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Antenatal corticosteroids for fetal lung maturation: an overview of Cochrane reviews (Protocol)

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Antenatal corticosteroids for fetal lung maturation: an overview of Cochrane reviews.
Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD012156.
DOI: 10.1002/14651858.CD012156.

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[Overview of Reviews Protocol]

Antenatal corticosteroids for fetal lung maturation: an overview of Cochrane reviews

Emma McGoldrick[1], Julie Brown[1], Philippa Middleton[2,3], Christopher JD McKinlay[1], David M Haas[4], Caroline A Crowther[1,3]

[1]Liggins Institute, The University of Auckland, Auckland, New Zealand. [2]Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, Adelaide, Australia. [3]ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [4]Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Contact address: Julie Brown, Liggins Institute, The University of Auckland, Auckland, New Zealand. j.brown@auckland.ac.nz.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2016.

Citation: McGoldrick E, Brown J, Middleton P, McKinlay CJD, Haas DM, Crowther CA. Antenatal corticosteroids for fetal lung maturation: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD012156. DOI: 10.1002/14651858.CD012156.

ABSTRACT

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

The objective is to summarise the available evidence from Cochrane systematic reviews for the effectiveness and safety of antenatal corticosteroid therapy to improve infant outcomes.

BACKGROUND

Description of the condition

Up to 10% of all births globally are preterm (born less than 37 weeks' gestational age) (March of Dimes 2012). Over one million babies die each year as a direct consequence of being born preterm (Lawn 2013). Preterm birth can have significant effects on short-term morbidity and mortality, and also long-term health and disability. The short-term sequelae of preterm birth include respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), retinopathy of prematurity, patent ductus arteriosus and sepsis (Haram 2003; Saigal 2008). RDS develops as a consequence of immature lung development and is the major cause of early neonatal morbidity and mortality in preterm infants. Prematurity can also predispose to the development of chronic lung disease (bronchopulmonary dysplasia) which may be associated with impaired airway function into adult life (Doyle 2006; Saigal 2008). In those infants who do survive there are increased risks of long-term neurodevelopmental disability (Saigal 2008), including cerebral palsy, and intellectual, visual and hearing impairment (Anderson 2003; Doyle 2001; Farooqi 2006; Wood 2000). Therefore prematurity and its associated sequelae has significant psychosocial and emotional effects on families caring for these infants (Saigal 2000; Singer 1999). Being born preterm also increases the risk of developing non-communicable diseases such as diabetes and hypertension in later life (Hovi 2007).

The rates of preterm birth are increasing in almost all countries with reliable data (Blencowe 2012). The greatest burden of preterm birth occurs in Africa and Asia (Blencowe 2012) where the use of interventions to mitigate the effects of preterm birth

varies substantially (Vogel 2014). Reasons for preterm birth vary by geographical location. In high-income countries the numbers of provider-initiated preterm births has been rising (Blencowe 2012). In France and the United States, over 30% of all preterm births were medically indicated in 2000 (Blondel 2012; Davidoff 2006). It is difficult to differentiate the cause of preterm birth in low- and middle-income countries due to the lack of population-based studies. However medically-indicated preterm births represent a much smaller proportion of all preterm births in low- and middle-income countries when compared with spontaneous preterm birth (Alhaj 2010; Nkyekyer 2006).

Overall, up to a third of all preterm births and up to half of very preterm births are provider-initiated (encompasses urgent, discretionary, iatrogenic and social) (Goldenberg 2008; Menon 2008; Steer 2005). The main maternal/fetal indications for preterm delivery are maternal pre-eclampsia, antepartum haemorrhage, and chronic or acute fetal compromise, including fetal distress and severe intrauterine growth restriction (Ananth 2006). The incidence of medically indicated preterm birth is likely to continue to rise due to increasing maternal disease, particularly in view of the world-wide epidemics of diabetes and obesity (Lawn 2013).

The aetiology of spontaneous preterm birth is not completely understood but it is likely to be multifactorial (Lawn 2013). In up to half of the cases the cause remains unknown (Menon 2008). Up to half of spontaneous preterm births occur following preterm prelabour rupture of membranes (Goldenberg 2008). Another important risk factor is multiple pregnancy, which is responsible for approximately 15% to 20% of all preterm births (Goldenberg 2008). A large contributor to the increasing incidence of multiple pregnancies has been advancing maternal age and the use of assisted reproductive techniques (Felberbaum 2007). Advancing maternal age has also been identified as an independent risk factor for spontaneous preterm birth (Goldenberg 2008).

The incidence of preterm birth is not equally distributed across all gestational ages. Only 5% of preterm births occur at less than 28 weeks' gestation, approximately 15% at 28 to 31 weeks', 20% at 32 to 33 weeks' and 60% to 70% at 34 to 36 weeks' gestation (Goldenberg 2008). However, these figures can also vary depending on geographical location. Recent data from Australia reported an overall incidence of preterm birth of 7.7%, of which 10% occurred at 20 to 27 weeks', 9% at 28 to 31 weeks and 81% at 32 to 36 weeks' gestation (Hilder 2014). Overall, the risks associated with prematurity are inversely related to gestational age (Saigal 2008).

Marked improvement in survival rates of preterm infants in recent decades, particularly those born very preterm, has been attributed to administration of antenatal corticosteroids, surfactant use, the use of assisted ventilation and changing attitudes towards intensive care (Doyle 1999; Roberts 2006; Rojas-Reyes 2012). However survival rates vary significantly depending on where preterm infants are born. The improvement in mortality in high-income countries is most marked at extremes of gestation and in infants of extremely low birthweight (Saigal 2008). Population-based cohort studies in Australia have demonstrated marked improvement in survival of extremely low birthweight infants from 25% in 1979, to 80% to 73% in 1997 (Doyle 2001). Similarly, a national cohort study in the UK demonstrated an increase in survival of infants born between 22 and 25 weeks' gestation between 1995 and 2006 from 40% to 53% (Costeloe 2012). However this trend is not reflected in low-income countries where more than 90% of very preterm infants (less than 28 weeks' gestation) die within the first few days of life compared with less than 10% in high-income settings (March of Dimes 2012).

Uncertainty still exists around the use of antenatal corticosteroids at later gestations. This question has become increasingly important in view of increasing numbers of caesarean sections at both term and late preterm gestations (McClure 2007). Undergoing a caesarean section predisposes the neonate to respiratory complications including RDS and transient tachypnoea of the newborn (Hook 1997; Maisels 1977; Morrison 1995). Opinion is divided on the necessity of antenatal corticosteroids at term, as approximately only 5% of these babies will require admission for respiratory distress and serious morbidity is uncommon (Stutchfield 2005). There is also some concern about the potential for long-term adverse effects of corticosteroid exposure in more mature fetuses (Aiken 2014; Steer 2005). As the risk of neonatal respiratory complications reduces with advancing gestational age (Morrison 1995; Zanardo 2004), delaying elective caesarean until 39 weeks or more appears to be an equally effective solution (Al Kiaat 2013; NICE 2011; Stutchfield 2005).

Description of the interventions

Antenatal corticosteroids are listed and recommended by the World Health Organization as a priority intervention in the prevention of RDS and mortality in preterm babies (PMNCH 2011; WHO 2015). However, rates of antenatal corticosteroid use in low- and middle-income countries remain low (Vogel 2014), indicating that there is an opportunity to improve outcomes for preterm babies through administration of antenatal corticosteroids (Dalziel 2014). An analysis conducted for the Global Action Report on Preterm Birth indicated if universal coverage (95%) of antenatal corticosteroids was achieved across the 75 priority countries by 2015, 373,000 additional infant deaths could be averted per year compared to 2010 figures (March of Dimes 2012). However, caution has been advised in upscaling antenatal corticosteroid administration (Althabe 2014), particularly in low-income countries where access to other effective interventions may be limited, such as accurate dating of the pregnancy, and the provision of effective neonatal resuscitation (Lawn 2013).

A single course of antenatal corticosteroids has been identified as a highly effective and safe intervention for women at risk of preterm birth to reduce neonatal mortality and morbidity (Crowley 1990; Roberts 2006). Their benefit was first described in the landmark trial conducted in New Zealand by Liggins and Howie in the late

1960s (Liggins 1972). Subsequently more than 20 clinical trials conducted in high- and middle-income countries and a number of systematic reviews have confirmed the efficacy of antenatal corticosteroids in significantly reducing the risk of RDS, neonatal death, IVH, NEC and early sepsis (Crowley 1990; Roberts 2006). Evidence suggests that in babies born more than seven days following antenatal corticosteroid treatment there is no reduction in the incidence of RDS compared to no antenatal corticosteroid treatment (Roberts 2006). Therefore repeat antenatal corticosteroids have been administered to women who remain at risk of preterm birth seven or more days after an initial course. Accumulating evidence has demonstrated that a repeat dose or doses of the synthetic corticosteroid, betamethasone is associated with a reduced risk of RDS and combined serious neonatal morbidity compared with a single course of antenatal corticosteroids (Crowther 2015). Uncertainty still exists around the effects of repeat antenatal corticosteroids of reduced birthweight and the long-term effects in both childhood and later life following repeat in utero exposure (Crowther 2015).

Reassuringly, long-term follow up of infants exposed to a single course of antenatal corticosteroids into early adulthood has not demonstrated any increased cardio-metabolic risk (Dalziel 2005; Dessens 2000) and follow up of infants up to early school-age after repeat antenatal corticosteroid exposure has been reassuring (Asztalos 2010; Asztalos 2013; Crowther 2007; McKinlay 2015; Peltonemi 2009; Wapner 2007). The long-term effects into adulthood of repeat corticosteroids on growth, the neuroendocrine system and the risk of developing cardiovascular and metabolic disease in later life is not yet known (Crowther 2015). Antenatal corticosteroids have been administered prior to elective section to minimise the risk of respiratory distress at late preterm and term gestations (Stutchfield 2005; Tita 2009). Infants born by caesarean at term are at greater risk of respiratory morbidity, including transient tachypnoea of the newborn and RDS compared with term infants born vaginally (Hansen 2008; Morrison 1995; Sotiriadis 2009). There are limited data on the long-term effects of exposure to antenatal corticosteroids prior to caesarean section at term.

The two main synthetic corticosteroids used in clinical practice are betamethasone and dexamethasone (NIH 1994; PMNCH 2011; RCOG 2010; ACS CPG 2015). Despite widespread use there is significant global variation in the type, preparation, dose and method of administration of antenatal corticosteroids (Aleman 2013; Erickson 2001; Hui 2007; Jobe 2004; Parant 2008; Pattanittum 2008; Spencer 2014; Vogel 2014). Currently, the optimal type of corticosteroid to use remains unclear (Brownfoot 2013). Both drugs are able to cross the placenta in their biologically active form and exert their effects with comparable efficiency (Jobe 2004). Intramuscular betamethasone can be administered in two different drug preparations: betamethasone sodium phosphate, which has a short half-life in maternal plasma of six hours; and betamethasone acetate which has a longer half-life in maternal plasma of approximately 12 hours (Ballard 1975; Buckingham 2006). Initially Liggins and Howie proposed that by using the two preparations in combination this would maximise drug efficacy (Liggins 1972). Antenatal corticosteroids have been administered in a variety of ways including orally (Egerman 1998), intramuscularly (Liggins 1972; Qublan 2001; Shanks 2010), intravenously (Petersen 1983), intra-amniotically (Lefebvre 1976; Murphy 1982) and as a direct intramuscular injection to the fetus (Ljubic 1999).

Betamethasone and dexamethasone, as antenatal corticosteroids, have been administered intramuscularly in a variety of regimens (Table 1; Table 2). Trial regimens of a single course of antenatal betamethasone have included administering a total dose of betamethasone between 12 mg to 48 mg in single or multiple doses, at varied time intervals between doses (immediate, eight hours, 12 hours and 24 hours between doses), compared to no antenatal corticosteroids (Table 1). Trial regimens of a single course of dexamethasone have included administering a total dose of dexamethasone between 20 mg to 24 mg in multiple divided doses, at varied time intervals between doses (eight hours, 12 hours and 24 hours), compared to no antenatal corticosteroids (Table 2). Trials have also compared administration of a repeat course or courses of antenatal corticosteroids compared to no repeat antenatal corticosteroids (Table 3). Predominantly these trials have administered betamethasone as the repeat course(s) apart from one trial that used dexamethasone (administered intramuscularly) as a repeat course (n = 31 participants) (Garite 2009) due to the temporary unavailability of betamethasone. The trial regimens of repeat antenatal betamethasone compared with no repeat antenatal corticosteroids have included administering a total dose of betamethasone between 11.4 mg to 24 mg per repeat course, in a single or multiple dose regimen (24 hours apart between doses). The time interval between the administration of repeat courses and number of repeat courses varied between trials.

Only one regimen of oral dexamethasone has been evaluated in a clinical trial (Egerman 1998; Regimen; four doses of 8 mg, 12 hours apart, total dose: 32 mg).

How the intervention might work

Glucocorticoids are known to have physiological and biochemical effects not only on the fetal lung, but in most fetal organ systems (Fowden 1998). They promote structural and functional maturation, preparing the fetus for life outside the womb. Synthetic corticosteroids promote a co-ordinated maturation response in fetal tissues similar to that occurring with the normal pre-partum surge in fetal corticosteroid production (Liggins 1994).

The effects of glucocorticoids have been investigated extensively in animal models and the fetal lung (Ballard 2000). Experimental studies in animals and human fetal lung explants have demonstrated that exposure of the preterm fetus to corticosteroids increases tissue and alveolar surfactant production, lung compliance, clearance of fluid from the lungs, maturation of parenchy-

mal structure and reduced vascular permeability (Ballard 1995). These effects help to moderate some of the consequences of being born preterm with immature lung structure and function (Ballard 1995).

At a molecular level glucocorticoids primarily act by inducing gene transcription via the glucocorticoid receptor. This leads to increased concentration of various enzymes and proteins, including lung phospholipids and surfactant proteins (Ballard 1995).

The finding that glucocorticoid action is reversible following dissociation of the steroid from the receptor and the clinical observation that corticosteroid effectiveness appears to diminish over time, if the fetus remains in utero, has resulted in the administration of repeat steroids to women who remain at risk of preterm birth (Ballard 1995; Liggins 1972). This was originally proposed by Liggins and Howie and has been supported further by experimental data showing that gene transcription can be repetitively induced (Ballard 1995; Ballard 1997; Willet 2001).

The available evidence from follow up of children exposed to repeat antenatal corticosteroids in utero compared to unexposed children has been reassuring, and has demonstrated no differences in mortality, neurosensory disability, measurements of growth, blood pressure or respiratory morbidity compared to no repeat exposure (Asztalos 2010; Asztalos 2013; Crowther 2007; McKinlay 2015; Peltonemi 2009; Wapner 2007). The pathophysiology underlying respiratory morbidity in infants born by elective caesarean section at term is thought to be different to that occurring after preterm birth (Brown 1983). A significant proportion of the respiratory morbidity in term infants after caesarean is due to retention of fetal lung fluid (Milner 1978; Morrison 1995). Administration of corticosteroids prior to elective section has been proposed based on the evidence that antenatal corticosteroids could help to facilitate the clearance of fluid from the fetal lung by increasing the number and function of sodium channels (Helve 2009; Jain 2006). The precise mechanism has not been confirmed and the long-term consequences of administration on child and adult health outcomes have not been established.

Why it is important to do this overview

Although the use of a single course of antenatal corticosteroids prior to preterm birth is generally accepted as one of the most effective interventions in perinatal medicine, there are several aspects of antenatal corticosteroid administration that remain uncertain, including:

- use of antenatal corticosteroids in late preterm gestations;
- use of antenatal corticosteroids at term gestations;
- use of repeat dose or doses of antenatal corticosteroids prior to preterm birth;
- optimal drug formulation, route and timing of administration;
- use of antenatal corticosteroids in different healthcare settings (low-, middle- and high-income countries).

This overview will aim to clarify these uncertainties, identify the health benefits and potential harms associated with antenatal corticosteroid administration and identify areas which should be the focus of future high-quality randomised trials. Ultimately this overview will provide a user-friendly, one-stop source of current evidence from Cochrane systematic reviews for the use of antenatal corticosteroids and should encourage uptake and appropriate administration of antenatal corticosteroids to all eligible mothers and their babies.

OBJECTIVES

The objective is to summarise the available evidence from Cochrane systematic reviews for the effectiveness and safety of antenatal corticosteroid therapy to improve infant outcomes.

METHODS

Criteria for considering reviews for inclusion

Only published Cochrane systematic reviews, including full reviews, protocols and registered titles will be considered for inclusion in this overview. Where necessary and feasible we will update the relevant Cochrane reviews.

Participants

- Women who have received antenatal corticosteroids by any route prior to birth to promote fetal maturation.

Interventions

Antenatal corticosteroids administered by any route to women or to the fetus to promote fetal maturation (preterm/term). Comparisons will include the following.

- A single course of antenatal corticosteroids will be compared to placebo or no treatment
- Repeat course(s) of antenatal corticosteroids will be compared to no repeat course(s)
- Head-to-head comparisons of different types of antenatal corticosteroids (for example, dexamethasone versus betamethasone)
- One antenatal corticosteroid regimen compared to a different antenatal corticosteroid regimen (dose, frequency and timing, and route of administration)

Outcomes of interest

The following maternal, infant, child and child as an adult primary and secondary outcomes have been selected for this overview.

Maternal

Primary

- Maternal sepsis (however defined by study authors)

Secondary

- Chorioamnionitis
- Pyrexia after trial entry requiring the use of antibiotics
- Intrapartum pyrexia
- Postnatal pyrexia
- Glucose tolerance (as defined by study authors)
- Breastfeeding

Infant

Primary

- Death (stillborn or death of a live born infant prior to primary hospital discharge)
- Respiratory distress syndrome

Secondary

- Intraventricular haemorrhage
- Birthweight (z score)
- Bronchopulmonary dysplasia (chronic lung disease) (as defined by study authors)
- Necrotising enterocolitis
- Admission to neonatal intensive care
- Composite of serious infant outcomes (as defined by authors)
- Systemic infection in the first 48 hours of life

Child

Primary

- Survival free of any disability (however defined by study authors)
- Neurodevelopmental impairment (however defined by study authors)

Secondary

- Total deaths
- Body size measurements (including z scores for weight, height, head circumference and body mass index (BMI))
- Asthma/wheeze
- Risk factors for cardiovascular disease
- Emotional and behavioural problems

Child as an adult

Primary

- Neurodevelopmental impairment at follow up (however defined by study authors)
- Survival free of cardio-metabolic disease

Secondary

- Growth measurements (including weight, head circumference, height, skin fold thickness and BMI)
- Age at puberty
- Abnormal lung function (including z scores for forced expiratory volume in one second, forced vital capacity and forced expiratory flow at 25% to 75% of forced vital capacity)
- Health-related quality of life
- Employment status

Search methods for identification of reviews

We will search the *Cochrane Database of Systematic Reviews* (*The Cochrane Library*) and Archie using the terms given in Appendix 1. We will not search any other sources.

Data collection and analysis

Selection of reviews

Two of the review authors will independently assess reviews that address the use of antenatal corticosteroids prior to:

- preterm birth for fetal maturation; or
- prior to term birth for fetal lung maturation.

Any disagreements will be resolved by consensus or by a third review author.

Where the Cochrane review search is out of date (search date is older than two years) and where feasible we will liaise with the Group to assess whether the review should be updated.

Data extraction and management

Two of the review authors (EM, JB, CM or DH) will independently extract data using an electronic form to be designed. We will resolve disagreements by consensus or by involving a third review author. We will extract and tabulate information as detailed. The overview will contain a 'Characteristics of included reviews' table. This table will include the following.

- The reference ID for each included review
- The review title
- The search date: when the review was last assessed as up-to-date. Defined as: whether the date of the review is greater than two years. The two-year period starts from the date on which the review was assessed as being up-to-date
- The population demographics of each included review: including a summary of the participant characteristics (inclusion and exclusion criteria)
- The review characteristics: the number of trials in the review, number of women and infants
- The specific interventions assessed within each review
- The control or comparisons interventions within each review
- The outcomes reported in each review
- Any major limitations of the review.

We will prepare an 'Overview of reviews' table for each comparison by outcome (Becker 2011 *Chapter 22 Cochrane Handbook, Figure 22.3b)* and will include the following.

- A statistical summary of the treatment effects and 95% confidence intervals for the selected primary and secondary outcomes
- The number of studies and participants for whom data are available for each specific outcome and treatment comparison
- The quality of the evidence for the selected primary and secondary outcomes (we will report the quality of the evidence using the GRADEpro GDT software

Assessment of methodological quality of included reviews

Quality of evidence in included reviews

We will use the GRADEpro Guideline Development Tool (GRADEpro GDT) to import data from Review Manager 5.3 (RevMan 2014) in order to create an 'Overview of reviews' table. We will obtain the data for each of our primary and secondary outcomes from the included systematic reviews and enter them into GRADEpro GDT. We will appraise the quality of the evidence for each of the outcomes for:

- the risk of bias of included trials;
- directness of evidence;
- precision of the evidence;
- heterogeneity;
- risk of publication bias (GRADE Handbook).

We will summarise the evidence for each of the selected clinical outcomes in an 'Overview of reviews' table which we will populate with the summary risk estimate and 95% confidence intervals. We will allocate a quality score for the strength of the clinical outcome evidence , ranging from HIGH to VERY LOW (as determined by GRADEpro GDT). The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication biases.

The quality of the body of evidence relating to the following outcomes for the main comparisons (single course versus placebo/no treatment; repeat course(s) versus no repeat course(s) and head-to-head comparisons of different types of antenatal corticosteroids (for example, dexamethasone versus betamethasone), and one antenatal corticosteroid regimen compared to a different antenatal corticosteroid regimen (dose, frequency and timing and route of administration) will be presented in separate tables.

Maternal

- Maternal sepsis (however defined by study authors)
- Chorioamnionitis
- Pyrexia after trial entry requiring the use of antibiotics
- Intrapartum pyrexia
- Postnatal pyrexia
- Glucose tolerance (as defined by study authors)
- Breast feeding

Infant

- Death (stillborn or death of a live born infant prior to primary hospital discharge)
- Respiratory distress syndrome
- Intraventricular haemorrhage
- Birthweight (z score)
- Bronchopulmonary dysplasia (chronic lung disease) (as defined by study authors)
- Necrotising enterocolitis
- Admission to neonatal intensive care
- Composite of serious infant outcomes (as defined by study authors)
- Systemic infection in the first 48 hours of life

Child

- Survival free of any disability (however defined by study authors)
- Neurodevelopmental impairment (however defined by study authors)
- Total deaths

- Body size measurements (including z scores for weight, height, head circumference and body mass index (BMI))
- Asthma/wheeze
- Risk factors for cardiovascular disease
- Emotional and behavioural problems

Child as an adult

- Neurodevelopmental impairment at follow up (however defined by study authors)
- Survival free of cardio-metabolic disease
- Growth measurements (including weight, head circumference, height, skin fold thickness and BMI)
- Age at puberty
- Abnormal lung function (including z scores for forced expiratory volume in one second, forced vital capacity and forced expiratory flow at 25% to 75% of forced vital capacity)
- Health-related quality of life
- Employment status

Methodological quality of included reviews

We will also use AMSTAR (A MeaSurement Tool to Assess systematic Reviews) (Shea 2007) and ROBIS (Risk of Bias in Systematic Reviws) (Whiting 2014) to assess the quality of the included reviews by tabulating whether the following items have been adequately addressed.

- Prespecified question and inclusion criteria
- Duplicate study selection and data extraction
- Comprehensive literature search
- Grey literature included
- Lists of included and excluded studies
- Describes characteristics of included studies
- Study quality assessed and documented
- Scientific quality of studies used appropriately to form conclusions
- Studies combined using appropriate methods
- Likelihood of publication bias considered/tested
- Potential for conflict of interest addressed
- Risk of bias in the review

Two review authors will independently complete the assessment of methodological quality We will resolve any disagreements by consensus or by consulting a third review author. The review authors completing the assessment of quality will be independent of the included systematic review (not named as an author on the systematic review).

Data synthesis

For each comparison, we will give a narrative description of the summary statistics from the included reviews. We will present the results for the primary and secondary outcomes by the intervention (Becker 2011; *Chapter 22 Cochrane Handbook, Figure 22.3b*), using tables and figures (e.g. characteristics of included reviews, overview of reviews tables, AMSTAR and ROBIS ratings for each systematic review). We will include other data, that may have been summarised in a narrative form, within the body of the text of the results.

ACKNOWLEDGEMENTS

We acknowledge the support of Cochrane Pregnancy and Childbirth Editorial and the Australian and New Zealand Pregnancy and Childbirth Satellite.

As part of the pre-publication editorial process, this protocol has been commented on by four peers (an editor and three referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers 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.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Trial regimens of a single course of antenatal betamethasone (administered intramuscularly) compared to no antenatal corticosteroids

Total dose	Interval between doses	(IM) Betamethasone regimen
12 mg	Immediate	1 dose 12 mg
12 mg	12 hours	2 doses of 6 mg 12 hours apart
24 mg	12 hours	2 doses of 12 mg 12 hours apart
24 mg	24 hours	2 doses of 12 mg 24 hours apart
24 mg	12 hours	4 doses of 6 mg 12 hours apart
	8 hours	6 doses of 4 mg 8 hours apart
28 mg	24 hours	2 doses of 14 mg 24 hours apart
48 mg	24 hours	2 doses of 24 mg 24 hours apart

Source: ACS CPG 2015; Roberts 2006
IM: intramuscular

Table 2. Trial regimens of a single course of antenatal betamethasone (administered intramuscularly) compared to no antenatal corticosteroids

Total dose	Interval between doses	(IM) Dexamethasone regimen
20 mg	12 hours	4 doses of 5 mg 12 hours apart
24 mg	24 hours	2 doses of 12 mg 24 hours apart
24 mg	12 hours	4 doses of 6 mg 12 hours apart
24 mg	8 hours	6 doses of 4 mg 8 hours apart

Source: ACS CPG 2015; Roberts 2006
IM: intramuscular

Table 3. Trial regimens of repeat antenatal betamethasone (administered intramuscularly) compared with no repeat antenatal corticosteroid

Total dose per repeat course	(IM) Betamethasone regimen per repeat course	Interval between repeat courses	Multiple repeat courses
12 mg	1 dose of 12 mg	Immediate	No
11.4 mg	1 dose	7 days	Yes
24 mg	2 doses of 12 mg 24 hours apart	Not applicable	No
24 mg	2 doses of 12 mg 24 hours apart	7 days	Yes
24 mg	2 doses of 12 mg 24 hours apart	14 days	Yes

Source: ACS CPG 2015; Roberts 2006
IM: intramuscular

APPENDICES

Appendix 1. Search terms

Cochrane Database of Systematic Reviews (*The Cochrane Library*)
(antenatal OR prenatal) AND (corticosteroid* OR glucocorticoid* OR betamethasone OR dexamethasone)
The terms will be restricted to title, abstract, or keywords.

WHAT'S NEW

Date	Event	Description
18 April 2016	Amended	Typo corrected.

CONTRIBUTIONS OF AUTHORS

The original concept of the review was generated by Caroline Crowther and Julie Brown.

Following a consultative process the review group (EM, JB, CM, DH, PM and CAC) agreed on the scope of the overview including the participants, interventions and outcomes that would be included in the overview.

Emma McGoldrick has taken the lead in preparing the draft protocol.

Julie Brown is the guarantor of this overview protocol and has provided methodological expertise in preparing the protocol.

Caroline Crowther, Julie Brown, Christopher McKinlay, Phillippa Middleton and David Haas have provided feedback on the drafts of the protocol and the final version.

DECLARATIONS OF INTEREST

Caroline Crowther (CAC), Philippa Middleton (PM), Chris McKinlay (CM), Emma McGoldrick (EM) and Julie Brown (JB) are authors of some of the Cochrane systematic reviews that are likely to be included in the overview when published. Other authors will be involved in the assessments of these reviews. CAC is principle investigator for the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) Trial. CM conducted in-depth studies on the ACTORDS children living in New Zealand at early school age. CAC and PM are investigators for the Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID) trial.

SOURCES OF SUPPORT

Internal sources

- Liggins Institute, University of Auckland, New Zealand.

Infrastructure support has been provided by staff within the Liggins Institute, University of Auckland, New Zealand.

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

External sources

- Cochrane Pregnancy and Childbirth Australia and New Zealand Satellite, Australia.

Funded by National Health and Medical Research Council