Version

This is the publisher’s version. This version is defined in the NISO recommended practice RP-8-2008 http://www.niso.org/publications/rp/

Suggested Reference


Copyright

Items in ResearchSpace are protected by copyright, with all rights reserved, unless otherwise indicated. Previously published items are made available in accordance with the copyright policy of the publisher.

This Protocol of a Cochrane Review was published in the Cochrane Database of Systematic Reviews 2016, 2. Cochrane Protocols and Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the Protocol.

For more information, see General copyright, Publisher copyright, SHERPA/RoMEO.
Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews (Protocol)

Shepherd E, Middleton P, Makrides M, McIntyre SJ, Badawi N, Crowther CA


www.cochranelibrary.com
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>1</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>5</td>
</tr>
<tr>
<td>METHODS</td>
<td>5</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>8</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>9</td>
</tr>
<tr>
<td>WHAT’S NEW</td>
<td>11</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>12</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>12</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>12</td>
</tr>
</tbody>
</table>
Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews

Emily Shepherd¹, Philippa Middleton¹,², Maria Makrides², Sarah J McIntyre³, Nadia Badawi⁴, Caroline A Crowther¹,⁵

¹ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. ²Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, Adelaide, Australia. ³Cerebral Palsy Alliance, The University of Sydney, Sydney, Australia. ⁴Grace Centre for Newborn Care, The Children’s Hospital at Westmead, Sydney, Australia. ⁵Liggins Institute, The University of Auckland, Auckland, New Zealand

Contact address: Emily Shepherd, ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, South Australia, 5006, Australia. emily.shepherd@adelaide.edu.au.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2016.


Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

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 aetiology or pathology. Discussion regarding the definition and classification was first recorded in English, French and German medical literature in the nineteenth century; for over 150 years, exactly what the term ‘cerebral palsy’ describes has been debated (Morris 2007). Definitions adopted by cerebral palsy registries internationally 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 muscu-
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 more than 28 days after birth and before the age of two to five; commonly, a cerebrovascular accident, spontaneous, associated with surgery or with complications of cardiac defects, or accidental and non-accidental head injuries (ACPR Group 2013). For the remaining over 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 known to be complex and multifactorial, with interrelated pathways contributing to cellular dysfunction and death, including accumulation of reactive oxygen species, the release of excitatory amino acids, energy depletion and apoptosis (Inder 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 other hearing, sight, and speech 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...
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).

In regards to life expectancy, 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 regards to survival trends overall has to date been presented, some improvements over time in survival have been observed 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).

Frequently used definitions for cerebral palsy today 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

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

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
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 EURO860,000 for men and EURO800,000 for women in Denmark (in 2000) (Kruse 2009), and $US921,000 for individuals in the United States (in 2003) (CDC 2004). In Australia, the financial cost of cerebral palsy was estimated $AU1.47 billion (in 2007); the value of lost well being (disability and premature death) was a further $AU2.4 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, the identification of primary preventive measures continues to be a key priority, as recognised by individuals with cerebral palsy and their families, clinicians and researchers (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 also by clinical subtype of cerebral palsy (Nelson 2008), it is reasonable to consider that successful primary preventive interventions may therefore also vary according to different aetiologies/cause 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 and/or maternal intrauterine infection and fetal systemic inflammation; quadriplegic cerebral palsy, especially with dyskinesia, is a subtype of cerebral palsy sometimes related to acute asphyxia during the birth process (Nelson 2008).

Primary preventive interventions may include public health strategies for the general population (e.g. periconceptional folic acid 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 2015). In this overview, therefore, we will include a broad range of antenatal and intrapartum interventions† (with varying primary aims/indications) that may mediate cerebral palsy risk (the examples presented below are not an exhaustive list), including:

- nutrition interventions in pregnancy, e.g. periconceptional folate supplementation; marine oil and other prostaglandin precursors; vitamins C and E;
- behaviour/advice interventions in pregnancy, e.g. for reducing alcohol/drug consumption; for supporting smoking cessation; for promoting hand-washing;
- interventions for predicting preterm birth 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 therapy and/or 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/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/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 programs;
- interventions for infection during pregnancy, e.g. prevention and treatment of viral infections (TORCH: toxoplasmosis (parasite), other infections, rubella, cytomegalovirus and herpes simples); interventions for urinary tract infections; interventions for other vaginal infections (i.e. bacterial vaginosis);
- interventions for preterm/term prelabour 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 cerebral palsy prevention.

**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; Oskouie 2013), it is possible that interventions to prolong gestation or reduce the risk of preterm birth will also reduce the risk of cerebral palsy (Chang 2015; O’Shea 2008). Specific approaches, supported by high level evidence, for prolonging pregnancy and/or preventing preterm birth include: interventions for primary prevention of preterm birth (e.g. smoking cessation programs 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 cerebral palsy risk. 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 antenatally administered drug with the potential to mediate cerebral palsy risk through protecting the developing fetal brain from injury, such as from intraventricular haemorrhage (Chang 2015; Nelson 2008; O’Shea 2008). Beyond antenatal corticosteroids and magnesium sulphate, a range of other potential 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 cerebral palsy risk (Chang 2015; Robertson 2012).

There are numerous other antenatal and intrapartum interventions with potential to contribute to cerebral palsy prevention for preterm and term infants, which may work through modifying known risk factors for cerebral palsy; for example: identification and subsequent management of maternal thyroid dysfunction (both hypo- and hyper-thyroidism) in pregnancy; identification and treatment of hypertension and pre-eclampsia in pregnancy; identification and management of perinatal infections (including chorioamnionitis) in pregnancy; and fetal monitoring (IA, CTG, ECG, fetal pulse oximetry) in labour for early recognition/prevention of birth asphyxia.

**Why it is important to do this overview**

A multitude of individual studies and Cochrane systematic reviews assessing a broad range of antenatal or intrapartum interventions (with varying primary aims/indications) recognise the potential for the intervention of interest to mediate cerebral palsy risk. With the acknowledgement that a multiplicity of risk factors impact on cerebral palsy risk, and thus, 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, to date, no ‘overview’ has brought together the evidence around interventions for cerebral palsy prevention from Cochrane systematic reviews together into one coherent document to be used by researchers, funding bodies, policy makers, clinicians and consumers to aid decision making and evidence implementation.

**OBJECTIVES**

The objective of this overview is to summarise the evidence from Cochrane systematic reviews regarding the effects of antenatal and intrapartum interventions for preventing cerebral palsy; and further, 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 of Cochrane systematic reviews, we will include only Cochrane systematic reviews of antenatal or intrapartum interventions, as long as cerebral palsy is reported as a primary or secondary review outcome. Cochrane protocols and titles will be
identified for future inclusion, and classified as 'Ongoing reviews' (in an Appendix).

We will make note of the publication and search dates of the reviews, however, we will not attempt to update the individual Cochrane systematic reviews. We will contact the Cochrane Pregnancy and Childbirth Editorial Base to identify any relevant new reviews or review updates that are being undertaken and/or near completion, in order to include the most up-to-date versions of the reviews, if and where possible.

Participants
We will consider reviews assessing interventions in pregnant women.

Interventions
We will consider all types of interventions used in the antenatal or intrapartum period for preventing cerebral palsy, compared with placebo, no treatment, or an alternative intervention.

We will include, for example, the following: pharmacological interventions, medical interventions, nutritional interventions, behavioural interventions, educational interventions (see Description of the interventions for further description of possible interventions).

Outcomes of interest

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

Secondary
- Cerebral palsy and death (e.g. in early childhood, and at the latest time point measured).
- Other composite outcomes that include cerebral palsy as a component.
- Severity of cerebral palsy (e.g. according to: Gross Motor Function Classification System (GMFCS); Manual Ability Classification System (MACS); Communication Function Classification System (CFCS)).
- 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/early childhood, and at the latest time point measured) (however defined by review authors/trialists)

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

Reviews that pre-specify cerebral palsy and a primary or secondary systematic review outcome, but have no reported data from included trials on this outcome, will be included as ‘Reviews awaiting further classification’ (and their results summarised in an Appendix), and will be re-considered in future updates of the overview.

*Wherever possible, we will extract data related to the cerebral palsy from any composite outcomes that include cerebral palsy. Where it is not possible to extract only the cerebral palsy data from such composite outcomes, we will report the composite outcome data; however we will report it separately to the data for our primary outcome (i.e. as a secondary outcome).

Search methods for identification of reviews
We will search the Cochrane Database of Systematic Reviews using the term: 'cerebral palsy.' The search term will be used to search 'all text', and not limited to 'title, abstract, or keywords'. We will not apply any language or date restrictions. No other databases will be searched. Citations retrieved through the search will be managed using Covidence (Covidence 2015).

Data collection and analysis
The methodology for data collection and synthesis will be based on Chapter 22 of the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2011). Where appropriate, the overview will be prepared using Covidence (Covidence 2015) and Review Manager Software (RevMan 2014).

Selection of reviews
Two overview authors will independently assess for inclusion all potential systematic reviews we identify that assess the effects of antenatal or intrapartum interventions and report on cerebral palsy. We will resolve any disagreement through discussion or, if required, we will consult a third member of the overview team.

Data extraction and management
Two overview authors will independently extract data from the reviews using a pre-defined data extraction form. We will resolve discrepancies through discussion or, if needed, through discussion with a third overview author. If any information from the reviews is unclear or missing, we will access the published papers of the individual studies. If the information cannot be obtained from the published papers, we will contact the individual review authors or authors of the original papers for further details.
Information will be extracted on the following.

• Review characteristics:
  ○ review title and authors;
  ○ date that the review was last assessed as up-to-date;
  ○ number of included trials, and number of participants (women and infants) in the trials and their characteristics (e.g. countries where the trials were conducted and inclusion criteria in the trials);
  ○ quality of the included trials (as reported by the review authors; see 'Quality of included studies within reviews' below under 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 'Quality of included reviews' under: 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) from comparisons and for outcomes relevant to this overview;
  ○ information required to assess and report on the quality of the evidence for the intervention effects extracted above (see 'Quality of evidence in included reviews' under: Assessment of methodological quality of included reviews).

*Where reviews were not able to perform meta-analyses and therefore did not report statistical summaries, we plan to extract from those reviews the narrative text relating to the results for our overview outcomes.

Assessment of methodological quality of included reviews

Quality of included reviews

We will assess 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, and the way they will assess review quality, are as follows.

• Was an ‘a priori’ design provided?
• Was there duplicate study selection and data extraction?
• Was a comprehensive literature search performed?
• Was the status of publication used as an inclusion criterion?
• Was a list of studies (included and excluded) provided?
• Were the characteristics of the included studies provided?
• Was the scientific quality of the included studies assessed and documented?
• Was the scientific quality of the included studies used appropriately in formulating conclusions?
• Were the methods used to combine the findings of studies appropriate?
• Was the likelihood of publication bias assessed?
• Was the conflict of interest stated?

For all items except item 4, a rating of ‘yes’ is considered adequate. For item 4, a rating of ‘no’ is considered adequate. A review that adequately meets all of the 11 criteria is considered to be a review of the highest quality. For this overview, we will consider reviews that achieve 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 will additionally use the new ROBIS (Risk Of Bias In Systematic reviews) tool (Whiting 2014). The tool considers risk of bias across four key domains.

• Study eligibility criteria.
• Identification and selection of studies.
• Data collection and study appraisal.
• Synthesis and findings.

A series of questions within each of the domains elicit information about possible limitations of the systematic review, leading to a judgement about the concerns within that domain (Low, High, or Unclear). The risk of bias of the review as a whole is then considered, with signalling questions and information to support overall judgement of risk of bias (Low, High, or Unclear) (Whiting 2014).

Two overview authors will independently assess the quality of the included reviews using AMSTAR and ROBIS, and another overview author will verify this assessment. We will resolve differences through discussion or, if needed, through discussion with a third overview author.

We will also note and report for each review the publication and search date.

Quality of included studies within reviews

We will not reassess the quality of included studies within reviews but instead will report study quality according to the review authors’ assessment. In the case that individual studies are included in two or more Cochrane reviews, we will report this, and any variation regarding review authors’ assessments of study quality. We will collect this information during the data extraction process.

Quality of evidence in included reviews

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

A narrative description of the characteristics of the included Cochrane reviews will be undertaken. We will summarise the main results of the included reviews by categorising their findings in the following framework (as has been used within previous Cochrane and non-Cochrane overviews, such as Farquhar 2015 and Lassi 2015), organised by antenatal or intrapartum intervention, and by intervention topic.

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

The choice of category will be based on the quality of the evidence for the primary overview outcome (cerebral palsy). Separate assessments may be made for different comparisons (e.g. where one intervention is compared with both placebo (or no treatment) and to an alternative intervention).

The above approach to summarising the evidence was based on an earlier Cochrane overview (Jones 2012), which categorised interventions as "What works," "What may work", and "Insufficient evidence to make a judgement".

**Acknowledgements**

We thank the Cochrane Pregnancy and Childbirth Editorial Base for their support.

As part of the pre-publication editorial process, this protocol has been commented on by five peers (an editor and four referees who are external to the editorial team) and the Group’s Statistical Adviser.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.
Additional references

Access Economics 2008

ACPR Group 2013

Badawi 2013

Bax 1964

Blair 1988

Blair 2001

Blair 2006

Cans 2000

CDC 2004

Chang 2015

Colver 2012

Colver 2014

Compagnone 2014

Covidence 2015

Davis 2010

Eliasson 2006

Ellenberg 2013

Farquhar 2015

Hemming 2005

Hidecker 2011

Hidecker 2012

Higgins 2011

Himpens 2008
Himpens E, Van den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and

Howard 2005

Iams 2008
Iams JD, Romero R, Culhane JF, Goldenberg RL. Preterm birth 2 - Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008;371(9607):164–75.

IMPACT for CP 2015

Inder 2000

Jacobs 2013

Jacobsson 2004

Jones 2003

Kruse 2009

Lagunju 2009

Larroque 2003

Lassi 2015

MacLennan 2015

McIntyre 2010

McIntyre 2011

McIntyre 2013

Moreno-De-Luca 2012

Morris 2004

Morris 2007

Mutch 1992

Nelson 2008

Nelson 2008b

Novak 2012

Oskoui 2013

Oskoui 2015
Oskoui M, Gazzellone MJ, Thiruvahindrapuram B, Zarrei M, Andersen J, Wéi J. Clinically relevant copy number

**O’Callaghan 2009**

**O’Shea 2008**

**Palisano 1997**

**Reid 2012**

**Reid 2016**

**RevMan 2014 [Computer program]**

**Robertson 2012**

**Rosenbaum 2007**

**Saliba 2001**

**Sanger 2003**

**Sankar 2005**

**Sellier 2015**

**Shea 2009**

**Smithers-Sheedy 2014**

**Strauss 2008**

**Vexler 2001**

**Volpe 2000**

**Whiting 2014**

**Wood 2000**

* Indicates the major publication for the study
WHAT'S NEW

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 February 2016</td>
<td>Amended</td>
<td>Affiliation corrected for Philippa Middleton and Maria Makrides</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

Emily Bain 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 draft.

DECLARATIONS OF INTEREST

The overview authors are likely to be authors on some of the Cochrane systematic reviews that may to be considered for inclusion in this review.

Therefore, assessment of eligibly of any and all of these reviews, and if included, data collection and analysis (including quality assessment) for these reviews, will be carried out by two overview authors not involved in the individual Cochrane reviews. We will document all such decisions made, relevant to any such reviews (with the full citations of these reviews), at review stage.

Maria Makrides serves on scientific advisory boards for Nestle, Fonterra and Nutricia. Associated honoraria are 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.

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

SOURCES OF SUPPORT

Internal sources

- ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- National Health and Medical Research Council, Australia Funding for the PCG Australian and New Zealand Satellite, Australia.
- Cerebral Palsy Alliance Research Foundation, Australia.

Project Grant: PG0914 - Interventions during the antenatal and neonatal period to prevent cerebral palsy: an overview of Cochrane systematic reviews (Bain E, Middleton P, Crowther CA)