2011	Low risk: Quote: "Patients were randomly allocated by means of a random number generator."	Unclear risk: No detail provided.	High risk: No blinding (assumed due to nature of interventions and control).	High risk: No blinding reported.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes. Outcomes not clearly pre-specified in methods, "maternal mortality and

						morbidity and perinatal mortality and morbidity."
Tangmanowutthikul 2019	Low risk: Quote: “using block randomisation by computer generated random number.”	Low risk: Quote: “sealed in opaque envelops.”	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Low risk: No apparent missing data (unclear as to whether 1 and 2 neonates are missing from NICU admission data, based on percentages reported).	Unclear risk: The study protocol is not available. Unclear whether the published report includes all pre-specified outcomes. No pre-specification of outcomes in trial registration (TCTR20180122001).
Terrone 2000	Low risk: Quote: "computer-generated random number allocation."	Low risk: Quote: "consecutively numbered opaque envelopes."	High risk: No blinding (assumed due to nature of intervention and control).	High risk: No blinding reported.	Unclear risk: Quote: "Patients who were considered to have treatment failure were excluded from further analyses because the time to tocolysis could not be assessed"; 148/160 women were included in analyses.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes.
Witlin 1997	Low risk: Quote: "Randomization was performed by the use of computer-generated tables of random numbers."	Low risk: Quote: "sealed, sequentially numbered, opaque envelopes."	Low risk: Placebo used. Quote: "Women randomized to placebo infusion received saline solution that was identical in appearance to the magnesium sulfate infusion and was likewise prepared in and dispensed by the hospital pharmacy."	Low risk: As above.	Low risk: No apparent missing data.	Unclear risk: The study protocol is not available. It is unclear whether the published report includes all pre-specified outcomes.

Non-randomised studies

Study	Were valid and reliable measures implemented consistently? (detection bias; confounding)	Any attempt to balance the allocation between the groups or match groups? (confounding)	Were important confounding variables not taken into account? (confounding)	Do the inclusion and/or exclusion criteria vary across groups? (selection bias) Does the strategy for recruiting participants differ across groups? (selection bias; confounding) Is the selection of the comparison group inappropriate? (selection bias; confounding)	Does the study fail to account for important variations from the proposed protocol? (performance bias)	Was the outcome assessor not blinded? (detection bias)	Was the length of follow-up different across groups? (attrition bias) In cases of high or differential loss to follow-up, was the impact assessed? (attrition bias; detection bias)	Are any important primary outcomes missing from the results? (selective outcome reporting) Are any important harms missing from the results? (selective outcome reporting)	Overall risk of bias
Adama-Hondegla 2013	Cannot determine: retrospective file review; limited detail/definitions provided	Cannot determine	Cannot determine	Not further assessed, although study reports that logistic regression was used, and aORs were presented in tables, no detail was provided of variables adjusted for					High
Alexander 2006	Yes: prospective data collection with use of database (verified accuracy); though outcomes not clearly	No	Yes	Not further assessed; no adjustment for confounders					High

	pre-defined in methods								
Alston 2016	Cannot determine: retrospective record review; limited detail/definitions provided	Yes	Yes	Not further assessed, although study reports a multivariable logistic regression model was used (considering variables found to differ in univariate comparisons), for the review outcomes of interest, there was no adjustment for confounders					High
Ambadkar 2017	Cannot determine: while neonatologists were reported to be 'blinded' to study, unclear if this was feasible and limited detail/definitions provided	Cannot determine, reported to be "matched"	Yes	Not further assessed; no adjustment for confounders					High
Bajaj 2018	Yes: prospectively collected data by trained research personnel using standard definitions	Yes	Partially: multivariable logistic regression analysis performed to assess the association between levels of resuscitation with selected morbidities after adjusting for centre, GA, SGA status, any antenatal steroids, and multiple birth	No	Cannot determine	Yes, not blinded	No	No	Moderate
Basu 2012	Yes: retrospective chart review, though detail/definitions provided	Yes	Partially: adjustment for GA, birthweight and multiple gestations (for PDA, ROP and LOS only)	No	Cannot determine	Yes, not blinded	No	No (though results of multivariate analysis for PDA, ROP and LOS were incompletely reported)	Moderate to high

Belden 2017	Yes: retrospective chart review, though detail/definitions provided	Yes	Partially: results of multivariate logistic regression incompletely reported	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Bertello Grecco 2019 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Black 2006	Yes: prospective outcome collection, detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Blackwell 2002	Yes: prospective outcome collection, detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Bonta 2000 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Bozkurt 2016	Cannot determine: retrospective record review, no detail/definitions for outcomes of interest	Yes	Yes	Not further assessed, although results of multinomial logistic regression analysis are reported for cerebral palsy; no adjustment for review outcomes of interest					High
Boyle 2018 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (though logistic regression was used for univariate and multivariable analyses for the composite outcome)					Unclear
Brazy 1982	Yes: retrospective collection, though detail/definitions provided	Yes: controls matched based on GA and birth order	Yes	Not further assessed; no adjustment for confounders					High
Brookfield 2015 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that multivariate techniques were used, controlling for GA, mode of anaesthesia, MgSO4 indication, total dose of MgSO4 and infant sex)					Unclear
Brookfield 2016* Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that multivariate logistic regression adjusted for diabetes, delivery route, other tocolytics, and GA at birth)					Unclear
Brown 2019 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (though controls were matched, and aORs, from logistic regression presented)					Unclear

Canterino 1999	Yes: retrospective collection, though detail/definitions provided	Yes	Partially: adjustment for GA, birthweight, antenatal steroids, chorioamnionitis, mode of birth, Apgar score < 7 at 5 minutes, RDS; or 'clinical group' (for abnormal sonograms, severe lesions only)	No	Cannot determine	No, blinded assessment by radiologist	No	No	Moderate
Cawyer 2016 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (though reports multivariable logistic regression was used to adjust for confounding)					Unclear
Cho 2014 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that a multiple linear regression model was used)					Unclear
Chowdhury 2009	Cannot determine: prospective collection, though limited detail/definitions provided (and some data self-reported by women who were discharged undelivered)	No	Yes	Not further assessed; no adjustment for confounders					High
Chun 2014 English abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; English abstract only (article in Korean)					Unclear
Cuff 2018	Yes: abstracted from PINS database (validated research database)	Yes	Partially: binary logistic regression controlling for race, PTL, gestational age, corticosteroid (betamethasone or dexamethasone), birthweight, and indomethacin exposure, to control	No	Cannot determine	Yes, not blinded	No	No	Moderate to high

			for potential confounding and co-linear variables, for IVH only						
Das 2015	Yes: prospective collection, with detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Deering 2005	Yes: retrospective database review, with detail/definitions provided	Yes	Partially: adjustment for GA, birthweight, chorioamnionitis and steroid use	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
De Jesus 2015	Yes: use of prospectively collected database, (limited) detail/definitions provided	Yes	Partially: adjustment for centre, GA, antenatal steroids and PIH/E (for delivery room intubation, day 1 MV, day 1 ET MV, day 3 MV, day 3 ET MV, hypotension and PDA treated)	No	Cannot determine	Yes, not blinded	No	No	Moderate
del Moral 2007	Cannot determine: prospective collection from maternal/newborn records using standardised forms; PDA only assessed for confirmation when suspected clinically (and no detail/definitions for IVH, PVL)	Yes	Partially: adjustment for GA or birthweight, race, gender, mode of birth, antenatal steroids, presence of chorioamnionitis, MgSO4 indication (for PDA only)	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
delValle 1998 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear

Derks 2016 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
De Silva 2018	Yes: use of prospectively collected database, detail/definitions provided	Yes	Partially: adjustment for multiple gestation, gender, GA at birth, birthweight < 10th centile, outborn status, mode of birth, antenatal corticosteroid use)	No	Cannot determine	Yes, not blinded	No	No	Moderate
de Veciana 1995	Cannot determine: retrospective chart review, limited detail/definitions provided (e.g. for IVH, NEC)	No	Yes	Not further assessed; no adjustment for confounders					High
Downey 2017	Yes: use of database (based on EMRs), (limited) detail/definitions provided	Yes	Partially: adjustment for site, GA at birth, multiple gestation, antenatal steroids, antibiotics, prolonged ROM, SGA, sex, discharge year, postnatal hydrocortisone, postnatal indomethacin)	No	Cannot determine	Yes, not blinded	No	No	Moderate
Drassinower 2015* Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that log-linear regression was used to control for potential confounders, and two outcomes (composite, intubation) reported to be adjusted for GA at birth, sepsis, SGA and alcohol use)					Unclear
Duffy 2012	Yes: retrospective collection from ERMs, detail/definitions provided	Yes	Yes	Not further assessed; although study reported multivariable logistic regression analyses, there was no adjustment for review outcomes of interest					High

Edwards 2018*	Cannot determine: prospective data collection in original RCT, with detail/definitions provided; however, authors acknowledge subjectivity of definition used for chorioamnionitis to define groups	Yes	Partially: adjustment for sex only	No	Cannot determine	No, original RCT was blinded	No	No	Moderate to high
Elimian 2002	Yes: retrospective chart review, detail/definitions provided	Yes	Partially: adjustment for antenatal confounding variables – assumed to be GA ≤ 28 weeks, antibiotics, antenatal steroids, and chorioamnionitis (for neonatal death only)	No	Cannot determine	Yes, blinding of steroid exposure for neurosonograms only	No	No	Moderate to high
Elliot 2003 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that multivariate analysis corrected for mode of delivery and exposure to antenatal steroids)					Unclear
Farkouh 2001	Yes: retrospective analysis using prospectively collected database (monitored for accuracy), though limited detail/definitions provided	Yes	Partially: controlled for GA and indication for therapy, antenatal steroids, terbutaline use, bleeding, caesarean section)	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
FineSmith 1997	Yes: retrospective record review, with blinded re-review of CUS	Yes: controls matched for GA range only	Partially: logistic regression included GA, MgSO4, Apgar scores at 1 and 5	Yes (CCS); no; no	Cannot determine	No, radiologist blinded to exposure/s	No	No	Moderate to high

			minutes, duration of intubation, reason for prematurity and type of birth)						
Gano 2016	Yes: prospective data collection, with detail/definitions provided	Yes	Partially: adjustment for postmenstrual age at MRI, VLBW, intubation at birth, prolonged MV, hypotension, symptomatic PDA, prenatal steroids)	No	Cannot determine	No, MRI review blinded to clinical history; and case note review blinded to MRI findings	No	No	Moderate
Garcia Alonso 2018	Yes: prospective data collection, detail/definitions provided	Yes: controls matched by GA and time period	Partially: for some outcomes (resuscitation, surfactant, BPD, ROP) control for GA and birthweight)	Yes; no; no	Cannot determine	Yes, not blinded	No	No (though results for some outcomes incompletely reported (e.g. P = NS; and "no longer statistically significant")	Moderate to high
Gasparyan 2017 English abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; English abstract only (article in Russian)					Unclear
Ghidini 2001	Yes: retrospective chart review, detail/definitions provided	Yes: controls matched by GA (similar) and gender	Partially: control for diagnosis of preterm labour only	Yes; no; no	Cannot determine	Yes, not blinded	No	No	Moderate to high
Gibbins 2013	Cannot determine: retrospective record review using standardised forms, however detail/definitions for some outcomes (e.g.	No	Yes	Not further assessed; no adjustment for confounding					High

	"individual morbidities") lacking								
Girsen 2015	Yes: retrospective review using prospectively collected database, with detail/definitions provided	Yes	Partially: adjustment for receipt of public insurance, maternal age, race type of birth, birthweight, GA at birth (for NICU admission and NICU admission ≥ 8 days)	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Gonzalez-Quintero 2001 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that logistic regression was used)					Unclear
Greenberg 2011	Yes: retrospective chart review, with detail/definitions provided	Yes	Partially: controlled for GA, Apgar score at 1 minute, birthweight, caesarean birth, severe PE	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Greenberg 2013	Yes: retrospective chart review, with detail/definitions provided	Yes	Partially: controlled for GA, public insurance, birthweight, caesarean birth, chronic hypertension and severe PE (for NICU admission only)	No	Cannot determine	Yes	No	No	Moderate to high
Grether 1998	Yes: retrospective review, with detail/definitions provided	Yes: controls matched for birthweight range, birth years and counties	Partially: below factors adjusted for separately (while controlling for birthweight, GA): placental infection definite, placental infection definite or possible, infection,	Yes; no; no	Cannot determine	Yes, not blinded (control data collected without knowledge of status; cases data collected with no blinding of case status)	No (though records complete for 85% cases, 90% controls; and additional cases excluded,	No	Moderate to high

			sex, maternal age, level of hospital care, maternal bleeding, presentation at birth, surgical birth, exposure to in utero corticosteroid, abruptio placentae, placenta praevia, hypertension				leaving 62% for analysis)		
Grimbly 2015 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Gulcan 2006	Cannot determine: prospective collection, though some outcomes lacking detail/definitions (e.g. RDS)	Yes: GA matching for some outcomes	Yes	Not further assessed; no control for confounders for review outcomes of interest					High
Gursoy 2015	Yes: prospective collection, with detail/definitions provided	Yes: matched for birthweight and GA	Yes	Not further assessed; no control for confounders					High
Havranek 2011	Cannot determine: limited detail/definitions provided re: clinical outcome collection methods	Yes	Yes	Not further assessed; though linear regression analysis was used for superior mesenteric artery blood flow velocity, there was no adjustment for confounders for review outcomes of interest					High
Hechtman 2002 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that multiple stepwise logistic regression was used, and reports results controlling for GA, betamethasone therapy, clinical chorioamnionitis, and delivery mode)					Unclear
Holcomb 1991	Cannot determine: categories for defining chest radiographs not well defined	Yes: matched for single/multiple	Yes	Not further assessed; no control for confounders					High

		gestation and GA			
Hom 2018 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only	Unclear
Hong 2019 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only	Unclear
Igarashi 1995 English abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; English abstract only (article in Japanese)	Unclear
Imamoglu 2014	Yes: prospective collection, with detail/definitions provided	No	Yes	Not further assessed; no control for confounders	High
James 2015	Yes: prospective collection, with detail/definitions (some limited) provided	Yes: matching for birthweight, GA, and mode of birth	Yes/Partially	Not further assessed; logistic regression used for CLD only and controlled only for antenatal steroid exposure; no control for confounders for other review outcomes	High
Jazayeri 2003	Yes: retrospective chart review, though detail/definitions provided	Yes: matching based on PPROM at same GA	Yes	Not further assessed; no control for confounders for review outcomes of interest	High
Jeanneteau 2014 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only	Unclear
Jones 2018 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only	Unclear
Jung 2018	Cannot determine: retrospective record review, detail/definitions (somewhat limited) provided	No	Yes	Not further assessed: no control for confounders	High
Kamilya 2005	Cannot determine: retrospective review; very limited detail	No	Yes	Not further assessed: no control for confounders	High

Kamyar 2015a Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report the use of multivariable models adjusting for GA, betamethasone exposure, mode of delivery, nulliparity, and PE)					Unclear
Kamyar 2015b Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report the use of a multivariable logistic regression model that included GA, betamethasone exposure, and nulliparity)					Unclear
Kamyar 2015c* Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report the use of multivariable models that included GA as a covariate)					Unclear
Kamyar 2016a*	Yes: prospective data collection in original RCT, detail/definitions provided; however, authors acknowledge subjectivity of definition used for chorioamnionitis to define inclusion	Yes	Partially: adjusted for GA at birth, maternal years of education, maternal race, IUGR, illicit drug use, smoking status, sex	No	Cannot determine	No, original RCT was blinded	No	No	Moderate to high
Kamyar 2016b*	Yes: prospective data collection in original RCT, detail/definitions provided (though recognition of lack of SIP data, and possibility of diagnostic overlap)	Yes	Partially: adjustment for birth GA, treatment group, fetal sex, SGA, chorioamnionitis, caesarean section, hypotension during initial resuscitation, postnatal exposure to indomethacin, sepsis, IVH	No	Cannot determine	No, original RCT was blinded	No	No	Moderate to high
Katayama 2011	Yes: retrospective chart review, though detail/definitions provided	Yes	Partially: adjusted for confounders “including” antenatal steroids, ritodrine tocolysis, PROM	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Kelly 1992 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Khodapanahandeh 2008	Yes: retrospective record review, though	Yes: controls also VLBW	Partially: multivariate analysis, included	Yes; no; no	Cannot determine	Yes, not blinded	No	No	Moderate to high

	detail/definitions provided		factors significant in univariate analyses: GA, birthweight, Apgar score at 5 minutes, resuscitation, tocolytic therapy, apnoea, MV, HMD, haematocrit, PaCO2 maximum in 1st 3 days, symptomatic hypotension 1st 3 days						
Kimberlin 1998	Yes: retrospective review of prospectively collected data, with detail/definitions provided	Yes	Partially: controlled for birthweight, GA, race, gender, mode of birth, chorioamnionitis, surfactant treatment, antenatal steroids)	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Koksal 2002	Yes: prospective collection with detail/definitions provided (though note: maternal interviews were used in conjunction with chart reviews)	No	Yes	Not further assessed: no control for confounders					High
Kuban 1992	Yes: prospective collection with detail/definitions provided (though note: maternal interviews were used in conjunction with chart/pharmacy sheet reviews)	Yes	Partially: stepwise logistic regression analysis included PE related variables; covariates (mode of birth, labour, birthweight, GA, intubation, lowest pH, antenatal steroids, mother's	No	Cannot determine	No, assessment of CUS blinded to exposures	No	No	Moderate to high

			weight/height were allowed to compete						
Lai 2017 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that multinomial logistic regression was used)					Unclear
Lee 2013 English abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; English abstract only (article in Korean; does present ORs adjusted for GA)					Unclear
Lee 2015 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that a multiple linear regression model was used)					Unclear
Leung 2016	Yes: prospective enrolment and retrospective record review, with detail/definitions provided	Yes	Partially: models included: GA, birthweight, Apgar scores at 1 and 5 minutes, antenatal exposure to betamethasone, MgSO4, an interaction term, maternal antibiotics, surfactant, CUS abnormalities, duration of ventilation, CLD, duration of furosemide, gentamicin and amphotericin, FIRS, PDA treatment with indomethacin)	No	Cannot determine	Yes, not blinded for review outcomes (blinding for placental histology)	No	No	Moderate
Leviton 1997	Yes: prospective collection, with definition provided (though note: maternal interview and record review used for some measures)	Yes	Partially: adjusted for GA, birthweight z score, antenatal corticosteroids, PE, PIH, route of birth and labour	No	Cannot determine	Yes, not blinded	No	No	Moderate to high

Lipsitz 1971	Cannot determine: prospective collection, however limited detail/definitions provided (particularly in methods)	No	Yes	Not further assessed: no control for confounders					High
Lloreda-Garcia 2016 English abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; English abstract only (article in Spanish)					Unclear
Martin 1998	Yes: retrospective review, though detail/definitions provided	Yes: matched by time period and GA range	Yes	Not further assessed; no control for confounders					High
Matsuda 1997	Yes: retrospective review, though detail/definitions provided	No: controls born in same period only	Yes	Not further assessed; no control for confounders					High
McGuiness 1980	Cannot determine: prospective collection, though outcomes not well defined in methods	Yes: controls in same GA range and also appropriately grown	Yes	Not further assessed; no control for confounders					High
McPherson 2014*	Yes: prospective data collection in original RCT, with detail/definitions provided	Yes	Yes	Not further assessed; no control for confounders for review outcomes of interest (multivariable regression analyses adjusted for confounders for CP/death assessment only)					High
Mikhael 2019	Cannot determine: methods for data collection not clearly reported	Yes	Partially: multivariate logistic regression analysis adjusted for significantly different baseline characteristics (maternal hypertension,	No	Cannot determine	Yes, not blinded	No	No	Moderate to high

			antenatal steroids, antenatal indomethacin) for composite outcomes only						
Mitani 2011	Yes: retrospective records review, with detail/definitions provided	Yes	Partially: reports that multivariate analyses/logistic regression used – assumed adjustment for GA on admission, corticosteroid, GA at birth, birthweight, Apgar scores at 1 and 5 minutes (for composite adverse outcome only)	No	Cannot determine	Yes (blinding for CP assessment, not review outcomes)	No	No	Moderate to high
Mittendorf 2005* Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that there was adjustment for confounding)					Unclear
Mittendorf 2009* Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that a logistic model controlling for birthweight and funisitis was used)					Unclear
Morag 2015	Cannot determine/no: retrospective review of prospective data, detail/definitions clear for 'cases'; data for term 'controls' collected from records	Yes: matched for birth date (within 2 weeks), gender, mode of birth	Partially: reports significant factors from multivariate analysis: maternal age, primiparity, antenatal steroids, SGA, caesarean birth, MgSO4 treatment	Yes; no; no/cannot determine	Cannot determine	Yes, not blinded	No	No	Moderate to high
Morag 2016	Yes: retrospective chart review, though detail/definitions provided	Yes	Yes	Not further assessed; though multiple linear regression analysis was conducted for neurodevelopmental follow up outcomes, no control for confounders for review outcomes of interest; additionally, protocol deviation in defining groups for comparison: "The mean iMgC was used as a cut-off in exposed infants as a second option because a comparison between those with normal serum concentrations, that is, 1.9 to 2.7 mg/dL,					High

				and those with elevated concentrations >2.7 did not reveal any difference between the groups."					
Moschos 2011 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report the results of logistic regression analysis)					Unclear
Murata 2005	Yes: retrospective record review, though detail/definitions provided	Yes	Partially: multivariate analysis included: Apgar score < 5 at 5 minutes, cord length > 40 cm, indomethacin exposure, birthweight and GA	No	Cannot determine	Yes (only placental assessment blinded)	No	No	Moderate to high
Nakamura 1991 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Narasimhulu 2017	Cannot determine: retrospective chart review, limited detail/definitions provided (some outcomes not pre-defined)	Yes	Yes	Not further assessed; for our comparison of interest, no control for confounding (though for comparisons of neonatal serum magnesium concentrations, logistic regression was used adjusting for birthweight and multiple gestation; and linear regression was used controlling for maternal MgSO4 dose)					High
Nassar 2006	Cannot determine: retrospective chart review, limited detail/definitions provided (some outcomes not pre-defined)	No	Yes	Not further assessed; no control for confounders					High
Nelson 1995	Cannot determine retrospective record review, with recognised limitations (e.g. for availability of CUS), and limited detail/definitions for outcomes of interest	Yes: controls matched for birthweight range, counties, and year	Yes	Not further assessed; while multivariate logistic regression analyses were conducted for CP, there was no control for confounders for review outcomes of interest					High

Nunes 2018	Yes: retrospective record review, though detail/definitions provided	No	Yes	Not further assessed; no control for confounders					High
Okusanya 2012	Cannot determine: prospective data collection, though limited detail/definitions provided, and reporting for perinatal mortality unclear	No	Yes	Not further assessed: no control for confounders; unclear reporting of perinatal mortality results					High
O Reilly 2016 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that the data were controlled for GA)					Unclear
Ozlu 2019	Yes: retrospective collection, though detailed definitions given	No	Yes	Not further assessed: no control for confounders					High
Palatnik 2019	Cannot determine: medical record review, with limited definitions provided	Yes: though no matching of cases and controls	Partially: factors associated with sepsis or death in bi-variable analyses were retained for further analyses (models of multivariable logistic regression for the outcome sepsis)	Yes, no, no	Cannot determine	Yes, not blinded	No	No	Moderate to high
Paneth 1991	Yes: prospective collection, with detail/definitions provided (note: maternal interviews also used)	Yes	Partially: adjustment for GA, fetal growth ratio, gender, multiple birth status, mode of birth, labour status, amnionitis, PE and pre-existing hypertension	No	Cannot determine: authors note in discussion some analyses not pre-specified	Yes, not blinded	No	No	Moderate

Perlman 1995 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that stepwise logistic regression was used)					Unclear
Petrov 2013 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Petrova 2012	Yes: retrospective collection with use of database/discharge files (though limited detail/definitions)	Yes: matching by GA and birthweight	Partially: controlled for PPROM, ventilation after birth, severity of distress	Yes; no; no	Cannot determine	Yes, no blinding (though matching was blinded)	No	No	Moderate to high
Qasim 2017 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that logistic regression correcting for GA and birthweight was used)					Unclear
Rantonen 2001	Yes: prospective data collection, with detail/definitions provided (limited for clinical outcomes)	No	Yes	Not further assessed: no adjustment for confounders (for outcomes of interest; in haemodynamic analyses, PV-IVH and graded ductal shunting were taken for covariates)					High
Rasch 1982	Yes: prospective data collection, with detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Rattray 2014	Cannot determine: retrospective collection, methods of collection not detailed	Yes	Partially: stepwise regression tested for an interaction effect between MgSO4 exposure and GA and SIP; a further model examined neonatal hydrocortisone and indomethacin exposure independently and as an interaction	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Rauf 2017	Cannot determine: retrospective record	No	Yes	Not further assessed; no adjustment for confounders					High

	review, outcomes not well defined								
Rhee 2012	Yes: prospective collection with detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Riaz 1998	Yes: prospective collection, including using records, with detail/definitions provided	Yes: matching by "similar gestation"	Yes	Not further assessed; no adjustment for confounders					High
Rizzolo 2019 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (though reports multivariate logistic regression models adjusted for patient characteristics)					Unclear
Sahin 2001	Cannot determine: prospective collection, though detail/definitions not provided	No	Yes	Not further assessed; no adjustment for confounders					High
Sakae 2017	Cannot determine: retrospective collection, with unclear methods for collection and limited detail/definitions	No	Yes	Not further assessed; while multiple logistic regression analysis was used to determine independent components of management protocol that contributed to the absence of serious neonatal complications, there was no adjustment for confounders for review outcome comparisons					High
Salafia 1995	Yes: retrospective record review, with detail/definitions provided	Yes	Partially: stepwise regression and multivariate regression analyses assessed specific factors related to early/late GM-IVH	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Sarkar 2009	Yes: retrospective collection using database/records,	Yes	Partially: stepwise logistic multivariate regression analysis assessed factors	No	Cannot determine	Yes, not blinded	No	No	Moderate to high

	with detail/definitions provided		related to severe IVH, controlling for effects of other potential confounders (GA, birthweight, prenatal steroid use, MgSO4, and 5-minute Apgar score < 6)						
Schanler 1997	Cannot determine: prospective data collection, but limited detail/definitions provided	Cannot determine: "similar women"	Yes	Not further assessed; no adjustment for confounders					High
Scudiero 2000	Yes: retrospective records review, with detail/definitions provided	Yes	Partially: multivariate logistic regression used to assess effect of > 48 g MgSO4, taking into account other possible predictors (delivery year, receipt of betamethasone, acute maternal disease, maternal race, birthweight, total dose of MgSO4)	No	Cannot determine	No, collection blinded to mortality outcomes	No	No	Moderate to high
Shalabi 2017	Yes: retrospective review using database, with detail/definitions provided (though limited for covariates)	Yes	Partially: multiple logistic regression included covariates: gender, GA, SGA, Apgar score < 7 at 5 minutes, MV on day 1, antenatal steroid use, prophylactic	No	Cannot determine	Yes, not blinded	No	No	Moderate

			indomethacin and indomethacin for PDA treatment						
Shamsuddin 2005	Cannot determine: prospective data collection with structured sheets, though some reporting by family members, limited detail/definitions	No/Cannot determine	Yes	Not further assessed; no adjustment for confounders					High
Shokry 2010	Yes: prospective data collection, detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Stetson 2019 Research Letter	Cannot determine: limited methodological detail provided	Yes	Yes/Partially	Not further assessed, multiple logistic regression analyses controlled for confounders for CP severity assessment, but no adjustment for outcomes of interest					High
Stockley 2018	Yes: data collected by CNN and CNFUN using standard manuals of operations and definitions; CNN has been shown to have high consistency and reliability	Yes	Partially: multivariable logistic regression analyses adjusting for: maternal hypertension, caesarean birth, multiple gestation, GA, male sex, and SNAP-II score > 20	No	Cannot determine	Yes, not blinded	No	No	Moderate
Suh 2015 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; English abstract only (articles in Korean)					Unclear
Teng 2006	Yes: retrospective record/database review, with detail/definitions provided	Yes	Partially: factors significantly associated with early hypotension (birthweight, GA, 1	No	Cannot determine	Yes, not blinded	No	No	Moderate to high

			and 5 minute Apgar scores, presence of labour, MgSO4, PE and RDS) were incorporated into multiple logistic regression model						
Verma 2006	Yes: retrospective record review, with detail/definitions provided	Yes	Partially: multivariate logistic regression controlled for maximum mean FiO2 and MAP during first 7 days of life, 1 and 5 min Apgar scores, GA and surfactant requirement	No	Cannot determine	No, blinded outcome assessments	No	No	Moderate to high
Weintraub 2001	Yes: retrospective collection using database, with detail/definitions provided	Yes	Partially: multivariate logistic regression included: tocolysis, antenatal steroid therapy, multiple birth, PROM, amnionitis, mode of birth, GA, birthweight, 1 and 5 minute Apgar scores, RDS, PDA, MV, pneumothorax, sepsis	No	Cannot determine	Yes, not blinded	No	No	Moderate to high
Weisz 2015	Yes: retrospective collection using database, with detail/definitions provided	Yes	Partially: adjusted for GA, sex, SGA, outborn status, chorioamnionitis, mode of birth, antenatal corticosteroid use and	No	Cannot determine	Yes, not blinded	No	No	Moderate

			multiple gestation (also accounting for correlated data within each site (or site effects))						
Whitsel 2004 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that multivariate logistic regression and analysis of covariance models were used to control for possible confounders)					Unclear
Whitten 2015 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only (does report that regression analysis was used as indicated)					Unclear
Wiswell 1996 Abstract	Cannot determine	Cannot determine	Cannot determine	Not further assessed; abstract only					Unclear
Wutthigate 2017	Yes: prospective data collection with detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High
Yokoyama 2010	Yes: retrospective record review, though detail/definitions provided	Yes: birthweight and GA were matched	Yes	Not further assessed; though logistic regression analyses was used to assess risks for increasing ALP concentrations, there was no adjustment for confounding for outcomes of interest					High
Young 1977	Cannot determine: NRT with limited detail/definitions provided	No	Yes	Not further assessed; no adjustment for confounders					High

Abbreviations: ALP: alkaline phosphatase; aOR: adjusted odds ratios; BPD: bronchopulmonary dysplasia; CCS: case-control study; CLD: chronic lung disease; CNFUN: Canadian Neonatal Follow-Up Network; CNN: Canadian Neonatal Network; CP: cerebral palsy; CUS: cranial ultrasound; E: eclampsia; EMR: electronic medical records; ET: endotracheal; FIRS: fetal inflammatory response syndrome; GA: gestational age; GM-IVH: germinal matrix intraventricular haemorrhage; HMD: hyaline membrane disease; IUGR: intrauterine growth restriction; IVH: intraventricular haemorrhage; LOS: length of stay; MAP: mean arterial pressure; MgSO4: magnesium sulphate; MRI: magnetic resonance imaging; MV: mechanical ventilation; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; NRT: non-randomised trial; NS: not significant; ORs: odds ratios; P: p value; PDA: patent ductus arteriosus; PE: pre-eclampsia; PIE: pregnancy induced hypertension; PINS: Perinatal Information System; PTL: preterm labour; PV-IVH: periventricular intraventricular haemorrhage; PPROM: preterm premature rupture of membranes; PROM: premature rupture of membranes; PVL periventricular leucomalacia; RCT: randomised controlled trial; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; ROM: rupture of membranes; SGA: small for gestational age; SIP: spontaneous intestinal perforation; SNAP: Score for Neonatal Acute Physiology-II; VLBW: very low birthweight

S3 Table. Adverse outcomes from non-randomised studies

Study; design; overall risk of bias	Participants; MgSO4 indication	Relevant comparison groups	Outcome measure(s)	Result(s)	Direction of effect, indicating benefit (✓), harm (×) or no clear difference (~)
Adama-Hondegla 2013; RCS with CCS(N); high	N = 170 women, 178 babies; E	1: Babies still living at the 7th day of life, N = 147 babies 2: Stillbirths and neonatal deaths in the 1st 7 days (perinatal deaths), N = 31 babies	MgSO4 exposure	aOR 1.04; P > 0.05	~
Alexander 2006; PCS; high	N = from 72004 births, 87 women with E and their babies included in analyses; GH/PE	1: No GH and no MgSO4 with E, N = 49 women and their babies 2: GH and MgSO4 with E, N = 11 and their babies 3: GH and no MgSO4 with E, N = 27 and their babies	Adverse outcome composite (cord pH < 7.0, Apgar score < 4 at 5 minutes, stillbirth or neonatal death, and an unanticipated admission of a term infant to the NICU)	12.2% vs. 9.1% vs. 11.1%	NR
			Perinatal death	6.1% vs. 0% vs. 11.1%	NR
Alston 2016; NCCS; high	N = 169 babies; T	1: MgSO4 use, N = 102 (90 babies in analyses) 2: No MgSO4 use, N = 67 (64 babies in analyses)	Hospital stay (days) (mean, no measure of variance)	P = 0.89	~
			Neonatal death	No events	~
			RDS	P = 0.17	~
			BPD	P = 0.10	~
			Sepsis	P = 0.74	~
			NEC	P = 0.40	~
			IVH	P = 0.47	~
Ambadkar 2017; PCS; high	N = 120 women and babies; PE/E	1: MgSO4, N = 60 babies 2: No MgSO4, N = 60 babies	Neonatal death	No events	~
			NICU admission	P = 0.007	×

			Hypotonia	P = 0.028	×
			RD	P = 0.143	~
			Meconium passage (< 6, 6-12, > 12 hours)	P > 0.05	~
		1: MgSO4 and NICU admission, yes, N = 13 babies 2: MgSO4 and no NICU admission, N = 47 babies	MgSO4 dose (categories: LD, LD + 1, LD + 2, LD + 3, LD + 4, LD + 5, LD + 7 doses)	P = 0.506	~
			Duration of MgSO4 (< 6, 6-12, 12-18, ≥ 18 hours)	P = 0.341	~
			Time between last MgSO4 dose and birth (1-2, 2-3, 3-4, 4-5, > 5 hours)	P = 0.0441 "the closer the last dose… the higher the rate"	×
Bajaj 2018; RCS; moderate	N = 7014 babies; NR	1: Routine care without resuscitation, N = 1684 babies 2: Oxygen or CPAP, N = 2279 babies 3: Bag and mask ventilation, N = 1831 babies 4: ETT intubation, N = 1034 babies 5: CPR, N = 186 babies	MgSO4 exposure (unadjusted)	P < 0.0001	✓
			MgSO4 exposure, 1 as reference, vs. 2 (adjusted for centre, GA, SGA status, any antenatal steroids, and multiple births)	aOR 0.96; 95% CI 0.81-1.14	~
			MgSO4 exposure, 1 as reference, vs. 3 (adjusted as above)	aOR 0.98; 95% CI 0.82-1.18	~
			MgSO4 exposure, 1 as reference, vs. 4 (adjusted as above)	aOR 0.65; 95% CI 0.52-0.81	✓
			MgSO4 exposure, 1 as reference, vs. 5 (adjusted as above)	aOR 0.40; 95% CI 0.24-0.67	✓
Basu 2012; RCS; moderate to high	N = 475 babies; FN	1: MgSO4, N = 289 babies 2: No MgSO4, N = 186 babies	Survival without IVH/PVL	P = 0.25	~
			Resuscitation	P = 0.42	~
			Intubation	P = 0.34	~
			BPD	P = 0.43	~
			IVH/PVL	P = 0.36	~
			Neonatal death	P = 0.52	~
			ROP	P = 0.02	×
			PDA	P = 0.01	×
			LOS (days) (mean ± SD)	P = 0.01	×
			PDA, ROP, LOS (days) (mean ± SD) (multivariate logistic regression, controlled for GA and birthweight; and multiple gestations)	"Multivariate analysis performed showed that… the increased incidences of PDA, ROP, LOS… were no longer statistically significant, although the odds of developing these complications were 1.6 times more	~

				likely than in those exposed to antenatal magnesium."	
Belden 2017; RCS with CCS(N); moderate to high	N = 83 babies; FN/PE	1: Enteral feeding intolerance, N = 49 babies 2: No feeding intolerance, N = 34 babies	MgSO4 dose (g) (mean ± SD)	P = 0.04	×
			MgSO4 dose (g) (mean ± SD) (multivariate logistic regression, accounting for differences between groups – assumed to be GA, birthweight, 1 and 5 minute Apgar scores)	"The strongest predictors were prematurity and cumulative maternal magnesium sulfate dose."	×
			MgSO4 dose (g) (mean ± SD), in relation to birthweight, < 1250 g, 1250-1500 g, > 1500 g	P = 0.47 P = 0.57 P = 0.48	~
		1: MgSO4 > 80 g, N = NR 2: MgSO4 ≤ 80 g, N = NR	Enteral feeding intolerance	P = 0.04	×
			Parenteral nutrition (days) (measure NR)^	P < 0.01	×
Bertello Grecco 2019; PCS; unclear Abstract	N = 93 women and their babies; PE	1: MgSO4 ≤ 24 hours, N = 51 women and their babies 2: MgSO4 < 24 hours, N = 42 women and their babies	"presence of respiratory depression, admission to intensive care unit, hypotonia, and neonatal mortality"	"No statistically significant differences were observed comparing both groups in neonatal variables."	~
Black 2006; PCS; high	N = 134 babies; PE/PIH/HELLP/T	1: MgSO4 with (N = 45)/without (N = 5) steroids, N = 50 babies 2: No MgSO4 with (N = 38)/without steroids (N = 46), N = 84 babies	Ventilation (days) (mean ± SD)	"no significant differences among groups."	~
			Methylxanthines (days) (mean ± SD)	"no significant differences among groups."	~
			NBRS (mean ± SD)^	"no significant differences among groups."	~
			IVH	"no differences among the groups on frequency or severity of IVH.""	~
Blackwell 2002; PCS; high	N = 39 babies; PE	1: MgSO4, N = 13 babies 2: No MgSO4, N = 26 babies	Troponin I ≥ 1.0 ng/mL (cardiac-specific protein used to detect myocardial injury)^	P = 0.4	~
Bonta 2000; PCS; unclear Abstract	N = 379 women and babies; T	1: MgSO4 < 72 hours, N = 199 babies 2: MgSO4 > 72 hours, N = 45 babies 3: No MgSO4, N = 135 babies	HsPDA treated with indomethacin	28.1% vs. 55.6% vs. 35.6%; "Incidence… was 2:1 (> 72 group vs < 72 group)"	×
Bozhurt 2016; RCS; high	N = 387 babies; PE	1: MgSO4, N = 59 babies 2: No MgSO4, N = 328 babies	RDS	"All of the p values are insignificant"	~
			BPD	"All of the p values are insignificant"	~
			Hypoglycaemia	"All of the p values are insignificant"	~

			Apnoea	"All of the p values are insignificant"	~
			PDA	"All of the p values are insignificant"	~
			IVH grade 3/4 and PVL	"All of the p values are insignificant"	~
			PVL only	"All of the p values are insignificant"	~
			Culture proven sepsis	"All of the p values are insignificant"	~
			NEC grade ≥ 2	"All of the p values are insignificant"	~
			ROP > 3	"All of the p values are insignificant"	~
Boyle 2018; RCS; unclear Abstract	N = 285 women and their babies; NR	1: MgSO4, N = 16 babies 2: No MgSO4, N = 271 babies [note discrepancy between total N and group Ns reported]	Composite adverse neonatal outcome (defined as Apgar score < 7 at 5 minutes, arterial cord pH < 7.1 and/or base deficit ≥ 12, admission to the NICU, need for immediate neonatal resuscitation beyond bulb suction and stimulation, or hospitalisation ≥ 3 days) (unadjusted OR from univariate logistic regression; aOR from multivariable logistic regression – confounders adjusted for NR)	OR 5.74; 95% CI 1.80-18.30; P < 0.01 aOR 4.29; 95% CI 1.24-14.81); P = 0.02	×
Brazy 1982; RCS; high	N = 56 babies; ESHP	1: Hypertensive women treated with MgSO4, N = 28 babies 2: Non-hypertensive women, with no MgSO4, N = 28 babies	Days hospitalised (mean ± SD)	P < 0.01	×
			Thrombocytopenia^	P < 0.05	×
			Leukopenia^	P < 0.001	×
			Neutropenia^	P < 0.01	×
			DIC^	P = NS	~
			Severe respiratory disease^	P = NS	~
			TTN^	P = NS	~
			Delayed adaptation	P < 0.01	×
			PDA	P < 0.01	×
			Hypotension	P = NS	~
			Delayed stooling (> 24 hours)	P < 0.05	×
			Ileus	P < 0.05	×
			Hypotonia	P < 0.05	×
			Other disease (CNS haemorrhage, air block, acute renal failure,^ NEC)	P = NS	~
			Neonatal death	7% vs. 7%	~
			Death after 28 days of age, before hospital discharge^	11% vs. 0%	×
			Stillbirth	No events	~

Brookfield 2015; PCS with CCS(N); unclear Abstract	N = 55 women and babies; FN/PE	1: Resuscitation, N = 27 babies 2: No resuscitation, N = 28 babies	MgSO4 dose (g) (mean ± SD)	P = 0.9	~
Brookfield 2016; RCS; unclear Abstract	N = 1496 women and babies; FN	1: MgSO4, N = 735 babies 2: No MgSO4, N = 761 babies	RDS (multivariate logistic regression, adjusted for diabetes, mode of birth, other tocolytics, GA at birth)	aRR 0.97; 95% CI 0.84-1.12	~
			Ventilation (adjusted as above)	aRR 0.93; 95% CI 0.81-1.07	~
Brown 2019; CCS; unclear Abstract	N = 218 babies; NR	1: SH, N = 109 babies 2: No SH, N = 109 babies	MgSO4 exposure (unadjusted P and aOR – confounders adjusted for NR)	P < 0.001 aOR 0.39; 95% CI: 0.20-0.75	✓
Canterino 1999; RCS; moderate	N = 918 babies; PE/T	1: MgSO4, N = 398 babies 2: No MgSO4, N = 520 babies	Apgar score < 7 at 5 minutes	P = 0.79	~
			RD	P = 0.38	~
			Neonatal death	P = 0.44	~
			Abnormal sonograms (any PVL or IVH)	P = 0.06	~
			Severe lesions (any PVL, PVL with IVH, or IVH grade 3/4)	P = 0.004	✓
			Severe lesions (any PVL, PVL with IVH, or IVH grade 3/4) (adjusted for clinical group)	aOR 1.11; 95% CI 0.73-1.68, P = 0.42	~
			Severe lesion (any PVL, PVL with IVH, or IVH grade 3/4) (adjusted for GA, birthweight, antenatal steroids, chorioamnionitis, mode of birth, Apgar score < 7 at 5 minutes, RDS)	aOR 1.10; 95% CI 0.70-1.74; P = 0.69	~
			Abnormal sonograms (any PVL or IVH) (adjusted for clinical group)	aOR 1.09; 95% CI 0.78-1.52; P = 0.40	~
			Abnormal sonograms (any PVL or IVH) (adjusted for GA, birthweight, antenatal steroids, chorioamnionitis, mode of birth, Apgar score < 7 at 5 minutes, RDS)	aOR 1.01; 95% CI 0.70-1.44; P= 0.97	~
		1: Abnormal sonograms, N = 39 babies 2: Normal findings, N = 125 babies	Duration of MgSO4 (mean, SD) (hours)	P = 0.78	~

		1: Severe lesions, N = 27 babies 2: Normal findings, N = 127 babies	Duration of MgSO4 (mean, SD) (hours)	P = 0.72	~
Cawyer 2019; RCS; unclear Abstract	N = 2468 women and their babies; PE	1: MgSO4, N = 1353 babies 2: No MgSO4, N = 1115 babies	Perinatal or neonatal death (unadjusted P)	P = 1.00	~
			NICU admission (adjusted for maternal age, race/ethnicity, BMI, primary source of payment, tobacco use, illicit drug use, diabetes, chronic hypertension)	aOR 0.94; 95% CI 0.74-1.2	~
Cho 2014; RCS; unclear Abstract	N = 570 babies; NR	1: MgSO4, N = 101 babies 2: No MgSO4 = 469 babies	Hypocalcaemia	"not different between groups."	~
Chowdhury 2009; PCS (or NRT); high	N = 630 women (529 babies born to antepartum/intrapartum cases); E	1: MgSO4 by Pritchard's regimen, N = 480 women (406 babies born to antepartum/intrapartum cases 2: MgSO4 by low-dose IV regimen, N = 150 women (123 babies born to antepartum/intrapartum cases)	Stillbirth	11.6% vs. 8.3%	~
			Early neonatal death due to birth asphyxia and prematurity (1st 7 days)	15.0% vs. 10.4%	~
			Perinatal death	OR 1.58; 95% CI 0.93-2.61; P = 0.075	~
Chun 2014; RCS; unclear English abstract	N = 209 women and babies; PE	1: MgSO4, N = 119 babies 2: No MgSO4, N = 90 babies	Apgar score < 7 at 1 minute, primiparous women	P = 0.031	×
			Apgar score < 7 at 1 minute, multiparous women	P = 0.147	~
			Apgar score < 7 at 5 minutes, primiparous women	P = 0.017	×
			Apgar score < 7 at 5 minutes, multiparous women	P = 0.792	~
			NICU admission, primiparous women	P = 0.001	×
			NICU admission, multiparous women	P = 0.179	~
Cuff 2018; RCS; moderate to high	N = 224 women and their babies: 44 women and 54 babies exposed to MgSO4 within 12 hours of birth; FN	1: 2014 (BEAM trial: 6 g IV LD; 2 g/hour IV MD for 12 hours), N = 18 babies exposed within 12 hours of birth 2: 2015 (PREMAG trial: 4 g IV MD; no MD), N = 36 babies	Apgar score < 7 at 5 minutes,	P = 0.55	~
			ROP grade 3/4	P = 0.57	~
			IVH grade 3/4 (binary logistic regression controlling for race, PTL, GA at delivery, corticosteroid exposure, birthweight, and indomethacin exposure)	P = 0.04 aOR 10.2; 95% CI 1.3-92	×

		exposed within 12 hours of birth			
Das 2015; PCS; high	N = 100 women and their babies; E	1: 8 g MgSO4, N = 20 babies 2: > 8 g MgSO4, N = 80 babies	Apgar score < 7 at 1 minute	P = 0.000	×
			Apgar score < 7 at 5 minutes	P = 0.021	×
			Apgar score ≤ 3 at 1 minute^	P = 0.002	×
			Apgar score ≤ 3 at 5 minutes^	P = 0.003	×
			Respiratory depression	P = 0.02	×
			Intubation in delivery room	P = 0.01	×
			Bradycardia^	P = 0.022	×
			Hypotonia	P = 0.012	×
			Hyporeflexia^	P = 0.025	×
			NICU admission	P = 0.03	×
			Significant respiratory support in NICU^	P = 0.000	×
			Time to 1st stool > 24 hours	P = 0.011	×
			Time to 1st void > 48 hours	P = 0.02	×
			Number of episodes of feeding intolerance ≥ 3^	P = 0.000	×
			Stillbirth	P = 0.008	×
			Neonatal death due to complications of hypermagnesemia	P = 0.043	×
Deering 2005; RCS; moderate to high	N = 221 babies; PE/T	1: MgSO4, N = 103 babies (77 preterm labour) 2: No MgSO4, N = 118 babies (108 preterm labour)	SNAP score in 1st 24 hours (mean ± SD) (multiple linear regression controlling for GA, birthweight, chorioamnionitis, steroid use)^	P = 0.005 (“significant decrease”)	✓
			SNAP score > 10 in 1st 24 hours (multiple linear regression as above)	P < 0.001	✓
			SNAP score in 1st 24 hours (mean ± SD), preterm labour only (multiple linear regression as above)^	P = 0.047	✓
			SNAP score > 10 in 1st 24 hours, preterm labour only (multiple linear regression as above)	P = 0.001	✓
De Jesus 2015; RCS; moderate	N = 1544 babies; FN/PIH/T	1: MgSO4, N = 1091 babies 2: No MgSO4, N = 453 babies	Delivery room resuscitation (PPV via bag and mask, any CPAP devices, intubation, chest compression and epinephrine)	P = 0.665	~
			Delivery room intubation	P = 0.157	~

			Delivery room intubation (multivariate logistic regression adjusted for centre, GA, antenatal steroids, and PIH/E)	aOR 1.20; 95% CI 0.88-1.65; P = 0.246	~
			Day 1 MV	P = 0.670	~
			Day 1 MV (multivariate logistic regression adjusted as above)	aOR 1.22; 95% CI 0.65-2.30; P = 0.540	~
			Day 1 ET MV	P = 0.023	✓
			Day 1 ET MV (multivariate logistic regression adjusted as above)	aOR 0.78; 95% CI 0.58-1.06; P = 0.109	~
			Day 3 MV	P = 0.190	~
			Day 3 MV (multivariate logistic regression adjusted as above)	aOR 0.65; 95% CI 0.40-1.04; P = 0.070	~
			Day 3 ET MV	P = 0.0002	✓
			Day 3 ET MV (multivariate logistic regression adjusted as above)	aOR 0.54; 95% CI 0.41-0.72; P <0.001	✓
			Day 1 hypotension	P = 0.043	✓
			Day 1 hypotension (multivariate logistic regression adjusted as above)	aOR 0.70; 95% CI 0.51-0.97; P = 0.031	✓
			PDA treated (medical or surgical)	P = 0.954	~
			PDA treated (medical or surgical) (multivariate logistic regression adjusted as above)	aOR 1.06; 95% CI 0.80-1.40; P = 0.696	~
			RDS	P = 0.747	~
			Pulmonary haemorrhage	P = 0.289	~
			Traditional BPD	P = 1.0	~
			Late onset sepsis/meningitis	P = 0.085	~
			NEC stage 2 or greater	P = 0.351	~
			ROP any stage	P = 0.359	~
			IVH or parenchymal haemorrhage	P = 0.294	~
			cPVL	P = 0.150	~
			Neonatal death	P = 0.223	~
			Cumulative days on MV (median, Q1, Q3)	P = 0.871	~
			Cumulative days on oxygen support (median, Q1, Q3)	P = 0.635	~
			LOS (median, Q1, Q3)	P = 0.621	~

del Moral 2007; RCS; moderate to high	N = 941 babies; PE/T	1: MgSO4, N = 546 babies 2: No MgSO4, N = 395 babies	PDA	P = 0.0178	×
			PDA (methods report co-variables: GA or birthweight, race, gender, mode of birth, antenatal steroids, presence of chorioamnionitis, MgSO4 indication)	"Logistic regression analysis showed that after controlling for confounding variables there was an increased risk of PDA in infants exposed to MgSO4."	×
			PDA, ≥ 26 weeks GA	P = 0.0399 "When stratified by gestational age the differences were significant only in the group of infants with a gestational age ≥ 26 weeks. Moreover, in these infants the incidence of PDA increased concomitantly with the dose of MgSO4 given to the mother."	×
			PDA, ≥ 26 weeks GA (methods report co-variables as above)	OR: 1.33; CI 1.12-1.58, per 50 g MgSO4 "Logistic regression analysis to adjust for co-variables indicated an increased risk of PDA with higher doses of MgSO4."	×
			PDA treated with surgical ligation	30% vs. 34% "not different."	~
			Neonatal death (up to hospital discharge)	18% vs. 22% "did not differ."	~
			IVH grade 3/4	12% vs. 13% "similar."	~
			PVL	2.3% vs. 1.1% "similar."	~
delValle 1998; PCS; unclear Abstract	N = 110 babies; NR	1: MgSO4, N = 34 babies 2. No MgSO4, N = 76 babies	Surfactant treatment, indomethacin treatment, PDA, NEC, IVH, PVL	"Infants exposed to maternal magnesium were comparable to non-exposed infants"	~
Derks 2016; NCCS; unclear Abstract	N = 207 babies; FN	1: Post MgSO4 implementation, N = 99 babies 2: Pre MgSO4 implementation, N = 108 babies	PWML at 30 weeks MRI^	P = 0.002	✓
			PWML at 40 weeks MRI^	"not [reduced]"	~
			"neonatal complications, including early intubation for respiratory insufficiency or hypotension."	"no increase"	~
De Silva 2018; RCS (within report of ITS); moderate	N = 14108 babies; FN	1: MgSO4 for FN, N = 5314 babies	Intensive resuscitation (either chest compressions or intubation and ventilation or epinephrine administration in the delivery room) (adjusted for	aOR 0.63; 95% CI 0.54-0.73; P < 0.001	✓

		2: No MgSO4, N = 7238 babies 3: MgSO4 for another indication, N = 1556 babies	multiple gestation, gender, GA at birth, birthweight < 10th centile, outborn status, mode of birth, antenatal corticosteroid use) 1 vs. 2		
			Intensive resuscitation (adjusted as above) 1 vs. 3	aOR 0.81; 95% CI 0.66-0.99; P = 0.04	✓
de Veciana 1995; RCS; high	N = 73 women, 80 babies; T	1: MgSO4, N = 44 women, 48 babies 2: No MgSO4, N = 29 women, 32 babies	Days in hospital (mean ± SD)	P = NS	~
			Days intubated (surviving neonates) (mean ± SD)	P = NS	~
			Days intubated (babies with RDS) (mean ± SD)	P = 0.43	~
			RDS mild to severe	P = NS	~
			RDS severe (requiring high pressure ventilation for more than 24 hours)	RR 0.47; CI 0.2-1.0; P = 0.04	✓
			IVH grade 1-4	P = NS	~
			NEC	P = NS	~
			Neonatal death	P = NS	~
			Apgar score < 7 at 5 minutes	P = NS	~
Downey 2017; RCS; moderate	N = 28035 babies; FN/PE/T	1: MgSO4, N = 11789 babies 1: No MgSO4, N = 16246 babies	SIP (adjusted for site, GA at birth, multiple gestation, antenatal steroid exposure, antenatal antibiotic exposure, prolonged ROM, SGA age, sex, discharge year, postnatal hydrocortisone exposure, and postnatal indomethacin exposure)	aOR 1.08; 95% CI 0.91-1.29	~
			Neonatal death in 1st 21 days of life (adjusted as above)	aOR 0.76; 95% CI 0.70-0.83	✓
			Surgical NEC (adjusted as above)	aOR 0.84; 95% CI 0.66-1.05	~
			Medical NEC (adjusted as above)	aOR 1.11; 95% CI 0.89-1.37	~
			Neonatal death, NEC or SIP (adjusted as above)	aOR 0.84; 95% CI 0.77-0.90	✓
			IVH grade 3/4 (adjusted as above)	aOR 0.97; 95% CI 0.88-1.06	~
Drassinower 2015; RCS; unclear Abstract	N = 1047 women and babies; FN	1: MgSO4, N = 461 babies 2: Placebo, N = 586 babies	Composite of immediate outcomes (Apgar score < 7 at 5 minutes, oxygen in delivery room, intubation, chest compressions, hypotension, hypotonicity) (adjusted for GA at birth, sepsis, SGA, and alcohol use) overall; and birth ≥ 30 weeks GA	OR 0.92; 95% CI 0.79-1.08; P = 0.12 OR 0.91; 95% CI 0.73-1.14; P = 0.24	~
			Apgar score < 7 at 5 minutes overall; and birth ≥ 30 weeks GA	OR 0.82; 95% CI 0.59-1.14; P = 0.25 OR 1.13; 95% CI 0.56-2.28; P = 0.74	~
			Oxygen bag, mask or both overall; and birth ≥ 30 weeks GA	OR 1.10; 95% CI 0.80-1.41; P = 0.62 OR 0.89; 95% CI 0.71-1.11; P = 0.61	~

			Intubation overall; and birth ≥ 30 weeks GA (adjusted for GA at birth, sepsis, SGA, and alcohol use)	OR 0.89; 95% CI 0.71-1.11; P = 0.05 OR 0.53; 95% CI 0.32-0.88; P = 0.01	✓
			Chest compressions overall; and birth ≥ 30 weeks GA	OR 1.2; 95% CI 0.6-2.5; P = 0.71 OR 2.39; 95% CI 0.2-26.5; P = 0.46	~
			Hypotension treated with vasopressors overall; and birth ≥ 30 weeks GA	OR 0.8; 95% CI 0.6-1.2; P = 0.30 OR 0.55; 95% CI 0.28-1.09; P = 0.08	~
			Generalised hypotonicity overall; and birth ≥ 30 weeks GA	OR 0.78; 95% CI 0.46-1.22; P = 0.35 OR 0.89; 95% CI 0.31-2.60; P = 0.83	~
			RDS overall; and birth ≥ 30 weeks GA	OR 0.96; 95% CI 0.75-1.22; P = 0.72 OR NR for ≥ 30 weeks GA	~
			MV overall; and birth ≥ 30 weeks GA	OR 0.84; 95% CI 0.66-1.07; P = 0.16 OR 0.80; 95% CI 0.54-1.18; P = 0.26	~
			Seizures overall; and birth ≥ 30 weeks GA	OR 0.99; 95% CI 0.37-2.67; P = 0.98 OR NR for ≥ 30 weeks GA	~
			IVH overall; and birth ≥ 30 weeks GA	OR 0.81; 95% CI 0.60-1.1; P = 0.16 OR NR for ≥ 30 weeks GA	~
			Neonatal death (assumed) overall; and birth ≥ 30 weeks GA	OR 1.27; 95% CI 0.78-2.08; P = 0.34 OR 2.35; 95% CI 0.69-7.90; P = 0.16	~
Duffy 2012; RCS; high	N = 5387 women and babies; PE	1: MgSO4, N = 248 babies 2: No MgSO4, N = 5139 babies	Composite adverse outcome (fetal acidemia, base excess ≤ -12.00, SCBU or NICU admission)	P = 0.11	~
Edwards 2018; RCS; moderate to high	N = 1944 women and babies; FN	1: Chorioamnionitis, N = 228 women and babies 2: No chorioamnionitis, N = 1716 women and babies	MgSO4 exposure	P = 0.76	~
			All below outcomes	Breslow-Day test P > 0.05 for all	~
		1: Chorioamnionitis and MgSO4, N = 109 babies 2: Chorioamnionitis and no MgSO4, N = 119 babies	IVH	OR 0.72; 95% CI 0.40-1.28; P = 0.26	~
			IVH (logistic regression adjusted for sex)	aOR 0.73; 95% CI 0.40-1.30	~
			NEC	OR 1.23; 95% CI 0.52-2.91; P = 0.64	~
			NEC (logistic regression adjusted for sex)	aOR 1.23; 95% CI 0.52-2.91	~
			BPD	OR 1.26; 95% CI 0.67-2.36; P = 0.48	~
			BPD (logistic regression adjusted for sex)	aOR 1.26; 95% CI 0.67-2.38	~
		1: No chorioamnionitis and MgSO4, N = 839 babies	IVH	OR 0.87; 95% CI 0.68-1.11; P = 0.26	~
			IVH (logistic regression adjusted for sex)	aOR 0.85; 0.66-1.09	~

		2: No chorioamnionitis and no MgSO4, N = 877 babies	NEC	OR 1.15; 95% CI 0.82-1.62; P = 0.42	~
			NEC (logistic regression adjusted for sex)	aOR 1.17; 95% CI 0.83-1.64	~
			BPD	OR 1.05; 95% CI 0.81-1.35; P = 0.73	~
			BPD (logistic regression adjusted for sex)	aOR 1.03; 95% CI 0.79-1.33	~
Elimian 2002; RCS; moderate to high	N = 401 babies; T	1: MgSO4, N = 190 babies 2: No MgSO4, N = 211 babies	Apgar score < 7 at 5 minutes	P = 0.79	~
			RDS	P = 0.40	~
			Surfactant	P = 0.42	~
			Antibiotics	P = 0.0001	✖
			PDA	P = 0.16	~
			IVH/PVL	P = 0.83	~
			NEC	P = 0.20	~
			Sepsis	P = 0.81	~
			Neonatal death (1st 28 days)	P = 0.27	~
			Neonatal death (1st 28 days) (adjustment for antenatal confounding variables)	aOR 0.66; 95% CI 0.28-1.54; P = 0.34	~
		1: MgSO4 > 24 hours, N = 79 babies 2. MgSO4 ≤ 24 hours, N = 111 babies	Apgar score < 7 at 5 minutes	P = 0.32	~
			RDS	P = 0.91	~
			Surfactant	P = 0.31	~
			Antibiotics	P = 0.19	~
			PDA	P = 0.72	~
			IVH/PVL	P = 0.93	~
			NEC	P = 0.70	~
			Sepsis	P = 1.0	~
			Neonatal death (1st 28 days)	P = 0.81	~
Elliot 2003; RCS; unclear Abstract	N = 9782 babies; T	1: MgSO4, N = 6186 babies 2: No MgSO4, N = 3596 babies	Neonatal death	7.2% vs. 7.3%	~
			IVH	5.7% vs. 4.4%	~
			NEC	4.3% vs. 4.8%	~
			ROP	5.2% vs. 3.2%	~
			Morbidities (as above)	"Multivariate analysis… showed no difference"	~
Farkouh 2001; RCS; moderate to high	N = 12876 babies; PE/T	1: MgSO4, N = 4612 babies 2: No MgSO4, N = 8264 babies	Neonatal death (death in NICU < 28 days)	OR 1.2; P = 0.06	~
			Neonatal death (death in NICU < 28 days) (stratified according to GA)	OR 0.67; 95% CI 0.54-0.84, P = 0.0005	✓

			Neonatal death (death in NICU < 28 days) (controlling for GA and MgSO4 indication)	aOR 0.70; 95% CI 0.56-0.89; P = 0.003 GA interaction: P = 0.653 MgSO4 indication interaction: P = 0.524	✓
			Neonatal death (death in NICU < 28 days) (logistic regression, controlling for: GA, antenatal steroids, terbutaline use, bleeding, caesarean section)	aOR 0.82; 95% CI 0.65-1.04; P = 0.108	~
FineSmith 1997; CCS; moderate to high	N = 54 babies; PE/T	1: cPVL, N = 18 babies 2: No cPVL, N = 36 babies	MgSO4 exposure	OR 0.19; 95% CI 0.039-0.988; P > 0.035	✓
			MgSO4 exposure (logistic regression including: GA, MgSO4, Apgar scores at 1 and 5 minutes, number of days intubation, reason for prematurity, type of birth)	Chi^2 = 23.4; df = 12; P = 0.014 R statistic P < 0.03; df = 1	✓
Gano 2016; PCS with CCS(N); moderate	N = 73 babies; FN/PE/T	1: MgSO4, N = 49 babies 2: No MgSO4, N = 24 babies	Cerebellar haemorrhage^	RR 0.45; 95% CI 0.26-0.81; P = 0.008	✓
			Cerebellar haemorrhage, size: < 3 mm vs. > 3 mm^	P = 0.018	✓
			Cerebellar haemorrhage, number of foci: 1-3 vs. > 3^	P = 0.028	✓
			WMI, absent/mild vs. moderate/severe^	P = 0.53	~
			IVH, none/grade 1 vs. grade 3/4	P = 0.23	~
		1: Cerebellar haemorrhage, N = 27 babies 2: No cerebellar haemorrhage, N = 46 babies	MgSO4 exposure (none, for PE/T, for FN)	P = 0.021	✓
			MgSO4 exposure (univariate logistic regression)	OR 0.26; 95% CI 0.092-0.72; P = 0.010	✓
			MgSO4 exposure (multivariable logistic regression: adjusting for postmenstrual age at MRI, VLBW, intubation at birth, prolonged MV, hypotensive, symptomatic PDA)	aOR 0.18; 95% CI 0.049-0.65; P = 0.009	✓
			MgSO4 exposure (multivariable logistic regression, adjusted as above, and further for prenatal steroid exposure)	aOR 0.11; 95% CI 0.025-0.50; P = 0.004	✓
			MgSO4 exposure (multivariable logistic regression, adjusted as above): MgSO4 for PE/T	aOR 0.21; 95% CI 0.053-0.83; P = 0.026	✓
			MgSO4 exposure (multivariable logistic regression, adjusted as above): MgSO4 for FN	aOR 0.12; 95% CI, 0.019-0.77; P = 0.025	✓
	N = 118 babies; FN	1: MgSO4, N = 62 babies	Resuscitation	P = 0.04	×

Garcia Alonso 2018; PCS; moderate to high		2: No MgSO4, N = 56 babies	Resuscitation (multivariate analysis in presence of GA and birthweight)	"no longer statistically significant"	~
			IMV	P = NS	~
			Surfactant	P = 0.03	×
			Surfactant (multivariate analysis as above)	"no longer statistically significant"	~
			BPD	P = 0.02	×
			BPD (multivariate analysis as above)	"no longer statistically significant"	~
			PDA	P = NS	~
			Neonatal death	P = 0.04	✓
			IVH	P = NS	~
			NEC	P = NS	~
			PVL	P = NS	~
			ROP	P = 0.03	×
			ROP (multivariate analysis as above)	"no longer statistically significant"	~
Gasparyan 2017; PCS; unclear English abstract	N = 62 women and babies; FN	1: MgSO4, N = 37 babies 2: No MgSO4, N = 25 babies	IVH	"the conduction of neuroprotection does not significantly reduce IVH frequency."	~
			IVH grade 3/4	27.7% vs. 69.2%; "pronounced influence"	✓
Ghidini 2001; CCS; moderate to high	N = 69 babies; PE/T	1: NEC, N = 23 babies 2: No NEC, N = 46 babies	MgSO4 exposure	OR 1.5; 95% CI 0.5-4.9; P = 0.4	~
			MgSO4 exposure (logistic regression, controlling for diagnosis of preterm labour)	P = 0.52	~
Gibbins 2013; RCS; high	N = 373 women and their babies (313 delivered < 32 weeks in analyses for relevant outcomes); FN (unclear whether also given for PE/T)	1: MgSO4, N = 223 babies 2: No MgSO4, N = 90 babies	Apgar score < 7 at 1 minute	P = 0.26	~
			Apgar score < 7 at 5 minutes	P = 0.58	~
			Resuscitation (none vs. oxygen vs. bag and mask vs. intubation vs. chest compressions)	P = 0.73	~
			Discharged alive	P = 0.52	~
			NICU admission	P > 0.99	~
			NICU LOS (days) (median range)	P = 0.93	~
			Individual morbidities	"did not differ significantly."	~
			Hypotonia	"There were no reports… in neonates exposed to magnesium."	NA
		1: MgSO4, N = 1747 babies	NICU admission	OR 1.9; 95% CI 1.4-2.7; P < 0.001	×

Girsen 2015; RCS; moderate to high	N = 2166 women and babies; PE	2: No MgSO4, N = 419 babies	NICU admission (multivariable logistic regression adjusted for potential confounding variables including receipt of public insurance, maternal age, race, type of birth, birthweight, GA at birth)	aOR 1.9; 95% CI 1.3-2.6	×
			NICU admission within 2 hours of birth	P = 0.01	×
			NICU LOS (days) (median, range)	P = 0.50	~
			LOS (days) (median, range)	P = < 0.001	×
			Apgar score < 7 at 1 minute	P = 0.01	×
			Apgar score < 7 at 5 minutes	P = 0.008	×
			Apgar score < 7 at 10 minutes^	P = 0.86	~
			RDS	P = 0.16	~
			Ventilation support within 24 hours of birth	P = 0.07	~
			Prolonged hypotonicity within 72 hours of birth	P = 0.08	~
			Seizures	No events	~
			Sepsis	P = 0.63	~
			HIE	P = 0.91	~
			Neonatal death	P = 0.44	~
			NICU LOS ≥ 8 days^	OR 0.7; 95% CI 0.4-1.4	~
			NICU LOS ≥ 8 days (multivariable logistic regression adjusted as above)^	aOR 0.7; 95% CI 0.3-2.3	~
Gonzalez-Quintero 2001; PCS; unclear Abstract	N = 851 babies; NR	1: MgSO4, N = 438 babies 2: No MgSO4, N = 413 babies	Overall survival	"similar"	~
			Early survival (alive at 7 days) Early survival, infants < 700 g	P < 0.01 "more apparent", P < 0.01	✓
			Severe RDS	"Similar rates"	~
			IVH	"Similar rates"	~
			PDA PDA, infants < 700 g	OR 1.64; 95% CI 1.21-2.21; P < 0.01 "more evident", P < 0.01	×
			Early PDA (< 7 days of life)	50% vs. 45%; "not different"	~
Greenberg 2011; RCS with CCS(N); moderate to high	N = 242 babies (note: discrepancies in text and tables); PE	1: NICU admission, N = 52 babies 2: Well baby nursery admission, N = 200 babies	Duration of MgSO4 (hours) (mean ± SD)	P < 0.001	×
			Duration of MgSO4 (hours) (mean ± SD) (multivariable regression analysis, controlled for GA, Apgar score at 1 minute, birthweight, caesarean birth, severe PE)	OR 1.06; 95% CI 1.02-1.10	×
			MgSO4 dose (g) (mean ± SD)	P < 0.001	×

			MgSO4 dose (g) (mean ± SD) (multivariable regression analysis controlled as above)	OR 1.03; 95% CI 1.01-1.05	×
			> 12 hours MgSO4 exposure (multivariable regression analysis controlled as above)	OR 2.81; 95% CI 1.31-6.03	×
			> 30 g MgSO4 exposure (multivariable regression analysis controlled as above)	OR 2.59; 95% CI 1.22-5.51	×
			Above outcomes, limited to neonates at ≥ 37 weeks GA, and controlling for operative birth for non-reassuring fetal status	"associations… remained… (data not shown)"	×
Greenberg 2013; RCS; moderate to high	N = 264 babies; PE	1: MgSO4, N = 190 babies 2: No MgSO4, N = 74 babies	Meconium stained AF	P = 0.9	~
			NICU admission	P = 0.04	×
			NICU admission (multivariable regression analysis, controlled for GA, public insurance, birthweight, caesarean birth, chronic hypertension and severe PE)	aOR 3.69, 95% CI 1.13 to 11.99	×
			Initial admission (NICU vs. well baby nursery)^	P = 0.6	~
			Primary NICU admission diagnosis (RD, rule out sepsis, hypotonia, hypothermia, LBW, hyperbilirubinaemia, hypermagnesemia, other)^	P = 0.06	~
			NICU LOS (days) (median, IQR)	P = 0.4	~
			Respiratory treatments needed^	P > 0.99	~
			Fluids/nutritional support needed	P = 0.04	×
			Antibiotics needed	P = 0.6	~
			Phototherapy needed	P = 0.6	~
		1: < 12 hours MgSO4 exposure (< 30 g), N = 132 babies 2: ≥ 12 hours (≥ 30 g), N = 58 babies	NICU admission	P = 0.004	×
			NICU admission (multivariable regression analysis, assumed to be controlled as above)	aOR 2.54; 95% CI 1.05 to 6.18	×
			NICU admission (logistic regression of MgSO4 dose (g) and MgSO4 exposure (hours))	"an increasing probability of NICU admission" [figures provided]	×
Grether 1998; CCS; moderate to high	N = 168 babies (128 analysed); T	1: Neonatal death, N = 53 babies 2: Survival to 3 years with no disabling CP, N = 75 babies	MgSO4 exposure	OR 0.11; 95% CI 0.03 to 0.40	✓
			MgSO4 exposure for PE	0% vs. 17.3%	✓
			MgSO4 exposure	OR 0.25; 95% CI 0.6-1.1	~

		1: Neonatal death no maternal PE, N = 21 babies 2: Survival to 3 years with no disabling CP no maternal PE, N = 35 babies	MgSO4 exposure (multiple linear logistic model adjusted for birthweight and GA)	aOR 0.09; 95% CI 0.01 to 0.93; P = 0.043	✓
			Above, adjusted for clinical or histologic diagnosis of placental infection	aOR 0.13; 95% CI 0.01-1.5	~
			Above, adjusted for clinical or histologic diagnosis of placental infection or suspected chorionitis	aOR 0.10; 95% CI 0.01-1.1	~
			Above adjusted clinical or histologic diagnosis of placental infection or maternal infection, including urinary tract infection versus no infection.	aOR 0.10; 95% CI 0.01-1.1	~
			Above adjusted for sex	aOR 0.09; 95% CI 0.01-0.96	✓
			Above, adjusted for maternal race	aOR 0.09; 95% CI 0.01-1.1	~
			Above, adjusted for maternal age	aOR 0.09; 95% CI 0.01-0.98	✓
			Above, adjusted for level of hospital care	aOR 0.09; 95% CI 0.01-0.93	✓
			Above, adjusted for maternal bleeding on admission	aOR 0.05; 95% CI 0.01-0.76	✓
			Above, adjusted for presentation at birth	aOR 0.11; 95% CI 0.01-1.2	~
			Above, adjusted for surgical birth	aOR 0.09; 95% CI 0.01-0.93	✓
			Above, adjusted for in utero exposure to corticosteroid	aOR 0.10; 95% CI 0.01-0.94	✓
			Above, adjusted for abruptio placentae	aOR 0.09; 95% CI 0.01-0.97	✓
			Above, adjusted for placenta praevia	aOR 0.07; 95% CI 0.01-0.83	✓
			Above, adjusted for hypertension or antihypertensive medications given during admission for birth	Not able to calculate due to 0 cells	NA
Grimbly 2015; RCS with CCS(N); unclear Abstract	N = 175 babies; NR	1: Hypoglycaemia, N = 69 babies 2: No hypoglycaemia, N = 106 babies	MgSO4 exposure	RR 0.67, P = 0.095 "antenatal administration of magnesium sulphate trended towards being protective"	~
Gulcan 2006; PCS; high	N = 200 babies; T	1: MgSO4, N = 35 babies 2: No MgSO4, N = 165 babies	RDS	0% vs. 27.9%	NR
Gursoy 2015; PCS; high	N = 50 babies; PE/T	1: MgSO4, N = 25 babies 2: No MgSO4, N = 25 babies	Hypotension	No events	~
			Hypertension	No events	~
			NEC	No events	~
			RDS	P = 0.3	~

			PDA	P = 0.83	~
			ICH stage I-2	P = 0.12	~
			Feeding intolerance	P = 0.3	~
Havranek 2011; RCS; high	N = 56 babies; PE/T	1: MgSO4 in 24 hours prior to birth, N = 27 babies 2: No MgSO4, N = 29 babies	Caffeine treatment	P = 0.11	~
			Ventilator support	P = 0.14	~
			Phototherapy	P = 0.54	~
			Umbilical artery catheter^	P = 0.57	~
			Enteral feedings day 1^	P = 0.60	~
			Neonatal death (assumed) during hospitalisation	3.7% vs. 6.9%	NR
			NEC	0% vs. 3.4%	NR
Hechtman 2002; RCS with CCS(N); unclear Abstract	N = 85 babies; T	1: Neonatal deaths, N = 19 babies 2: Survivors, N = 66 babies	MgSO4 exposure	P = 0.2	~
			MgSO4 dose (g) (median, range)	P = 0.2	~
			MgSO4 dose > 48 g	P = 0.4	~
			As above	"After controlling for GA, betamethasone therapy, clinical chorioamnionitis, and delivery mode, neither MgSO4 exposure nor total dose of antenatal MgSO4 had an impact on neonatal survival."	~
Holcomb 1991; NCCS; unclear	N = 23 women, 33 babies; T	1: MgSO4 > 7 days, N = 11 babies 2: No MgSO4 or < 3 days, N = 22 babies	Definitely abnormal chest radiograph (bones) (proximal humeri, radiographic abnormalities: transverse radiolucent and/or sclerotic bands)	P < 0.001	×
Hom 2018; RCS; unclear Abstract	N = 52 women and babies; FN	1: MgSO4, N = 26 babies 2: No MgSO4, N = 26 babies	IVH	P = 0.35	~
Hong 2019; RCS; unclear Abstract	N = 598 babies; NR (includes FN)	1: MgSO4 for FN not adopted (16.2% exposure), N = 270 babies 2: MgSO4 for FN routine (60.6% exposure), N = 264 babies 3: MgSO4 abandoned (14.0% exposure), N = 64 babies	Neonatal death	"not significantly different among the three periods"	~
			Neonatal death due to NEC	P = 0.347	~
			NEC	P = 0.346	~
			NEC (grade ≥ 2)	"not significantly different among the three periods"	~
			Other neonatal outcomes^	"not significantly different among the three periods"	~
		1: MgSO4, N = 213 babies	Neonatal death	"two groups were similar"	~

		2: No MgSO4, N = 385 babies	Neonatal death due to NEC	P = 0.885	~
			NEC	P = 0.171	~
			NEC (grade ≥ 2)	"two groups were similar"	~
			Other neonatal outcomes^	"two groups were similar"	~
Imamoglu 2014; PCS; high	N = 53 babies; PE/T	1: MgSO4, N = 20 babies 2: No MgSO4, N = 33 babies	RDS	P = 0.8	~
			PDA	P = 0.7	~
			IVH	P = 0.52	~
			Caffeine treatment	P = 0.8	~
			Ibuprofen^	P = 0.54	~
			Inotrope use	P = 0.87	~
			Phototherapy	P = 0.9	~
Igarashi 1995; RCS; unclear English abstract	N = 42 babies; T	1: Hypermagnesemic infants exposed to MgSO4, N = 27 babies (with (N = 15) and without (N = 12) complications) 2: Infants born to "normal mothers", N = 15 babies	See right	"In both control group and non-complication group, respiratory and cardiovascular symptoms were less found than in complication group. But the infants in complication group only had more symptoms such as respiratory depression, hypotonia, and hypotension than those in other groups. They required prolonged dopamine and calcium gluconate infusion. We speculated that complications could be attributed to disorders rather than hypermagnesemia."	NR
James 2015; PCS; high	N = 38 babies; FN	1: MgSO4 within 4 hours of birth, N = 19 babies 2: No MgSO4, N = 19 babies	IVH grade 3/4	P = 0.2	~
			Inotropes (1st week)	P = 1.0	~
			Pulmonary haemorrhage	P = 0.1	~
			NEC	P = 0.3	~
			CLD	P = 0.04	✖
			CLD (logistic regression, controlling for antenatal steroids)	P = 0.06	~
			Neonatal death (assumed) before discharge	P = 0.2	~
			Early onset sepsis	No events	~

			Invasive ventilation, day 1	P = 1.0	~
			Invasive ventilation, day 2	P = 1.0	~
			PDA, day 1	"all infants"	~
			PDA, day 2	89.5% vs. 89.5%	~
Jazayeri 2003; RCS; high	N = 72 women and babies; T	1: MgSO4, N = 36 babies 2: No MgSO4, N = 36 babies	NICU LOS (days) (mean ± SE)	P > 0.05	~
			Meconium	P = NS	~
			RDS	P = NS	~
			IVH	P = NS	~
			NEC	P = NS	~
			Sepsis	P = NS	~
			Neonatal death	P = NS	~
Jeanneteau 2014; RCS; unclear Abstract	N = 119 women and their babies; FN	1: MgSO4, N = 81 women 2: No MgSO4, N = 38 women	Apgar score < 7 at 5 minutes	P = 0.03	✓
			Closed cardiac massage^	P = 0.003	✓
			Adrenaline	P = 0.01	✓
			"neonatal morbi-mortality"^	"no difference"	~
Jones 2018; RCS; unclear Abstract	N = 120 babies; PE/T	1: MgSO4, N = NR 2: No MgSO4, N = NR	Adverse bowel events^	No events	~
Jung 2018; RCS; high	N = 184 women and their babies; T	1: MgSO4, N = 143 women and babies 2: No MgSO4, N = 41 women and babies	Stillbirth, all infants, PPROM 23-27+6 weeks GA, 28-31+6 weeks GA	P = 0.0012; P = 0.0070; P = 0.4873	✓, ✓, ~
			Neonatal death, all infants, PPROM 23-27+6 weeks GA, 28-31+6 weeks GA	P = 0.6902; P = 0.8696; P = 0.4695	~, ~, ~
			Early neonatal death	P = 0.9169	~
			Perinatal death, all infants, PPROM 23-27+6 weeks GA, 28-31+6 weeks GA	P = 0.0375; P = 0.0651; P = 0.9051	✓, ~, ~
			Apgar score < 7 at 5 minutes	P = 0.7066	~
			Pulmonary hypoplasia^	P = 0.8039	~
			RDS	P = 0.7255	~
			BPD	P = 0.5091	~
			NEC	P = 0.7437	~
			Early onset sepsis	P = 0.2239	~
			ROP	P = 0.7134	~
			ROP grade 2/3	P = 0.7759	~
			Hearing impairment	P = 0.9028	~
			NICU LOS (days) (mean ± SD)	P = 0.6597	~

			IVH, all infants, PPROM 23-27+6 weeks GA, 28-31+6 weeks GA	RR 0.40; 95% CI 0.25-0.88 RR 0.35; 95% CI 0.17-0.71 RR 0.66; 95% CI 0.23-1.91	✓, ✓, ~
			IVH grade 3/4	RR 0.37; 95% CI 0.06-2.14	~
			PVL, all infants, PPROM 23-27+6 weeks GA, 28-31+6 weeks GA	RR 0.60; 95% CI 0.39-0.94 RR 0.48; 95% CI 0.25-0.91 RR 0.71; 95% CI 0.39-1.29	✓, ✓, ~
			Bone abnormalities	1: 4 cases (exposed for 4, 5, 20, 45 days respectively)	NA
Kamilya 2005; NCCS; high	N = 1205 babies; E	1: 2002-2004 (MgSO4 use), N = 481 babies 2: 1995-1997 (no MgSO4 use), N = 724 babies	Perinatal death	24.3% vs. 54.8%; "Recent changes in eclampsia management protocol by MgSO4 therapy and early CS have been instrumental in bringing down MMR and PNM in eclampsia cases."	✓
Kamyar 2015a; RCS; unclear Abstract	N = 271 babies; FN/PE/T	1: MgSO4, N = 133 babies 2: No MgSO4, N = 138 babies	Composite morbidity (IVH, PVL, BPD, NEC, RDS, ROP and/or neonatal death) (multivariable model)	OR 1.19; CI 0.51-2.78; P = 0.69	~
			Neonatal death (multivariable model)	OR 0.79; CI 0.31-2.02; P = 0.74	~
			Individual morbidities (multivariable model)	"were also not increased."	~
Kamyar 2015b; RCS; unclear Abstract	N = 1246 babies; FN/PE/T	1: MgSO4, N = 457 babies 2: No MgSO4, N = 789 babies	Composite morbidity (IVH, BPD, NEC, and/or neonatal death prior to hospital discharge) (multivariable model)	OR 1.20; CI 0.91, 1.57; P = 0.20	~
			Neonatal death (multivariable model)	OR 0.41; CI 0.16, 1.06; P = 0.07	~
Kamyar 2015c; RCS; unclear Abstract	N = 2431 babies; FN	Males, N = 1147 babies 1: MgSO4, N = 643 babies 2: No MgSO4, N = 504 babies	Composite severe morbidity (IVH grade 3/4, PVL, BPD, NEC, and/or neonatal death) Males (multivariable model including GA as covariate)	OR 1.27; 0.94-1.72; P = 0.12	~
		Females, N = 1284 babies 1: MgSO4, N = 536 babies 2: No MgSO4, N = 748 babies	Composite severe morbidity (IVH grade 3/4, PVL, BPD, NEC, and/or neonatal death) Females (multivariable model including GA as covariate)	OR 1.06; 0.74-1.49; P = 0.72	~
		Males vs. females	Interaction term for gender as above	P = 0.44	~
Kamyar 2016a; RCS; moderate to high	N = 396 babies; FN	1: MgSO4, N = 192 babies 2: Placebo, N = 204 babies	Stillbirth or death by age 1: all babies, and ≤ 28 weeks GA (adjusted multivariable log-binomial model, using backwards elimination (P < 0.20) for	RR 1.68; 95% CI 0.85-3.32 RR 1.34; 95% CI 0.47-2.73	~, ~

			covariates: GA at birth, maternal years of education, maternal race/ethnicity, IUGR, illicit drug use, smoking status, and sex)		
			Severe composite morbidity (1 or more of: sepsis, severe IVH, PVL, NEC stage 2/3, BPD): all babies, and ≤ 28 weeks GA (adjusted as above)	RR 1.10; 95% CI 0.88-1.38 RR 1.07; 95% CI 0.86-1.34	~, ~
			Sepsis: all babies, and ≤ 28 weeks GA (adjusted as above)	RR 1.03; 95% CI 0.71-1.50 RR 1.01; 95% CI 0.67-1.51	~, ~
			Severe IVH: all babies, and ≤ 28 weeks GA (adjusted as above)	RR 0.36; 95% CI 0.10-1.27 RR 0.41; 95% CI 0.12-1.49	~, ~
			PVL: all babies, and ≤ 28 weeks GA (adjusted as above)	RR 0.37; 95% CI 0.08-1.78 RR 0.64; 95% CI 0.12-3.38	~, ~
			NEC stage 2/3: all babies, and ≤ 28 weeks GA (adjusted as above)	RR 1.36; 95% CI 0.58-3.20 RR 1.36; 95% CI 0.47-3.91	~, ~
			BPD: all babies, and ≤ 28 weeks GA (adjusted as above)	RR 1.29; 95% CI 0.91-1.82 RR 1.13; 95% CI 0.80-1.58	~, ~
			Neonatal death before hospital discharge: all babies, and ≤ 28 weeks GA (adjusted as above)	RR 1.46; 95% CI 0.64-3.33 RR 1.45; 95% CI 0.47-2.89	~, ~
Kamyar 2016b; RCS with CCS(N); moderate to high	N = 697 babies; FN	1: MgSO4, N = 332 babies 2: No MgSO4, N = 365 babies	Neonatal death before NICU discharge and/or NEC stage 2/3 (multivariable regression, adjusted for confounders: birth GA, treatment group, fetal sex, SGA, chorioamnionitis, caesarean section, hypotension during initial resuscitation, postnatal exposure to indomethacin, sepsis, IVH)	OR 1.01; 95% CI 0.69-1.47; P = 0.965	~
			Neonatal death before NICU discharge (multivariable regression, adjusted as above)	"MgSO4 was also not associated with elevated odds of the individual outcomes… in multivariable models (data not shown)."	~
			NEC stage 2/3 (multivariable regression, adjusted as above)	As above	~
		1: MgSO4, N = 148 babies delivered < 26 weeks GA	Neonatal death before NICU discharge and/or NEC stage 2/3 (unadjusted)	OR 1.82; 95% CI 1.10-3.03; P = 0.021	×

		2: No MgSO4, N = 145 babies delivered < 26 weeks GA	Neonatal death before NICU discharge and/or NEC stage 2/3 (multivariable regression, controlled for confounders including birth GA and SGA)	aOR 1.90; 95% CI 1.12-3.22; P = 0.017	×
			Neonatal death before NICU discharge (multivariable regression, adjusted as above)	aOR of 1.83; 95% CI 1.03-3.27; P = 0.040	×
			NEC stage 2/3 (multivariable regression, adjusted as above)	aOR 1.38, 95% CI 0.64-3.00; P = 0.414	~
		MgSO4 exposed babies 1: Neonatal death before NICU discharge and/or NEC stage 2/3, N = 73 babies 2: Survival without NEC stage 2/3, N = 259 babies	MgSO4 infusing at birth	P = 0.700	~
			Total amount of MgSO4 received (g) (mean ± SD)	P = 0.595	~
Katayama 2011; RCS; moderate to high	N = 160 babies; T	1: MgSO4, N = 41 babies 2: No MgSO4, N = 119 babies	Early closure of the DA^	P = 0.002	×
			Symptomatic PDA	P = 0.006	×
			Successful response to indomethacin of PDA^	P = 0.210	~
			PDA treated with surgery	P = 0.210	~
			Failure of early closure of DA after indomethacin (univariate analysis)^	OR 3.73; 95% CI 1.69-8.23	×
			Failure of early closure of DA after indomethacin (multivariate logistic regression analysis, adjusted for confounders including antenatal steroids, ritodrine tocolysis, PROM)^	aOR 4.03; 95% CI 1.65-9.80; P = 0.002	×
			Symptomatic PDA (univariate analysis)	OR 2.81; 95% CI 1.33-5.92	×
			Symptomatic PDA (multivariate logistic regression analysis, adjusted for confounders, assumed to be as above)	aOR 2.26; 95% CI 1.01-5.04; P = 0.047	×
		MgSO4 1: Low dose (< 50 g), N = 19 babies 2: High dose (≥ 50 g), N = 22 babies	Early closure of the DA^	59% vs. 58%;"No significant differences"	~
			Symptomatic PDA	50% vs. 42%; "No significant differences"	~
			Successful response to indomethacin of PDA^	73% vs. 63%; "No significant differences"	~

			PDA treated with surgery	27% vs. 37%; "No significant differences"	~
Kelly 1992; PCS; unclear Abstract	N = 10 women and babies; T	1: MgSO4, N = 5 babies 2: No MgSO4, N = 5 babies	See right^	"Infants… did not sustain any increase in morbidity as a result of their in utero MgSO4 exposure."	~
Khodapanahandeh 2008; CCS; moderate to high	N = 121 babies; T	1: IVH grade 3/4, N = 39 babies 2: No IVH grade 3/4, N = 82 babies	MgSO4 exposure	P = 0.021	×
			MgSO4 exposure (multivariate logistic regression analysis, including factors significant in univariate analyses: GA, birthweight, Apgar score at 5 minutes, resuscitation, tocolytic therapy, apnoea, MV, HMD, haematocrit, PaCO2 maximum in 1st 3 days, symptomatic hypotension 1st 3 days)	OR 4.4; 95% CI 1.10-24.5	×
Kimberlin 1998; RCS; moderate to high	N = 308 babies (363 in death analyses); T	1: MgSO4, N = 124 babies (138 for death analyses) 2: No MgSO4, N = 184 babies (225 for death analyses)	Neonatal death ≤ 2 days^	10.1% vs. 18.2%; "lower"	✓
			Neonatal death between 3-120 days	P = 0.10	~
			Intact survival (survival to hospital discharge or 120 days without any serious morbidities)^	P = 0.54	~
			Intact survival (multiple logistic regression, controlling for birthweight, GA, race, gender, mode of birth, chorioamnionitis, surfactant treatment, antepartum steroid treatment)^	OR 1.07; 95% CI 0.60-1.92	~
			Neonatal death at ≥ 2 days and < 120 days	P = 0.67	~
			IVH grade 3/4	P = 0.34	~
			IVH grade 3/4 (multiple logistic regression as above)	OR 0.71; 95% CI 0.36-1.42	~
			ROP grade 3/4	P = 0.59	~
			ROP grade 3/4 (multiple logistic regression as above)	OR 1.38; 95% CI 0.66-2.87	~
			Abnormal neurological evaluation^	P = 0.91	~
			Abnormal neurological evaluation (multiple logistic regression as above)^	OR 1.44; 95% CI 0.66-3.16	~
			Seizure activity	P = 0.35	~
			Seizure activity (multiple logistic regression as above)	OR 0.76; 95% CI 0.29-1.95	~
			NEC requiring surgery	P = 0.33	~

			NEC requiring surgery (multiple logistic regression as above)	OR 0.39; 95% CI 0.12-1.25	~
			Oxygen dependence at discharge	P = 0.97	~
			Oxygen dependence at discharge (multiple logistic regression as above)	OR 1.37; 95% CI 0.71-2.66	~
			Duration of ventilation (days) (median, measure of variance NR)	P = 0.08	~
			NICU LOS (days) (mean ± SD)	P = 0.07	~
Koksal 2002; PCS with CCS(N); high	N = 120 babies; T	1: GMH-IVH grade 3/4 or PVL, N = 18 babies 2: GMH-IVH grade 1/2 or no abnormalities, N = 102 babies	MgSO4 exposure	P < 0.05	✓
Kuban 1992; PCS; moderate to high	N = 449 babies; PE/T	1: MgSO4, N = 90 babies 2: No MgSO4, N = 359 babies	GMH-IVH	4.4% vs. 18.9%	NR
			GMH-IVH (risk among babies born to women with hypertension and proteinuria vs. neither condition): with MgSO4 vs. with no MgSO4	OR 0.4; 95% CI 0.1-3.1 vs. OR 0.4; 9% CI 0.1-1.4	~; ~
			GMH-IVH (risk among babies born to women with PE): with MgSO4; with no MgSO4	OR 0.7; 9% CI 0.1-7.3; NC due to value of 0 in 1 cell	~; NA
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): vaginal birth vs. abdominal birth	OR 0.2; 95% 0-1.2 vs. OR 0.3; 95% 0.1-1.2	~; ~
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): any labour vs. no labour	OR 0.3; 95% CI 0.1-0.99 vs. NC	~; NA
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): birthweight < 1000 g vs. birthweight ≥ 1000 g	OR 0.1; 95% 0-0.7 vs. OR 0.3; 95% CI 0.1-1.5	✓; ~
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): GA ≤ 30 weeks; GA > 30 weeks	OR 0.1; 95% CI 0-0.6 vs. OR 0.7; 95% CI 0.2-3.6	✓; ~
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): intubation vs. no intubation	OR 0.1; 95% CI 0-0.7 vs. OR 0.5; 95% CI 0.1-2.2	✓; ~

			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): lowest pH < 7.2 vs. lowest pH ≥ 7.2	NC; OR 0.3; 95% CI 0.1-0.8	NA; ✓
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): antenatal steroids vs. no antenatal steroids	OR 0.1; 95% CI 0-0.98 vs. OR 0.3; 95% CI 0.1-1.3	✓; ~
			GMH-IVH (risk among babies born to women who received MgSO4 vs. did not receive MgSO4): mother's weight/height > 75th percentile vs. mother's weight/height ≤ 75th percentile	OR 0.2; 95% CI 0-1.7 vs. OR 0.2; 95% CI 0.1-1.0	~; ~
			See right	"In an attempt to identify which of the preeclampsia variables contributed unique and significant information about GMH risk and to control for possible confounding, we carried out a stepwise logistic regression analysis. An initial model included as potential predictors of GMH-IVH all of the preeclampsia-related variables described above. Only two variables, however, remained in the model when a .05 significance level was needed for entry. Diagnosis of preeclampsia conveyed the most information about reduced risk of GMH-IVH, followed closely by receipt of magnesium sulfate. The other preeclampsia variables (eg, pregnancyinduced hypertension, hypertension not identified as pregnancy induced, and proteinuria) did not provide additional unique information. Very similar results were obtained when covariates (eg, gestational age, birth weight,	✓

				intubation, ratio of prepregnancy maternal weight to height, etc) were allowed to compete."	
Lai 2017; RCS; unclear Abstract	N = NR; PE	1: MgSO4, N = NR 2: No MgSO4, N = NR	Muscle tone scores (units NR)^	"lower in the MgSO4-exposed neonates… the difference did not reach statistical significance."	~
			SCBU admission (multinomial logistic regression)^	OR 5.02; 95% CI 1.98-12.70	×
			NICU admission (multinomial logistic regression)	OR 3.90; 95% CI 0.49-30.99	~
			Delayed adaptation	"the rate… was higher in the MgSO4-exposed neonates, but again the difference was not statistically significant."	~
Lee 2013; RCS; unclear English abstract	N = 81 babies; PE	1: MgSO4, N = 20 2: No MgSO4, N = 61	RDS (adjusted for GA)	P = 0.076 aOR 1.34; 95% CI 0.32-5.53; P = 0.69	~
			Ventilation (adjusted for GA)	P = 0.277 aOR 0.99; 95% CI 0.26-3.88; P = 0.99	~
			sPDA (adjusted for GA)	P = 0.002 aOR 4.13; 95% CI 1.25-13.62; P = 0.02	×
			PDA treated with operation (adjusted for GA)	P = 1.0 aOR 1.02; 95% CI 0.07-15.75; P = 0.99	~
			ROP (adjusted for GA)	P = 0.149 aOR = 1.97; 95% CI 0.11-36.53; P = 0.65	~
			NEC (adjusted for GA)	P = 0.440 aOR = 0.35; 95% CI 0.41-2.98; P = 0.335	~
			IVH grade ≥ I (adjusted for GA)	P = 0.364 aOR 0.39; 95% CI 0.17-1.31; P = 0.13	~
			PVL (adjusted for GA)	P = 0.216 aOR 0.24; 95% CI 0.43-1.30; P = 0.10	~
			Neonatal death (adjusted for GA)	P = 1.0 aOR 1.12; 95% CI 0.25-4.96; P = 0.88	~
		1: MgSO4 and sPDA, N = 15 babies	MgSO4 dose (g) (mean ± SD)	P = 0.34	~

		2: MgSO4 and no sPDA, N = 5 babies			
Lee 2015; RCS; unclear Abstract	N = 570 women and babies; T	1: MgSO4, N = 101 babies 2: No MgSO4, N = 469 babies	Hypocalcaemia	"incidence… was not different between two groups"	~
Leung 2016; PCS with CCS(N); moderate	N = 289 babies; PE/E/T	1: Passed hearing screen, N = 244 babies 2: Failed hearing screen, N = 45 babies	MgSO4 exposure	OR 0.38; 95% CI 0.2-0.74; P = 0.004	✓
			MgSO4 and betamethasone exposure	OR 0.31; 95% CI 0.16-0.60; P < 0.001	✓
			MgSO4 and betamethasone exposure (logistic regression model A: survivors failing hearing screen; factors entered into stepwise regression: GA, birthweight, Apgar score at 1 and 5 minutes, antenatal exposure to betamethasone, MgSO4 and an interaction term of betamethasone plus MgSO4, maternal antibiotics exposure, surfactant treatment, CUS abnormalities, duration of ventilation, CLD, duration on furosemide, gentamicin and amphotericin, FIRS, PDA treated with indomethacin)	OR: 0.37 (95% CI 0.11-0.81); P = 0.013	✓
			MgSO4 and betamethasone exposure (logistic regression model B: event-free survival, death (before discharge) or failure of hearing screen; factors entered into stepwise regression as above)	OR 0.33; 95% CI 0.17-0.66; P = 0.002	✓
Leviton 1997; PCS; moderate to high	N = 1331 women and 1518 babies; unclear PE/PIH/T	1: MgSO4, N = 678 babies 2: No MgSO4, N = 840 babies	IVH (logistic regression adjusted for GA, birthweight z score, antenatal corticosteroids, PE, PIH, route of birth and labour)	RR 1.0; 95% CI 0.7-1.3; P = 0.94	~
			PEA: early (logistic regression adjusted as above)^	RR 1.3; 95% CI 0.8-2.2; P = 0.29	~
			PEA: late (logistic regression adjusted as above)^	RR 0.8; 95% CI 0.5-1.5; P = 0.57	~
			PEA: any (logistic regression adjusted as above)^	RR 1.0; 95% CI 0.7-1.5; P = 0.86	~
			PEA: hypoechoic image (logistic regression adjusted as above)^	RR 1.2; 95% CI 0.7-2.0; P = 0.50	~
			PEA: late hypoechoic image (logistic regression adjusted as above)^	RR 1.2; 95% CI 0.7-2.2; P = 0.51	~
			Ventriculomegaly^	RR 1.1; 95% CI 0.7-1.7; P = 0.62	~
Lipsitz 1971; PCS (or NRT); high	N = 37 babies; PE/E	1: MgSO4 IV LD and MD, N = 29 babies	Apgar score < 7 at 1 minute	75.9% vs. 37.5%	✗
			Apgar score < 7 at 5 minutes	48.3% vs. 37.5%	✗

		2: MgSO4 IV LD, IM MD, N = 8 babies	Clinical score of 3^	44.8% vs. 37.5%	×
			Clinical score > 0 (the higher the score, with a maximum of 3, the greater the apparent toxicity of excess Mg: 1 point for flaccidity and hyporeflexia, 1 for resuscitation or assisted ventilation, 1 for week or absent cry unrelated to tracheal intubation)^	82.8% vs. 62.5%	×
			Neonatal death	17.2% vs. 0%	×
			Resuscitation	48.3% vs. 37.5%	×
			Assisted ventilation	24.1% vs. 12.5%	×
			Summary see right	"When magnesium sulfate is given intramuscularly to the mother, the newborn is usually not compromised by excess magnesium but may be affected. If continuous intravenous infusion of magnesium sulfate is used and especially if given for more than 24 hours, one can anticipate a newborn manifesting all the signs of hypermagnesemia"	×
Lloreda-Garcia 2016; NCCS; unclear English abstract	N = 107 babies; FN	1: MgSO4, N = 56 babies 2: No MgSO4, N = 51 babies	Resuscitation overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = NS, P = NS	~, ~, ~
			Apgar score ≤ 5 at 1 minute overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = NS, P = NS	~, ~, ~
			Apgar score ≤ 5 at 5 minutes	P = NS	~
			CPAP/nasal IMV overall, < 30 weeks GA, ≥ 30 weeks GA	P = 0.03, P = NS, P = NS	×, ~, ~
			CMV overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = 0.016, P = NS	~, ✓, ~
			HFOV	P = NS	~
			Surfactant treatment overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = 0.074, P = NS	~, ~, ~
			PDA treated overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = NS, P = NS	~, ~, ~
			Vasoactive drugs overall, < 30 weeks GA, ≥ 30 weeks GA^	P = NS, P = 0.053, P = NS	~, ~, ~

			Blood products overall, < 30 weeks GA, ≥ 30 weeks GA^	P = NS, P = NS, P = 0.043	~, ~, ×
			Sepsis confirmed overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = NS, P = NS	~, ~, ~
			Pathological brain ultrasound overall, < 30 weeks GA, ≥ 30 weeks GA^	P = NS, P = NS, P = NS	~, ~, ~
			No stools at 48 hours overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = 0.019, P = NS	~, ✓, ~
			No bowel movements at 72 hours^	P = NS	~
			NEC overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = NS, P = NS	~, ~, ~
			Neonatal death overall, < 30 weeks GA, ≥ 30 weeks GA	P = NS, P = NS, P = NS	~, ~, ~
			CRIB (median, range)^	P = NS	~
			Meconium evacuation delay	P = NS	~
			Parenteral nutrition^	P = NS	~
Martin 1998; RCS; high	N = 193 women and babies; PE/T	1: MgSO4, N = 118 babies 2: No MgSO4, N = 75 babies	IVH	P = 0.09	~
Matsuda 1997; RCS with CCS(N); high	N= 139 babies born to 114 women; and a further 51 control babies; PE/T	1: MgSO4, N = 114 women and 139 babies 2: No MgSO4, N = 51 babies	Bone abnormalities	P = 0.0101	×
		1: MgSO4 and bone abnormalities, N = 13 women 2: MgSO4 and no bone abnormalities, N = 101 women	GA at start of MgSO4 (weeks) (mean ± SD)	P < 0.05	×
			Duration of MgSO4 (days) (mean ± SD)	P < 0.05	×
			MgSO4 dose (g) (mean ± SD)	P < 0.05	×
McGuiness 1980; NRT; high	N = 37 women and their babies; PE	1: MgSO4, N = 23 women and their babies 2: Dextrose-water or dextrose-saline, N = 14 women and their babies	Significant birth asphyxia	No events	~
			Hypocalcaemia	"Although magnesium sulfate infusion cause a significant decline in maternal total calcium and ionized calcium levels, it was not associated with neonatal hypocalcemia."	~
McPherson 2014; RCS; high	N = 933 women and their babies; FN	1: MgSO4 < 12 hours, N = 356 women and babies	Apgar score < 7 at 5 minutes	2 vs. 1: OR 0.95; 95% CI 0.64-1.41 3 vs. 1: OR 0.73; 95% CI 0.46-1.16 P = 0.37	~, ~, ~

		2: MgSO4 12-18 hours, N = 341 women and babies 3: MgSO4 > 18 hours, N = 236 women and babies	Resuscitation in delivery room (oxygen blow-by, oxygen bag, mask or both, intubation, chest compressions)	P = 0.07	~
			NEC	2 vs. 1: OR 0.97; 95% CI 0.58-1.63 3 vs. 1: OR 1.11; 95% CI 0.61-1.86 P = 0.96	~, ~, ~
			ROP	2 vs. 1: OR 1.16; 95% CI 0.81-1.64 3 vs. 1: OR 1.73; 95% CI 0.48-1.12 P = 0.09	~, ~, ~
			RDS	2 vs. 1: OR 0.98; 95% CI 0.73-1.32 3 vs. 1: OR 0.92; 95% CI 0.66-1.28 P = 0.87	~, ~, ~
			MV	2 vs. 1: OR 0.93; 95% CI 0.69-1.25 3 vs. 1: OR 0.86; 95% CI 0.62-1.20 P = 0.68	~, ~, ~
			BPD	2 vs. 1: OR 0.96; 95% CI 0.66-1.41 3 vs. 1: OR 0.87; 95% CI 0.56-1.36 P = 0.84	~, ~, ~
			Seizures	2 vs. 1: OR 1.25; 95% CI 0.38-3.39 3 vs. 1: OR 0.91; 95% CI 0.21-3.83 P = 0.88	~, ~, ~
			Any IVH	2 vs. 1: OR 0.86; 95% CI 0.58-1.27 3 vs. 1: OR 0.92; 95% CI 0.60-1.41 P = 0.76	~, ~, ~
			IVH grade 3/4	2 vs. 1: OR 1.28; 95% CI 0.34-4.83 3 vs. 1: OR 0.36; 95% CI 0.04-2.25 P = 0.42	~, ~, ~
			NICU admission	"not different among groups after adjusting for gestational age at delivery (data not shown)."	~
Mikhael 2019; RCS; moderate to high	N = 302 babies; NR (includes FN)	1: MgSO4 ≤ 7 days prior to birth, N = 210 babies 2: No MgSO4 ≤ 3 days prior to birth, N =192 babies	Death; all babies, and < 26 weeks GA	P = 0.69; P = 0.76	~
			Early death; all babies, and < 26 weeks GA	P = 0.28; P = 0.31	~
			Postnatal steroids	P = 0.67	~
			NEC; all babies, and < 26 weeks GA	P = 0.89; P = 0.42	~

			Early NEC; all babies, and < 26 weeks GA	P = 0.61; P = 0.52	~
			SIP; all babies, and < 26 weeks GA	P = 0.82; P = 0.73	~
			Early SIP; all babies, and < 26 weeks GA	P = 0.68; P = 0.79	~
			SIP or NEC or death: all babies, and < 26 weeks GA (unadjusted P); for all babies: aOR and P – adjusted for maternal hypertension, antenatal steroids, and antenatal indomethacin)	P = 0.81; P = 0.46 aOR 0.69; 95% CI 0.35-1.38; P = 0.29	~
			Early SIP or NEC or death: all babies, and < 26 weeks GA (unadjusted P); for all babies: aOR and P – adjusted for maternal hypertension, antenatal steroids, and antenatal indomethacin)	P = 0.79; P = 1.0 aOR 1.7; 95% CI 0.73-3.75; P = 0.22	~
			Late onset-sepsis	P = 0.075	~
			Postnatal NSAIDs for PDA	P = 0.15	~
			IVH ≥ grade 3	P = 0.4	~
		1: MgSO4 ≤ 3 days prior to birth, N = 179 babies 2: No MgSO4 ≤ 3 or 7 days prior to birth, N = 123 babies	Death; all babies, and < 26 weeks GA	P = 0.23; P = 0.27	~
			Early death; all babies, and < 26 weeks GA	P = 0.44; P = 0.43	~
			NEC; all babies, and < 26 weeks GA	P = 0.98; P = 0.31	~
			Early NEC; all babies, and < 26 weeks GA	P = 0.97; P = 0.84	~
			SIP; all babies, and < 26 weeks GA	P = 0.57; P = 0.36	~
			Early SIP; all babies, and < 26 weeks GA	P = 0.54; P = 0.44	~
			SIP or NEC or death; all babies, and < 26 weeks GA	P = 0.58; P = 0.29	~
			Early SIP or NEC or death; all babies, and < 26 weeks GA	P = 0.8412; P = 0.9	~
		1: MgSO4 ≤ 3 days prior to birth, N = 179 babies 2: No MgSO4 ≤ 3 days prior to birth, N = 31 babies	Death; all babies, and < 26 weeks GA	P = 0.13; P = 0.16	~
			Early death; all babies, and < 26 weeks GA	P = 0.87; P = 1.0	~
			NEC; all babies, and < 26 weeks GA	P = 0.87; P = 0.51	~
			Early NEC; all babies, and < 26 weeks GA	P = 0.56; P = 0.65	~
			SIP; all babies, and < 26 weeks GA	P = 0.53; P = 0.3	~
			Early SIP; all babies, and < 26 weeks GA	P = 0.75; P = 0.69	~
			SIP or NEC or death; all babies, and < 26 weeks GA	P = 0.55; P = 0.44	~
			Early SIP or NEC or death; all babies, and < 26 weeks GA	P = 0.99; P = 0.83	~
		1: Pre MgSO4 protocol, N = 112 babies	Death; all babies, and < 26 weeks GA	P = 0.3; P = 0.4	~
			NEC; all babies, and < 26 weeks GA	P = 0.5; P = 0.8	~

		2: Post MgSO4 protocol, N = 190 babies	SIP; all babies, and < 26 weeks GA	P = 0.6; P = 0.1	~
		1: MgSO4 ≤ 3 days prior to birth, N = 179 babies	SIP or NEC or death, logistic regression modelling, each 10 g increase in MgSO4 cumulative dose	"correlated with an 18.9% decrease in SIP/NEC/death prior to discharge (95% CI 2.2–32.8%, *p* = 0.028)"	✓
			SIP or NEC or death, logistic regression modelling, number of MgSO4 loading doses	"no significant association… OR = 1.07 (95% CI 0.53–2.1, *p* = 0.86)"	~
			Early SIP or NEC or death, logistic regression modelling, each 10 g increase in MgSO4 cumulative dose	"correlated with … a 21.9% decrease in early SIP/NEC/death (95% CI 1.4 38.1%, *p* = 0.037)"	✓
			Early SIP or NEC or death, logistic regression modelling, number of MgSO4 loading doses	"no significant association … early SIP/NEC/death, OR = 1.08 (95% CI 0.48–2.4, *p* = 0.86)"	~
		1: MgSO4 ≤ 7 days prior to birth, N = 210 babies 2: No MgSO4 ≤ 7 days prior to birth, N = 92 babies	SIP or NEC or death, SGA status	"found to be correlated with a reduction… by a likelihood ratio test with p = 0.07"	~
			Early SIP or NEC or death; SGA babies only, and non-SGA babies only	OR 0.23; 95% CI 0.04-1.19; P = 0.079 OR 1.19; 95% CI 0.58-2.47; P = 0.63	~
Mitani 2011; RCS with CCS(N); moderate to high	N = 425 babies; T	1: MgSO4, N = 236 babies 2: No MgSO4, N = 189 babies	Perinatal death	P = 0.185	~
			Apgar score < 7 at 1 minute	P = 0.246	~
			Apgar score < 7 at 5 minutes	P = 0.817	~
			RDS	P = 0.543	~
			IVH	P = 0.879	~
			PVL	P = 0.630	~
		1: Adverse outcome (IVH, PVL, CP, infantile death), N = 80 babies 2: Good outcome, N = 315 babies	MgSO4 exposure	P = 0.801	~
			MgSO4 exposure (multivariate logistic regression analysis; confounders NR)	OR 0.93; 95% CI 0.57-1.52 aOR 0.82; 95% CI 0.48-1.40	~
		1: < 2 days MgSO4, N = 49 babies 2: > 2 days MgSO4, N = 174 babies	Combined adverse outcome (infantile death, IVH, PVL, CP)	P > 0.999	~
			IVH	P = 0.339	~
			PVL	P = 0.416	~

		1: MgSO4 and adverse outcome, N = 49 babies 2: MgSO4 and good outcome, N = 174 babies	Duration of MgSO4 (hours) (median, range)	P = 0.31	~
Mittendorf 2005; RCS; unclear Abstract	N = 146 babies; FN/T	1: MgSO4 0-4 g, N = 90 babies 2: MgSO4 5-49 g, N = 23 babies 3: MgSO4 ≥ 50 g, N = 33 babies	IVH grade 3 and/or LSV (adjusted for confounding), 2 vs. 3^	aOR 0.13; 95% CI -Inf to 0.96; P = 0.045	✓
			IVH grade 3 and/or LSV (adjusted for confounding), 1 vs. 2^	"trended toward neuopathogenesis (not significant; StatXact)."	~
Mittendorf 2009; RCS; unclear Abstract	N = 140 babies; FN/T	1: MgSO4 > 0 to < 10 g, N = 27 babies 2: MgSO4 10 to < 30 g, N = 8 babies 3: 30 to < 50 g, N = 11 babies 4: ≥ 50 g, N = 30 babies	TSV (Cochran-Armitage trend test of increasing exposures to MgSO4)^	P = 0.22	~
			TSV (logistic model controlling for birthweight and funisitis), tocolytic MgSO4 : ≥ 50 g^	P = 0.03	×
Morag 2015; RCS; moderate to high	N = 645 women and 705 babies (235 preterm babies further considered); PE	1: Preterm infants with MgSO4 exposure, N = 10 women 2: Preterm infants with no MgSO4 exposure, N = 168 women	Respiratory disease (including RDS, TTN and disorders of air leak such as pneumothorax and pneumomediastinum) (multivariate logistic regression analysis - factors from multivariate analysis: maternal age, primiparity, antenatal steroids, SGA, caesarean birth, MgSO4 treatment)^	OR 5.17; 95% CI 1.29-20.64; P = 0.020	×
Morag 2016; RCS; high	N = 190 babies; FN/PE	1: MgSO4, N = 145 babies 2: No MgSO4, N = 45 babies	Apgar score < 7 at 1 minutes	P = 0.28	~
			Apgar score < 7 at 5 minutes	P = 0.03	×
			IV (days) (mean ± SD)^	P = 0.01 "explained by out unit protocol, which recommended delay of enteral feeding in infants whose Mg concentrations are elevated."	×
			Treated early hypotension	P = 0.16	~
			Intubation	P = 0.44	~
			Oxygen at 28 days	P = 0.41	~
			Oxygen at 36 weeks	P = 0.34	~
			Proven NEC	P = 0.10	~
			Sepsis	P = 0.11	~

			IVH 3-IV/PVL	P = 0.55	~
			Discharge (week) (mean ± SD)^	P = 0.22	~
			Neonatal death	P = 0.37	~
Moschos 2001; CCS; unclear Abstract	N = 75 babies; NR	1: NEC, N = 25 babies 2: No NEC, N = 50 babies	MgSO4 exposure (logistic regression analysis)	OR 4; CI: 1.367-12.743; P = 0.016	✓
Murata 2005; RCS with CCS(N); moderate to high	N = 201 babies; T	1: cPVL, N = 35 babies 2: No cPVL, N = 166 babies	MgSO4 exposure (univariate analysis)	OR 0.14; 95% CI 0.040-0.95; P = 0.03	✓
			MgSO4 exposure (multivariate analysis including variables that were significant in the univariate analysis [Apgar score < 5 at 5 minutes, cord length > 40 cm, indomethacin exposed], with birthweight and GA by the logistic procedure)	OR 0.058; 95% CI 0.007-0.498; SE: 1.1	✓
Nakamura 1991; RCS with CCS(N); unclear Abstract	N = 58 women and their babies; PE	1: Ileus, N = NR 2: No ileus, N = NR	MgSO4 dose (g) (mean ± SD)	P < 0.05	×
Narasimhulu 2017; RCS; high	N = 304 women and babies; FN/PE	1: MgSO4, N = 237 women and babies 2: No MgSO4, N = 67 women and babies	Apgar score ≤ 5 at 1 minute	P = 0.79	~
			Apgar score ≤ 5 at 5 minutes	P = 0.49	~
			Delivery room resuscitation	P = 0.56	~
			Hypotension	P = 0.01	×
			Hypocalcaemia	P = 0.01	×
			IVH grade 3/4	P = 0.29	~
			BPD	P = 0.02	×
			ROP grade 3+	P = 0.07	~
			PVL	P = 0.42	~
			Intubation	P = 0.36	~
			NEC	P = 0.75	~
			PDA	P = 0.02	×
			Neonatal death	P = 0.93	~
			Composite outcome (neonatal death, IVH grade 3/4, BPD, ROP grade 3+, PVL, NEC)	P = 0.06	~
			NICU LOS (days) (median, Q1-Q3)	P < 0.01	×
Nassar 2006; RCS; high	N = 155 women, 198 babies; T	1: MgSO4 > 48 hours, N = 78 women, 112 babies	Apgar score < 4 at 1 minute^	P = 0.597	~
			Apgar score < 7 at 5 minutes	P = 0.772	~
			Hypotonia	P = 0.635	~

		2: $MgSO_4$ ≤ 48 hours, N = 77 women, 86 babies	IVH	P = 0.210	~
			Neonatal deaths (per 1,000)	P = 0.614	~
			Abnormal bone mineralisation	1: 3 cases vs. 2: 0 cases; "Abnormal bone mineralization was encountered in 3 neonates whose mothers received 4,400 and 5,500 g of $MgSO_4$"	NA
Nelson 1995; CCS: high	N = 117 babies; 75 babies considered for review; PE/T	1: No CP, $MgSO_4$, N = 27 babies [discrepancy in text/table 29 vs. 27] 2: No CP, no $MgSO_4$, N = 48 babies	Apgar score < 6 at 5 minutes	23% vs. 9%; "None of these differences alone was statistically significant"	~
			ICH/IVH, among those who underwent neuroimaging, among all	OR 0.33; 95% CI .12-1.0 OR 0.52; 95% CI .20-1.5	~ ~
Nunes 2018; RCS; high	N = 75 women, 99 babies (94 available for analyses); FN	1: $MgSO_4$, N = 26 babies 2: No $MgSO_4$, N = 68 babies	Heart rate (normal vs. abnormal)^	OR 1.17; 95% CI 0.45-3.12; P = 0.106	~
			Respiratory rate (normal vs. abnormal)^	OR 0.94; 95% CI 0.35-2.62; P = 0.017 (unclear why P value does not reflect OR)	~
			Temperature (normal vs. abnormal)^	OR 1.06; 95% CI 0.34-3.09; P = 0.011 (unclear why P value does not reflect OR)	~
			Oxygen saturation (≥ 95% vs. < 95%)^	OR 1.47; 95% CI 0.40-7.11; P = 0.319	~
			Hemoglucotest (normal vs. abnormal)^	OR 1.20; 95% CI 0.42-3.72; P = 0.114	~
			Hemoglobin (≥ 16.4 vs. < 16.4 g/dL)^	OR 1.00; 95% CI 0.36-2.64; P < 0.001 (unclear why P value does not reflect OR)	~
			Ventilation (non-invasive vs. ET)	OR 2.01; 95% CI 0.80-5.23; P = 0.07	~
Okusanya 2012; NRT; high	N = 103 women and their babies; PE/E	1: 10 g $MgSO_4$ LD, N = 54 (25 severe PE; 29 E) and their babies 2: 14 g $MgSO_4$ LD, N = 49 (30 severe PE; 19 E) women and their babies	Apgar score < 7 at 5 minutes: severe PE women	P = 0.2373	~
			Apgar score < 7 at 5 minutes: E women	P = 0.9396	~
			Perinatal death: severe PE women	Results not clear 1: reports 19 livebirths, 6 perinatal deaths, and PMR 240 per 1000 vs. 2: reports 26 livebirths, 1 perinatal death, and PMR 35 per 1000	NR
			Perinatal death: E women	Results not clear 1: reports 6 perinatal deaths, and PMR 241 per 1000 [note: all women had	NR

				IUFD prior to MgSO4] vs. 2: reports 0 perinatal deaths	
O Reilly 2016; RCS; unclear Abstract	N = 100 babies; FN	1: MgSO4, N = 55 babies 2: No MgSO4, N = 45 babies	Duration of intubation (hours) (median, variance measure NR) (controlled for GA)	P = 0.0011	✓
		1: MgSO4, N = 55 babies	Duration of intubation (hours) (median, variance measure NR)	"Babies born to mothers who had received MgS04 closest to time of delivery remained intubated for a longer median of hours compare to those born to mothers who received it the longest amount of time before delivery."	×
			Duration of intubation (hours) (subgroups as reported to right)	"There was a notably variation in the length of hours of intubation among the subgroups who received MgS04 at different time periods before delivery. Subgroups were divided into babies whose mothers received MgS04 < 1, 0-4, > 4 h prior to delivery."	NR
Ozlu 2019; RCS; high	N = 280 babies; FN	1: 2014-2016 (post MgSO4 implementation), N = 108 babies 2: 2011-2012 (pre MgSO4 implementation), N = 172 babies	Neonatal death	P = 0.64	~
			Resuscitation at birth	P = 0.89	~
			RDS	P = 0.01	✓
			Ventilator support	P = 0.85	~
			Ventilation (days) (mean ± SD, and median, minimum and maximum)	P = 0.82	~
			BPD	P = 0.36	~
			Oxygen use (days) (mean ± SD, and median, minimum and maximum)	P = 0.65	~
			NEC	"None of the babies had necrotizing enterocolitis."	~
			Early neonatal sepsis	P = 0.25	~
			Feeding intolerance	P = 0.96	~
			Could not get full enteral feeding^	1: 6.4% vs. 2: 6.4%	NR
			Could not start any enteral feeding^	1: 19.4% vs. 2: 19.8%	NR

			Starting day of enteral feeding (day) (mean ± SD, and median, minimum and maximum)^	P = 0.12	~
			Time of full enteral feeding (day) (mean ± SD, and median, minimum and maximum)^	P = 0.82	~
			PDA	P = 0.63	~
			ROP	P = 0.11	~
			IVH	P = 0.32	~
			IVH grade 3/4	P = 0.09	~
			Duration of hospital stay (days) (mean ± SD, and median, minimum and maximum)	P = 0.56	~
Palatnik 2019; CCS; moderate to high	N = 779 babies; NR	1: Early onset sepsis or death in 1st week, N = 73 babies 2: No early onset sepsis or death in 1st week, N = 706 babies	MgSO4 exposure	P = 0.024	✓
			MgSO4 exposure, model 1 (multivariable logistic regression, including GA at birth and birthweight as continuous variables, and the interaction between them) (confounders: maternal obesity, receipt of antibiotics prior to birth, receipt of 1 dose of steroids prior to birth, MgSO4 in labour, fever in labour, presence of meconium, GA at birth, birthweight)	aOR 0.82; 95% CI 0.35-1.94	~
			MgSO4 exposure, model 2 (multivariable logistic regression, including GA at birth as a continuous variable, birthweight dichotomised by VLBW, and the interaction between them) (confounders as above)	aOR 0.84; 95% CI 0.36-1.95	~
			MgSO4 exposure, model 3 (multivariable logistic regression, including GA at birth dichotomised by < 28 weeks, birthweight as a continuous variable, and the interaction between them) (confounders as above)	aOR 0.86; 95% CI 0.37-2.00	~
Paneth 1991; PCS; moderate	N = 1037 babies; PE/PEH/T	1: MgSO4, N = 362 babies 2: No MgSO4, N = 675 babies	GM/IVH	OR 0.89; 95% CI 0.65-1.20	~
			GM/IVH (multiple logistic regression adjusted for GA, fetal growth ratio, gender, multiple birth status, mode of birth, labour status, amnionitis, PE, and pre-existing hypertension)	aOR 0.89; 95% CI 0.64-1.25	~

			PEL/VE^	OR 0.96; 95% CI 0.62-1.47	~
			PEL/VE (multiple logistic regression adjusted as above)^	aOR 0.94; 95% CI 0.59-1.49	~
			Neonatal death in 1st 28 days	OR 0.77; 95% CI 0.54-1.10	~
			Neonatal death in 1st 28 days (multiple logistic regression adjusted as above)	aOR 0.83; 95% CI 0.53-1.30	~
Perlman 1995; RCS; unclear Abstract	N = 1025 babies; PIH	1: MgSO4, N = 192 babies 2: No MgSO4, N = 833 babies	PV-IVH	OR 2.1; 95% CI 1.4-3.3; P < 0.05 (and stepwise logistic regression "shows that GA and Mg+ are the most significant predictors of PV-IVH")	✓
			PV-IVH, infants < 28 weeks	P = 0.70	~
			PV-IVH, infants 28-31 weeks	OR 3; 95 %CI 1.2-7.4; P < 0.05	✓
			IVH grade 3/4	P < 0.05	✓
Petrov 2013; NRT; unclear Abstract	N = 140 women and babies; FN	1: MgSO4, N = 80 babies 2: Placebo, N = 60 babies	Range of neurological complications^	RR 0.55; 95% CI 0.32-0.95	✓
			Haemodynamic complications^	P > 0.05	~
Petrova 2012; RCS with CCS(N); moderate to high	N = 178 babies; T	1: IVH, N = 89 babies 2: No IVH, N = 89 babies	MgSO4 exposure	OR 0.494; 95% CI 0.271-0.901	✓
			MgSO4 exposure (multiple logistic regression model, controlling for observed differences in frequency of PPROM, ventilation after birth, severity of distress - Apgar scores at 1 minute)	aOR 0.471; 95% CI 0.241-0.906	✓
Qasim 2017; PCS with CCS(N); unclear Abstract	N = 105 babies; NR	1: MgSO4, N = 95 babies 2: No MgSO4, N = 10 babies	HsPDA (Pearson correlation analysis)	Negative correlation, r = -0.364, P < 0.001	✓
			HsPDA (regression model)	Negative linear relationship, -0.525, P < 0.001	✓
Rantonen 2001; PCS; high	N = 55 babies (17 in ritrodrine exposure group not further considered); PE/T	1: MgSO4, N = 19 babies 2: No MgSO4, N = 19 babies	See right	Note: below P values are reported for intergroup differences between groups 1, 2 and 3 (ritrodrine exposure)	
			Dexamethasone	P = 0.07	~
			Dopamine^	P = 0.3	~
			Dobutamine^	P = 0.8	~
			Surfactant	P = 0.7	~
			PDA	5.3% vs. 10.5%; P = 0.02	P value relates to

					group 2 vs. group 3 (ritodrine)
			PIVH grade 1-4	P = 0.03	✓
			PIVH grade 3/4	P = 0.07	~
			HIE/increased echodensity	P = 0.8	~
			RDS and MV	P = 0.2	~
			NICU admission	All babies	~
			Neonatal death	No events	~
			Blood-culture confirmed septicaemia	No events	~
Rasch 1982; PCS; high	N = 79 babies; PE	1: Born to PE women treated with MgSO4, N = 36 babies 2: Born to PE women with no MgSO4, N = 18 babies 3: Born to normal women, N = 25 babies	Poor sucking and cry response, 1 vs. 2 and 3^	"poorer… until 48 hours of age"	~
			Cyanosis during feedings	1: 2 events	NA
			Requirement for IV fluid treatment^	38.9% vs. 5.6% vs. 0%	×
			Neurologic section of the Dubowitz examination at birth, over 24 hours after birth, 1 vs. 2 and 3^	P < 0.001	×
			Individual measures on the Dubowitz examination^	"those tasks which required repetitive muscle activity (head lag and ventral suspension) were accomplished less effectively by infants in Group A. Ability to perform single or low-frequency responses (arm and leg recoil) was also diminished at birth in Group A infants, but was similar for all groups by 6 hours of age."	×
			Neuromuscular transmission at 6 and 12 hours, "significant fade" 1 vs. 2 and 3 combined^	P < 0.005	×
			Neuromuscular transmission at 24 hours, "significant fade", 1 vs. 2 and 3 combined^	P < 0.01	×
Rattray 2014; NCCS; moderate to high	N = 155 babies; FN	1: Pre-MgSO4 FN protocol (50.6% MgSO4), N = 81 babies 2: During MgSO4 FN protocol (78.3% MgSO4), N = 23 babies	Postnatal hydrocortisone	P = 0.44	~
			Postnatal NSAIDs	P = 0.21	~
			SIP or neonatal death (before discharge), 1 vs. 2 vs. 3	P = 0.45	~
			SIP or neonatal death (before discharge), 1 and 3 vs. 2	P = 0.28	~

		3: After MgSO4 FN protocol (60.8% MgSO4), N = 51 babies	SIP or neonatal death (before discharge) (multivariable analysis, MgSO4 dose (g) x GA)	P < 0.01	×
			SIP, 1 vs. 2 vs. 3	P = 0.09	~
			SIP, 1 and 3 vs. 2	P = 0.03	×
			Neonatal death (before discharge), 1 vs. 2 vs. 3	P = 0.07	~
			Neonatal death (before discharge), 1 and 3 vs. 2	P = 0.02	×
Rauf 2017; RCS; high	N = 107 women and babies; FN	1: MgSO4, N = 46 babies 2: No MgSO4, N = 61 babies	Active resuscitation at birth (ET intubation)	P = 0.015	×
			NICU LOS (days) (mean ± SD)	P = 0.929	~
			Respiratory support, MV, nasal CPAP, nasal SIMV, oxygen hood	P = 0.006	×, ✓ [group 1: higher rates of respiratory support, MV, nasal CPAP; lower rates of nasal SIMV, oxygen hood]
			IVH	P = 0.049	✓
			IVH grade 1-4	P = 0.91	~
			PVL	P = 0.43	~
			Convulsion	P = 0.63	~
			Hypotonia	P = 0.032	×
			Encephalopathy	P = 0.57	~
			ROP	P = 0.04	×
			Neonatal death	P = 0.015	×
Rhee 2012; PCS; high	N = 23 women and 22 babies; PE/T	1: MgSO4, N = 11 women, 10 babies 2: No MgSO4, N = 12 women, 12 babies	NICU admission	P = 0.02	×
			Apgar score < 7 at 5 minutes	P = 0.22	~

Riaz 1998; PCS with CCS(N); high	N = 52 babies; PIH/T	1: MgSO4, N = 26 babies 2: No MgSO4, N = 26 babies	Hypotonia	P < 0.001 "However, there was no association between either hypotonia at birth or Apgar scores, with… total maternal dose or duration of MgSO4 administered (p ≥ 0.29 [data not shown])."	×
			Delivery room support (bag and mask ventilation)	P = 0.19	~
			NICU admission	P = 0.49	~
			Delayed adaptation	P = 0.46	~
			Presumed or ruled-out sepsis	P = 0.75	~
			Delayed feeding (1st feeding ≥ 8 hours after birth)^	P = 0.12	~
			Feeding intolerance	P = 0.54	~
			Hospital stay (days) (mean ± SD)	P = 0.11	~
			Apnoea density (mean ± SD)^	P = 0.37	~
			Apnoea ≥ 15 seconds (associated with bradycardia) (mean ± SD)^	P = 0.96	~
			Apnoea ≥ 10 seconds (mean ± SD)^	P = 0.16	~
			Pathologic apnoea (≥ 15 seconds associated with bradycardia)	P = 1.0	~
		1: MgSO4 and NICU admission, N = 12 babies 2: MgSO4 and no NICU admission, N = 14 babies	MgSO4 dose (g) (mean ± SD),	P = 0.91	~
			Duration of MgSO4 (hours) (mean ± SD)	P = 0.97	~
Rizzolo 2019; RCS; unclear Abstract	N = 3788 babies; FN	1: MgSO4, N = NR 2: No MgSO4, N = NR	Death or SNI (grade ≥ 3 IVH and/or PVL) (adjusted for GA, SGA, mode of birth, sex, multiple pregnancy and SNAP > 20)	aOR 0.87; 95% CI 0.71-1.05	~
Sahin 2001; PCS; high	N = 40 babies; PE/E	1: MgSO4, N = 20 babies 2: No MgSO4, N = 20 babies	Not voiding in 1st 24 hours	No events	~
			Residual urine after 1st micturition (> 5 mL)^	No events	~
			Urinary tract abnormality^	No events	~
			Neurologic pathology^	No events	~
Sakae 2017; NCCS; high	N = 45 women, 48 babies; PE	1: Post-protocol: April 2013 onwards (100% MgSO4 use), N = 17 women, 19 babies	Composite of serious complications (1 or more of: neonatal death, assisted ventilation with ETT > 24 hours, RDS, PPH, PDA, BPD, cPVL, IVH grade ≥ 3,	aOR 10.07; 95% CI 1.70-103.71; P = 0.009	×

		2: Pre-protocol: prior to April 2013 (36% MgSO4 use), N = 28 women, 29 babies	NEC and sepsis) (multiple logistic regression analysis, using the components of our management protocol (antenatal corticosteroids, IV nicardipine, MgSO4, indication for birth) as predictor variables)		
		1: > 48 hours MgSO4, N = 17 women, 19 babies 2: ≤ 48 hours MgSO4, N = 10 women, 10 babies 3: No MgSO4, N = 18 women, 19 babies	Composite of serious complications	1 vs. 2: P = 0.33 1 vs. 3: P = 0.003 2 vs. 3: P = 0.018	~ ✗ ✗
Salafia 1995; RCS with CCS(N; moderate to high	N = 406 women and their babies; T	1: Early GM-IVH, N = 44 babies 2: Late GM-IVH, N = 21 babies 3: No GM-IVH, N = 341 babies	MgSO4 exposure (factors significantly related to early GM-IVH in multivariate logistic regression: GA, MgSO4, antenatal steroids, volume expansion in 1st 2 days, pressor agents in 1st 3 days, acute amnion inflammation)	OR 2.33; 95% CI 1.128-4.814; P = 0.022; β = 0.846	✗
Sarkar 2009; RCS with CCS(N); moderate to high	N = 59 babies; NR	1: IVH grade 3, N = 28 babies 2: IVH grade 4, N = 31 babies	MgSO4 exposure	P = 0.06	~
			MgSO4 exposure (multivariate logistic regression analysis, including GA, birthweight, prenatal steroid use, MgSO4 and Apgar score < 6 at 5 minutes)	OR 0.3; 95% CI 0.07-0.9; P = 0.04	✓
Schanler 1997; PCS; high	N = 31 women, 41 babies; T	1: MgSO4; N = 16 women, 22 babies 2: No MgSO4, N = 15 women, 19 babies	Apgar score < 7 at 5 minutes	22.7% vs. 10.5%	~
			LOS (days) (mean ± SD)	46 ± 38 vs. 35 ± 22	~
			HMD	36.4% vs. 10.5%	~
			PDA	13.6% vs. 0%	~
			IVH	22.7% vs. 10.5%	~
			NEC	4.5% vs. 0%	~
			Birth depression^	No events	~
			Oxygen treatment	68.2% vs. 68.4%	~
			Oxygen treatment > 1 month^	13.6% vs. 5.3%	~
			MV	50.0% vs. 47.4%	~
			MV > 1 week^	9.10% vs. 0%	~
			Methylxanthine treatment for apnoea	40.9% vs. 47.4%	~

			Clinical diagnoses (as above)	"similar between groups"	~
Scudiero 2000; RCS with CCS(N); moderate to high	N = 127 babies; T	1: Fetal or neonatal deaths (perinatal deaths), N = 18 babies 2: Survivors, N = 109 babies	MgSO4 for T > 48 g	P = 0.03	×
			MgSO4 for T ≤ 48 g vs > 48 g (multivariable logistic regression analysis, included year of birth, receipt of betamethasone, acute maternal disease, maternal race, birthweight, MgSO4 dose)	OR 4.72; 95% CI 1.12, 19.97; P = 0.035	×
		1: MgSO4 ≤ 24 g, N = 43 babies 2: MgSO4 > 24 but ≤ 48 g, N = 25 babies 3: MgSO4 > 48 g, N = 59 babies	Perinatal death (Cochrane–Armitage trend test)	P = 0.03	×
			Perinatal death (1 vs. 2 only)	P = 1.0	~
Shalabi 2017; RCS; moderate	N = 4355 babies; any	1: MgSO4, N = 2055 babies 2: No MgSO4, N = 2300 babies	Apgar score < 7 at 5 minutes	P < 0.0001	✓
			SNAP-2 score > 20	P = 0.0005	✓
			MV day 1	P < 0.0001	✓
			Prophylactic indomethacin^	P < 0.0001	×
			PDA treated with indomethacin	P = 0.31	~
			Postnatal steroids for hypotension^	P = 0.37	~
			Postnatal steroid for BPD	P = 0.59	~
			PDA treated with indomethacin or ibuprofen	P = 0.33	~
			Postnatal steroid for BPD or hypotension; PDA treated with indomethacin or ibuprofen^	P = 0.10	~
			NEC stage 2 or higher: all, 22-25 weeks GA, 26-27 weeks GA	P = 0.75; P = 0.45; P = 0.86	~, ~, ~
			NEC stage 2 or higher (multiple logistic regression, covariates included: gender, GA, SGA, Apgar score < 7 at 5 minutes, MV on day 1, antenatal steroid use, prophylactic indomethacin and indomethacin for PDA): all, 22-25 weeks GA, 26-27 weeks GA	aOR 0.92; 95% CI 0.75-1.14; P = 0.45 aOR 0.96; 95% CI 0.72-1.27; P = 0.81 aOR 0.88; 95% CI 0.65-1.20; P = 0.36	~ ~ ~
			SIP: all, 22-25 weeks GA, 26-27 weeks GA	P = 0.99; P = 0.69; P = 0.75	~, ~, ~
			SIP (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA	aOR 1.05; 95% CI 0.75-1.48; P = 0.75 aOR 1.13; 95% CI 0.74-1.72; P = 0.79 aOR 0.93; 95% CI 0.53-1.62; P = 0.69	~ ~ ~
			NEC or SIP: all, 22-25 weeks GA, 26-27 weeks GA^	P = 0.62; P = 0.92; P = 0.53	~, ~, ~

			NEC or SIP (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA^	aOR 0.88; 95% CI 0.73-1.07; P = 0.21 aOR 0.91; 95% CI 0.71-1.18; P = 0.43 aOR 0.85; 95% CI 0.64-1.13; P = 0.41	~ ~ ~
			Neonatal death prior to discharge: all, 22-25 weeks GA, 26-27 weeks GA	P < 0.0001; P < 0.0001; P = 0.56	✓, ✓, ~
			Neonatal death prior to discharge (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA	aOR 0.84; 95% CI 0.71-1.00; P = 0.054 aOR 0.75; 95% CI 0.61-0.93; P = 0.02 aOR 1.04; 95% CI 0.78-1.39; P = 0.74	~ ✓ ~
			NEC or SIP associated death: all, 22-25 weeks GA, 26-27 weeks GA	P = 0.18; P = 0.57; P = 0.21	~, ~, ~
			NEC or SIP associated death (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA	aOR 0.8; 95% CI 0.59-1.09; P = 0.16 aOR 0.89; 95% CI 0.61-1.31; P = 0.44 aOR 0.72; 95% CI 0.43-1.19; P = 0.17	~ ~ ~
			IVH grade 3/4 or PVL: all, 22-25 weeks GA, 26-27 weeks GA	P = 0.002; P = 0.001; P = 0.41	✓, ✓, ~
			IVH grade 3/4 or PVL (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA	aOR 0.91; 95% CI 0.78-1.07; P = 0.26 aOR 0.80; 95% CI 0.65-0.99; P = 0.048 aOR 1.07; 95% CI 0.85-1.35; P = 0.98	~ ✓ ~
			ROP stage 3 or above or ROP treated: all, 22-25 weeks GA, 26-27 weeks GA	P = 0.09; P = 0.06; P = 0.4	~, ~, ~
			ROP stage 3 or above or ROP treated (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA	aOR 0.81; 95% CI 0.65-0.999; P = 0.049 aOR 0.77; 95% CI 0.6-1.001; P = 0.063 aOR 0.88; 95% CI 0.6-1.29; P = 0.23	✓ ~ ~
			BPD: all, 22-25 weeks GA, 26-27 weeks GA	P = 0.18; P = 0.36; P = 0.24	~, ~, ~
			BPD (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA	aOR 0.92; 95% CI 0.79-1.06; P = 0.23 aOR 0.9; 95% CI 0.72-1.12; P = 0.82 aOR 0.93; 95% CI 0.77-1.12; P = 0.42	~ ~ ~
			Nosocomial infection: all, 22-25 weeks GA, 26-27 weeks GA^	P = 0.04; P 0.0007; P = 0.85	✗, ✗, ~
			Nosocomial infection (multiple logistic regression, covariates as above): all, 22-25 weeks GA, 26-27 weeks GA^	aOR 1.08; 95% CI 0.94-1.25; P = 0.26 aOR 1.26; 95% CI 1.03-1.53; P = 0.04 aOR 0.93; 95% CI 0.76-1.13; P = 0.76	~ ✗ ~
			Asphyxia	18.6% vs. 27.6%; (“poorer” in group 2)	✓

Shamsuddin 2005; NRT; high	N = 265 women and their babies (207 antepartum/intrapartum PE/E cases); PE/E	1: MgSO4 LD at home before referral to hospital, N = 102 women and their babies 2: No MgSO4 before referral to hospital, N = 105 women and their babies	Stillbirth	P < 0.001	✓
Shokry 2010; PCS; high	N = 48 women and their babies; T	1: MgSO4, N = 28 women and their babies 2: No MgSO4, N = 20 women and their babies	RDS	P = 0.762	~
			PIVH	P = 0.036	✓
			Seizures	P = 0.011	✓
			MV	P = 0.836	~
			Surfactant use	P = 0.874	~
			Inotropic drug use	P = 0.498	~
			PDA	P = 0.042	×
			Neonatal death	P = 0.480	~
Stetson 2019; NCCS; high Research Letter	N = 110 babies; FN/PE	1: 2002-2008 (pre-BEAM trial, 36% uptake MgSO4), N = 42 babies 2: 2009-2014 (post-BEAM trial, 62% uptake MgSO4), N = 68 babies	BPD 1: 67% babies exposed to MgSO4 vs. 56% not exposed 2: 86% babies exposed to MgSO4 vs. 73% not exposed	P = 0.049	×
			IVH 1: 40% babies exposed to MgSO4 vs. 56% not exposed 2: 60% babies exposed to MgSO4 vs. 62% not exposed	P = 0.41	~
Stockley 2018; RCS; moderate	N = 336 babies; NR	Growth restriction (fetal standards) 1: MgSO4, N = 112 babies 2: No MgSO4, N = 224 babies	Death in NICU and post-discharge (adjusted for GA, sex, mode of birth, multiple birth, SNAP-II > 20, maternal hypertension)	aOR (95% CI): 0.42 (0.19-0.95)	✓
			Apgar score < 7 at 5 minutes	P = 0.65	~
			Chest compression or epinephrine	P = 0.70	~
			SNAP-II score > 20	P = 0.36	~
			BPD (adjusted as above)	aOR 0.84; 95% CI 0.46-1.52	~
			NEC (adjusted as above)	aOR 0.38; 95% CI 0.15-1.00	~
			Late-onset sepsis (adjusted as above)	aOR 0.89; 95% CI 0.49-1.61	~
			ROP stage 3/4/5 or treated (adjusted as above)	aOR 0.80; 95% CI 0.34-1.88	~

			IVH grade 1/2 (adjusted as above)	aOR 1.02; 95% CI 0.53-1.94	~
			IVH grade 3/4 (adjusted as above)	aOR 0.55; 95% CI 0.20-1.51	~
		Growth restriction (neonatal standards) 1: MgSO4, N = 61 babies 2: No MgSO4, N = 116 babies	Death in NICU and post-discharge (adjusted as above)	aOR 0.37; 95% CI 0.15-0.95	✓
			Apgar score < 7 at 5 minutes	P = 0.83	~
			Chest compression or epinephrine	P = 0.49	~
			SNAP-II score > 20	P = 0.60	~
			BPD (adjusted as above)	aOR 1.10; 95% CI 0.47-2.61	~
			NEC (adjusted as above)	aOR 0.57; 95% CI 0.16-2.00	~
			Late-onset sepsis (adjusted as above)	aOR 0.71; 95% CI 0.32-1.56	~
			ROP stage 3/4/5 or treated (adjusted as above)	aOR 0.96; 95% CI 0.34-2.73	~
			IVH grade 1/2 (adjusted as above)	aOR 0.54; 95% CI 0.20-1.42	~
			IVH grade 3/4 (adjusted as above)	aOR 0.68; 95% CI 0.20-2.34	~
Suh 2015; RCS; unclear English abstract	N = 150 babies (of relevance); HD	1: MgSO4, N = 40 babies 2: No MgSO4, N = 110 babies	LOS (days) (mean ± SD)	P = 0.181	~
			Duration of ventilation(days) (mean ± SD)	P = 0.078	~
			Duration of oxygen (days) (mean ± SD)	P = 0.205	~
			RDS	P = 0.242	~
			BPD	P = 0.264	~
			Moderate to severe BPD	P = 0.576	~
			PDA treated (medication ± operation)	P = 0.534	~
			ROP treated with laser	P = 0.086	~
			NEC	P = 0.528	~
			IVH grade ≥ 2	P = 0.151	~
			PVL	P = 0.053	~
			Neonatal death	P = 0.320	~
Teng 2006; RCS with CCS(N); moderate to high	N = 184 babies; PE/T	1: Early hypotension, N = 75 babies 2: No early hypotension, N = 109 babies	MgSO4 exposure (identified as one of eight variables associated with hypotension, by univariate analysis)	OR 2.83; 95% CI 1.52-5.27; P < 0.01	✗
			MgSO4 exposure (incorporated into multiple logistic regression model)	No longer associated	~
			Positive blood culture	No events	~
	N = 45 babies; PE/T	1: PIE^, N = 11 babies	MgSO4 dose (g) (mean ± SD)	P = 0.02	✗

Verma 2006; RCS with CCS(N); moderate to high		2: No PIE, N = 34 babies	MgSO4 dose ≥ 10 g	P = 0.01	×
			MgSO4 dose ≥ 10 g (multivariate logistic regression analysis model, controlling for maximum mean FiO2 and MAP during 1st 7 days of life, Apgar scores at 1 and 5 minutes, GA and surfactant requirement)	OR 19.8; 95% CI 1.5-263; P = 0.01	×
Weintraub 2001; RCS; moderate to high	N = 2794 babies (have not considered the 263 babies and 177 infants exposed to ritodrine and indomethacin)	1: MgSO4, N = 341 babies 2: No MgSO4, N = 2013 babies	PVH/IVH grade 3/4	10.0% vs. 15.1%; P < 0.01 (P relates to univariate analysis, considering tocolytic groups: 1: MgSO4, 2: no tocolysis, 3: ritodrine, and 4: indomethacin)	NR
			PVH/IVH grade 3/4 (multivariate logistic regression analysis; considered for inclusion: tocolysis, antenatal steroids, multiple birth, PROM, amnionitis, mode of birth, GA, birthweight, Apgar score at 1 minute, Apgar score at 5 minutes, RDS, PDA, MV, pneumothorax, sepsis)	aOR 0.8; 95% CI 0.5-1.2	~
Weisz 2015; RCS; moderate	N = 6015 babies; FN/PE/T/UK	1: MgSO4 for FN, N = 1387 babies 2: No MgSO4, N = 3868 babies	Any resuscitation (mask CPAP or PPV, ETT intubation and ventilation, chest compressions or epinephrine)	P < 0.01	×
			CPAP only^	P < 0.01	×
			Bag/mask or neopuff ventilation	P < 0.01	✓
			Intubation and ventilation	P = 0.03	✓
			Chest compressions	P < 0.01	✓
			Epinephrine (ETT or IV)	P = 0.02	✓
			Apgar score < 7 at 5 minutes	P = 0.20	~
			Surfactant use	P = 0.06	~
			SNAP-2 score > 20	P = 0.28	~
			Intensive resuscitation (intubation and ventilation, or chest compressions or epinephrine administration in delivery room), unadjusted, and multiple logistic regression (with GEE to account for correlated data within each site/site effects), adjusted for: GA, sex, SGA, outborn status,	OR 0.87; 95% CI 0.76-0.98; P = 0.02 aOR 0.88; 95% CI 0.66-1.17	✓, ~

			chorioamnionitis, mode of birth, antenatal corticosteroid use, multiple gestation		
			Neonatal death, unadjusted, and adjusted as above	OR 0.73; 95% CI 0.58-0.92; P < 0.01 aOR 0.61; 95% CI 0.40-0.94	✓, ✓
			BPD, unadjusted, and adjusted as above	OR 1.09; 95% CI 0.93-1.18; P = 0.28 aOR 1.13; 95% CI 0.92-1.38	~, ~
			NEC stage ≥ 2, unadjusted, and adjusted as above	OR 1.19; 95% CI 0.91-1.55; P = 0.20 aOR 0.99; 95% CI 0.73-1.34	~, ~
			IVH grade 3/4 or PVL, unadjusted, and adjusted as above	OR 0.95; 95% CI 0.79-1.15; P = 0.62 aOR 1.01; 95% CI 0.76-1.34	~, ~
			ROP stage ≥ 3, unadjusted, and adjusted as above	OR 1.01; 95% CI 0.74-1.36; P = 0.95 aOR 0.88; 95% CI 0.61-1.28	~, ~
			Sepsis, unadjusted, and adjusted as above	OR 1.09; 95% CI 0.92-1.29; P = 0.32 aOR 0.96; 95% CI 0.80-1.14	~, ~
			Composite outcome (morality or any major morbidity), unadjusted, and adjusted as above	OR 1.00; 95% CI 0.88-1.14; P = 0.97 aOR 1.03; 95% CI 0.83-1.29	~, ~
		23-28 weeks GA 1: MgSO4 for FN, N = 731 babies 2: No MgSO4, N = 1813 babies	Intensive resuscitation, and adjusted as above	OR 0.79 (0.66 to 0.94); P < 0.01 aOR 0.89 (0.67 to 1.18)	✓, ~
			Neonatal death, unadjusted, and adjusted as above	OR 0.65 (0.51 to 0.85); P < 0.01 aOR 0.65 (0.43 to 1.00)	✓, ~
			BPD, unadjusted, and adjusted as above	OR 1.03 (0.85 to 1.25); P = 0.75 aOR 1.30 (1.03 to 1.65)	~, ~
			NEC stage ≥ 2, unadjusted, and adjusted as above	OR 1.15 (0.84 to 1.57); P = 0.38 aOR 1.05 (0.78 to 1.42)	~, ~
			IVH grade 3/4 or PVL, unadjusted, and adjusted as above	OR 0.96 (0.77 to 1.19); P = 0.69 aOR 1.11 (0.77 to 1.60)	~, ~
			ROP stage ≥ 3, unadjusted, and adjusted as above	OR 0.96 (0.70 to 1.31); P = 0.79 aOR 0.86 (0.59 to 1.25)	~, ~
			Sepsis, unadjusted, and adjusted as above	OR 0.97 (0.79 to 1.18); P = 0.76 aOR 0.91 (0.75 to 1.11)	~, ~
			Composite outcome, unadjusted, and adjusted as above	OR 0.92 (0.77 to 1.09); P = 0.33 aOR 1.24 (0.97 to 1.61)	~, ~
		29-31 weeks GA	Intensive resuscitation, and adjusted as above	OR 0.67 (0.53 to 0.83); P < 0.01 aOR 0.82 (0.57 to 1.19)	✓, ~

		1: MgSO4 for FN, N = 656 babies 2: No MgSO4, N = 2055 babies	Neonatal death, unadjusted, and adjusted as above	OR 0.44 (0.18 to 1.05); P = 0.06 aOR 0.74 (0.36 to 1.51)	~, ~
			BPD, unadjusted, and adjusted as above	OR 0.67 (0.44 to 0.99); P = 0.05 aOR 0.73 (0.49 to 1.07)	✓, ~
			NEC stage ≥ 2, unadjusted, and adjusted as above	OR 1.06 (0.63 to 1.78); P = 0.81 aOR 1.03 (0.57 to 1.85)	~, ~
			IVH grade 3/4 or PVL, unadjusted, and adjusted as above	OR 0.67 (0.43 to 1.04); P = 0.07 aOR 0.66 (0.40 to 1.06)	~, ~
			ROP stage ≥ 3, unadjusted, and adjusted as above	OR 1.53 (0.36 to 6.46); P = 0.56 aOR NC	~, ~
			Sepsis, unadjusted, and adjusted as above	OR 1.23 (0.81 to 1.58); P = 0.48 aOR 1.23 (0.91 to 1.67)	~, ~
			Composite outcome, unadjusted, and adjusted as above	OR 0.77 (0.59 to 1.01); P = 0.05 aOR 0.77 (0.59 to 1.01)	~, ~
		1: MgSO4 for FN, N = 1387 babies 2: MgSO4 for PE/T = 214 babies 3: MgSO4 for UK = 546 babies	Any resuscitation, 1 vs. 2; 1 vs. 3	P = 0.97; P = 0.76	~, ~
			CPAP only, 1 vs. 2; 1 vs. 3^	P < 0.01; P < 0.01	×, ×
			Bag/mask or neopuff ventilation, 1 vs. 2; 1 vs. 3	P = 0.04; P = 0.35	✓, ~
			Intubation and ventilation, 1 vs. 2; 1 vs. 3	P < 0.01; P < 0.28	×, ~
			Chest compressions, 1 vs. 2; 1 vs. 3	P = 0.82; P = 0.60	~, ~
			Epinephrine (ETT or IV) , 1 vs. 2; 1 vs. 3	P = 0.99; P = 0.54	~, ~
			Apgar score < 7 at 5 minutes, 1 vs. 2; 1 vs. 3	P = 0.14; P = 0.12	~, ~
			Surfactant use, 1 vs. 2; 1 vs. 3	P = 0.33; P = 0.53	~, ~
			SNAP-2 score > 20, 1 vs. 2; 1 vs. 3	P < 0.01; P < 0.01	✓, ✓
		1: MgSO4 for any indication, N = 2147 babies 2: No MgSO4, N = 3868 babies	Intensive resuscitation, and adjusted as above	OR 0.81; 95% CI 0.73-0.90; P < 0.01 aOR 0.87; 95% CI 0.69-1.13	✓, ~
			Neonatal death, unadjusted, and adjusted as above	OR 0.67; 95% CI 0.54-0.82; P < 0.01 aOR 0.64; 95% CI 0.46-0.89	✓, ✓
			BPD, unadjusted, and adjusted as above	OR 1.05; 95% CI 0.92-1.21; P = 0.44 aOR 1.11; 95% CI 0.94-1.30	~, ~
			NEC stage ≥ 2, unadjusted, and adjusted as above	OR 0.99; 95% CI 0.79-1.27; P = 0.99 aOR 0.89; 95% CI 0.768-1.17	~, ~
			IVH grade 3/4 or PVL, unadjusted, and adjusted as above	OR 0.86; 95% CI 0.73-1.01; P = 0.06 aOR 1.02; 95% CI 0.76-1.36	~, ~
			ROP stage ≥ 3, unadjusted, and adjusted as above	OR 0.99; 95% CI 0.76-1.29; P = 0.94	~, ~

				aOR 0.86; 95% CI 0.59-1.25	
			Sepsis, unadjusted, and adjusted as above	OR 1.12; 95% CI 0.97-1.30; P = 0.11 aOR 1.02; 95% CI 0.87-1.20	~, ~
			Composite outcome, unadjusted, and adjusted as above	OR 0.93; 95% CI 0.83-1.04; P = 0.19 aOR 1.03; 95% CI 0.85-1.24	~, ~
Whitsel 2004; RCS; unclear Abstract	N = 118 babies; NR	1: MgSO4, N = NR 2: No MgSO4, N = NR	Neonatal death	"did not change the mortality rate"	~
			Late bacterial sepsis	P = 0.046	✖
Whitten 2015; RCS with CCS(N); unclear Abstract	N = 6791 babies; NR	1: LOS ≤ 3 days^, N = 6472 babies 2: LOS ≥ 4 days, N = 319 babies	MgSO4 exposure	OR 6.72; P = 0.000	✖
Wiswell 1996; PCS; unclear Abstractf	N = 137 babies; T/PIH	1: MgSO4, N = 61 babies 2: No MgSO4, N = 76 babies	NEC	P = 0.042	✓
			ICH grade 3/4	P = 0.009	✓
			cPVL in survivors ≥ 21 days	P = 0.088	~
			ICH grade 3/4 or cPVL	OR 4.1; 95% CI 2.0-8.5; P = 0.0001	✓
Wutthigate 2017; PCS with CCS(N); high	N = 57 women, 63 babies; PIH/T	1: Apnoeic episodes, N = 8 babies 2: No apnoeic episodes, N = 55 babies	MgSO4 dose (reported as mg/dL) (mean ± SD)	P = 0.06	~
Yokoyama 2010; RCS; high	N = 117 babies; T	1: MgSO4, N = 58 babies 2: No MgSO4, N = 59 babies	RDS	P = 0.709	~
			IVH	P = 0.496	~
			PDA	P = 0.829	~
			ROP	P = 0.053	~
			Neonatal death	P = 0.243	~
			NEC	No events	~
			Bone change (abnormalities: osteopenic radiolucent bands at metaphyses of long bones; not suggestive of rickets)	P = 0.496	~
Young 1977; NRT; high	N = 144 women and their babies; PE/E	1: MgSO4 'push' IV, N = 97 women and babies 2: MgSO4 continuous IV, N = 47 women and babies	Perinatal death	1: 2.1% vs. 2: 2.1%	~

^Indicates an outcome reported by a single study

Abbreviations: aOR: adjusted odds ratio; aRR: adjusted risk ratio; BMI: body mass index; BPD: bronchopulmonary dysplasia; CCS; case-control study; CCS(N): nested case-control study; CI: confidence interval; CMV: continuous mandatory *ventilation*; CPAP: continuous positive airway pressure; CPR: cardiopulmonary resuscitation; cPVL: cystic periventricular leucomalacia; CRIB: clinical risk *index* for babies; E: eclampsia; ETT: endotracheal tube; FN: fetal neuroprotection; g: grams; GA: gestational age; HD: hypertensive disorders; HFOV: high frequency oscillatory ventilation; HsPDA: haemodynamically significant patent ductus arteriosus; ICH: intracranial haemorrhage; IMV: intermittent mandatory ventilation; IV: intravenous; IVH: intraventricular haemorrhage; LD: loading dose; LOS: length of stay; LSV: lenticulostriate vasculopathy; MD: maintenance dose; MgSO4: magnesium sulphate; MRI: magnetic resonance imaging; N: number; MV: mechanical ventilation; N: number; NCCS: non-concurrent cohort study; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; NR: not reported; NRT: non-randomised trial; NS: non-significant; OR: odds ratio; P: p value; PCS: prospective cohort study; PDA: patent ductus arteriosus; PE: pre-eclampsia; PEA: parenchymal echo abnormality; PEL/VE: parenchymal lesions/ventricular enlargement; PIE: pulmonary interstitial emphysema; PIH: pregnancy-induced hypertension; ; PTL: preterm labour; PV-IVH: periventricular intraventricular haemorrhage; PVL: periventricular leucomalacia; PWML: punctate white matter lesions; RCS: retrospective cohort study; RCT: randomised controlled trial; RD: respiratory distress; RDS: respiratory distress syndrome; ROM: rupture of membranes; ROP: retinopathy of prematurity; RR: risk ratio; SCBU: special care baby unit; SD: standard deviation; SGA: small-for-gestational age; SH: systematic hypertension; SIP: spontaneous intestinal perforation; SNAP: Score For *Neonatal* Acute Physiology; SNI: severe neurological injury; sPDA: significant patent ductus arteriosus; T: tocolysis; TSV: thalamostriate or mineralising vasculopathy; VLBW: very low birthweight; WMI: white matter injury

S4 Table. Adverse outcomes from case reports

Common adverse outcome	Authors' conclusions	Setting	Neonatal characteristics	MgSO4 regimen	MgSO4 indication	Study
Neonatal death						
Twin A: Apgar scores 1/1/0; resuscitated (including intratracheal epinephrine receipt); death at 30 minutes of age Twin B: Apgar scores 4/6/8; resuscitated (intubated); hypermagnesemic; elevated serum cardiac troponin T levels; non-specific ST-T wave abnormalities	"it is conceivable that the mechanism of death… may be directly related to the toxic effects of magnesium on the myocardium of twin A, whereas the myocardium of twin B, although compromised, was sufficiently functional to maintain life."	USA Year NR	2 neonates; twins; preterm; LBW	4 g IV LD; 2.5 g/hour MD for ~ 1 day; total dose: 51.4 g	T	Herschel 2001
42 neonates: diagnosis of poisoning; abnormal clinical signs (suck failure, cyanosis, hypoactivity, hypotonia, hyporeflexia); IV calcium gluconate receipt; death of 7/27 neonates exposed to $MgSO_4$ as a single agent	"in fact only two (2.7%) patients died of the secondary effects of overdose of drugs (one of them due to magnesium sulfate."	Turkey 1975 to 1997	42 neonates with a diagnosis of poisoning; exposed to $MgSO_4$ (27 as a single agent)	18 to 40 g IV for 12 to 48 hours prior to birth	PE/E	Kurtoglu 2000
Cardiopulmonary arrest after gentamicin exposure following hypermagnesemia at birth						
Respiratory arrest and cardiac arrest following IM gentamicin at 24 hours for suspected sepsis (in context of hypermagnesemia at birth with abnormal neuromuscular function tracings and clinical examination: peripheral motor weakness, rapid shallow respirations, poor suck, poor Moro reflex, decreased grasp reflexes)	"aminoglycosides may potentiate a magnesium-induced impairment of neuromuscular transmission and cause muscular weakness in neonates."	USA Year NR	1 neonate; term	24 g in 32 hours prior to birth	PE	L'Hommedieu 1983
Respiratory and cardiac arrest following IV gentamicin at 48 hours for suspected sepsis (in context of hypermagnesemia at birth with neuromuscular compromise: ulnar nerve stimulation studies and neurologic examination)	"depressed NMF [neuromuscular function] in a hypermagnesemic infant may be further compromised by aminoglycoside therapy."	USA Year NR	1 neonate; term	28 g	PE	Rasch 1981
Clinical features of magnesium 'toxicity' or 'intoxication' at birth						
Flaccid, apnoeic, cyanotic at birth (muscular paralysis, absent reflexes, respiratory failure); Apgar score 2 at 1 minute; endotracheal intubation, ventilation and calcium gluconate receipt; hypermagnesemic	"Magnesium Intoxication… "in our patient, peak serum levels from the mother's first intramuscular dose could have coincided with the peak serum level from her second	USA 1966	1 neonate; very preterm; LBW	3 g IV, 6 g IM, and 2 g IV, 3.5 hours, 2.5 hours, 0.5 hours	PE	Brady 1967

	intravenous dose… the toxic effects of motor and respiratory paralysis were immediately reversed when the serum magnesium level lowered during an exchange transfusion."			prior to birth respectively		
Depressed, hypotonic, cyanotic, apnoeic, partially responsive to initial resuscitation; hypermagnesemic	"a newborn with a history of maternal use of magnesium sulfate, who presented hypermagnesemia."	Chile Year NR	1 neonate; preterm	17 hours IV prior to birth	PE	Cruz 2009
"CNS disturbances"	"For appropriate treatment of neonates, it is necessary to take into consideration maternal medication use during pregnancy and delivery."	USA Year NR	~25 neonates [225 neonates with RDS, 11% with symptoms of "Magnezium Sulfate intoxication"]	NR	NR	Jashi 2014
"clinical and biochemical changes associated with hypermagnesemia in newborns": Neonate 1: low Apgar score at 1 minute (intubation, ventilation), flaccid, unresponsive, shallow respirations, respiratory arrest Neonate 2: low Apgar score at 1 minute, bradycardia, minimal activity, weak cry Neonate 3: low Apgar score at birth, hypotonia, hyporeflexia Neonate 4: low Apgar score at 1 minute (intubation, ventilation), floppy, poor shallow respiratory movement, poor activity, weak cry Neonates 5 and 6: low Apgar scores (intubation and ventilation), flaccid, death [not attributed to MgSO4; rather HMD] Neonate 6: low Apgar at 1 minute (intubation and ventilation), flaccid, weak cry, poor reflexes, poor muscle tone	"clinical and biochemical changes associated with hypermagnesemia in newborns."	USA 1965-1966	7 neonates [detailed case reports]; 3 term, 4 preterm (1 set of twins) [Note: only detailed cases included; others presented as case series]	1: 51.5 g in 33.5 hours 2: 21 g in 24 hours 3: 30 g in 19 hours 4: 31 g in 20 hours 5: 41.3 g in 30 hours 6: 60.4 g in 44 hours	PE/E	Lipsitz 1967
Apgar scores 2/6, severe respiratory distress (intubated) at birth, hyporeflexic, hypotonic, lethargic; hypermagnesemic; hypocalcaemic; ventilated and IV calcium gluconate receipt	"Hypermagnesemia was judged to be the cause of the newborn's clinical presentation."	Taiwan 1989	1 neonate; preterm; LBW	50 g IV in 46 hours prior to birth	PE	Teng 1989

Microcolon or 'meconium-plug syndrome'						
Microcolon, with clinical signs and symptoms: failure to pass meconium within first 24 hours with progressive abdominal distention	"In summary, the microcolon seen in our very premature infants seems secondary to functional obstruction on the basis of ganglion cell dysfunction and depressive effects of magnesium sulfate."	USA 1980 to 1984	4 neonates with non-organic intestinal obstruction; very preterm; VLBW	NR	PE	Amodio 1986
No passage or delayed massage of meconium and abdominal distension; findings consistent with "meconium plug syndrome"	"The role of magnesium in depression smooth muscle cells and passing the placenta has been well documented and was contributory in some of our patients."	USA Year NR	8 neonates; LBW/VLBW; preterm [12 neonates not exposed to $MgSO_4$ excluded]	NR	PE/E	Krasna 1996
Abdominal distention and failure to pass meconium ("Meconium-plug syndrome") 1 neonate: depressed, shallow respirations, hypotonic, hyporeflexic; hypermagnesemic; hypocalcaemic 1 neonate: lethargic, hypotonic, rapid and grunting respiration, lower extremities hypotonic, absent deep tendon reflexes; hypermagnesemic; hypocalcaemic; calcium gluconate IV receipt	"We believe that the hypermagnesemia depressed function of the intestinal smooth muscle as well as skeletal striated muscle in these babies."	USA Year NR	2 neonates; 1 term, LBW; 1 preterm	41 and 25 g in 24 hours prior to birth respectively	PE/E	Sokal 1972
Nonoliguric hyperkalaemia						
Neonatal non-oliguric hyperkalaemia (high risk for developing life-threatening cardiac arrhythmia) at 2 hours after birth; insufficient urinary K excretion; hypermagnesemic; not hypocalcaemic with calcium sulphate receipt; transiently hyponatraemic	"Maternal and fetal hypermagnesemia can induce rapidly progressive hyperkalemia in neonates.	Japan Year NR	1 neonate; preterm; VLBW	0.1 g/hour IV on day 1; 0.5 g/hour IV on days 2 to 5; 1 g/hour IV days 6 to 12; 2 g/hour IV on day 12	PE	Tanaka 2018
Bone abnormalities with prolonged $MgSO_4$ for tocolysis						
Laboratory abnormalities ("especially hypermagnesemia and hypocalcemia") and skeletal abnormalities including osteopenia and fractures	"The postmarket… data support an association between prolonged maternal administration of MgSO4 and neonatal hypermagnesemia, hypocalcemia, and skeletal abnormalities."	USA 1986 to 2011	18 neonates; identified through the FDA Adverse Event Reporting System	Prolonged IV administration	Not clear (PE/T)	Ahmad 2013

Radiographic changes in the metaphyses of long bones (discrete band of osteopenic metaphyseal bone); hypermagnesemic; not hypocalcaemic; elevated alkaline phosphatase	"we believe it likely the abnormal ossification was due to hypermagnesemia."	USA Year NR	1 neonate; very preterm; LBW	1 to 4 g/hour IV from ~18 weeks until birth at 28 weeks	T	Cumming 1989
Diffuse osteopenia of long bones (diffuse metaphyseal osteopenia); probable rib fracture (2 neonates); hypermagnesemic; severely hypocalcemic; elevated alkaline phosphatase; relative hypoparathyroidism; calcium and calcitriol receipt (5 neonates)	"Premature infants who are exposed to large doses of MgSO4, especially those of multiple pregnancies, have an increased risk of developing hypocalcemia, osteopenia, and fractures."	USA Year NR	10 neonates (twins or triplets); preterm; LBW or VLBW	Average mean parenteral dose: 3.66 (SD: 0.8) kg per pregnancy over a mean of 10.0 (SD: 0.5) weeks (1.75 to 3 g/hour for 9 to 11 weeks)	T	Kaplan 2006
Triplets B and C: bone abnormalities "mimicking genetic bone disease": at 3 weeks thin, demineralised bones with multiple fractures of the ribs, humeri and clavicle; skull bones were demineralised; very wide fontanelles, white sclera; not hypocalcaemic; mildly hypermagnesemic; elevated alkaline phosphatase; low bone density persisting at 3 months	"The bone abnormalities were presumed to be related to prolonged prenatal exposure to magnesium, with genetic bone disease unlikely… This case points out the necessity of including prolonged magnesium therapy in the differential diagnosis of the newborn infant with multiple fractures."	NR	2 neonates (from triplets); very preterm	2.5 g/hour IV for 8.5 weeks	T	Kogan 2003
Radiological, biochemical or clinical features of rickets 1 neonate: radiographic bony abnormalities: frank rachitic changes and dental enamel hypoplasia; hypotonic, respiratory distress at birth; hypermagnesemic; hypocalcaemic; elevated alkaline phosphatase; IV calcium gluconate receipt (dental enamel hypoplasia persisting at 3 years) 3 neonates: no bony abnormalities; mild respiratory distress; 1 hypotonic; hypermagnesemic; 1 hypocalcaemic	"We hypothesize that prolonged infusion of magnesium sulfate, especially when imitated during the second trimester, may lead to fetal parathyroid gland suppression with consequent abnormalities resembling rickets."	USA Year NR	4 neonates; preterm [1 neonate exposed to combination tocolysis excluded]	1 neonate: 4 g IV LD; 2-3 g/hour IV MD for 13 weeks 3 neonates: doses similar to above, for 4 to 6 weeks	T	Lamm 1988
Abnormal radiological findings: abnormal mineralisation of long-bone metaphyses Twin 1A and 1B: hypotonic, poor sucking capacity; widening of anterior ends of ribs and widening of femora and humeri metaphyses with radiolucency; hypermagnesemic	"abnormal radiological findings consisting of abnormal mineralisation of long-bone metaphyses owing to fetal hypermagnesaemia." Twin 2A not affected: "intrauterine growth restriction may be a protective factor against	Lebanon Year NR	3 neonates (from 2 sets of twins); preterm; LBW [twin 2A VLBW, excluded]	Twins 1A and B: 3 to 3.5 g/hour IV for 12 weeks Twins 2A and B: 3 to 4 g/hour IV for 8 weeks	T	Malaeb 2004

Twin 2B: radiolucency of metaphyses, mainly humeri; hypermagnesemic	the development of bone abnormalities secondary to prolonged fetal hypermagnesaemia."					

Abbreviations: CNS: central nervous system; E: eclampsia; g: grams; HMD: hyaline membrane disease; IM: intramuscular; IV: intravenous; LBW: low birthweight; LD: loading dose; MD: maintenance dose; $MgSO_4$: magnesium sulphate; NR: not reported; PE: pre-eclampsia; RDS: respiratory distress syndrome; SD: standard deviation; T: tocolysis; USA: United States of America; VLBW: very low birthweight

S1 Text. Protocol

Project Title
Neonatal and infant adverse effects of antenatal magnesium sulphate for improving outcomes for mothers and babies: a systematic review

Chief Investigator	
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Research Plan

BACKGROUND

Antenatal magnesium sulphate for cerebral palsy prevention

Two landmark observational studies published in the 1990s provided the first descriptions of an association between in utero magnesium sulphate exposure and a reduced risk of cerebral palsy.[1,2] Due to the limitations and discrepancies of findings from observational studies, a need to establish reliable evidence, through the conduct of randomised trials, was realised. From 1995 to 2004, five placebo-controlled randomised trials (ACTOMgSO4;[3] BEAM;[4] MagNET;[5] PREMAG[6]; MAGPIE[7]) were conducted, testing the hypotheses that antenatal magnesium sulphate reduces brain injury, cerebral palsy, or mortality for preterm infants.

In the meta-analysis of the aforementioned trials in the 2009 Cochrane review, magnesium sulphate administered with neuroprotective intent reduced the risk of death or cerebral palsy (RR 0.85, 95% CI 0.74-0.98; 4 trials, 4,446 infants).[8] Overall magnesium sulphate reduced the risk of cerebral palsy (RR 0.68, 95% CI 0.54-0.87; 5 trials, 6,145 infants). This review confirmed the neuroprotective role for magnesium sulphate – 63 babies (95% CI 44-155) need to be exposed to magnesium sulphate in utero to benefit one preterm baby by avoiding cerebral palsy.[8]

Additional systematic reviews and meta-analyses have reached similar conclusions.[9,10] This has been regarded as a very important finding, as few interventions have been found to prevent the devastating consequences of cerebral palsy. Importantly, in a recent cost-effectiveness analysis, magnesium sulphate prior to very preterm birth was shown to be cost-effective from a societal and health system perspective.[11]

Following this compelling evidence from randomised trials and reviews, in many countries, including Australia, New Zealand, the United Kingdom, Canada and the United States, clinical practice guidelines[12,13] and opinion papers[14-17] have recommended use of this therapy. Australian and New Zealand clinical practice guidelines, *Antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child, endorsed by the* National Health and Medical Research Council (NHMRC) in 2010, provided guidance in the form of nine evidence-based recommendations and six practice points.[12]

With passive guideline dissemination alone, it was not anticipated that all health professionals would immediately begin using antenatal magnesium sulphate.[18] The WISH Project (*Working to Improve Survival and Health for babies born very preterm*) was thus designed, funded by the Cerebral Palsy Alliance Research Foundation, to improve and monitor the use of this therapy in Australia and New Zealand.[19] Through WISH, audit studies at lead hospitals have highlighted rapid translation – at the Women's and Children's Hospital, South Australia uptake increased from 30% in 2010, to 78% in 2011-13,[20,21] and in 2012, uptake at Auckland City Hospital, New Zealand, was 82%.[22] While encouragingly in 2011, 76%, and in 2013, almost all Australian and New Zealand tertiary maternity hospitals had local practices to implement this therapy, fewer were formally auditing use, and uptake estimates have varied.[23,24] The Australian and New Zealand Neonatal Network (ANZNN) data report increasing uptake bi-nationally (2012: 44%; 2013: 60%).[25,26]

Maternal adverse effects of antenatal magnesium sulphate: a systematic review

Given the extensive use of antenatal magnesium sulphate in obstetric care, to prevent or treat pre-eclampsia (beneficial),[27,28] for acute and maintenance tocolytic therapy for women during and following threatened preterm labour (not beneficial),[29,30] and most recently, for fetal neuroprotection and cerebral palsy prevention (beneficial),[8] the potential adverse effects for the mother are well known.

High quality evidence regarding maternal adverse effects can be drawn from a recent systematic review (led by CI Bain), *'Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: a systematic review'*.[31] This review included 143 publications – 21 randomised controlled trials, 14 non-randomised comparative studies, 32 case series, and 74 reports of individual cases – reporting adverse effects of

magnesium sulphate when given for treatment of pre-eclampsia, for cerebral palsy prevention, or for preterm labour tocolysis. Reassuringly, this review showed that antenatal magnesium sulphate was not associated with an increased risk of maternal death, cardiac arrest or respiratory arrest.[31] In this review, individual case reports, did, however support an association between iatrogenic overdose of magnesium sulphate and life-threatening consequences.[31,32] Appropriate administration of therapy was shown to increase the risk of 'any adverse maternal effects' (RR 4.62, 95% CI 2.42 to 8.83; 4 trials, 13,322 women), and treatment cessation due to maternal adverse effects (RR 2.77, 95% CI 2.32 to 3.30; 5 trials, 13,666 women).[31] This systematic review concluded that for each antenatal indication for use, further trials designed to determine optimal regimens (aimed at achieving maximal effectiveness with minimal adverse effects) may be beneficial, and called for vigilance in the use of this therapy, in order to ensure women's safety.[31]

Potential neonatal or infant adverse effects of antenatal magnesium sulphate

With the increased, widespread use of antenatal magnesium sulphate for cerebral palsy prevention, concern has been raised about potential unintended neonatal or infant adverse effects. In a recent evaluation of barriers and enablers to implementing antenatal magnesium sulphate for cerebral palsy prevention (as part of The WISH Project), the uncertainty surrounding adverse effects for very preterm neonates was specifically raised by health professionals, particularly neonatologists, as a potential barrier to increased use.[33]

Magnesium has fundamental roles in many cellular process (such as gating of calcium channels; muscle contraction; neuronal activity; control of vasomotor tone; cardiac excitability; and neurotransmitter release)[34], and thus above normal magnesium concentrations (associated with magnesium sulphate therapy), can plausibly be associated with fetal, neonatal or infant adverse effects. Magnesium is known to cross the placenta readily, with fetal serum concentrations correlated with maternal serum magnesium concentrations,[35] and/or total maternal dose of magnesium sulphate given.[36] Where there is delayed fetal urinary excretion, fetal serum and amniotic fluid concentrations can exceed maternal concentrations.

In the Cochrane systematic reviews assessing magnesium sulphate for treating pre-eclampsia,[27,28] for cerebral palsy prevention,[8] and for preterm labour tocolysis,[29] no clear increased risks of adverse neonatal or infant outcomes were reported, however a borderline increased risk of total death (fetal, neonatal, infant) with prolonged use for tocolysis was observed (RR 4.56, 95% CI 1.00 to 20.86; 2 trials, 257 babies).[29] These reviews were restricted to assessing randomised controlled trial evidence, and a limited number of pre-specified outcomes.

Recently, a systematic review (including randomised trials and prospective observational studies) summarised the effects of magnesium sulphate given for treating pre-eclampsia, for cerebral palsy prevention, and for preterm labour tocolysis specifically on fetal heart rate.[37] This review suggested a small negative effect on fetal heart rate, variability and accelerative pattern, *"not sufficient clinically to warrant medical intervention".*[37] To date, a comprehensive systematic review of all available evidence surrounding potential unintended neonatal or infant adverse effects of antenatal magnesium sulphate has not been conducted.

While secondary analyses from the BEAM trial (one of the five randomised trials assessing magnesium sulphate for cerebral palsy prevention) have shown no clear effects of magnesium sulphate on neonatal resuscitation,[38,39] and other cardiovascular parameters in the first 24 hours of life,[40] numerous published observational studies have indicated higher risks of some adverse outcomes, necessitating further evaluation.

For example, a retrospective cohort study (of 6,654 women and their babies) has shown increasing maternal serum magnesium concentrations (when given for pre-eclampsia) to be associated with lower one and five-minute Apgar scores, and higher risks of intubation in the delivery room, admission to special care nursery and neonatal hypotonia.[41] Two retrospective cohort studies (of 160 neonates born at less than 28 weeks gestation; and 954 neonates born 500 to 1000 g), and one prospective case-control study (of 48 neonates born 30 to 34 weeks gestation), have shown antenatal magnesium sulphate exposure (when given for pre-eclampsia or for tocolysis) to be associated with an increased risk of neonatal patent ductus arteriosus.[42-44] A recent retrospective cohort study (of 155 neonates born less than 1000 g) has shown magnesium sulphate (when given for cerebral palsy prevention), to be associated with spontaneous intestinal perforation; with higher doses associated with spontaneous intestinal

perforation and death among infants with the lowest birthweights.[45] Observational studies (including retrospective cohort studies and case reports) have shown prolonged magnesium sulphate exposure (when given for tocolysis) to be associated with abnormal bone metabolism for the neonate or infant,[46] and rarely, bone fracture at birth.[47]

Why it is important to conduct a systematic review of adverse effects for the neonate or infant

Strong evidence from randomised trials and systematic reviews supports the use of antenatal magnesium sulphate for cerebral palsy prevention.[3-6,8,48] Rapid translation into clinical practice across Australia and New Zealand has been observed.[20,23,24] Concerns have however been raised surrounding potential neonatal and infant adverse effects of therapy, warranting further evaluation. A systematic review of all available evidence is thus now required in order to determine whether such adverse effects are associated with magnesium sulphate therapy, and if so, whether they vary according to factors such as different regimens for administration, or indications for use. Implementation of antenatal magnesium sulphate for cerebral palsy prevention can be strengthened, and safety improved, if clinical practice guidelines and their recommendations can be based on such knowledge.

AIMS

The primary aim of this systematic review is to assess whether antenatal exposure to magnesium sulphate, given to improve outcomes for mothers or their babies, including for cerebral palsy prevention, is associated with adverse effects for the neonate or infant.

Secondary aims are to assess whether there are variations in adverse effects according to pregnancy and birth characteristics for the women/neonate (such as: indication for use of antenatal magnesium sulphate, antenatal co-interventions, mode of birth, gestational age at birth, and birthweight) or characteristics of the magnesium sulphate regimen received by women (such as: dose, route of administration, timing before birth, and duration of treatment).

METHODS

Research design

Systematic review of adverse effects.

Criteria for considering studies for inclusion

Studies

We will include interventional (e.g. randomised, cluster-randomised, quasi-randomised and non-randomised comparative trials) and observational studies (e.g. cohort, case-control and cross-sectional studies, case series and case reports). We will include studies available as abstract only, along with full-text publications.

Participants

We will include neonates or infants who were exposed to antenatal magnesium sulphate, regardless of their gestational age at exposure or birth.

Interventions and comparators

We will include studies where antenatal magnesium sulphate was given for pre-eclampsia or eclampsia, for tocolysis to women in or following threatened preterm labour, or for neuroprotection of the fetus to women at risk of preterm birth (for cerebral palsy prevention). We will exclude studies where oral magnesium sulphate was given, and where magnesium sulphate was given as an adjuvant during anaesthesia. We will include studies in which magnesium sulphate was compared to no treatment, placebo, or a different magnesium sulphate regimen; and/or, for observational studies, we will include studies in which magnesium sulphate was assessed as an 'exposure.'

Outcomes

Primary: perinatal mortality (defined as stillbirth, neonatal or infant mortality up to the time of primary hospital discharge).

Secondary outcomes for the neonate or infant will be comprehensive, including anticipated or unanticipated adverse effects, such as:

- Stillbirth
- Neonatal or infant death
- Low Apgar scores at one and five minutes
- Need for active resuscitation at birth
- Neonatal respiratory depression
- Neonatal hypotension
- Need for neonatal nursery admission and duration of admission
- Lethargy, hypotonia, or hyporeflexia
- Patent ductus arteriosus
- Spontaneous intestinal perforation
- Osteopenia or bone fractures
- Other unanticipated adverse effects

Search methods

A comprehensive search of the following bibliographic databases will be performed: MEDLINE (PubMed/OVID which includes the Cochrane Library), EMBASE (OVID), CINAHL, Lilacs, Scopus, ISI Web of Science and Toxline, from their inceptions. We will use a combination of MeSH and free-text terms, and will not apply date or language restrictions.

We will search research registers of ongoing trials (clinicaltrials.gov, international clinical trials registry), and search engines Google Scholar and Google using key words. The reference lists of eligible articles or reviews identified will be checked for additional references.

Data collection and synthesis

The methodology for data collection and synthesis will be based on current recommendations of the Cochrane Adverse Effects Methods Group.[49] Where appropriate, the overview will be prepared using CAST[50] and Review Manager Software.[51]

Study selection

After screening all titles and abstracts, we will obtain the full-text article for any study which seems to meet the inclusion criteria based on the title and/or abstract, along with any reviews that may provide relevant references. Each stage will be carried out by two reviewers. We will resolve any discrepancies through discussion, or if required, we will consult a third reviewer.

Data extraction and management

Once a study is included, data will be extracted using a standardised form. Data extracted will include information regarding study design, participants, the magnesium sulphate regimen(s), the control or comparison if applicable, neonatal or infant adverse effects reported and results relevant to the review, the risk of bias, confounding and relevance. Extraction will be carried out by two reviewers independently. We will resolve any discrepancies through discussion, or if required, we will consult a third reviewer.

Quality assessment

The levels of evidence will be assessed using the Australian National Health and Medical Council Levels of Evidence, and the quality (risk of bias) of randomised trials assessed using established guidelines provided in the Cochrane Handbook.[52] The quality assessment of non-randomised studies will be based on recommendations from Cochrane (ACROBAT-NRSI).[53] As it has been suggested that the quality of adverse effect detection and reporting is not always adequately assessed, the methods used to detect adverse effects and how rigorous these methods were, will also be considered, along with incomplete reporting.[54,55]

Data synthesis

The analysis and presentation of results will be categorised by study design, and according to indication for use. Statistical analyses will be performed using Review Manager.[51]

For interventional studies we will present quantitative data from individual studies where possible as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes. For all outcomes, we will carry out analyses as far as possible on an intention-to-treat basis. Pooled estimates (summary RR with 95% CI) will be calculated using fixed-effect meta-analysis where there is a sufficient quantity of data, with clinical homogeneity. Where we consider that there is clinical heterogeneity sufficient to expect that the underlying effects differ between trials, or there is substantial statistical heterogeneity (where I^2 is greater than 30% and either Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test), summary estimates will be calculated using random-effects meta-analysis.

Separate comparisons will be performed for those studies assessing magnesium sulphate versus no treatment or placebo, and those comparing different magnesium sulphate regimens.

For observational studies (e.g. cohort, case-control and cross-sectional studies, and case series) we will present effect estimates where possible as percentages, RR or odds ratios (OR) with 95% CIs, or adjusted RR or OR if reported with 95% CIs, in tabular format based on study type; we will use narrative synthesis to summarise the results. Data from case reports will be tabulated, subsequently grouped according to common outcomes, and summarised narratively.

Analysis of subgroups

Subgroup analyses will be carried out if sufficient data are available based on pregnancy and birth characteristics, and characteristics of the magnesium sulphate regimens:

Characteristics of the pregnancy and birth

- Indication for magnesium sulphate administration (e.g. fetal neuroprotection and cerebral palsy prevention, pre-eclampsia/eclampsia treatment, preterm labour tocolysis, other)
- Gestational age at magnesium sulphate administration (e.g. < 28, 28 to < 32, 32 to < 37, ≥ 37 weeks gestation)
- Birthweight (e.g. < 500, 500 to < 1000, 1000 to < 1500, 1500 to < 2500, 2500 to < 4000, ≥ 4000 g)
- Mode of birth (vaginal birth, caesarean section)
- Concomitant maternal treatment including: antenatal or intrapartum drug therapy (e.g. corticosteroids, tocolytic agents, agents for pain relief).

Characteristics of the magnesium sulphate regimen

- Route of administration of magnesium sulphate (intravenous (IV), intramuscular (IM))
- Concentrated solution requiring dilution or pre-mixed solution
- Dose of magnesium sulphate
    - Loading dose only, loading and maintenance dose, maintenance dose only
    - Loading dose: none, ≤ 4 g, > 4 g
    - Maintenance dose: none, ≤ 1 g/hour IV, > 1 g/hour IV (OR none, ≤ 10 g IM every 4 hours, > 10 g IM every 4 hours)
    - Total dose prior to birth (< 4, 4 to < 14, 14 to < 28, ≥ 28 g)
    - Interval between treatment and birth (0 to < 1, 1 to < 4, 4 to < 8, 8 to < 12, 12 to < 24, ≥ 24 hours)

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S2 Text. Search strategies

CINAHL

Date searched: 30/05/2016; with top-up searches conducted on 10/08/2018 and 03/09/2019
Total records retrieved: **422**

1. (MH "magnesium sulfate+")
2. “magnesium sulfate” or “magnesium sulphate” or mgso4
3. S1 or S1
4. (MH “Prenatal Care”)
5. (MH “Pregnancy+”)
6. (MH “Perinatal Care”)
7. (MH “Maternal Exposure”)
8. (pregnan* or labor or laboring or labour* or antepart* or prenatal* or antenatal* or perinatal* or intranatal* or obstetric* or intrapart* or preterm or prematur* or tocoly* or “maintenance therapy” or preeclamp* or pre-eclamp* or “pre eclamp*” or eclamp* or neuroprotection* or “cerebral palsy”)
9. S4 OR S5 OR S6 OR S7 OR S8
10. (MH "Infant+")
11. (MH "Infant, Newborn, Diseases+")
12. (MH "Intensive Care, Neonatal+")
13. (fetus* or fetal* or foetus* or foetal* or baby or babies or neonat* or infan* or newborn* or “new born”)
14. S10 OR S11 OR S12 OR S13
15. S3 AND S9 AND S14

Cochrane Library

Date searched: 30/05/2016; with top-up search conducted on 10/08/2018 and 03/09/2019
Total records retrieved: **494**

1. MeSH descriptor: [Magnesium Sulfate] explode all trees
2. ((magnesium next sulfate) or (magnesium next sulphate) or MgSO4):ti,ab,kw
3. #1 or #2
4. MeSH descriptor: [Pregnancy] explode all trees
5. MeSH descriptor: [Pregnancy Complications] explode all trees
6. MeSH descriptor: [Prenatal Care] explode all trees
7. MeSH descriptor: [Perinatal Care] explode all trees
8. MeSH descriptor: [Maternal Exposure] explode all trees
9. (pregnan* or labor or laboring or labour* or antepart* or prenatal* or antenatal* or perinatal* or intranatal* or obstetric* or intrapart* or preterm or prematur* or tocoly* or (maintenance NEXT therapy) or preeclamp* or pre-eclamp* or (pre NEXT eclamp*) or eclamp* or neuroprotection* or (cerebral NEXT palsy)):*ti,ab,kw*
10. #4 or #5 or #6 or #7 or #8 or #9
11. MeSH descriptor: [Infant] explode all trees
12. MeSH descriptor: [Infant, Newborn, Diseases] explode all trees
13. MeSH descriptor: [Intensive Care, Neonatal] explode all trees
14. (fetus* or fetal* or foetus* or foetal* or baby or babies or neonat* or infan* or newborn* or (new NEXT born)):*ti,ab,kw*
15. #11 or #12 or #13 or #14
16. #3 and #10 and #15

LILACS

Date searched: 30/05/2016; with top-up search conducted on 10/08/2018 and 03/09/2019
Total records retrieved: **58**

("magnesium sulphate" or "magnesium sulfate" or mgso4) and (fetus$ or fetal$ or foetus$ or foetal$ or baby or babies or neonat$ or infan$ or newborn$ or "new born")

MEDLINE and Embase (OVID)

Date searched: 30/05/2016; with top-up search conducted on 10/08/2018 and 03/09/2019
Total records retrieved: **4044**

1. exp Magnesium Sulfate/
2. ((magnesium adj sulfate) or (magnesium adj sulphate) or MgSO4).mp.
3. or/1-2
4. exp Pregnancy/
5. exp Pregnancy Complications/
6. exp Prenatal Care/
7. exp Perinatal Care/
8. exp Maternal Exposure/
9. (pregnan$ or labor or laboring or labour$ or antepart$ or prenatal$ or antenatal$ or perinatal$ or intranatal$ or obstetric$ or intrapart$ or preterm or prematur$ or tocoly$ or (maintenance adj therapy) or preeclamp$ or pre-eclamp$ or (pre adj eclamp$) or eclamp$ or neuroprotection$ or (cerebral adj palsy)).mp.
10. or/4-9
11. exp Infant/
12. exp Infant, Newborn, Diseases/
13. Intensive Care, Neonatal/
14. (fetus$ or fetal$ or foetus$ or foetal$ or baby or babies or neonat$ or infan$ or newborn$ or (new adj born)).mp.
15. or/11-14
16. 3 and 10 and 15
17. exp Animals/
18. exp Humans/
19. 17 not 18
20. 16 not 19
21. Remove duplicates from 20

TOXLINE

Date searched: 30/05/2016; with top-up search conducted on 10/08/2018 and 03/09/2019
Total records retrieved: **319**

(“magnesium sulphate” OR “magnesium sulphate” OR MgSO4) AND (fetus* or fetal* or foetus* or foetal* or baby or babies or neonat* or infan* or newborn* or “new born”)

Web of Science

Date searched: 30/05/2016; with top-up search conducted on 10/08/2018 and 03/09/2019
Total records retrieved: **553**

1. TS=("magnesium sulphate" OR "magnesium sulphate" OR MgSO4) *Timespan=All years*
2. TS=(fetus* or fetal* or foetus* or foetal* or baby or babies or neonat* or infan* or newborn* or "new born") *Timespan=All years*
3. TS=(pregnan* OR labor OR laboring OR labour* OR antepart* OR prenatal* OR antenatal* OR perinatal* OR intranatal* OR obstetric* OR intrapart* OR preterm OR prematur* OR tocoly* OR "maintenance therapy" OR preeclamp* OR pre-eclamp* OR "pre eclamp*" OR eclamp* OR neuroprotection* OR "cerebral palsy*") *Timespan=All years*
4. #3 AND #2 AND #1 *Timespan=All years*
5. #3 AND #2 AND #1 Refined by: Databases: (BCI OR SCIELO OR WOS OR BIOSIS OR KJD OR CCC OR CABI OR RSCI)

S3 Text. Articles excluded at full-text screening due to absence of English translation

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S4 Text. References for included studies

Randomised controlled trials

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