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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 Precht’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 in-

clude 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 (GMFMS), 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 addition 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: toxoplasmosis (parasite), other infections, rubella, cytomegalovirus, herpes 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 pri-

mary 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. periconceptual 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. periconceptual 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 cere-

bral 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 re-considered 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-

assessment. 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).

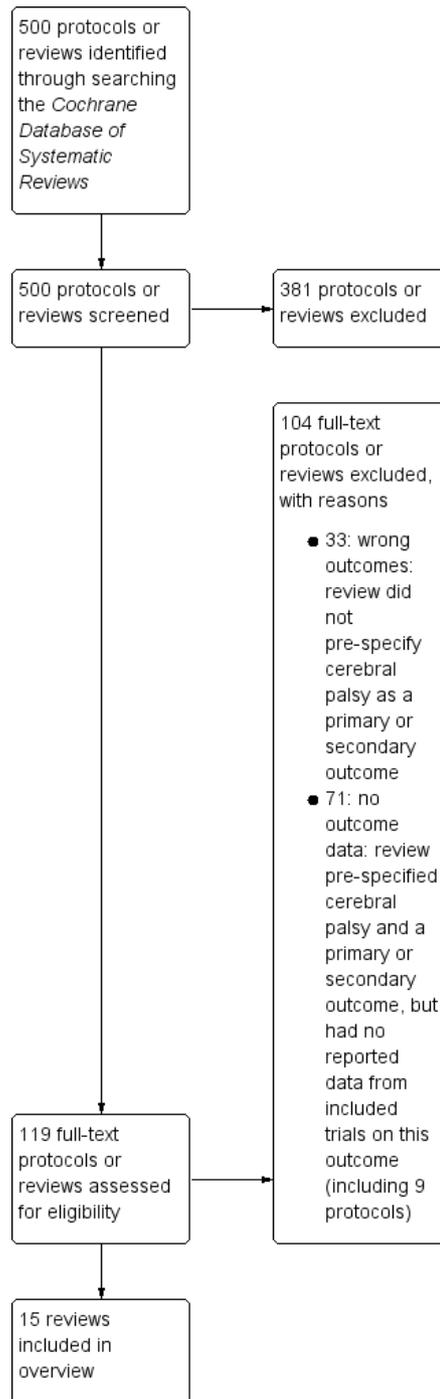
We listed 71 protocols and reviews in the appendices.

- 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 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Neurodevelopment at age two. No outcome data for this outcome.
Buchanan 2010	Secondary neonatal outcomes included: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> • Disability at time of childhood follow-up. No outcome data for this outcome
East 2014	Primary outcomes included: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Any neurological disability at follow-up. No outcome data for this outcome.
Hofmeyr 2015	Primary outcomes included: <ul style="list-style-type: none"> • Perinatal or infant death (excluding fatal anomalies) or disability in childhood. Secondary long-term infant outcomes included: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Neonatal neurodevelopment. No outcome data for this outcome.
Kiiza 2015	Protocol. Secondary baby outcomes will include: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Long-term sequelae: neurologic impairment and chronic lung disease. No outcome data for this outcome.
Thomas 2007	Outcomes included: <ul style="list-style-type: none"> • 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 (pre-specified 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 <ul style="list-style-type: none"> • 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)

<p>Dodd 2013</p>	<p>14 January 2013</p>	<p>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</p>	<p>8523 women and their babies</p>	<p>pregnant women considered to be at increased risk of preterm birth:</p> <ul style="list-style-type: none"> • 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 	<p>progesterone versus placebo or no treatment (11 RCTs, 1899)</p>	<p>cerebral palsy re- ported as a secondary review outcome motor dysfunc- tion, pre- specified as mo- tor impairment, reported as secondary review outcome</p>
<p>Doyle 2009</p>	<p>Search: 31 Au- gust 2008 Up-to-date: 5 November 2008</p>	<p>5 RCTs No. RCTs in: Australia and New Zealand: 1 France: 1 USA: 2 international; 1 (predom- inately in devel- oping countries) RCTs published in: 2000s: 5</p>	<p>5560 women and their 6145 babies</p>	<p>women consid- ered to be at risk of preterm birth</p>	<p>mag- nesium sulphate versus placebo (5 RCTs, 6145 babies)</p>	<p>cerebral palsy; cerebral palsy or death; severity of cerebral palsy (mild, moderate, moderate to se- vere, severe cere- bral palsy); com- posite outcomes includ- ing cerebral palsy (any neurologic impairment; ma- jor neurological disability; death or any neuro- logic im- pairment; death or major neuro-</p>

Table 2. Characteristics of included reviews (Continued)

						<p>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</p>
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Table 2. Characteristics of included reviews (Continued)

						<p>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)</p>
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Table 2. Characteristics of included reviews (Continued)

<p>Duley 2010</p>	<p>Search: 4 June 2010 Up-to-date: 1 September 2010</p>	<p>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</p>	<p>15,570 women and their babies</p>	<p>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</p>	<p>magnesium sulphate versus placebo or no anticonvulsant (6 RCTs, 11,444 women)</p>	<p>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'</p>
<p>Flenady 2013</p>	<p>Search: 31 August 2013 Up-to-date: 3 October 2013</p>	<p>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</p>	<p>7837 women and their babies</p>	<p>women thought to be in preterm labour with intact membranes, between 20 and 36 completed weeks of gestation</p>	<p>any antibiotics versus no antibiotics (14 RCTs, 7837 women)</p>	<p>cerebral palsy reported as a primary review outcome pre-specified outcome was 'major long-term infant neurosensory impairment'</p>
<p>Magee 2003</p>	<p>Search: 4 July 2012 (<i>results added to Studies awaiting classification</i>) Up-to-date: 30 January 2004</p>	<p>29 RCTs No. RCTs in: Argentina: 1 Australia: 2 Brazil: 1 England: 5 Fr Caribbean: 1 France: 3</p>	<p>2548 women and their babies</p>	<p>women with mild to moderate hypertension during pregnancy, however defined</p>	<p>beta-blockers versus placebo or no beta-blocker (13 RCTs, 1480 women)</p>	<p>Cerebral palsy reported as a review outcome, rather than primary or secondary pre-specified</p>

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

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

Crowther 2014	<p>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”</p>
Crowther 2015	<p>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”</p>
Dodd 2013	<p>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”</p>
Doyle 2009	<p>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”</p>
Duley 2010	<p>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”</p>
Flenady 2013	<p>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)</p>

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

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

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)

Alfirevic 2013	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUALITY
Churchill 2013	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUALITY
Crowther 2010	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUALITY
Crowther 2010a	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUALITY
Crowther 2014	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11/11 HIGH QUALITY
Crowther 2015	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11/11 HIGH QUALITY
Dodd 2013	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUALITY
Doyle 2009	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	9/11 HIGH QUALITY
Duley 2010	✓	✓	✓	✓	✓	✓	✓	✓	?	×	×	8/11 HIGH QUALITY
Flenady 2013	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUALITY

Table 4. AMSTAR assessments for included reviews (Continued)

Magee 2003	✓	✓	✓	✓	✓	✓	✓	✓	?	×	×	8/11 HIGH QUAL- ITY
Neilson 2014	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	10/11 HIGH QUAL- ITY
Roberts 2006	✓	✓	✓	✓	✓	✓	✓	✓	?	×	✓	9/11 HIGH QUAL- ITY
Stock 2016	✓	✓	✓	✓	✓	✓	✓	✓	N/A	✓	×	9/10 HIGH QUAL- ITY

✓: 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 criteria	eligibility	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 quadri-paresis with a severe pseudo-bul-bar 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 RCTs	(2)	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							
Pre-natal administration of progesterone 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 fetal maturation or neuroprotection							
Phenobarbital versus placebo or no treatment prior to preterm birth for preventing neonatal periventricular	Cerebral palsy at 18 months to 3 years <ul style="list-style-type: none"> 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)

<p>ular haemorrhage (Crowther 2010a)</p>	<p>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</p> <ul style="list-style-type: none"> • 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) 						<p>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</p>
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Table 6. Summary of findings: all comparisons measuring cerebral palsy (Continued)

<p>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)</p>	<p>Cerebral palsy at 7 years, definition not clear; method of assessment not clear</p>	<p>79 per 1000 (12/151)</p>	<p>61 per 1000 (26 to 140)</p>	<p>RR 0.77 (95% CI 0.33 to 1.76)</p>	<p>299 (1 RCT)</p>	<p>VERY LOW</p>	<p>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</p>
<p>Magnesium sulphate versus placebo for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009)</p>	<p>Cerebral palsy at 18 months to 2 years</p> <ul style="list-style-type: none"> • 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 	<p>50 per 1000 (154/3093)</p>	<p>34 per 1000 (27 to 43)</p>	<p>RR 0.68 (95% CI 0.54 to 0.87)</p>	<p>6145 (5 RCTs)</p>	<p>HIGH</p>	<p>Not downgraded</p>

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

	<p>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</p> <ul style="list-style-type: none"> • 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 						
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Table 6. Summary of findings: all comparisons measuring cerebral palsy (Continued)

	<ul style="list-style-type: none"> ● 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 						
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Table 6. Summary of findings: all comparisons measuring cerebral palsy (Continued)

<p>Antenatal corticosteroids versus placebo for accelerating fetal lung maturation for women at risk of preterm birth (Roberts 2006)</p>	<p>Cerebral palsy at 2 to 6 years</p> <ul style="list-style-type: none"> • 1 RCT: defined as any of hemiparesis, diplegia, tetraplegia, quadriplegia; assessed using detailed physical and neurologic examination (including of motor coordination) 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) 	<p>68 per 1000 (28/414)</p>	<p>41 per 1000 (23 to 70)</p>	<p>RR 0.60 (95% CI 0.34 to 1.03)</p>	<p>904 (5 RCTs)</p>	<p>LOW</p>	<p>study limitations (-1): 2 RCTs with unclear and 1 RCT with inadequate allocation concealment imprecision (-1): wide confidence intervals crossing line of no effect</p>
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Table 6. Summary of findings: all comparisons measuring cerebral palsy (Continued)

<p>Repeat doses of corticosteroids versus single course for women at risk of preterm birth (Crowther 2015)</p>	<p>Cerebral palsy at 18 months to 3 years</p> <ul style="list-style-type: none"> • 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 	<p>27 per 1000 (52/1891)</p>	<p>28 per 1000 (20 to 41)</p>	<p>RR 1.03 (95% CI 0.71 to 1.50)</p>	<p>3800 RCTs)</p>	<p>(4 MODERATE</p>	<p>imprecision (-1); wide confidence intervals crossing line of no effect</p>
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Table 6. Summary of findings: all comparisons measuring cerebral palsy (Continued)

	<p>Rosenbaum 2007; assessed by paediatric neurologist or paediatrician using specific neurological examination at 2 years</p> <ul style="list-style-type: none"> • 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 fetal compromise							
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 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 RCT)	(1	Chi ² = 1.52, df = 1 (P = 0.22), I ² = 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 RCT)	(1	
		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 RCTs)	(2	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 RCTs)	(2	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 RCT)	(1	Chi ² = 1.52, df = 1 (P = 0.22), I ² = 34%
			Unclear	77 per 1000	195 per 1000 (85 to 451)	RR 2.54 (95% CI 1.10 to 5.86)	173 RCT)	(1	
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 RCT)	(1	Not applicable
Prophylactic antibiotics versus no antibiotics for inhibit-	Cerebral palsy at 7 years	Type of antibiotic	Beta-lactams alone	16 per 1000	19 per 1000 (6 to 57)	Average RR 1.22 (95% CI 0.41 to 3.63)	1049 RCT)	(1	Chi ² = 1.41, df = 2 (P = 0.49), I ² = 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 RCT)	(1	
			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 RCT)	(1	
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 RCT)	(1	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 RCT)	(1	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 RCTs)	(2	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 RCT)	(1	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 RCTs)	(4	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 RCT)	(1	

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 RCTs	(1		
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 RCTs	(2	Chi ² = 1.28, df = 1 (P = 0.26), I ² = 22.	
	Multiple	53 per 1000	28 per 1000 (11 to 67)	RR 0.52 (95% CI 0.21 to 1.25)	527 RCTs	(2		
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 RCTs	(5	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 RCTs	(2		
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 RCTs	(4	Chi ² = 1.33, df = 1 (P = 0.25), I ² = 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 RCTs	(1		
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 RCTs	(2	Chi ² = 0.44, df = 1 (P = 0.51), I ² = 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 RCTs	(3		
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 RCTs	(2	Chi ² = 2.94, df = 3 (P = 0.40), I ² = 0% (Performed by overview authors)	
	Loading dose (4 g)	33 per 1000	27 per 1000 (18 to 41)	average RR 0.81 (95% CI 0.51 to 1.25)	2848 RCTs	(2		

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 RCT)	(1	
			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 RCT)	(1	
		Retreatment permitted	Yes	59 per 1000	35 per 1000 (24 to 50)	RR 0.59 (95% CI 0.40 to 0.85)	2444 RCT)	(1	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 RCTs)	(3	
			Unclear	38 per 1000	35 per 1000 (8 to 170)	RR 0.94 (95% CI 0.20 to 4.53)	165 RCT)	(1	
			High antenatal corticosteroids	66 per 1000	44 per 1000 (35 to 56)	RR 0.67 (95% CI 0.53 to 0.86)	4493 RCTs)	(4	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 RCTs)	(2	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 RCTs	(2	Chi ² = 1.05, df = 2 (P = 0.59), I ² = 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 RCT	(1			
	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 RCTs	(2				

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 fetal maturation 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 fetal maturation 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 <ul style="list-style-type: none"> 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)

<ul style="list-style-type: none"> 1 RCT: definition not clear; paediatricians evaluated motor function at 2 years; if examination was not possible, parent telephone interview was used 							
<p>Moderate cerebral palsy at 2 years</p> <ul style="list-style-type: none"> 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 RCTs	(2)	MODERATE	imprecision (-1); wide confidence intervals crossing line of no effect
<p>Moderate to severe cerebral palsy at 2 years</p> <ul style="list-style-type: none"> 1 RCT: 	32 per 1000 (72/2218)	21 per 1000 (14 to 30)	RR 0.64 (95% CI 0.44 to 0.92)	4387 RCTs	(3)	HIGH	not downgraded

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

<p>definition: not walking at 2 years but likely to do so (moderate); not likely to walk (severe); assessed by developmental paediatrician at 2 years</p> <ul style="list-style-type: none"> • 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 								
<p>Severe cerebral palsy at 2 years</p> <ul style="list-style-type: none"> • 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 RCTs)	(2	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							
<ul style="list-style-type: none"> 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 'neurosensory 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 fetal maturation 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 RCTs	(2)	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 RCTs	(2)	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 RCTs	(2)	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: <ul style="list-style-type: none"> • 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 RCTs	(2	HIGH	not downgraded

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

	<p>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)</p> <ul style="list-style-type: none"> • 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 RCTs	(2) 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)

	<p>as:</p> <ul style="list-style-type: none"> • 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) 						<p>attrition bias and high risk of other bias inconsistency (-1): substantial heterogeneity ($I^2 = 88%$)</p>
	<p>Major neurosensory disability at 2 to 3 years, defined as:</p> <ul style="list-style-type: none"> • 1 RCT: definition: severe or moderate neurosensory disability: severe neurosensory 	<p>110 per 1000 (71/643)</p>	<p>119 per 1000 (34 to 415)</p>	<p>Average RR 1.08 (95% CI 0.31 to 3.76)</p>	<p>1256 RCTs</p>	<p>(2) LOW</p>	<p>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-</p>

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

	<p>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</p> <ul style="list-style-type: none"> • 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) 						<p>ing line of no effect</p>
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Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component
(Continued)

	<p>Disability at 2 years, defined as:</p> <ul style="list-style-type: none"> • 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
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Table 10. Summary of findings: all comparisons measuring other composite outcomes that include cerebral palsy as a component
(Continued)

<p>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)</p>						
<p>Composite serious outcome at 18 months to 2 years, defined as:</p> <ul style="list-style-type: none"> • 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; 	<p>227 per 1000 (356/1571)</p>	<p>224 per 1000 (197 to 254)</p>	<p>RR 0.99 (95% CI 0.87 to 1.12)</p>	<p>3164 RCTs</p>	<p>(2) HIGH</p>	<p>not downgraded</p>

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

	<p>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)</p> <ul style="list-style-type: none"> • 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) 						
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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 fetal compromise							
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
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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							
Pre-natal 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 neuro-motor 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 RCTs)	(4	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 RCTs)	(4	MODERATE	inconsistency (-1): substantial heterogeneity ($I^2 = 65%$)

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

APPENDICES

Appendix I. Ongoing reviews

Protocol citation	Overview of pre-specified outcomes in protocol
Amorim 2011	<p>Secondary pre-specified perinatal and neonatal outcomes include:</p> <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2012, Issue 4	<p>Primary pre-specified outcomes for the baby include:</p> <ul style="list-style-type: none"> • Serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood). <p>Secondary pre-specified outcomes for the baby include:</p> <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2016, Issue 1	<p>Primary pre-specified outcomes for the infant include:</p> <ul style="list-style-type: none"> • Major neurodevelopmental disability at childhood follow-up. <p>Secondary pre-specified outcomes for the child include:</p> <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2012, Issue 1	<p>Secondary pre-specified outcome for the child include:</p> <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2012, Issue 11	<p>Secondary pre-specified outcomes for the child include:</p> <ul style="list-style-type: none"> • 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.

(Continued)

Haruna M, Matsuzaki M, Ota E, Shiraishi M, Hanada N, Mori R. Guided imagery for treating hypertension in pregnancy. <i>Cochrane Database of Systematic Reviews</i> 2014, Issue 10	Secondary pre-specified outcomes for the neonate include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2015, Issue 5	Secondary pre-specified outcomes for the child include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2016, Issue 3	Secondary pre-specified outcomes for the child include: <ul style="list-style-type: none"> • Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy.
Martis R, Emilia O, Nurdianti DS. Intermittent auscultation (IA) of fetal heart rate in labour for fetal well-being. <i>Cochrane Database of Systematic Reviews</i> 2010, Issue 9	Secondary pre-specified outcomes for the baby include: <ul style="list-style-type: none"> • Cerebral palsy.

Appendix 2. Reviews awaiting further classification

Review citation	Overview of pre-specified outcomes in review with no outcome data	Main conclusion(s) of review
Abdel-Latif 2010	Primary outcomes include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2013, Issue 8	Secondary outcomes for the infant/child include: <ul style="list-style-type: none"> • 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 con-

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		trol 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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, Crowther CA, et al. Interventions for managing asthma in pregnancy. Cochrane Database of Systematic Reviews 2014, Issue 10	Secondary outcomes for the infant, child, and for the child as an adult include: <ul style="list-style-type: none">• 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).	“Based on eight included trials, of moderate quality overall, no firm conclusions about optimal interventions for managing asthma in 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 pharma-

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		<p>cist-led management, the evidence to date is insufficient to draw definitive conclusions</p> <p>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.”</p>
<p>Bricker L, Reed K, Wood L, Neilson JP. Nutritional advice for improving outcomes in multiple pregnancies. <i>Cochrane Database of Systematic Reviews</i> 2015, Issue 11</p>	<p>Secondary outcomes for the child include:</p> <ul style="list-style-type: none">• Cerebral palsy.	<p>No included trials.</p> <p>“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.”</p>
<p>Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in pregnancy. <i>Cochrane Database of Systematic Reviews</i> 2013, Issue 1</p>	<p>Secondary outcomes for the neonate include:</p> <ul style="list-style-type: none">• Cerebral palsy at childhood follow-up.	<p>“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 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.”</p>
<p>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. <i>Cochrane Database of Systematic Reviews</i> 2013, Issue 8</p>	<p>Primary outcomes for the child include:</p> <ul style="list-style-type: none">• 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). <p>Primary outcomes for the child as an adult</p>	<p>“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 betametha-</p>

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	<p>include:</p> <ul style="list-style-type: none">● 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. <p>Secondary outcomes for the child include:</p> <ul style="list-style-type: none">● Cerebral palsy (however defined by authors);	<p>sone, 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.”</p>
<p>Chawanpaiboon S, Laopaiboon M, Lumbiganon P, Sangkomkarn US, Dowswell T. Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes. <i>Cochrane Database of Systematic Reviews</i> 2014, Issue 3</p>	<p>Secondary outcomes for the neonate include:</p> <ul style="list-style-type: none">● Neurological sequelae (general intelligence, hearing, vision, cerebral palsy, and disability).	<p>“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.”</p>
<p>Cluett ER, Burns E. Immersion in water in labour and birth. <i>Cochrane Database of Systematic Reviews</i> 2009, Issue 2</p>	<p>Primary outcomes for the neonate include:</p> <ul style="list-style-type: none">● Neurological pathology, e.g. seizures, cerebral palsy.	<p>“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 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.”</p>
<p>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. <i>Cochrane Database of Systematic Reviews</i> 2012, Issue 2</p>	<p>Primary outcomes for the infant include:</p> <ul style="list-style-type: none">● 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.	<p>“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. Further-</p>

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	<p>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).</p>	<p>more, 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.”</p>
<p>Dickinson H, Bain E, Wilkinson D, Middleton P, Crowther CA, Walker DW. Creatine for women in pregnancy for neuroprotection of the fetus. <i>Cochrane Database of Systematic Reviews</i> 2014, Issue 12</p>	<p>Primary outcomes for the infant and child include:</p> <ul style="list-style-type: none">• 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). <p>Secondary outcomes for the infant/child include:</p> <ul style="list-style-type: none">• 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).• 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).	<p>No included trials.</p> <p>“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 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.”</p>
<p>Dodd JM, Dowswell T, Crowther CA. Specialised antenatal clinics for women with a multiple pregnancy for improving maternal and infant outcomes. <i>Cochrane Database of Systematic Reviews</i> 2015, Is-</p>	<p>Secondary outcomes for the infant include:</p> <ul style="list-style-type: none">• Disability at childhood follow-up (including deafness, blindness, neurodisability, or cerebral palsy).	<p>“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’ ante-</p>

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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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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

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		a matter of personal preference.”
Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. <i>Cochrane Database of Systematic Reviews</i> 2007, Issue 2	Outcomes for the child include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2010, Issue 12	Secondary outcomes for the child include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2010, Issue 8	Secondary outcomes for the baby include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2013, Issue 7	Secondary outcomes for the child include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 1999, Issue 4	Outcomes for the baby include: <ul style="list-style-type: none"> • 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. <i>Cochrane Database of Systematic Reviews</i> 2014, Issue 6	Primary outcomes include: <ul style="list-style-type: none"> • 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 	“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

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	<p>cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient (DQ) or intelligence quotient (IQ) less than two standard deviations below mean))).</p>	<p>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.”</p>
<p>Flenady V, Wojcieszek AM, Papatsonis DNM, Stock OM, Murray L, Jardine LA, et al. Calcium channel blockers for inhibiting preterm labour and birth. <i>Cochrane Database of Systematic Reviews</i> 2014, Issue 6</p>	<p>Primary outcomes include:</p> <ul style="list-style-type: none">• 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 (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))). <p>Secondary outcomes for the infant or child include:</p> <ul style="list-style-type: none">• Blindness, deafness, cerebral palsy.	<p>“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 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</p>

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		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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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 threatened preterm labor. Cochrane Database of Systematic Reviews 2015, Issue 11	Secondary outcomes for the fetus, neonate, or infant include: <ul style="list-style-type: none">• 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 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))).	“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 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: <ul style="list-style-type: none">• 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

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		<p>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</p>
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		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: <ul style="list-style-type: none">• 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, Sangkomkarn US. Cyclo-oxygenase (COX) inhibitors for preventing preterm labour. Cochrane Database of Systematic Reviews 2012, Issue 10	Secondary neonatal outcomes include: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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.”

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<p>McNamara HC, Crowther CA, Brown J. Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour. <i>Cochrane Database of Systematic Reviews</i> 2015, Issue 12</p>	<p>Primary outcomes for the infant or child include:</p> <ul style="list-style-type: none">• 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 leuco malacia (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)). <p>Secondary outcomes for the child include:</p> <ul style="list-style-type: none">• Cerebral palsy (mild, moderate, or severe, evaluated separately).	<p>“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 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</p>
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		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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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.”

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<p>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</p>	<p>Primary outcomes include:</p> <ul style="list-style-type: none"> • Any neurological disability at paediatric follow-up (impairment of vision, hearing, intelligence, or cerebral palsy). 	<p>“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.”</p>
<p>Nanda K, Cook LA, Gallo MF, Grimes DA. Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth. Cochrane Database of Systematic Reviews 2002, Issue 4</p>	<p>Outcomes for the infant include:</p> <ul style="list-style-type: none"> • Neurological sequelae (general intelligence, hearing, vision, cerebral palsy, and disability). 	<p>“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.”</p>
<p>Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database of Systematic Reviews 2015, Issue 12</p>	<p>Secondary outcomes for the fetus include:</p> <ul style="list-style-type: none"> • Cerebral palsy. 	<p>“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.”</p>
<p>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</p>	<p>Primary outcomes for the infant or child include:</p> <ul style="list-style-type: none"> • Death or cerebral palsy. • Cerebral palsy (abnormality of tone with motor dysfunction (as diagnosed at 18 months of age or later)). <p>Secondary outcomes for the child include:</p> <ul style="list-style-type: none"> • Any neurological disabilities (defined as developmental delay or intellectual impairment, blindness (corrected visual acuity worse than 6/60 in the better eye), 	<p>“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</p>

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	<p>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 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.</p> <ul style="list-style-type: none"> • 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)). 	<p>also require evaluation.”</p>
<p>Ohlsson A, Shah VS, Stade BC. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. <i>Cochrane Database of Systematic Reviews</i> 2014, Issue 12</p>	<p>Secondary intellectual impairment outcomes include:</p> <ul style="list-style-type: none"> • Long-term neurological sequelae, which may include cognitive delay, cerebral palsy, cortical blindness, deafness, hydrocephalus, or a combination. 	<p>“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.</p>

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		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. Cochrane Database of Systematic Reviews 2013, Issue 10	Primary outcomes include: <ul style="list-style-type: none">• 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, cerebral palsy, or developmental delay or intellectual impairment).	“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, 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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 MgSO ₄ , 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 to-

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		colytic 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Cerebral palsy. 	No included trials. “Monoamniotic twins are rare, and there is insufficient randomised controlled evidence on which to draw strong conclusions

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		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 thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. <i>Cochrane Database of Systematic Reviews</i> 2015, Issue 9	Primary outcomes for the infant as a child include: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• Cerebral palsy.	“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 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. <i>Cochrane Database of Systematic Reviews</i> 2015, Issue 6	Secondary outcomes for the neonate pre-specified include: <ul style="list-style-type: none">• 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)

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		. 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 	"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

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	<p>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).</p>	<p>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.”</p>
<p>Waterfall H, Grivell RM, Dodd JM. Techniques for assisting difficult delivery at caesarean section. Cochrane Database of Systematic Reviews 2016, Issue 1</p>	<p>Secondary outcomes for the infant include:</p> <ul style="list-style-type: none">• Cerebral palsy.	<p>“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.”</p>
<p>Whitworth M, Quenby S. Prophylactic oral betamimetics for preventing preterm labour in singleton pregnancies. Cochrane Database of Systematic Reviews 2008, Issue 1</p>	<p>Primary outcomes include:</p> <ul style="list-style-type: none">• 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).	<p>“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.”</p>
<p>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</p>	<p>Secondary outcomes for the infant include:</p> <ul style="list-style-type: none">• Disability at childhood follow-up (including deafness, blindness, neurodisability, or cerebral palsy).	<p>“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.”</p>

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<p>Wilkinson D, Shepherd E, Wallace EM. Melatonin for women in pregnancy for neuroprotection of the fetus. Cochrane Database of Systematic Reviews 2016, Issue 3</p>	<p>Primary outcomes for the infant or child include:</p> <ul style="list-style-type: none">• 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. <p>Secondary outcomes for the infant or child include:</p> <ul style="list-style-type: none">• 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).• 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).	<p>No included trials.</p> <p>“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 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.”</p>
<p>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</p>	<p>Secondary outcomes for the child include:</p> <ul style="list-style-type: none">• Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay, and cerebral palsy.	<p>“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.”</p>

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Yamasmit W, Chaithongwongwathana 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: <ul style="list-style-type: none">• 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.”
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Key (in order of appearance)

FENO-based - Fractional exhaled nitric oxide-based algorithm
PMR - progressive muscle relaxation
PTB - preterm birth
IVH - intraventricular haemorrhage
NICU - neonatal intensive care unit
CCB - calcium channel blockers
hPL - human placental lactogen
GBS - Group B Streptococcus
MgSO₄ - magnesium sulphate
PROM - preterm rupture of membranes

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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INDEX TERMS

Medical Subject Headings (MeSH)

*Parturition; Antibiotic Prophylaxis; Cerebral Palsy [epidemiology; *prevention & control]; Fetal Distress [therapy]; Hypertension [therapy]; Infant, Premature; Magnesium Sulfate [therapeutic use]; Neuroprotective Agents [therapeutic use]; Pre-Eclampsia [therapy]; Pregnancy Complications, Cardiovascular [therapy]; Premature Birth [prevention & control]; Prenatal Care [*methods]; Randomized Controlled Trials as Topic; Review Literature as Topic

MeSH check words

Female; Humans; Pregnancy