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Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term (Review)

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[Intervention Review]

Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term

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ABSTRACT

Background

Infants born at term by elective caesarean section are more likely to develop respiratory morbidity than infants born vaginally. Prophylactic corticosteroids in singleton preterm pregnancies accelerate lung maturation and reduce the incidence of respiratory complications.

Objectives

The objective of this review was to assess the effect of prophylactic corticosteroid administration before elective caesarean section at term, as compared to usual management without corticosteroids, in reducing neonatal respiratory morbidity and admission to special care with respiratory complications.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (14 June 2017), and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials comparing prophylactic antenatal corticosteroid administration (betamethasone or dexamethasone) with placebo or with no treatment, given before elective caesarean section at term (at or after 37 weeks of gestation).

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We assessed the quality of the evidence using the GRADE approach.

Main results

We included four trials (3956 women and 3893 neonates) at a moderate risk of bias, comparing prophylactic administration of betamethasone or dexamethasone versus placebo or usual treatment without steroids in term elective caesarean section. Women randomised to treatment group received either two intramuscular doses of betamethasone in the 48 hours before delivery, or intramuscular dexamethasone (two or four doses) prior to delivery (at 37 weeks' gestation or 48 hours before delivery), and were compared to the control group who received a saline placebo or treatment as usual.

Prophylactic antenatal corticosteroid administration appeared to decrease the risk of respiratory distress syndrome (RDS) (risk ratio (RR) 0.48; 95% confidence interval (CI) 0.27 to 0.87; 4 studies; 3817 participants; low-quality evidence), transient tachypnoea of the neonate (TTN) (RR 0.43; 95% CI 0.29 to 0.65; 4 studies; 3821 participants; low-quality evidence), admission to the neonatal intensive care unit (NICU) for respiratory morbidity (RR 0.42; 95% CI 0.22 to 0.79; 3 studies; 3441 participants), and admission to neonatal special care (all levels) for respiratory complications (RR 0.45; 95% CI 0.22 to 0.90; 1 study; 942 participants; low-quality evidence). Administration of antenatal corticosteroids also appeared to reduce admission to neonatal special care (RR 0.62; 95% CI 0.43 to 0.89; 2 studies; 2169 participants) and neonatal intensive care (RR 0.14; 95% CI 0.03 to 0.61; 1 study; 452 participants) for any indication, compared to placebo or usual care. Finally, prophylactic antenatal corticosteroids also appeared to reduce the length of stay in NICU by 2.70 days (mean difference (MD) -2.70; 95% CI -2.76 to -2.64; 2 studies; 32 participants).

No reduction was found in the need for mechanical ventilation (RR 0.67; 95% CI 0.27 to 1.68; 3 studies; 3441 participants; very-low quality), perinatal death (RR 0.67; 95% CI 0.11 to 4.10; 4 studies; 3893 participants) or neonatal sepsis (RR 1.00; 95% CI 0.06 to 15.95; 2 studies; 2214 participants).

There were no reported events of neonatal respiratory complications (other than RDS and tachypnoea of the newborn (TTN)), chronic lung disease, duration of mechanical ventilation or maternal postpartum infection, therefore results on these outcomes are non-estimable. The studies did not provide data on other pre-defined outcomes.

The quality of evidence, as assessed using GRADE was low for the outcomes of RDS, TTN and admission to NICU for respiratory morbidity, indicating that the true effect could potentially be substantially different from our estimate of effect.

Authors' conclusions

The results from the four trials are promising, but more high-quality studies with larger sample sizes that are adequately powered to detect the effect of prophylactic antenatal corticosteroids on outcomes of respiratory morbidity are needed, given the potential of the current studies for bias. Consideration should be given to the balance between statistical significance and clinical significance, particularly in view of the low event rates of significant respiratory morbidity (RDS or admission to NICU for respiratory complications) in this population. In addition, further trials on the long-term outcomes of these infants are needed to identify any potential harms and complications of antenatal corticosteroid administration at term.

PLAIN LANGUAGE SUMMARY

Corticosteroids for preventing respiratory complications in the newborn after caesarean section at term

What is the issue?

Babies born at term (at or after 37 weeks) by planned (elective) caesarean section and before onset of labour are more likely to develop respiratory complications than babies born vaginally. The giving of injections called 'corticosteroids' to the mother has been shown to reduce the risk of newborn babies having breathing problems in babies born before 34 weeks, but it is not clear if they are useful after this stage.

Why is this important?

The risk of respiratory complications, mostly respiratory distress syndrome and transient tachypnoea, decreases from 37 weeks to 39 weeks of gestation, at which stage it is low. The aim of this review was to investigate if corticosteroids can reduce the rates of respiratory problems and the need for admission into special care units when given before planned (not emergency) caesarean section at term.

What evidence did we find?

The review identified four randomised controlled studies involving 3956 women and 3893 babies, which compared corticosteroids with usual care or placebo. Giving the mother intramuscular antenatal corticosteroids may reduce the chances of a baby needing special care for respiratory problems, and may reduce the chances of the baby being admitted to a neonatal intensive care unit. Much larger numbers of women would be needed to confirm differences in the rates of the respiratory problems themselves and any possible harms of giving the corticosteroids, for the mother and the baby.

Quality of evidence

The quality of evidence from the included randomised trials was low. This means that we can not be completely confident that future trials will come to the same conclusions about the treatment benefits for the babies of mothers receiving a course of antenatal corticosteroids prior to caesarean section.

What does this mean?

Evidence suggest that there might be a beneficial effect of intramuscular corticosteroids in respiratory outcomes of the neonate in the immediate period after birth. Given that only one study has examined the long-term effects, we cannot be certain about whether there are

risks and what is their magnitude. Larger randomised trials should be conducted in order to confirm the short- and long-term effects of this intervention in the general population of women undergoing elective caesarean section.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. GRADE 'Summary of findings' table

Corticosteroids compared to placebo or standard care for elective cesarean at term

Patient or population: elective cesarean at term

Setting: general population - hospital settings in Egypt and UK

Intervention: corticosteroids

Comparison: placebo or standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard care	Risk with corticosteroids				
Respiratory distress syndrome	Study population		RR 0.48 (0.27 to 0.87)	3817 (4 RCTs)	⊕⊕⊕⊕ LOW 1,2	
	54 per 1,000	26 per 1,000 (15 to 47)				
Transient tachypnoea of the new-born	Study population		RR 0.43 (0.29 to 0.65)	3821 (4 RCTs)	⊕⊕⊕⊕ LOW 1,2	
	54 per 1,000	23 per 1,000 (16 to 35)				
Admission to neonatal special care for respiratory morbidity (all levels of care or intensive care unit)	Study population		RR 0.45 (0.22 to 0.90)	942 (1 RCT)	⊕⊕⊕⊕ LOW 1,2	
	51 per 1,000	23 per 1,000 (11 to 45)				
Need for mechanical ventilation	Study population		RR 0.67 (0.27 to 1.68)	3441 (3 RCTs)	⊕⊕⊕⊕ 1,2,3 VERY LOW	
	15 per 1,000	10 per 1,000 (4 to 24)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- ¹ Study limitations (additional outcomes reported that were not pre-specified in trial methods; 2 trials did not use a placebo and personnel were not blinded to group allocation) (-1)
- ² Imprecision (limited number of trials; low event rates) (-1)
- ³ Inconsistency (heterogeneity in results $I^2 = 40\%$) (-1)

BACKGROUND

Description of the condition

Caesarean section is a risk factor for the development of neonatal respiratory complications, mostly respiratory distress syndrome (RDS) and transient tachypnoea of the neonate (TTN), both in term and preterm infants (Dani 1999; Gerten 2005; Levine 2001; Morrison 1995; Nielsen 1984; Reed 1978; White 1985). Neonates born at term by caesarean delivery are more likely to develop respiratory morbidity than those born vaginally, and this risk increases furthermore for the subgroup of neonates born after elective caesarean section, i.e. before onset of labour (Bowers 1982; Gerten 2005; Morrison 1995), with potentially severe implications (Roth-Kleiner 2003). The risk decreases with advancing gestational age, and neonates born between 37 + 0 and 37 + 6 weeks are at 1.7 times more risk for respiratory complications than those born between 38 + 0 and 38 + 6 weeks, which in turn are at 2.4 times more at risk than those born between 39 + 0 and 39 + 6 weeks (Morrison 1995). This trend is particularly pronounced for RDS, where the risk decreases from about 39/1000 for the period between 37 + 0 to 37 + 6 weeks to about 8/1000 for the period between 39 + 0 to 39 + 6 weeks, with the odds ratio in comparison to vaginal delivery similarly decreasing from 12.9 before 39 weeks to 1.1 from 39 + 0 weeks onwards (Zanardo 2004). There is little or no conflicting evidence on how mode of anaesthesia (Nielsen 1984; Van den Berg 2001) and fetal gender (Dani 1999; Van den Berg 2001) further affects this risk.

In view of this evidence, it is currently recommended that elective caesarean section should be deferred to 39 weeks (NICE 2004). However, approximately 10% to 15% of women planned for caesarean may deliver before 39 weeks, and there may be concerns on waiting in the presence of specific clinical indications or previous history. Prophylactic corticosteroids in singleton preterm pregnancies accelerate lung maturation and reduce the incidence of RDS, and administration of steroids is currently recommended between 24 and 34 weeks in cases of threatened preterm labour, antepartum haemorrhage, preterm rupture of membranes or in any condition requiring elective preterm delivery (RCOG 2004).

Description of the intervention

In 1972, Liggins and Howie (Liggins 1972), were the first to demonstrate the efficacy of a single course of antenatal corticosteroids in reducing the incidence of RDS in the preterm infants enrolled in their randomised control trial. Subsequently, a number of systematic reviews have been completed and have demonstrated the benefits associated with administration of single (Roberts 2017) and repeat course/s (Crowther 2015) of antenatal corticosteroids in women at risk of preterm birth. The evidence for administration of corticosteroids after 35 weeks is more controversial. The most recent version of the Cochrane review on prophylactic corticosteroids for accelerating fetal lung maturation showed in a subgroup analysis of gestational age at trial entry, that there was no evidence that gestational age at trial entry led to different rates of death, RDS, Intraventricular haemorrhage (IVH) or birthweight. This subgroup analysis compared women whose gestational age at trial entry was less than or equal to 35 weeks + 0 days or more than 34 weeks and 0 days (Roberts 2017). However, there was some overlap in the gestational age subgroups and the infants included in these randomised trials were born vaginally or by caesarean section. Additionally, one of the randomised trials

included in the systematic review reported an increased rate of neonatal hypoglycaemia in the infants exposed to betamethasone antenatally compared to the placebo group (Gyamfi-Bannerman 2017).

How the intervention might work

Respiratory morbidity in cases of term elective caesarean births appears to have a different pathophysiology than in preterm birth, with lack of the physiological catecholamine surge (Brown 1983; Irestedt 1984), and fluid retention in the lungs (Avery 1966) being the most likely causes. Interestingly, recent evidence indicates that, apart from the traditional mechanical concept of 'vaginal squeeze', molecular mechanisms (predominantly lung epithelial sodium channels) promote alveolar fluid drainage, and these channels may be underactive in fetuses not exposed to the process of labour (Jain 2006). Glucocorticoids appear to increase the number and function of sodium channels, as well as the responsiveness to catecholamines and thyroid hormones (Jain 2006), providing a rationale for their exogenous administration in cases of elective caesarean.

Why it is important to do this review

The practical impact of routine steroid administration in scheduled term caesarean delivery is important to assess. This is even more apparent when taking into consideration that caesarean births represent 30% to 40% of all births in some countries (McClure 2007), and approximately half of them are elective at term; therefore the use or not of steroids in this setting is a common question for obstetricians. This is an update of the review which was first published in 2009 (Sotiriadis 2009).

OBJECTIVES

The objective of this review was to assess the effect of prophylactic corticosteroid administration before elective caesarean section at term, as compared to usual management without corticosteroids, in reducing neonatal respiratory morbidity and admission to special care with respiratory complications.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials comparing prophylactic antenatal corticosteroid administration with placebo or with no treatment, given before elective caesarean section at term (at or after 37 + 0 weeks of gestation) in order to reduce neonatal respiratory morbidity. Quasi-randomised and cluster-randomised controlled trials were eligible for inclusion but none were identified. We did not consider emergency caesarean deliveries at term, as steroid administration is not an appropriate intervention for these cases. Cross-over trials were not eligible for inclusion.

Types of participants

Women with singleton or twin pregnancies at term (37 + 0 weeks or more) who underwent elective caesarean section under general or regional anaesthesia. We did not consider triplet pregnancies due to their low prevalence and low likelihood to reach term.

Types of interventions

Prophylactic maternal corticosteroid administration compared with placebo or no treatment.

Types of outcome measures

The primary outcomes were the most clinically important ones for the infant, whereas the secondary outcomes included maternal complications and long-term follow-up of the infant as a child.

Primary outcomes

1. Respiratory distress syndrome (RDS) (as defined by the authors of primary reports)
2. Transient tachypnoea of the neonate (TTN) (as defined by the authors of primary reports)
3. Admission to neonatal special care for respiratory morbidity (all levels of care or intensive care unit (NICU))
4. Need for mechanical ventilation

Secondary outcomes

1. Admission to neonatal special care for any indication (all levels of special care or NICU)
2. Development of neonatal respiratory complications (pneumonia, air leak syndrome)
3. Development of non-respiratory complications (e.g. sepsis)
4. Perinatal death
5. Chronic lung disease (need for oxygen supplementation beyond 28 days of life)
6. Length of stay in the NICU
7. Duration of mechanical ventilation
8. Readmission for respiratory problems after initial discharge
9. Maternal development of postpartum infection/pyrexia
10. Trauma infection
11. Long-term infantile morbidity
12. Survival free of neurodevelopmental disability (defined as cerebral palsy and/or deafness and/or blindness and or developmental delays/intellectual impairment (mental developmental index (MDI) or Psychomotor Development Index (PDI) <70)
13. Cognitive impairment (as defined by authors)
14. Emotional and behavioural problems

Different levels of neonatal special care may not be directly comparable in different reports. In the context of this review, we considered the definitions of the American Pediatric Association (specialty neonatal care - level II (resuscitation and stabilisation of preterm and/or ill infants before transfer to a facility at which newborn intensive care is provided) versus subspecialty neonatal care - level III (NICU)) (Stark 2004) and the British Association of Perinatal Medicine (special care versus high dependency and intensive care) (BAPM 2001).

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (14 June 2017).

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the [Cochrane Pregnancy and Childbirth Group](#) in the Cochrane Library and select the '**Specialized Register**' section from the options on the left side of the screen.

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.
7. scoping searches of [ClinicalTrials.gov](#) and the WHO International Clinical Trials Registry Platform (ICTRP).

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections ([Included studies](#); [Excluded studies](#); [Studies awaiting classification](#); [Ongoing studies](#)).

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see [Sotiriadis 2009](#).

For this update, the following methods were used for assessing the three new studies that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors independently extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software ([RevMan 2014](#)) and checked for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

For each included study we assessed the method as being at:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For each included study we described the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as being at:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

For each included study we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as being at:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

For each included study we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as being at:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses that we undertook.

We assessed methods as being at:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as being at:

- low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

For each included study we described any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it was likely to have an impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses (Sensitivity analysis).

Assessment of the quality of the evidence using the GRADE approach

For this update the quality of the evidence was assessed using the GRADE approach as outlined in the [GRADE handbook](#) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparison, antenatal corticosteroids versus no steroids.

1. Respiratory distress syndrome (RDS) (as defined by the authors of primary reports)
2. Transient tachypnoea of the neonate (TTN) (as defined by the authors of primary reports)
3. Admission to neonatal special care for respiratory morbidity (all levels of care or intensive care unit (NICU))
4. Need for mechanical ventilation

We used the [GRADEpro](#) Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. 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 bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CIs).

Continuous data

We used the mean difference (MD) if outcomes were measured in the same way between trials. We planned to use the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different measurement methods.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were identified for inclusion. In future updates, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes or standard errors (SEs) using the methods described in the Handbook [Section 16.3.4 or 16.3.6] using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population.

If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

This study design was not eligible for inclusion.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it using formal statistical tests

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects. The results were presented as the average treatment effect with 95% CIs,

and the estimates of τ^2 and I^2 . When only a few studies were available with an I^2 more than 0%, we used the Hartung-Knapp-Sidik-Jonkman (HKSJ) approach, which uses a Student's t -distribution instead of a normal distribution for tests of the effect and confidence intervals (IntHout 2014). This method applies an ad hoc correction and yields more conservative inferences.

Subgroup analysis and investigation of heterogeneity

We defined an a-priori subgroup analysis to investigate if there are differences between different types of corticosteroids (betamethasone and dexamethasone) and gestational age at birth (37 + 0 to 37 + 6 weeks; 38 + 0 to 38 + 6 weeks; 39 + 0 weeks or later) in neonatal respiratory outcomes because of their different biologic mode of action. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We also wanted to assess the following outcomes in subgroup analyses.

1. Respiratory distress syndrome (RDS) (as defined by the authors of primary reports)
2. Transient tachypnoea of the neonate (TTN) (as defined by the authors of primary reports)

3. Admission to neonatal special care for respiratory morbidity (all levels of care or intensive care unit (NICU))
4. Need for mechanical ventilation

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result. However, there were too few studies included in this update to carry out any meaningful sensitivity analysis.

RESULTS

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.

Figure 1. (Continued)

synthesis
(meta-analysis)

For this update, we retrieved 10 new trial reports to assess and also reassessed one previously ongoing study for potential inclusion. We have included three new trials (reported in four sources) ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#)), and added one additional trial report to [Stutchfield 2005](#). We excluded three new trials ([Christofori 2011](#); [Jain 2005](#); [Sananes 2017](#)). Two trials are ongoing ([Ahmadpourkacho 2015](#); [Custo 2007](#)), and we required further clarification on the methods used one trial ([Ammar 2013](#)), therefore this trial remains in *Studies awaiting classification*.

Included studies

A total of 3956 women (and 3893 infants) were included in the four trials that met the pre-specified inclusion criteria for this review ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)).

One study was conducted in the UK (Antenatal Steroids for Term Elective Caesarean Section (ASTECS)) and compared prophylactic administration of betamethasone (12 mg x 2, 24 hours apart intramuscular, N = 467 women) versus usual treatment without antenatal corticosteroids (N = 475 women) in women undergoing term elective caesarean section (planned at 37 weeks' gestation and beyond) ([Stutchfield 2005](#)). Women randomised to the treatment group received two intramuscular doses of betamethasone in the 48 hours before delivery, whereas the control group received treatment as usual.

The other three studies were conducted in Egypt ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#)) and compared prophylactic administration of dexamethasone with placebo or standard care. The [Ahmed 2015](#) trial randomised women undergoing elective caesarean section from 37 + 0 to 39 + 6 weeks to either dexamethasone (12 mg x 2, 24 hours apart intramuscular, N = 228) at 37 weeks, or standard care without antenatal corticosteroids (N = 224). The [Nada 2016](#) trial randomised women undergoing elective caesarean section between 38 + 0 and 38 + 6 weeks to either dexamethasone (8 mg x 4, 12 hours apart intramuscular, N = 645) or placebo (normal saline intramuscular, N = 645) 48 hours prior to the operation ([Nada 2016](#)). The [Nooh 2018](#) trial randomised women undergoing planned caesarean section at 38 weeks gestation or beyond to either dexamethasone 8 mg three times at eight hours apart intramuscular, N = 636) 24 hours prior to the operation, whereas the control group (N = 636) received treatment as usual. For the purpose of this review we only included the data in the group of patients who were at 38 weeks of gestation.

The primary outcomes were similar between studies. In the three trials ([Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)) that specified their primary and secondary outcome measures, the primary outcome was: neonatal intensive care unit (NICU) admission with respiratory distress in the [Nada 2016](#) trial, admission to special care baby unit in the [Stutchfield 2005](#) trial, and admission to NICU with respiratory morbidity in the [Nooh 2018](#) trial. The [Ahmed 2015](#) trial did not distinguish between primary and secondary outcome measures, however did include NICU admissions as an outcome measure. The secondary outcomes were also very similar between groups. All four trials included respiratory distress syndrome (RDS)

as an outcome. Both the [Ahmed 2015](#) and [Stutchfield 2005](#) trials reported on severity of respiratory distress and three of the trials ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#)) included rates of transient tachypnoea of the neonate (TTN) as a secondary outcome. The [Nooh 2018](#) trial included the need for mechanical ventilation as a secondary outcome. The [Stutchfield 2005](#) trial includes some follow-up data on a cohort of patients from their original trial using questionnaires. These questionnaires included a strengths and difficulties questionnaire, an international study of asthma and allergies in childhood, and a general health and school performance survey.

Dates of studies, funding sources and declarations of interest

Date of the studies were reported as follows: in [Ahmed 2015](#) the study was conducted from July 2012 to December 2013; in [Nada 2016](#) the study was conducted from November 2011 to December 2014; in [Nooh 2018](#) the study was conducted from September 2012 to August 2016; and in [Stutchfield 2005](#) the study was conducted from February 1995 to December 2002.

Funding sources for the studies were as follows: in [Ahmed 2015](#) no financial support was received; in [Nada 2016](#) no funding was declared; in [Nooh 2018](#) no financial support was received by the authors for the research, authorship or publication of the manuscript; and in [Stutchfield 2005](#) the funding sources was reported as being Wales Office of Research and Development in health and social care (WORD) and Conwy and Denbighshire NHS Trust.

Declarations of interest among primary researchers of the study were reported as follows: in all of the studies no conflicts of interest were declared ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)).

For further details see [Characteristics of included studies](#).

Excluded studies

We excluded four studies. One study ([Langer 2008](#)) compared prophylactic betamethasone in women planned to have caesarean section at 38 weeks versus deferring the caesarean to 39 weeks and therefore does not fulfil our inclusion criteria. The second trial included women outside the gestational age of inclusion for this review. The [Christofori 2011](#) trial included women undergoing caesarean section from 34 to 36 weeks' of gestation. The [Sananes 2017](#) trial compared women undergoing an elective caesarean section at 38 weeks' of gestation and received a course of antenatal corticosteroids versus a caesarean section at 39 weeks of gestation without antenatal corticosteroids. Due to the different gestational ages of participants among the treatment and control groups, we excluded this trial from this systematic review. The [Jain 2005](#) study was terminated due to slow enrolment and lack of funding. No trial data were available to include in this review.

For further details see [Characteristics of excluded studies](#).

Risk of bias in included studies

Overall, the trials were judged to be at moderate risk of bias. For further details on the risk of bias in individual studies, see [Figure 2](#) and also, see [Characteristics of included studies](#).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmed 2015	?	?	-	+	?	-	-
Nada 2016	+	?	+	+	+	-	-
Nooh 2018	+	+	-	-	+	?	-
Stutchfield 2005	+	+	-	-	+	?	-

Allocation

Adequate sequence generation was reported for three trials. For [Nada 2016](#); [Nooh 2018](#), and the ASTECS study ([Stutchfield 2005](#)), a randomisation sequence was generated using a computer-based random number generator. The method of sequence generation was unclear in [Ahmed 2015](#). The method of allocation concealment was adequately reported in the ASTECS ([Stutchfield 2005](#)) and ([Nooh 2018](#)) trials. In the ASTECS trial the treatment allocation was kept centrally at the trial centre and midwives were informed of the participants group allocation following completion of a signed

consent form. In the [Nooh 2018](#) trial, allocation concealment was performed using the closed envelope technique. Opaque sealed envelopes were used. The method of allocation concealment was adequate in the [Nooh 2018](#) trial. The method of allocation concealment was unclear in both the [Ahmed 2015](#) and [Nada 2016](#) trials. [Ahmed 2015](#) does not report on the methods used to try and conceal the allocation sequence. In [Nada 2016](#), allocation concealment was performed using a closed envelope technique. Further information was obtained by the authors of this review and allocation was performed by one of the co-authors with the

assistance of resident doctors at the antenatal clinic resulting in an unclear risk of bias.

Blinding

No placebo was used in three of the trials ([Ahmed 2015](#); [Nooh 2018](#); [Stutchfield 2005](#)). In the ASTECS ([Stutchfield 2005](#)) and [Nooh 2018](#) studies neither the participants nor the clinicians were blinded. Lack of blinding in randomised studies can potentially predispose to some exaggeration of the intervention effects for some outcomes through multiple pathways (different expectations from the two groups, biased assessment of the effect and/or differential administration of co-interventions) ([Higgins 2008](#)). This may be particularly true for outcomes involving subjective choices, e.g. whether admission to a special/intensive care unit will be preferred. Adequate blinding was reported in the [Nada 2016](#) trial where a placebo was used and participants, clinicians and outcome assessors were unaware of group allocations. The [Ahmed 2015](#) study did not use a placebo and therefore was at risk of performance bias, however the outcome assessors were unaware of group allocation therefore providing adequate concealment and minimising detection bias.

Incomplete outcome data

Three of the trials demonstrated adequate follow-up of patients and accounted for any missing participants ([Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)).

The ASTECS trial ([Stutchfield 2005](#)) was assessed as having a low risk of attrition bias. Between allocation and delivery, 7% of the treatment group and 4% of the control group were lost to follow-up, with 17% overall lost to follow-up or deviated from the protocol. In the [Nada 2016](#) trial, 645 participants were randomised to the treatment group and 645 to the control group. Data are reported on 616 participants in the intervention group and 611 participants in the control. Further information was obtained from the authors who adequately accounted for the dropout or exclusion of participants. The overall attrition rate was adequate (less than 5%). In the [Nooh 2018](#) trial, 700 participants were randomised to both the treatment and control groups. The data report on 636 participants in both the intervention group and the control groups. The authors reported on those participants that were lost to follow-up or not included in the analysis for both intervention and control groups. The overall attrition rate was adequate at 9%. In the [Ahmed 2015](#) trial there were no reports of dropout of cases from randomisation to ascertainment, which is unusual given the study design and the participants involved resulting in an assessment of an unclear risk of bias.

Selective reporting

All four trials included additional outcomes in their results that were not pre-specified in their methods ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)). In addition, [Ahmed 2015](#) did not pre-specify primary and secondary outcomes. The [Nada 2016](#) trial reported on admission to NICU for respiratory morbidity, however the primary outcome was admission to NICU with respiratory distress. Figures reported in the text of the results also reported on NICU admission rate, however the figures reported correspond to admission to primary baby care unit (PCBU). For the [Nada 2016](#) trial, the results do not report or mention the pre-specified secondary outcomes of air leak syndrome and pneumonia which are included in their methods. The [Nooh 2018](#) trial reports on

subgroup analysis of gestational age which was not pre-specified in their methods. In [Stutchfield 2005](#) no maternal outcomes were included and adverse maternal outcomes/events were reported, as well as additional outcomes that had not been pre-specified.

Other potential sources of bias

The [Ahmed 2015](#) trial did not report on the formal sample size calculation used to determine the sample size prior to commencing the trial. The [Nada 2016](#) trial calculated the sample size based on previous trial data. However due to the low event rates a sample sizes based on previous trial data when event rates of RDS are low may overestimate the true treatment effect. In [Nooh 2018](#), the low event rate could result in a type two error, although a power calculation was made. The study was not registered with a recognised trial registry. However, the study authors did comment that the study was approved by the local research and ethics committee of the hospital. Only the [Stutchfield 2005](#) trial reports on any assessment of long-term outcomes, but the non-blinded design potentially creates conditions for performance and detection bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) GRADE 'Summary of findings' table

We included four trials ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)), involving 3956 women and 3893 neonates.

Primary outcomes

Data were available for all the pre-specified primary outcomes.

All four trials, reported information on respiratory distress syndrome (RDS) and transient tachypnoea of the neonate (TTN). Prophylactic antenatal corticosteroids appeared to decrease the risk of RDS (risk ratio (RR) 0.48; 95% confidence interval (CI) 0.27 to 0.87; 4 studies; 3817 participants; low-quality evidence) [Analysis 1.1](#), and TTN (RR 0.43; 95% CI 0.29 to 0.65; Hartung-Knapp-Sidik-Jonkman (HKSJ) CI 0.20 to 0.68; 4 studies; 3821 participants; low-quality evidence) [Analysis 1.2](#).

Only one trial ([Stutchfield 2005](#)) reported data on admission to neonatal special care units (all levels) for respiratory complications. Prophylactic administration of corticosteroids was associated with a reduction in admission to neonatal special care for respiratory complications (RR 0.45; 95% CI 0.22 to 0.90; 1 study; 942 participants; low-quality evidence) [Analysis 1.3](#).

Three of the included trials reported data on admission to neonatal intensive care unit (NICU) for respiratory complications and demonstrated a difference in favour of administration of prophylactic corticosteroids (RR 0.42; 95% CI 0.22 to 0.79; HKSJ CI 0.19 to 0.83) [Analysis 1.4](#).

The risk differences were -0.01 (i.e. 1% reduction, 95% CI -2% to -0%) for RDS, -0.04 (i.e. 4% reduction, 95% CI -5% to -0%) for tachypnoea of the newborn (TTN) and -0.02 (i.e. 2% reduction, 95% CI -4% to -1%) for admission to NICU, highlighting the low rates of the two outcomes and better illustrating the actual gain from steroid administration.

In contrast, no reduction was found in the need for mechanical ventilation among the three trials that reported data on this

outcome (RR 0.67; 95% CI 0.27 to 1.68; HKSJ CI 0.22 to 1.75; 3 studies; 3441 participants; very low-quality evidence) ([Analysis 1.5](#)).

Subgroup analyses

There were too few trials included in any comparison for meaningful subgroup analysis. Results for separate subgroups are presented below.

Gestational age at birth

Due to the small number of events in the subgroups, a significant reduction in the incidence of TTN (RR 0.37; 95% CI 0.23 to 0.59; HKSJ CI 0.20 to 0.71) [Analysis 1.2](#) could only be shown for the interval 38 + 0 to 38 + 6 gestational weeks. There was no evidence of a subgroup difference (Test for subgroup differences: $\chi^2 = 2.26$, $df = 2$ ($P = 0.32$), $I^2 = 11.6\%$).

Specific corticosteroid used

Betamethasone was shown to decrease the risk for special care unit or NICU admission for respiratory complications (RR 0.47; 95% CI 0.23 to 0.94, and RR 0.15; 95% CI 0.03 to 0.64, respectively) [Analysis 2.3](#); [Analysis 2.4](#).

Dexamethasone appears to decrease the risk for RDS (RR 0.50; 95% CI 0.26 to 0.94) [Analysis 2.1](#), TTN (RR 0.37; 95% CI 0.25 to 0.54; HKSJ CI 0.20 to 0.64) [Analysis 2.2](#) and admission to NICU for respiratory complications (RR 0.51; 95% CI 0.31 to 0.84; HKSJ CI 0.11 to 0.86) [Analysis 2.4](#).

Secondary outcomes

All four trials reported data on the outcome of perinatal death. No association was found between prophylactic administration of antenatal corticosteroid and the rates of perinatal death (RR 0.67; 95% CI 0.11 to 4.10; 4 studies; 3893 participants) [Analysis 1.9](#).

Prophylactic antenatal corticosteroids appeared to reduce the overall rate of admission to neonatal special care (all levels) for any indication (i.e. respiratory and non-respiratory indications) (RR 0.62; 95% CI 0.43 to 0.89; 2 studies; 2169 participants) ([Analysis 1.6](#)) in the two trials that provided data, as well as the rate of admission to NICU for any indication, reported in one trial (RR 0.14; 95% CI 0.03 to 0.61; 1 study; 452 participants) [Analysis 1.7](#). Two of the included trials reported data on length of stay in the NICU. Antenatal steroids were associated with a reduction in the length of stay in the NICU (mean difference (MD) -2.70 days; 95% CI -2.76 to -2.64; HKSJ CI -2.80 to -2.52; 2 studies; 32 participants [Analysis 1.10](#)).

There were no reported events of neonatal sepsis, or maternal trauma infection; therefore results on these outcomes are non-estimable. The studies did not provide data on neonatal respiratory complications other than RDS and TTN, as well as on chronic lung disease, duration of mechanical ventilation, readmission after discharge, maternal postpartum infection or long-term infantile morbidity.

DISCUSSION

Summary of main results

The overall observed rate of respiratory distress syndrome (RDS) and transient tachypnoea of the newborn (TTN) in the control group was 1.7% and 5.4%, respectively, in the included studies ([Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#); [Stutchfield 2005](#)). Approximately 3.4%

of neonates in the control group were admitted to the neonatal intensive care unit (NICU) because of respiratory symptoms.

Prophylactic antenatal corticosteroids (betamethasone or dexamethasone pooled together) appeared to decrease the risk for RDS, TTN and admission to NICU for respiratory complications.

Specifically, prophylactic administration of antenatal corticosteroids appeared to reduce the rate of RDS by approximately 52% and the rate of TTN by approximately 57%. It also reduced the need for NICU admission, both due to respiratory morbidity (by approximately 58%) and for any indication. The reduction of NICU admissions due to respiratory reasons is consistent with the reduction of respiratory morbidity after corticosteroid administration. The reasons for the reduction in admissions due to non-respiratory morbidity are less clear; however, they may have some association of the non-blinded design of most studies and the potential (biased) inclination of the neonatologists that it was easier to admit neonates who had not received antenatal steroids.

The subgroup analysis was underpowered to detect differences for most comparisons, due to the small and variable number of events in the subgroups.

Overall completeness and applicability of evidence

Prophylactic antenatal corticosteroids reduce the rates of RDS, TTN and admission to special care or NICU for respiratory complications after elective caesarean section ([Ahmed 2015](#); [Nada 2016](#); [Stutchfield 2005](#)). Based on the summary effect sizes, 19 women would need to be administered antenatal corticosteroids to prevent one admission to NICU, 76 women would need to be administered prophylactic antenatal corticosteroids to prevent one case of RDS in the infant and 26 women would need to be administered a course of antenatal corticosteroids to prevent one case of TTN.

Currently there are only a limited number of trials which evaluate the effects of prophylactic antenatal corticosteroid administration. Four [Ahmed 2015](#); [Nada 2016](#); [Nooh 2018](#) - included; [Ammar 2013](#) - awaiting classification) are from Egypt, and two of the studies ([Ammar 2013](#) (awaiting classification) and ([Nada 2016](#)) come from the same hospital, covering different time periods and limiting the generalisability of the results. One of the trials ([Stutchfield 2005](#)) was a multicentre pragmatic study, and therefore the favourable results demonstrated may also reflect the true effect in regular clinical practice. However, it should be noted that two ([Ahmed 2015](#); [Stutchfield 2005](#)) of the three studies were not blinded, and admission to a special care or intensive care unit is largely a subjective choice and may be affected by knowledge of treatment assignment. Therefore, this outcome should be interpreted with caution.

Much larger numbers of participants are needed to adequately power clinical trials to evaluate the true impact of prophylactic antenatal corticosteroid administration on respiratory outcomes with associated morbidity (e.g. RDS) or uncommon maternal and neonatal complications. This is particularly important in view of the low rates of RDS and admission to NICU in this population, and therefore clinicians need to consider carefully the balance of statistical significance versus the clinical significance of the outcomes and the impact on the mother or baby.

The balance of risk is particularly important, as currently there is only limited evidence on any long-term follow-up of these infants. In a cohort of infants from the ASTECS trial ([Stutchfield 2005](#)), nearly twice as many betamethasone-exposed children did not attain English proficiency (13% versus 7%), and they were twice as likely to be ranked in the lower quartile of academic ability by teachers (18% versus 9%) ([Stutchfield 2013](#)). Although this follow-up study suffered from high attrition rate (49%), it highlights the need for caution and for future trials to consider long-term outcomes in their study design.

Quality of the evidence

Current evidence comes from four studies with some significant methodological concerns with regards to their conduct. The overall quality of the evidence for the primary outcomes was found to be low and very low ([Summary of findings for the main comparison](#)).

The main concern with a number of the included trials was the selective reporting of study outcomes. In specific instances the pre-specified study outcomes were not reported in the results, or the outcome was reported differently. In addition, a number of the trials were at high risk of performance bias, as both participants and health professionals were aware of their group allocation. Although all outcomes may be affected, it is likely that more subjective management decisions or assessments of outcome are more susceptible to bias arising from lack of blinding, as compared to more objective ones ([Higgins 2008](#)). Admission of neonates to special care is one such example - clinicians potentially biased in favour of the intervention may have been more likely to organise an admission to NICU for babies not exposed to corticosteroids. Such bias was possible, but less likely for radiological diagnosis of RDS or TTN by independent specialists. Similarly, admission to lower levels of special care may be more prone to bias than referral to NICU, as the latter would require more clinical and laboratory findings.

Two of the three studies ([Ahmed 2015](#); [Stutchfield 2005](#)) listed specific criteria used for the diagnosis of respiratory distress, which in turn was the criterion for admission to special care; however, this does not guarantee that the appraisal was totally objective and fail-proof for all cases.

The limitations of the evidence are reflected on its assessment as per the GRADE handbook. As shown in the [Summary of findings for the main comparison](#) for the outcomes of RDS, TTN and NICU admission for respiratory morbidity, the quality of the evidence was downgraded by one level for study limitations and one level for imprecision. Therefore, the quality of the evidence for these outcomes was judged as low. We additionally downgraded by one level for heterogeneity for the outcome of need for mechanical ventilation, therefore the quality for this outcome was judged as very low. In practical terms, this means that the true effect may be (or it is likely to be, for the outcome of need for mechanical ventilation) substantially different from our estimates, and the results should therefore be interpreted with caution.

A further potential concern is the lack of long-term outcomes in the studies, which could result in preferentially favouring antenatal corticosteroid administration, when potential long-term harms remain unknown.

Potential biases in the review process

We endeavoured to minimise the potential bias of the review process by ensuring an up-to-date search was undertaken to try and identify all relevant trials pertinent to the review. Two or more review authors independently appraised and extracted the trial data required and the data extraction process was complete and without missing data that would potentially exclude eligible studies. In the rare case where data were missing, or in order to adequately assess the risk of bias of the trial additional data was sought from the trial authors, who responded on average in a timely and clear manner. Two of the review authors conducted a GRADE assessment of the evidence for the primary outcomes included in the review. The analysis of the retrieved data was performed by using methods that take into account not only the potential within-study heterogeneity when present, but the scarcity of studies, therefore the presented point estimates and confidence intervals are more likely to represent unbiased estimates.

Agreements and disagreements with other studies or reviews

The favourable effect of antenatal corticosteroids on fetuses at risk for preterm birth has been reported in multiple trials and systematic reviews. Steroids were first tried as a means to accelerate fetal lung maturation and reduce perinatal respiratory morbidity; the latest update of the Cochrane systematic review reaffirms that antenatal steroids reduce the incidence of RDS (RR 0.66, 95% CI 0.56, 0.77) and moderate/severe RDS (RR 0.59, 95% CI 0.38 to 0.91). In contrast, there is no evidence that they affect the risk of chronic lung disease (RR 0.86, 95% CI 0.42 to 1.79); however this latter outcome included data from 818 infants only ([Roberts 2017](#)).

Antenatal corticosteroids appear to be equally effective in reducing neonatal respiratory morbidity in term infants delivered by elective caesarean section. Our results indicate that steroids reduce the risk of RDS by approximately 50% (RR 0.48, 95% CI 0.27 to 0.87) and TTN by about 60% (RR 0.43, 95% CI 0.29, 0.65). Transient tachypnoea was not an outcome in the review focusing on preterm infants ([Roberts 2017](#)), as it is a mild condition with normally good prognosis. However, TTN is a relevant outcome for the group of term neonates, as it increases the burden of neonatal units, and indeed the need for NICU admission for respiratory complications was reduced by 60% for cases having received antenatal steroids in our review (RR 0.42, 95% CI 0.22 to 0.79).

Apart from respiratory morbidity, antenatal corticosteroids in fetuses at risk for preterm birth can also reduce neonatal mortality (RR 0.69, 95% CI 0.59 to 0.81) and severe neonatal morbidity, including necrotising enterocolitis (RR 0.50, 95% CI 0.32 to 0.78) and intraventricular haemorrhage (RR 0.55, 95% CI 0.40 to 0.76), without increasing maternal and perinatal complications ([Sotiriadis 2015](#)). Moreover, there is some evidence, partly derived from non-randomised trials, that steroids in fetuses at risk for preterm birth can also reduce severe neurological morbidity in childhood ([Sotiriadis 2015](#)). Such events are uncommon in term infants and we therefore had either no data or very few data for these outcomes.

A common clinical question is whether either of betamethasone or dexamethasone is superior to the other regarding their effectiveness and safety profile. The paradigm of fetuses at risk

for preterm birth shows that there are no substantial differences between the two agents and the sample sizes for dexamethasone are usually much smaller than those for betamethasone, resulting in wide confidence intervals for the for the former drug (Roberts 2017). The reverse pattern was observed in our review, where there were much more abundant data for dexamethasone for most of the respiratory outcomes. As a result, the confidence intervals for the outcomes of RDS, TTN and the need for mechanical ventilation did not include the unit for dexamethasone but did so for betamethasone.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from four randomised controlled trials suggests that prophylactic corticosteroids before elective caesarean section at term may reduce the rates of respiratory distress syndrome (RDS), transient tachypnoea of the neonate (TTN) and admission to neonatal intensive care unit (NICU) for respiratory morbidity. Reduction in NICU admissions may be important in the light of increasing rates of caesarean section and overcrowding of neonatal units; however, caution is needed in interpreting these potential benefits, given the low quality of the evidence. Moreover, much larger samples and longer follow-up would be needed to identify potential differences in outcomes with recognised respiratory morbidity and potential long-term harms.

Implications for research

More studies with larger sample sizes are needed to investigate the effect of prophylactic betamethasone in the incidence of the more rare events of RDS, stratify the effectiveness of antenatal steroids according to gestational age at caesarean and provide more data on potential uncommon side effects and complications.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ahmed 2015

Methods	Parallel randomised control trial.
Participants	Location: 1 hospital in Egypt. Tmeframe: July 2012-December 2013. Eligibility: 452 women with a singleton pregnancy (228 intervention, 224 control) undergoing an elective caesarean section from 37 + 0 weeks' gestation to 39 + 6 weeks' gestation. Exclusion: women with multiple gestations or a fetus with a major congenital anomaly and those with other medical or obstetrical conditions warranting early or immediate delivery and/or women who had received prophylactic dexamethasone during the current pregnancy were excluded.
Interventions	Intervention: 2 doses of 12 mg IM dexamethasone administered 24 hours apart. n = 228. Control group: usual care (without antenatal steroids) n = 224.
Outcomes	Rates of RDS. Rates of TTN. Severity of RDS* (mild, moderate or severe according to the level of oxygen or ventilatory support). Rates of admission to the NICU.

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Ahmed 2015 (Continued)

Notes

All participants in the intervention group received the antenatal corticosteroids at 37 weeks' gestation irrespective of gestational age at delivery.

* severity of RDS was only assessed for the NICU admitted cases.

Funding source of study: no financial support received.

Declarations of interest among primary researchers of the study: no conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment on how the randomisation was conducted.
Allocation concealment (selection bias)	Unclear risk	No mention of how participants were randomised.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to a lack of placebo blinding was not possible for participants or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The attending paediatrician was blinded to the neonates in either group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data on dropout cases from randomisation to ascertainment or potentially no loss to follow-up.
Selective reporting (reporting bias)	High risk	Study did not pre-specify primary and secondary outcomes. Additional outcomes were included that were not mentioned in the methods.
Other bias	High risk	The study was not registered. Low event rate could result in a type 2 error. In view of the fact that participants were not stratified at trial entry it is unusual that there is 50% in both groups in the gestations of 39 - 39 + 6 in both groups. Baseline appears to be ok but no long-term follow-up appears to be planned. No formal sample size calculation presented.

Nada 2016

Methods	Parallel randomised control trial.
Participants	Location: 1 hospital in Egypt. Timeframe: November 2011-December 2014. Eligibility criteria: women with a singleton pregnancy (as calculated from the first day of their last menstrual period) between 38 and 38 + 6 weeks' of pregnancy, aged between 20 and 40 years of age undergoing an elective caesarean section. Exclusion criteria: women with multiple gestations or any medical problems that could affect fetal well-being, or a fetus with a major congenital anomaly, intrauterine growth restriction, oligohydramnios or

Nada 2016 (Continued)

	hydramnios. Women who developed spontaneous labour or had uterine contractions, or tenderness were excluded.
Interventions	Intervention: 4 doses of 8 mg of dexamethasone administered intramuscularly 12 hours apart, 48 hours prior to elective caesarean section. n = 645. Placebo: in the placebo group: women received IM saline prior to elective caesarean section. n = 645.
Outcomes	Primary outcome: rates of NICU admissions with respiratory distress. Secondary outcomes: 1. rates of RDS 2. rates of TTN; 3. development of neonatal respiratory complications (pneumonia, air leak syndrome, perinatal death (within the first 24 hours); 4. the need for mechanical ventilation.
Notes	Consent: verbal informed consent. Funding source of study: not declared Declarations of interest among primary researchers of the study:None declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using computer-based tables. Further information was obtained from the author. The randomisation was performed by 1 of the co-authors in the antenatal clinic.
Allocation concealment (selection bias)	Unclear risk	Allocation was performed using the closed envelope technique. The trial authors were contacted and explained this was done by one of the co-authors in the clinic. The authors and residents of the clinic were aware of the allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A placebo was used in the study. Participants were blinded to the group allocation. Further information was obtained by the authors: who reported that while the trial authors and residents of the antenatal clinic were aware of the group allocation and administered the ACS or placebo, individuals performing the caesarean section and assessing the infants were not aware of group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No direct mention but due to placebo it is unlikely that assessor knew the group allocation of the infants. However author provided further information that surgeons performing the operation and paediatricians assessing the infants were not aware of the allocation of the intervention/placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome group: Report no loss to follow-up, however fewer numbers are reported in the results table. Further information provided by the authors: losses were due to spontaneous labour and PPROM, therefore participants were excluded. Attrition < 5%.
Selective reporting (reporting bias)	High risk	Report on admission to NICU however their primary outcome is admission to NICU with respiratory distress. Figures reported on this outcome are for admission to the primary baby care unit (PBCU). Also the study reports on NICU admission for respiratory morbidity however the primary outcome was reported as respiratory distress. No mention of secondary outcomes of air leak syn-

Nada 2016 (Continued)

drome and pneumonia. The authors also report on Apgar scores however this was not included in their outcomes.

Other bias	High risk	No long-term follow-up appears to be planned. Sample size is based on previous trial data but event rates of RDS are low and therefore the sample size calculation may overestimate the true treatment effect.
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Nooh 2018

Methods	Randomised controlled trial
Participants	Location: 1 hospital in Egypt. Timeframe: September 2012-August 2016. Eligibility criteria: women with a singleton pregnancy in the cephalic presentation planned to have a cesarean section at 38 weeks' gestation of pregnancy or beyond. Exclusion criteria: women with multiple gestations or any obstetric disorders (such as pre-eclampsia, antepartum haemorrhage, intrauterine growth restriction, breech presentation etc) or medical disorders (such as asthma, hypertension, diabetes, intrauterine infection etc) or history of smoking or peptic ulceration were excluded.
Interventions	Intervention: 3 doses of 8 mg/2mL of dexamethasone administered intramuscularly 8 hours apart, 24 hours after the last dose n = 636. Placebo: in the placebo group: usual care (without antenatal steroids)n = 636.
Outcomes	Primary: admission to NICU with respiratory morbidity Secondary: incidence of TTN, RDS and need for mechanical ventilation.
Notes	Additional outcomes including neonatal death and neonatal sepsis were reported on. Funding source of study: no financial support was received by the authors for the research, authorship or publication of the manuscript. Declarations of interest among primary researchers of the study: no conflicts disclosed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using a computer-generated randomisation sequence using serial number, opaque sealed envelopes.
Allocation concealment (selection bias)	Low risk	Allocation was performed using the closed envelope technique. Opaque sealed envelopes were used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to a lack of placebo blinding was not possible for participants or personnel.
Blinding of outcome assessment (detection bias)	High risk	The authors comment that blinding of participants and health care givers was neither desirable or possible.

Nooh 2018 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	1400 women were recruited resulting in 700 in each group. Sixty-four patients were lost/not included in both groups. Reasons were provided for exclusions.
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes were reported. However a number of additional outcomes were reported. A subgroup analysis was conducted which was not pre-specified in the methods.
Other bias	High risk	The low event rate could result in a type two error, however a power calculation was made. The study was not registered with a recognised trial registry. However, the authors did comment that the study was approved by the local research and ethics committee of the hospital.

Stutchfield 2005

Methods	Parallel randomised control trial.
Participants	Location: 10 hospitals in the UK. Timeframe: February 1995-December 2002. Eligibility: women with a singleton pregnancy undergoing a planned elective cesarean section at or after 37 weeks' gestation. Exclusion: women with severe maternal hypertension, history of peptic ulceration, severe fetus rhesus sensitisation and evidence of intrauterine infection were excluded. Stutchfield 2013 : follow-up of participants (now aged 8-15 years) from the 4 largest recruiting centres from the original trial.
Interventions	Intervention: 2 doses of 12 mg of betamethasone administered intramuscularly 24 hours apart, 48 hours before delivery. n = 467. Control: treatment as usual (without antenatal corticosteroids). n = 475.
Outcomes	Primary outcome: admission to special care baby unit with respiratory distress. Secondary outcomes: 1. severity of respiratory distress (mild, moderate or severe, according to reported arterial gases and oximetry measurements); 2. level of care needed. Stutchfield 2013 : assessment of long-term behavioural, cognitive or developmental outcome, and the risk of asthma or atopic disease using questionnaires and general health and school performance.
Notes	Funding source of study: Wales Office of Research and Development in health and social care (WORD) and Conwy and Denbighshire NHS Trust. Declarations of interest among primary researchers of the study: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation through a random number generator in MS Excel at the trial centre.

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Stutchfield 2005 (Continued)

Allocation concealment (selection bias)	Low risk	The list of treatment allocation (centrally kept) was concealed from all participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel were not blinded to the participants group allocation potentially influencing outcomes. Participants were not blinded to their group allocation, which could impact on maternal outcomes reported but is unlikely to influence other outcomes. Stutchfield 2013: unclear risk of bias as no comment on whether professionals (teachers) were aware of treatment allocation. Participants (mothers) were aware of group allocation which could influence outcome (survey response).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded to the participants group allocation potentially influencing outcomes. Participants were not blinded to their group allocation which could impact on maternal outcomes reported but is unlikely to influence other outcomes. Stutchfield 2013: unclear risk of bias as no comment on whether professionals (teachers) were aware of treatment allocation prior to completing questionnaire. Participants (mothers) were aware of group allocation which could influence outcome (survey response).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rate of loss between allocation and delivery: 7% in treatment group and 4% in controls; total losses or deviations from protocol 17%, described in detail by authors. Stutchfield 2013: high risk of attrition bias. 862 participants from the 4 largest recruiting centres were eligible, 824 (96%) were traced and 799 (93%) were successfully contacted 51% completed the questionnaire (217 treatment versus 190 control). 386 of the 407 completed maternal questionnaires, gave consent for schools to be contacted regarding performance and 352 reports (91%) were received.
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes were pre-specified. However, no maternal outcomes were included and adverse maternal outcomes/events were reported. Additional outcomes were reported including: Apgar scores at 1 and 5 minutes, time in special care, time on oxygen and maximum inspired oxygen.
Other bias	High risk	The non-blinded design potentially creates conditions for performance and detection bias.

ACS: antenatal corticosteroids

IM: intramuscular

NICU: neonatal intensive care unit

PPROM: preterm prelabour rupture of the membranes

RDS: respiratory distress syndrome

TTN: tachypnoea of the newborn

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Christofori 2011	This trial was conducted in women from 34-36 weeks of gestation.
Jain 2005	This trial was terminated due to slow enrolment and lack of funding.
Langer 2008	Comparison groups are of different gestational age.

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Study	Reason for exclusion
Sananes 2017	Comparison groups are of different gestational age.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ammar 2013

Methods	Parallel randomised control trial.
Participants	Location: 1 hospital in Egypt. Timeframe: March 2010-March 2011. Eligibility: women scheduled to undergo elective caesarean section at or after 37 completed weeks (based on the last menstrual period). Exclusion criteria: women with obstetric complications (including pre-eclampsia, antepartum haemorrhage, fetal anomaly, hypertensive disease), chronic disease (including diabetes mellitus and renal disease) or preoperative infection were excluded.
Interventions	Intervention: 2 doses of 12 mg dexamethasone administered intramuscularly 12 hours apart, 48 hours before delivery. n = 300. Control: usual care (without antenatal corticosteroids) n = 300.
Outcomes	1. Admission to NICU with RDS 2. TTN 3. RDS 4. Need for mechanical ventilation
Notes	Trial methods reports this is a double-blinded prospective randomised study and that patients were randomly allocated to 2 groups by closed envelope technique. The trial authors were contacted for further information to confirm how randomisation was conducted.

NICU: neonatal intensive care unit
RDS: respiratory distress syndrome
TTN: tachypnoea of the newborn

Characteristics of ongoing studies *[ordered by study ID]*

Ahmadpour-kacho 2015

Trial name or title	Effect of antenatal steroid before elective cesarean section (C/S) on prevention of respiratory morbidity of term neonates
Methods	Parallel randomised control trial.
Participants	Location: 2 hospitals in Iran. Timeframe: August 2015-February 2015 Eligibility: women undergoing repeat elective caesarean sections at or after 39 weeks' gestation (based on USS and by the researcher's physical examination after birth using the Ballard Scoring System).

Ahmadpour-kacho 2015 (Continued)

Exclusion criteria: premature delivery, infection, diabetes, premature rupture of membranes and the use of steroids before birth and caesarean sections for other indications (underlying medical or obstetric disease, e.g. cephalopelvic disproportion, retinal detachment and macrosomia). Women with a fetus with underlying disease such as intrauterine growth restriction, macrosomia, perinatal infection and congenital anomalies were excluded.

Interventions	Intervention: 2 doses of 12 mg of betamethasone administered 24 hours apart, 48 hours prior to caesarean section. Control group: usual care (without antenatal corticosteroids).
Outcomes	Need for resuscitation Respiratory distress Need for oxygen administration Admission to the neonatal unit Admission to the neonatal intensive care unit (and doing diagnostic and therapeutic studies) Need for hospitalisation Length of hospital stay
Starting date	03/08/2015
Contact information	Dr Mousa Ahmadpour-Kacho Babol University of Medical Sciences Gangafrooz Babol Mazandaran Iran 00981132197667/00989111122855 mousa_ahmadpour@hotmail.com
Notes	Recruitment completed. IRCT registration number: IRCT2015090923963N1

Custo 2007

Trial name or title	Use of antenatal dexamethasone in late pregnancy and its effect on incidence of neonatal respiratory distress after elective caesarean sections.
Methods	Randomised controlled trial.
Participants	Women planned to deliver by caesarean section after 37 completed gestational weeks.
Interventions	Intervention: dexamethasone, 12 mg x 2. Control: usual care (no steroids).
Outcomes	Admission to special care baby unit with respiratory distress.

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Custo 2007 (Continued)

Apgar scores.

Starting date	Not known.
Contact information	Custo R. Obstetrics and Gynaecology Department St. Luke's Hospital Malta.
Notes	

DATA AND ANALYSES
Comparison 1. Antenatal corticosteroids versus no steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	4	3817	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.87]
1.1 Birth before 38 + 0 weeks	2	215	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.08, 1.07]
1.2 Birth 38 + 0 to 38 + 6 weeks	4	2406	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.28, 1.16]
1.3 Birth at or after 39 + 0 weeks	3	1196	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.07, 3.07]
2 Transient tachypnoea of the neonate	4	3821	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.29, 0.65]
2.1 Birth before 38 + 0 weeks	2	221	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.08, 10.58]
2.2 Birth 38 + 0 to 38 + 6 weeks	4	2406	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.59]
2.3 Birth at or after 39 + 0 weeks	3	1194	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.29, 2.19]
3 Admission to neonatal special care (all levels) for respiratory complications	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.22, 0.90]
3.1 Birth before 38 + 0 weeks	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.16, 1.57]
3.2 Birth 38 + 0 to 38 + 6 weeks	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.17, 1.14]
3.3 Birth at or after 39 + 0 weeks	1	368	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Admission to neonatal intensive care unit for respiratory complications	3	3441	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.79]
5 Need for mechanical ventilation	3	3441	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.27, 1.68]
6 Admission to neonatal special care (all levels) for any indication	2	2169	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.43, 0.89]
6.1 Birth before 38 + 0 weeks	1	145	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.28, 1.71]
6.2 Birth 38 + 0 to 38 + 6 weeks	2	1656	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.34, 0.94]
6.3 Birth at or after 39 + 0 weeks	1	368	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.36, 3.36]
7 Admission to neonatal intensive care unit for any indication	1	452	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.61]
8 Neonatal sepsis	2	2214	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.95]
9 Perinatal death	4	3893	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.11, 4.10]
10 Length of stay in neonatal intensive care unit	2	32	Mean Difference (IV, Random, 95% CI)	-2.70 [-2.76, -2.64]
11 Wound infection	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 1 Respiratory distress syndrome.

Analysis 1.2. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 2 Transient tachypnoea of the neonate.

Analysis 1.3. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 3 Admission to neonatal special care (all levels) for respiratory complications.

Analysis 1.4. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 4 Admission to neonatal intensive care unit for respiratory complications.

Analysis 1.5. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 5 Need for mechanical ventilation.

Analysis 1.6. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 6 Admission to neonatal special care (all levels) for any indication.

Analysis 1.7. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 7 Admission to neonatal intensive care unit for any indication.

Analysis 1.8. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 8 Neonatal sepsis.

Study or subgroup	Antenatal corticosteroids n/N	Placebo/no corticosteroid n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					
			Favours treatment 0.02 0.1 1 10 50 Favours control		

Analysis 1.9. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 9 Perinatal death.

Study or subgroup	Antenatal corticosteroids n/N	Placebo/no corticosteroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ahmed 2015	0/228	0/224			Not estimable
Nada 2016	1/616	2/611		57.16%	0.5[0.05,5.46]
Nooh 2018	1/636	1/636		42.84%	1[0.06,15.95]
Stutchfield 2005	0/467	0/475			Not estimable
Total (95% CI)	1947	1946		100%	0.67[0.11,4.1]
Total events: 2 (Antenatal corticosteroids), 3 (Placebo/no corticosteroid)					
Heterogeneity: Tau ² =0; Chi ² =0.14, df=1(P=0.71); I ² =0%					
Test for overall effect: Z=0.43(P=0.66)					
			Favours treatment 0.02 0.1 1 10 50 Favours control		

Analysis 1.10. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 10 Length of stay in neonatal intensive care unit.

Study or subgroup	Antenatal corticosteroids		Placebo/no corticosteroid		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Ahmed 2015	2	1.1 (0)	14	3.8 (0.1)		99.97%	-2.7[-2.76,-2.64]
Stutchfield 2005	2	2.5 (2.1)	14	4.6 (3.4)		0.03%	-2.14[-5.58,1.3]
Total ***	4		28			100%	-2.7[-2.76,-2.64]
Heterogeneity: Tau ² =0; Chi ² =0.1, df=1(P=0.75); I ² =0%							
Test for overall effect: Z=84.2(P<0.0001)							
					Favours treatment -4 -2 0 2 4 Favours control		

Analysis 1.11. Comparison 1 Antenatal corticosteroids versus no steroids, Outcome 11 Wound infection.

Study or subgroup	Antenatal corticosteroids n/N	Placebo/no corticosteroid n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Stutchfield 2005	0/467	0/475			Not estimable
Total (95% CI)	467	475			Not estimable
Total events: 0 (Antenatal corticosteroids), 0 (Placebo/no corticosteroid)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
			Favours treatment 0.02 0.1 1 10 50 Favours control		

Comparison 2. Antenatal corticosteroids versus no steroids (subgroup analysis by type of steroid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	4	3893	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.25, 0.83]
1.1 Dexamethasone	3	2951	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.94]
1.2 Betamethasone	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.73]
2 Transient tachypnoea of the neonate	4	3893	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.28, 0.56]
2.1 Betamethasone	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.25, 1.14]
2.2 Dexamethasone	3	2951	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.25, 0.54]
3 Admission to neonatal special care (all levels) for respiratory complications	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.94]
3.1 Betamethasone	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.94]
3.2 Dexamethasone	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Admission to neonatal intensive care unit for respiratory complications	3	3441	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.27, 0.67]
4.1 Betamethasone	1	942	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.64]
4.2 Dexamethasone	2	2499	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.31, 0.84]
5 Need for mechanical ventilation	3	3441	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.34, 1.19]
5.1 Betamethasone	1	942	Risk Ratio (M-H, Fixed, 95% CI)	4.07 [0.46, 36.27]
5.2 Dexamethasone	2	2499	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.25, 0.99]

Analysis 2.1. Comparison 2 Antenatal corticosteroids versus no steroids (subgroup analysis by type of steroid), Outcome 1 Respiratory distress syndrome.

Study or subgroup	Antenatal corticosteroid n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Dexamethasone					
Ahmed 2015	2/228	8/224		24.41%	0.25[0.05,1.14]
Nada 2016	4/616	10/611		30.36%	0.4[0.13,1.26]
Nooh 2018	8/636	10/636		30.24%	0.8[0.32,2.01]
			Favours treatment 0.01 0.1 1 10 100 Favours control

Analysis 2.2. Comparison 2 Antenatal corticosteroids versus no steroids (subgroup analysis by type of steroid), Outcome 2 Transient tachypnoea of the neonate.

Analysis 2.3. Comparison 2 Antenatal corticosteroids versus no steroids (subgroup analysis by type of steroid), Outcome 3 Admission to neonatal special care (all levels) for respiratory complications.

Analysis 2.4. Comparison 2 Antenatal corticosteroids versus no steroids (subgroup analysis by type of steroid), Outcome 4 Admission to neonatal intensive care unit for respiratory complications.

Analysis 2.5. Comparison 2 Antenatal corticosteroids versus no steroids (subgroup analysis by type of steroid), Outcome 5 Need for mechanical ventilation. **WHAT'S NEW**

Date	Event	Description
14 June 2017	New search has been performed	Search updated and and three new included studies have been added to the review in this update. A 'Summary of findings' table has been added.
14 June 2017	New citation required but conclusions have not changed	The protective effect of antenatal corticosteroids was slightly attenuated for the respiratory outcomes of the neonate but the inferences did not change for all comparisons.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 4, 2009

Date	Event	Description
3 May 2011	Amended	Corrected typo.

CONTRIBUTIONS OF AUTHORS

For the protocol: Alexandros Sotiriadis (AS) prepared the first draft and revised it in response to editorial comments. George Makrydimas (GM) and John PA Ioannidis (JI) commented on the drafts.

For this review: AS and GM assessed potential studies. Stefania Papatheodorou (SP) and AS extracted the data, entered it into RevMan, assessed studies for risk of bias, and tabulated the results. All authors contributed in preparation of the review.

For the update of this systematic review 2017, AS and EM assessed potential studies, extracted the data and entered the data into RevMan. EM and AS also assessed studies for risk of bias, tabulated the results and completed the GRADE 'Summary of findings' table. All authors commented on drafts.

DECLARATIONS OF INTEREST

Alexandros Sotiriadis: none known.

George Makrydimas: none known.

Stefania Papatheodorou: none known.

John PA Ioannidis: none known.

Emma McGoldrick: I am an author of an overview relating to antenatal corticosteroids ([McGoldrick 2016](#)). This review is potentially eligible for inclusion in the overview. I will not be involved in any assessment or data extraction and two independent review authors will assess this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original outcome "Admission to the neonatal special care unit or above" was split into a primary outcome (Admission to neonatal special care for respiratory morbidity (all levels of care or intensive care unit (NICU))) and a secondary outcome (Admission to neonatal special care for any indication (all levels of care or intensive care unit (NICU))). This was done because, in the case of non-blinded trials, there is a possibility of bias, as infants in the treatment group may have been less likely to have had their reason for admission classified as 'respiratory' because they were known to have received corticosteroids. Furthermore, special care was split into two categories "special care - all levels" and "special care - NICU", as different levels of care may reflect different severity of respiratory distress.

The updated review includes three additional outcomes which look at the long-term outcomes of administration of antenatal corticosteroids to the infant as a child. The authors felt that these outcomes were important to include in view of concerns regarding long-term effects of antenatal corticosteroid administration.

A 'Summary of findings' table has been incorporated for this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Apnea [prevention & control]; Betamethasone [*therapeutic use]; Cesarean Section [*adverse effects]; Dexamethasone [*therapeutic use]; Elective Surgical Procedures; Intensive Care Units, Neonatal; Patient Admission [statistics & numerical data]; Prenatal Care; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; Respiratory Distress Syndrome, Newborn [*prevention & control]; Tachypnea [epidemiology]; Term Birth

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy