National Institute for Health and Care Excellence

Draft for consultation

Preterm labour and birth

[B] Evidence review for effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation

NICE guideline NG25 (update)

Evidence review underpinning recommendations 1.9.4 to 1.9.6 and a research recommendation in the NICE guideline

February 2022

Draft for consultation

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation

Review question

What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Introduction

Babies born preterm have immature lungs which can lead to respiratory difficulties and they may require oxygen therapy or ventilation. This can lead to chronic lung disease, also known as bronchopulmonary dysplasia, which can affect the baby until they are a year old; some babies may go on to develop problems with lung health into childhood and later life.

There is good evidence for the effectiveness of maternal corticosteroids aiding lung maturation to prevent acute complications. These should be administered prior to a premature birth. Predicting when women are likely to go into preterm labour is difficult: women may present with signs indicating that preterm birth may be imminent and so be given maternal corticosteroids. However, in some cases, the preterm birth does not occur, but women may present again days or even weeks later, again at risk of preterm birth. In this situation it is not known if a repeat course of maternal corticosteroids should be given, as there remain several concerns about the adverse effects of repeat courses of corticosteroids, particularly relating to birthweight, growth and neurodevelopmental delay.

The aim of this review is to determine the effectiveness of repeat courses of maternal corticosteroids, and to determine if the benefits of repeat courses outweigh the risks.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Pregnant women who are considered to be at risk of preterm labour and birth because they have a history of: ○ spontaneous preterm birth ○ second stage caesarean birth at full cervical dilatation ○ preterm pre-labour rupture of membranes ○ mid-trimester loss ○ cervical trauma (including surgery – for example, previous cone biopsy [cold knife or laser], large loop excision of the transformation zone [LLETZ – any number] and radical diathermy). • Pregnant women who are considered to be at risk of preterm labour and birth because they have a short cervix that has been identified on ultrasound scan and/or bulging membranes in the current pregnancy • Pregnant women with preterm pre-labour rupture of membranes. • Pregnant women clinically suspected to be in preterm labour • Women diagnosed to be in spontaneous preterm labour • Women having a planned preterm birth. • Women who received a single course of corticosteroids prior to being randomised to receive either a repeat course or placebo/ no further treatment • Women with multi-fetal pregnancies
Intervention	• Repeat courses of corticosteroids (for example, betamethasone, dexamethasone) administered to the women intravenously, intramuscularly or orally
Comparison	• Placebo • No further treatment (that is, single dose of corticosteroid)
Outcome	**Critical** • Perinatal mortality • Neurodevelopmental delay at 2 years (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) ○ Severe (score of >2 SD below normal on validated assessment scales, or on Bayley assessment scale of MDI or PDI <70 or complete inability to assign score due to CP or severe cognitive delay) ○ Moderate (score of 1-2 SD below normal on validated assessment scales, or on Bayley assessment scale of MDI or PDI 70-84) • Neonatal admission **Important** • Intraventricular haemorrhage • Chronic lung disease (for example, BPD, oxygen dependency at 36 weeks) • Birthweight • Growth at 2 years (weight, head circumference)

BPD: bronchopulmonary dysplasia; CP: cerebral palsy; LLETZ: large loop excision of the transformation zone; MDI: mental developmental index; PDI: psychomotor developmental index; SD: standard deviation.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Outcomes from the individual included studies were meta-analysed to give overall effect estimates and stratified effect estimates, the latter of which were reported in a hierarchy as

per the protocol. Sub-group effect estimates reported in the individual patient data (IPD) which corresponded to stratifications itemised in the protocol were included in a separate GRADE table, but could not be analysed in a hierarchy due to insufficient information (sample size and standard deviation). In cases where the stratified outcomes meta-analysed from the individual studies reported on the same sub-group as the IPD sub-group analyses (for example, perinatal mortality, ≤7 days between repeat courses), effect estimates were reported from the IPD sub-group analyses to avoid over-reporting.

Statistical significance was used to determine benefits and harms for the sub-group effect estimates reported in the IPD; this was because 90% confidence intervals could not be calculated from the available information to determine minimally important differences as per the protocol.

Effectiveness evidence

Included studies

One IPD meta-analysis (Crowther 2019) including 11 randomised controlled trials (RCTs) was included (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, TEAMS, and Wapner 2006). Two additional RCTs were included (Atarod 2014 and Ernawati 2016).

The included studies are summarised in Table 2.

All studies compared at least one repeat course of corticosteroids to a single course of corticosteroids. All studies included participants who had already received a single course of corticosteroids prior to randomisation.

With the exception of one study which included participants who were diagnosed with preterm preeclampsia (Ernawati 2016), all studies included women who were at risk of preterm labour and birth or who had a history of preterm labour and birth. The interval between repeat courses varied: 9 studies had an interval of ≤7 days (Aghajafari 2002, Crowther 2006, Ernawati 2016, Guinn 2001, Mazumder 2008, McEvoy 2002, TEAMS, Peltoniemi 2007 and Wapner 2006) and 4 studies had an interval of 8 to ≤14 days between repeat courses (Atarod 2014, Garite 2009, McEvoy 2010 and Murphy 2008). Three studies administered one repeat course only (Garite 2009, McEvoy 2010 and Peltoniemi 2007), 1 study administered a maximum of 2 repeat courses (Atarod 2014) and 8 studies administered repeat courses until 33 to 34 weeks gestational age or until birth, whichever came first (Aghajafari 2002, Crowther 2006, Guinn 2001, Mazumder 2008, McEvoy 2002, Murphy 2008, TEAMS, and Wapner 2006). These 12 studies all administered betamethasone by intramuscular (IM) injection and the total dose per course varied from ≤12 mg (Crowther 2006, Peltoniemi 2007) to 24 mg (Aghajafari 2002, Atarod 2014, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, TEAMS and Wapner 2006). One study administered an intravenous (IV) course of 25 mg methylprednisolone for 7 days, lowering to 12.5 mg until birth, following an initial course of dexamethasone (Ernawati 2016).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Atarod 2014 Randomised controlled trial Iran	N = 1348 women, GA 28-35 weeks at risk of preterm birth, history of preterm birth, placenta previa, chronic detachment and cerclage history, who had received a single course of betamethasone (2 x 12 mg, every 24 hours) 10 days previously	2 x 12 mg betamethasone IM (24 hours apart), repeated every 10 days (maximum of 3 total courses)	2 x placebo IM, every 24 hours, repeated every 10 days for up to 2 (maximum of 3 total courses)	• Perinatal mortality • Birthweight
Crowther 2019 Individual participant data meta-analysis United States, Canada, Australia, New Zealand, Finland, India, United Kingdom	K = 11 (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, TEAMS, Wapner 2006) N = 4857 women at risk of preterm birth who had received a single course of corticosteroids ≥ 7 days previously; 5915 babies	Repeat courses of betamethasone IM (12- 24 mg, every 7- 14 days)	Placebo or no intervention	• Perinatal mortality • Neurodevelop mental delay at 2 years • Neonatal admission • Intraventricular haemorrhage • Chronic lung disease • Birthweight • Growth at 2 years (weight, head circumference)
Ernawati 2016 Randomised controlled trial Indonesia	N = 48 women, GA 30-34 weeks, with preterm preeclampsia who had received a single course of dexamethasone IM (4 x 6mg every 12 hours) for fetal lung maturation 48 hours previously	25 mg of methylprednisolone IV for 7 days, followed by 12.5 mg IV daily until birth	25 mg of matching placebo IV for 7 days followed by placebo IV daily until birth	• Perinatal mortality • Intraventricular haemorrhage • Birthweight

GA: gestational age; IM: intramuscular; IV: intravenous; mg: milligrams

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

All studies randomised participants after they had received an initial single repeat course of corticosteroids to receive repeat courses or no further treatment (or placebo). Estimates calculated from meta-analysis of individual studies stratify by total dose per repeat course, which refers to the total amount of corticosteroids given for each individual repeat course. Effect estimates taken from the IPD meta-analysis are stratified by total overall dose, which refers to the overall total amount of betamethasone the individual received over all repeat courses.

In terms of perinatal mortality, 10 RCTs provided very low to moderate quality evidence that there was no important difference for women who received an initial single course followed by repeat courses of corticosteroids compared to women who received an initial single course of corticosteroids only and either placebo or no further intervention. The effect did not differ when the evidence was stratified in a hierarchy by the pre-specified variables: interval between repeat courses, number of repeat courses, type of corticosteroid, total dose per course. Subgroup effect estimates from the IPD meta-analysis provided moderate quality evidence of an important benefit on perinatal mortality (reported as death at any time) for women who received an overall total dose between 24 mg to 48 mg betamethasone from repeat courses compared to women who received an initial single course. There was low to moderate quality evidence of no important difference in perinatal mortality for any of the other sub-groups included in the IPD meta-analysis: gestational age (at time of first dose), interval between repeat courses, reason the women was at risk of preterm labour and birth (PTLB) or other overall total doses of corticosteroids.

Two RCTs provided very low to low quality evidence of no important difference in terms of severe neurodevelopmental delay for babies of women who received repeat courses of corticosteroids compared to babies of women who received a single course of corticosteroids. Both studies administered ≥1 course of betamethasone IM at ≤7 day intervals between courses. In terms of moderate neurodevelopmental delay, there was low to moderate quality evidence of a possible important benefit of repeat courses of corticosteroids compared to a single course, however, when the data was stratified by total dose of betamethasone per course, effect estimates from the individual studies provided no evidence of important difference for babies of women who received ≤12 mg per repeat course and evidence of no important difference for babies of women who received >12 mg to 24 mg per repeat course compared to women who received a single course only.

Two RCTs provided high quality evidence of no important difference in terms of neonatal admission for babies of women who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone. Both studies administered more than 1 course of betamethasone IM and the effect did not differ when the evidence was stratified by interval between repeat courses (≤7 days and 8 to ≤14 days) and total dose per course (≤12 mg per course and >12 mg to 24 mg per course).

In terms of intraventricular haemorrhage (IVH), the outcome was reported as all grades of IVH and grades III-IV IVH only. Overall, for all grades of IVH, there was moderate quality evidence from 6 RCTs of no important difference for babies of women who received repeat courses of corticosteroids compared to babies of women who received a single course of corticosteroids. There was very low to low quality evidence of no important difference for this comparison when the evidence was stratified by the pre-specified variables and no evidence of important difference for women who received 1 course of IM betamethasone, 8 to ≤14 days between courses with a total dose per course of >12 mg to 24 mg. In terms of IVH grades III-IV, there was low quality evidence from 7 RCTs of no important difference for the overall estimate for babies of women who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone and when the evidence was stratified to include only women who received ≥1 repeat courses of IM betamethasone with ≤7 days between repeat courses or when stratified by women who

received IM betamethasone with 8 to ≤14 days between repeat courses. When the evidence was further stratified by the pre-specified variables, there was no evidence of important difference, indicating a lack of statistical power to detect differences.

Overall, there was no evidence of important difference from 8 RCTs in terms of chronic lung disease for babies of women who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone. When the evidence was stratified by the pre-specified variables, the quality of the evidence ranged from low to moderate. There was evidence of no important difference when the evidence was stratified by ≤7 days between repeat courses of IM betamethasone for women receiving ≥1 repeat course for both ≤12 mg per course and >12 mg to 24 mg per course stratifications. There was evidence of no important difference for women receiving 1 repeat course of ≤12 mg IM betamethasone at an interval of 8 to ≤14 days. Sub-group effect estimates from the IPD meta-analysis provided low to moderate quality evidence of no important difference for babies of women who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone and this did not differ by gestational age (GA), number of repeat courses, reason the women was at risk of PTLB or overall total dose of betamethasone.

In terms of birthweight (as measured in grams), overall, 11 RCTs provided high quality evidence of an important harm for babies of women who received repeat courses of corticosteroids compared to babies of women who received a single course of corticosteroids. When the evidence was stratified by pre-specified variables there was an important harm for babies of women who received ≥1 repeat course of >12 mg to 24 mg of betamethasone IM with an interval of 8 to ≤14 days between repeat courses compared to women who received a single course. There was evidence of no important difference for women who received ≥1 repeat course of ≤12 or >12 mg to 24 mg per course of betamethasone IM or 25 mg for 7 days, followed by 12.5 mg until birth of methylprednisolone IV at an interval of ≤7 days or for women who received 1 repeat course only of ≤12 or >12 mg to 24 mg per course of betamethasone IM at an interval of 8 to ≤14 days between repeat courses, compared to babies of women who received a single course.

Sub-group effect estimates from the IPD meta-analysis provided high quality evidence of important harm in terms of birthweight (as measured by z-scores) for babies of women who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone. In terms of birthweight by GA, there was an important harm for women with GA <30 weeks, but evidence of no important difference for babies of women with a GA 30 to <34 weeks for those who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone. In terms of birthweight by interval between courses, there was an important harm on birthweight for babies of women who received repeat courses with an interval of ≤7 days, and evidence of no important difference for babies of women who received repeat courses with an interval of ≥8 days, compared to babies of women who received a single course only. There was evidence of no important difference in terms of birthweight by the reason women were considered to be at risk of PTLB. In terms of birthweight by overall total dose of betamethasone, there was evidence of no important difference on birthweight for babies of women who received ≤12 mg or >12-24 mg and an important harm for babies of women who received >24-48 mg and >48 mg, compared to babies of women who received a single course only.

In terms of growth outcomes (weight and head circumference) at 2 years, there was moderate to high quality evidence from 3 studies of no important difference for babies of women who received repeat courses of betamethasone compared to babies of women who received a single course of betamethasone.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

No evidence was identified which was applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the cost of corticosteroids are relatively cheap and therefore the committee considered that recommendations were unlikely to have a significant resource impact to the NHS.

Unit costs

Resource	Unit costs	Source
Dexamethasone	£19.17 [1]	BNF (2021)
Betamethasone	£58.24 [2]	BNF (2021)

[1] Based on 2 doses of 12mg and Dexamethasone 3.3mg/1ml solution for injection ampoules at £23.96 for 10 ampoules
[2] Based on 2 doses of 12mg and Betamethasone 4mg/1ml solution for injection ampoules at £48.53 for 5 ampoules

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The aim of this review was to assess the effectiveness of repeat courses of maternal corticosteroids in women at risk of preterm labour and birth. The committee therefore chose 3 critical outcomes: perinatal mortality, neurodevelopmental delay at 2 years and neonatal admission. These outcomes were selected as the most direct indicators of the efficacy and safety of repeat courses of maternal corticosteroids in women at risk of preterm labour and birth. As exposure to maternal corticosteroids during pregnancy may be associated with neurodevelopmental impairment in the infant, the committee wanted to include neurodevelopmental delay at 2 years.

The committee identified 4 additional important outcomes: intraventricular haemorrhage (IVH), chronic lung disease, birthweight and growth at 2 years (weight and head circumference). As preterm birth may be associated with IVH and chronic lung disease, the committee wanted to determine whether repeat courses of maternal corticosteroids may be effective in preventing these problems in babies of mothers at risk of preterm birth. As a risk of exposure to corticosteroids during pregnancy is reduced birthweight and reduced long-term growth outcomes, the committee considered it was important to capture whether there was any differential harm on these outcomes between repeat courses compared to a single course of corticosteroids.

The quality of the evidence

One IPD meta-analysis and two additional RCTs were included in this review. The quality of the evidence ranged from low to high, as assessed using GRADE.

The main reason for downgrading was imprecision, where confidence intervals around effect estimates were wide. Additionally, some outcomes were also downgraded for risk of bias due to incomplete outcome data reporting. The perinatal mortality outcome from the IPD was downgraded for indirectness as it reported death at any time.

Benefits and harms

Babies born before 34 weeks of gestational age may be at an increased risk of respiratory complications in the immediate postnatal period and later in life. The committee considered the evidence on the benefits and harms of repeat courses of corticosteroids compared to a single course for fetal lung maturation in improving preterm neonatal outcomes.

Overall, the committee noted that there were few benefits of repeat courses of corticosteroids and important harms in terms of birthweight. For the majority of outcomes, including severe neurodevelopmental delay, neonatal admission, chronic lung disease, IVH and growth at 2 years, there were no important differences between repeat courses and a single course of maternal corticosteroids. The committee used the outcomes reported as part of the stratified analyses to identify the possible benefits and harms in terms of the dose, number of courses, interval between courses and gestational age at first dose.

The committee discussed the evidence of an important benefit in terms of perinatal mortality for babies of women receiving repeat courses of corticosteroids with a total dose of between 24 mg to 48 mg; while they agreed that the effect estimate and confidence intervals indicated a clinically important benefit, they needed further granularity on the interval between courses and the gestational age the first course was given to guide decision-making. Perinatal mortality outcomes stratified by number of courses and interval between courses did not show any important differences between women receiving repeat courses and women receiving a single course of maternal corticosteroids. The committee also noted the benefit in terms of moderate neurodevelopmental delay at 2 years follow-up with repeat courses of corticosteroids. The committee weighed these important benefits against the birthweight outcomes and noted that harms were associated with higher total doses, higher number of courses and shorter intervals between courses of corticosteroids for women receiving repeat courses. Although there was a harm identified based on statistical significance in terms of birthweight for babies of women receiving a repeat course of corticosteroids, the committee noted that the absolute impact on the weight in grams or on the z-score was small, with mean difference in weight of 50 g to 100 g in most of the analyses. They also noted that weight and head circumference at 2 years were not different between the 2 groups, indicating that the repeat dose may not have had an effect on growth in the longer term.

The committee considered this evidence in the context of their knowledge and expertise that courses of maternal corticosteroids were effective at reducing respiratory complications in preterm babies. Acute respiratory outcomes were not included in the review protocol as the committee considered that any acute neonatal harms would be captured within the neonatal admission outcome. Although there was evidence of no difference in terms of neonatal admission from the meta-analysis of 2 individual studies, this outcome was not reported in the IPD meta-analysis. the committee therefore discussed qualitatively the finding reported in the IPD meta-analysis that repeat courses of maternal corticosteroids reduced the likelihood of babies needing respiratory support after birth. They agreed that the evidence supported a recommendation to consider a single repeat course of corticosteroids for women less than 34+0 weeks gestational age at risk of preterm birth, where the first course was received more than 7 days previously. They noted that in practice, deciding which women at risk of preterm birth to give corticosteroids to was often based on how soon they believed the woman would give birth, as ideally, the corticosteroids should be given in the 48 hours prior to birth to avoid any potential adverse neurodevelopmental outcomes. The committee agreed that the woman's likelihood of birth within 48 hours should therefore be considered when deciding whether to give a single repeat course of corticosteroids and, where possible, other

tests that could help determine the likely risk of preterm birth (such as cervical length scans or fetal fibrinonectin tests) should be used to guide decision-making.

Based on the committee's knowledge and expertise, and on the evidence of reduced birthweight for women who received repeat courses of corticosteroids with a 1st dose at less than 30 weeks gestational age, the committee wanted to emphasize that the woman's gestational age, the age when the first dose was given and the fetal growth should be taken into account when deciding whether to give a repeat course of maternal corticosteroids. This would allow a balance of risks to be considered: the risk of preterm birth occurring, the risk of the baby developing respiratory distress after birth, and the risk of a reduction in the birthweight.

Based on the evidence that had shown increased harm relating to birthweight with increased numbers of courses of corticosteroid courses, the committee agreed to recommend that not more than 2 course of corticosteroids should be given.

The committee discussed that sometimes pregnant women required corticosteroids for other conditions, notably for the treatment of Covid-19, and discussed whether corticosteroids administered for other reasons would count as a course, when deciding how many courses a woman could receive. The committee agreed that corticosteroids administered in pregnancy for another reason would not count as one of the courses used prior to preterm labour and birth for the purposes of facilitating neonatal lung maturation. However, they noted that the Royal College of Obstetricians and Gynaecologists guideline for the treatment of Covid-19 in pregnancy did provide a suggested regimen for use specifically in women who were at risk of preterm labour and birth AND who required corticosteroids for Covid-19, and that if this regimen were used then this course would count as one of the courses. The recommendation advising that not more than 2 courses of corticosteroids should be administered was therefore revised to clarify that this was 2 courses 'for preterm labour'.

Overall, the committee were concerned with the lack of evidence for longer-term neurodevelopmental outcomes beyond 2 years of age which they agreed were important for decision-making. Furthermore, the committee wanted more evidence on single repeat courses of corticosteroids as they agreed that the current evidence base did not give a clear picture of the optimal regimen and in which situations babies of women in advanced preterm labour would benefit. They therefore made a research recommendation for studies to explore the short and long-term safety and effectiveness of a single repeat dose or a repeat course of maternal corticosteroids compared to a single course.

Cost effectiveness and resource use

Offering a single repeat course of corticosteroids to women at risk of preterm labour is likely to increase the proportion of women who are given a repeat course of corticosteroids, although overall impact on use will be balanced by reducing the use of 3 or more courses. The overall impact on usage is therefore likely to be minimal. In addition, considering the low cost of this intervention and the relatively small population of women for whom this will be considered and the potential benefits on perinatal mortality, this recommendation is unlikely to result in a significant cost.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.9.4 to 1.9.6 and the research recommendation on the effectiveness of a single repeat dose or course of maternal corticosteroids.

References

Effectiveness

Atarod 2014

Atarod Z, Taghipour M, Roohanizadeh H et al. (2014) Effects of single course and multicourse betamethasone prior to birth in the prognosis of the preterm neonates: A randomized, double-blind placebo-control clinical trial study. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 19(8): 715-719

Crowther 2019

Crowther, Caroline A., Middleton, Philippa F., Voysey, Merryn et al. (2019) Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: An individual participant data meta-analysis. PLoS medicine 16(4): e1002771

Ernawati 2016

Ernawati, Gumilar, Erry, Kuntoro et al. (2016) Expectant management of preterm preeclampsia in Indonesia and the role of steroids. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(11): 1736-40

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021277553
Review title	Effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation
Review question	What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?
Objective	To update recommendations for the clinical effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes. Stakeholders have identified an individual patient meta-analysis regarding the effectiveness of repeat courses of steroids, which reports a reduced likelihood of the infant needing respiratory support after birth and an updated Cochrane review which has reported that repeat courses are safe and effective for women with suspected preterm labour. The guideline will be updated to consider the benefits and harms of repeat courses of maternal corticosteroids in light of this new evidence.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database (IHTA) Searches will be restricted by:

Field	Content
	• Date (2015-) • English language • Human studies Other searches: • Inclusion lists of systematic reviews Key papers • Crowther 2015 (Cochrane review) • Crowther 2019 (Individual patient meta-analysis) The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Preterm labour and birth; fetal lung maturation; corticosteroids
Population	• Pregnant women who are considered to be at risk of preterm labour and birth because they have a history of: ○ spontaneous preterm birth ○ second stage caesarean birth at full cervical dilatation ○ preterm pre-labour rupture of membranes ○ mid-trimester loss ○ cervical trauma (including surgery – for example, previous cone biopsy [cold knife or laser], large loop excision of the transformation zone [LLETZ – any number] and radical diathermy). • Pregnant women who are considered to be at risk of preterm labour and birth because they have a short cervix that has been identified on ultrasound scan and/or bulging membranes in the current pregnancy. • Pregnant women with preterm pre-labour rupture of membranes. • Pregnant women clinically suspected to be in preterm labour. • Women diagnosed to be in spontaneous preterm labour. • Women having a planned preterm birth. • Women who received a single course of corticosteroids prior to being randomised to receive either a repeat course or placebo/

Field	Content
	no further treatment • Women with multi-fetal pregnancies
Intervention	• Repeat courses of corticosteroids (for example, betamethasone, dexamethasone) administered to the women intravenously, intramuscularly or orally
Comparator	• Placebo • No further treatment (that is single dose of corticosteroid)
Types of study to be included	• Include published full-text papers: ○ Systematic reviews of RCTs ○ Parallel RCTs (individual, cluster) Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	• Population ○ Women in labour at term If any study or systematic review includes <1/3 of women with the above characteristics, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.
Context	This guideline will partly update the following: Preterm labour and birth (NG25)
Primary outcomes (critical outcomes)	• Perinatal mortality • Neurodevelopmental delay at 2 years (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) ○ Severe (score of >2 SD below normal on validated assessment scales, or on Bayley assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) ○ Moderate (Score of 1-2 SD below normal on validated assessment scales, or on Bayley assessment scale of MDI or PDI 70-84) • Neonatal admission (includes neonatal intensive care unit [NICU] and special care baby unit [SCBU])
Secondary	• Intraventricular haemorrhage

Field	Content
outcomes (important outcomes)	• Chronic lung disease (for example, bronchopulmonary dysplasia [BPD], oxygen dependency at 36 weeks) • Birthweight • Growth at 2 years (weight, head circumference)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • CheckMAP tool for IPD meta-analysis • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster randomised trials The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through

Field	Content
	subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • All-cause mortality: statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes.
Analysis of sub-groups	Evidence will be stratified by: • Gestational age at first dose: less than 24, 24 to less than 27, 27 to less than 32, 32 to less than 34 and more than 34 completed weeks • Interval between courses: ≤7 days, 8 to ≤14, >14 days • Number of repeat courses: 1, 2, 3, 4, 5 or more • Reason the woman was considered to be at risk of preterm labour and birth (as outlined in ID 6 – population) • Type of corticosteroid given: betamethasone, dexamethasone • Planned dose of corticosteroid given per treatment: <12mg, ≥12mg to 24 mg, >24 mg/per week • Method of treatment administration: intramuscular, intra-amniotic, intravenous, oral Stratifications will be dealt with in a hierarchy (this is, where possible, stratify first by gestational age at first dose, then by interval between courses, then by number of repeat courses, then by reason why the woman was considered to be at risk of PTLB, then by type of corticosteroid given, then by planned dose of corticosteroid given per treatment, and then by method of treatment administration). Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Singleton vs multi-fetal pregnancy • Country where the study was conducted: high income countries versus low and middle income countries (as defined by the OECD) Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations

Field	Content			
	should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	15 September 2021			
Anticipated completion date	23 June 2022			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☐
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑

Field	Content
Named contact	5a. Named contact National Guideline Alliance 5b. Named contact e-mail PTLB@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	From the National Guideline Alliance: • NGA Senior Systematic Reviewer • NGA Systematic Reviewer
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10174
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=277553

Field	Content
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	preterm labour and birth; fetal lung maturation; corticosteroids
Details of existing review of same topic by same authors	Not applicable
Additional information	Not applicable
Details of final publication	www.nice.org.uk

BPD: bronchopulmonary dysplasia; CDSR: Cochrane Database of Systematic Reviews; CP: cerebral palsy; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; LLETZ: large loop excision of the transformation zone; MDI: mental developmental index; MID: minimally important difference; NGA: National Guideline Alliance; NICU: neonatal intensive care unit; NHS: National health service; NICE: National Institute for Health and Care Excellence; PDI: psychomotor developmental index; RCT: randomised controlled trial; RoB: risk of bias; SCBU: special care baby unit; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Review question search strategies

Databases: Medline; and Medline In-Process

Date of last search: 27/09/2021

#	Searches
1	exp OBSTETRIC LABOR, PREMATURE/
2	exp INFANT, PREMATURE/
3	exp INFANT, LOW BIRTH WEIGHT/
4	(pre term or preterm or pre matur* or prematur* or premmie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
5	or/1-4
6	exp ADRENAL CORTEX HORMONES/
7	(Corticosteroid? or Adrenal Cortex Hormone? or 17-Ketosteroid? or Androstenedione or Androsterone or Dehydroepiandrosterone or Estrone or Etiocholanolone or Glucocorticoid? or Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or (Fluticasone adj3 Salmeterol) or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Hydroxycorticosteroid? or 11-Hydroxycorticosteroid? or Aldosterone or Corticosterone or Hydrocortisone or 18-Hydroxycorticosterone or Tetrahydrocortisol or 17-Hydroxycorticosteroid? or Cortisone or Cortodoxone or Tetrahydrocortisol or Tetrahydrocortisone or Desoxycorticosterone or 18-Hydroxydesoxycorticosterone or Pregnenolone or 17-alpha-Hydroxypregnenolone).mp.
8	or/6-7
9	exp RESPIRATORY DISTRESS SYNDROME, NEWBORN/
10	((respirat* or breath*) adj3 (distress* or difficult* or problem? or fail* or complication? or morbidit* or support* or care)).ti,ab.
11	RDS.ti,ab.
12	FETAL ORGAN MATURITY/
13	LUNG/em [Embryology]
14	((lung? or pulmonar?) adj3 (matur* or develop*)).ti,ab.
15	or/9-14
16	5 and 8 and 15
17	limit 16 to english language
18	limit 17 to yr="2015 -Current"
19	LETTER/
20	EDITORIAL/
21	NEWS/
22	exp HISTORICAL ARTICLE/
23	ANECDOTES AS TOPIC/
24	COMMENT/
25	CASE REPORT/
26	(letter or comment*).ti.
27	or/19-26
28	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
29	27 not 28
30	ANIMALS/ not HUMANS/
31	exp ANIMALS, LABORATORY/
32	exp ANIMAL EXPERIMENTATION/
33	exp MODELS, ANIMAL/
34	exp RODENTIA/
35	(rat or rats or mouse or mice).ti.
36	or/29-35
37	18 not 36
38	META-ANALYSIS/
39	META-ANALYSIS AS TOPIC/
40	(meta analy* or metanaly* or metaanaly*).ti,ab.
41	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
42	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
43	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

#	Searches
44	(search* adj4 literature).ab.
45	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
46	cochrane.jw.
47	or/38-46
48	randomized controlled trial.pt.
49	controlled clinical trial.pt.
50	pragmatic clinical trial.pt.
51	randomi#ed.ab.
52	placebo.ab.
53	randomly.ab.
54	CLINICAL TRIALS AS TOPIC/
55	trial.ti.
56	or/48-55
57	37 and 47
58	37 and 56
59	or/57-58

Databases: Embase; and Embase Classic

Date of last search: 27/09/2021

#	Searches
1	PREMATURE LABOR/
2	PREMATURITY/
3	exp LOW BIRTH WEIGHT/
4	(pre term or preterm or pre matur* or prematur* or premmie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
5	or/1-4
6	exp CORTICOSTEROID/
7	(Corticosteroid? or Adrenal Cortex Hormone? or 17-Ketosteroid? or Androstenedione or Androsterone or Dehydroepiandrosterone or Estrone or Etiocholanolone or Glucocorticoid? or Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or (Fluticasone adj3 Salmeterol) or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Hydroxycorticosteroid? or 11-Hydroxycorticosteroid? or Aldosterone or Corticosterone or Hydrocortisone or 18-Hydroxycorticosterone or Tetrahydrocortisol or 17-Hydroxycorticosteroid? or Cortisone or Cortodoxone or Tetrahydrocortisol or Tetrahydrocortisone or Desoxycorticosterone or 18-Hydroxydesoxycorticosterone or Pregnenolone or 17-alpha-Hydroxypregnenolone).mp.
8	or/6-7
9	NEONATAL RESPIRATORY DISTRESS SYNDROME/
10	((respirat* or breath*) adj3 (distress* or difficult* or problem? or fail* or complication? or morbidit* or support* or care)).ti,ab.
11	RDS.ti,ab.
12	FETUS LUNG MATURITY/
13	((lung? or pulmonar?) adj3 (matur* or develop*)).ti,ab.
14	or/9-13
15	5 and 8 and 14
16	limit 15 to english language
17	limit 16 to yr="2015 -Current"
18	letter.pt. or LETTER/
19	note.pt.
20	editorial.pt.
21	CASE REPORT/ or CASE STUDY/
22	(letter or comment*).ti.
23	or/18-22
24	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
25	23 not 24
26	ANIMAL/ not HUMAN/
27	NONHUMAN/
28	exp ANIMAL EXPERIMENT/
29	exp EXPERIMENTAL ANIMAL/
30	ANIMAL MODEL/
31	exp RODENT/
32	(rat or rats or mouse or mice).ti.
33	or/25-32
34	17 not 33
35	SYSTEMATIC REVIEW/
36	META-ANALYSIS/

#	Searches
37	(meta analy* or metanaly* or metaanaly*).ti,ab.
38	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
39	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41	(search* adj4 literature).ab.
42	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43	((pool* or combined) adj2 (data or trials or studies or results)).ab.
44	cochrane.jw.
45	or/35-44
46	random*.ti,ab.
47	factorial*.ti,ab.
48	(crossover* or cross over*).ti,ab.
49	((doubl* or singl*) adj blind*).ti,ab.
50	(assign* or allocat* or volunteer* or placebo*).ti,ab.
51	CROSSOVER PROCEDURE/
52	SINGLE BLIND PROCEDURE/
53	RANDOMIZED CONTROLLED TRIAL/
54	DOUBLE BLIND PROCEDURE/
55	or/46-54
56	34 and 45
57	34 and 55
58	or/56-57

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews

Date of last search: 27/09/2021

#	Searches
#1	MeSH descriptor: [Obstetric Labor, Premature] explode all trees
#2	MeSH descriptor: [Infant, Premature] explode all trees
#3	MeSH descriptor: [Infant, Low Birth Weight] explode all trees
#4	("pre term" or preterm or "pre matur*" or prematur* or premmie* or premie or premies or "low birth weight*" or "low birthweight*" or LBW* or VLBW*):ti,ab
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#7	(Corticosteroid* or "Adrenal Cortex Hormone*" or "17-Ketosteroid*" or Androstenedione or Androsterone or Dehydroepiandrosterone or Estrone or Etiocholanolone or Glucocorticoid* or Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or "Fluocinolone Acetonide" or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or "Fluticasone Salmeterol" or "Melengestrol Acetate" or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Hydroxycorticosteroid* or "11-Hydroxycorticosteroid*" or Aldosterone or Corticosterone or Hydrocortisone or "18-Hydroxycorticosterone" or Tetrahydrocortisol or "17-Hydroxycorticosteroid*" or Cortisone or Cortodoxone or Tetrahydrocortisol or Tetrahydrocortisone or Desoxycorticosterone or "18-Hydroxydesoxycorticosterone" or Pregnenolone or "17-alpha-Hydroxypregnenolone"):ti,ab
#8	#6 or #7
#9	MeSH descriptor: [Respiratory Distress Syndrome, Newborn] explode all trees
#10	((respirat* or breath*) near/3 (distress* or difficult* or problem* or fail* or complication* or morbidit* or support* or care)):ti,ab
#11	RDS:ti,ab
#12	MeSH descriptor: [Fetal Organ Maturity] this term only
#13	MeSH descriptor: [Lung] this term only and with qualifier(s): [embryology - EM]
#14	((lung* or pulmonar*) near/3 (matur* or develop*)):ti,ab
#15	#9 or #10 or #11 or #12 or #13 or #14
#16	#5 and #8 and #15
#17	#5 and #8 and #15 with Cochrane Library publication date Between Jan 2015 and Sep 2021, in Cochrane Reviews
#18	#5 and #8 and #15 with Publication Year from 2015 to 2021, in Trials

Databases: International Health Technology Assessment

Date of last search: 27/09/2021

#	Searches
	All: "Respiratory Distress Syndrome, Newborn"[mh]
	OR All: "respiratory distress" or "respiratory complication" or "respiratory morbidity"

#	Searches
	OR All: "Fetal Organ Maturity"[mh]
	OR All: "lung maturity" or "lung development" or "pulmonary maturity" or "pulmonary development"

Health economics search strategies

Databases: Medline; and Medline In-Process

Date of last search: 11/10/2021

#	Searches
1	exp OBSTETRIC LABOR, PREMATURE/
2	exp INFANT, PREMATURE/
3	exp INFANT, LOW BIRTH WEIGHT/
4	(pre term or preterm or pre matur* or prematur* or premmie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
5	or/1-4
6	exp ADRENAL CORTEX HORMONES/
7	(Corticosteroid? or Adrenal Cortex Hormone? or 17-Ketosteroid? or Androstenedione or Androsterone or Dehydroepiandrosterone or Estrone or Etiocholanolone or Glucocorticoid? or Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or (Fluticasone adj3 Salmeterol) or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Hydroxycorticosteroid? or 11-Hydroxycorticosteroid? or Aldosterone or Corticosterone or Hydrocortisone or 18-Hydroxycorticosterone or Tetrahydrocortisol or 17-Hydroxycorticosteroid? or Cortisone or Cortodoxone or Tetrahydrocortisol or Tetrahydrocortisone or Desoxycorticosterone or 18-Hydroxydesoxycorticosterone or Pregnenolone or 17-alpha-Hydroxypregnenolone).mp.
8	or/6-7
9	exp RESPIRATORY DISTRESS SYNDROME, NEWBORN/
10	((respirat* or breath*) adj3 (distress* or difficult* or problem? or fail* or complication? or morbidit* or support* or care)).ti,ab.
11	RDS.ti,ab.
12	FETAL ORGAN MATURITY/
13	LUNG/em [Embryology]
14	((lung? or pulmonar?) adj3 (matur* or develop*)).ti,ab.
15	or/9-14
16	5 and 8 and 15
17	limit 16 to english language
18	limit 17 to yr="2015 -Current"
19	LETTER/
20	EDITORIAL/
21	NEWS/
22	exp HISTORICAL ARTICLE/
23	ANECDOTES AS TOPIC/
24	COMMENT/
25	CASE REPORT/
26	(letter or comment*).ti.
27	or/19-26
28	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
29	27 not 28
30	ANIMALS/ not HUMANS/
31	exp ANIMALS, LABORATORY/
32	exp ANIMAL EXPERIMENTATION/
33	exp MODELS, ANIMAL/
34	exp RODENTIA/
35	(rat or rats or mouse or mice).ti.
36	or/29-35
37	18 not 36
38	ECONOMICS/
39	VALUE OF LIFE/
40	exp "COSTS AND COST ANALYSIS"/
41	exp ECONOMICS, HOSPITAL/
42	exp ECONOMICS, MEDICAL/
43	exp RESOURCE ALLOCATION/
44	ECONOMICS, NURSING/
45	ECONOMICS, PHARMACEUTICAL/
46	exp "FEES AND CHARGES"/
47	exp BUDGETS/
48	budget*.ti,ab.

#	Searches
49	cost*.ti,ab.
50	(economic* or pharmaco?economic*).ti,ab.
51	(price* or pricing*).ti,ab.
52	(financ* or fee or fees or expenditure* or saving*).ti,ab.
53	(value adj2 (money or monetary)).ti,ab.
54	resourc* allocat*.ti,ab.
55	(fund or funds or funding* or funded).ti,ab.
56	(ration or rations or rationing* or rationed).ti,ab.
57	ec.fs.
58	or/38-57
59	37 and 58

Databases: Embase; and Embase Classic

Date of last search: 11/10/2021

#	Searches
1	PREMATURE LABOR/
2	PREMATURITY/
3	exp LOW BIRTH WEIGHT/
4	(pre term or preterm or pre matur* or prematur* or premmie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
5	or/1-4
6	exp CORTICOSTEROID/
7	(Corticosteroid? or Adrenal Cortex Hormone? or 17-Ketosteroid? or Androstenedione or Androsterone or Dehydroepiandrosterone or Estrone or Etiocholanolone or Glucocorticoid? or Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or (Fluticasone adj3 Salmeterol) or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Hydroxycorticosteroid? or 11-Hydroxycorticosteroid? or Aldosterone or Corticosterone or Hydrocortisone or 18-Hydroxycorticosterone or Tetrahydrocortisol or 17-Hydroxycorticosteroid? or Cortisone or Cortodoxone or Tetrahydrocortisol or Tetrahydrocortisone or Desoxycorticosterone or 18-Hydroxydesoxycorticosterone or Pregnenolone or 17-alpha-Hydroxypregnenolone).mp.
8	or/6-7
9	NEONATAL RESPIRATORY DISTRESS SYNDROME/
10	((respirat* or breath*) adj3 (distress* or difficult* or problem? or fail* or complication? or morbidit* or support* or care)).ti,ab.
11	RDS.ti,ab.
12	FETUS LUNG MATURITY/
13	((lung? or pulmonar?) adj3 (matur* or develop*)).ti,ab.
14	or/9-13
15	5 and 8 and 14
16	limit 15 to english language
17	limit 16 to yr="2015 -Current"
18	letter.pt. or LETTER/
19	note.pt.
20	editorial.pt.
21	CASE REPORT/ or CASE STUDY/
22	(letter or comment*).ti.
23	or/18-22
24	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
25	23 not 24
26	ANIMAL/ not HUMAN/
27	NONHUMAN/
28	exp ANIMAL EXPERIMENT/
29	exp EXPERIMENTAL ANIMAL/
30	ANIMAL MODEL/
31	exp RODENT/
32	(rat or rats or mouse or mice).ti.
33	or/25-32
34	17 not 33
35	HEALTH ECONOMICS/
36	exp ECONOMIC EVALUATION/
37	exp HEALTH CARE COST/
38	exp FEE/
39	BUDGET/
40	FUNDING/
41	RESOURCE ALLOCATION/
42	budget*.ti,ab.

#	Searches
43	cost*.ti,ab.
44	(economic* or pharmaco?economic*).ti,ab.
45	(price* or pricing*).ti,ab.
46	(financ* or fee or fees or expenditure* or saving*).ti,ab.
47	(value adj2 (money or monetary)).ti,ab.
48	resourc* allocat*.ti,ab.
49	(fund or funds or funding* or funded).ti,ab.
50	(ration or rations or rationing* or rationed).ti,ab.
51	or/35-50
52	34 and 51

Database: Cochrane Central Register of Controlled Trials

Date of last search: 11/10/2021

#	Searches
#1	MeSH descriptor: [Obstetric Labor, Premature] explode all trees
#2	MeSH descriptor: [Infant, Premature] explode all trees
#3	MeSH descriptor: [Infant, Low Birth Weight] explode all trees
#4	("pre term" or preterm or "pre matur*" or prematur* or premmie* or premie or premies or "low birth weight*" or "low birthweight*" or LBW* or VLBW*):ti,ab
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#7	(Corticosteroid* or "Adrenal Cortex Hormone*" or "17-Ketosteroid*" or Androstenedione or Androsterone or Dehydroepiandrosterone or Estrone or Etiocholanolone or Glucocorticoid* or Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or "Fluocinolone Acetonide" or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or "Fluticasone Salmeterol" or "Melengestrol Acetate" or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Hydroxycorticosteroid* or "11-Hydroxycorticosteroid*" or Aldosterone or Corticosterone or Hydrocortisone or "18-Hydroxycorticosterone" or Tetrahydrocortisol or "17-Hydroxycorticosteroid*" or Cortisone or Cortodoxone or Tetrahydrocortisol or Tetrahydrocortisone or Desoxycorticosterone or "18-Hydroxydesoxycorticosterone" or Pregnenolone or "17-alpha-Hydroxypregnenolone"):ti,ab
#8	#6 or #7
#9	MeSH descriptor: [Respiratory Distress Syndrome, Newborn] explode all trees
#10	((respirat* or breath*) near/3 (distress* or difficult* or problem* or fail* or complication* or morbidit* or support* or care)):ti,ab
#11	RDS:ti,ab
#12	MeSH descriptor: [Fetal Organ Maturity] this term only
#13	MeSH descriptor: [Lung] this term only and with qualifier(s): [embryology - EM]
#14	((lung* or pulmonar*) near/3 (matur* or develop*)):ti,ab
#15	#9 or #10 or #11 or #12 or #13 or #14
#16	#5 and #8 and #15
#17	#5 and #8 and #15 with Publication Year from 2015 to 2021, in Trials
#18	MeSH descriptor: [Economics] this term only
#19	MeSH descriptor: [Value of Life] this term only
#20	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#21	MeSH descriptor: [Economics, Hospital] explode all trees
#22	MeSH descriptor: [Economics, Medical] explode all trees
#23	MeSH descriptor: [Resource Allocation] explode all trees
#24	MeSH descriptor: [Economics, Nursing] this term only
#25	MeSH descriptor: [Economics, Pharmaceutical] this term only
#26	MeSH descriptor: [Fees and Charges] explode all trees
#27	MeSH descriptor: [Budgets] explode all trees
#28	budget*:ti,ab
#29	cost*:ti,ab
#30	(economic* or pharmaco?economic*):ti,ab
#31	(price* or pricing*):ti,ab
#32	(financ* or fee or fees or expenditure* or saving*):ti,ab
#33	(value near/2 (money or monetary)):ti,ab
#34	resourc* allocat*:ti,ab
#35	(fund or funds or funding* or funded):ti,ab
#36	(ration or rations or rationing* or rationed):ti,ab
#37	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
#38	#17 and #37

Databases: International Health Technology Assessment

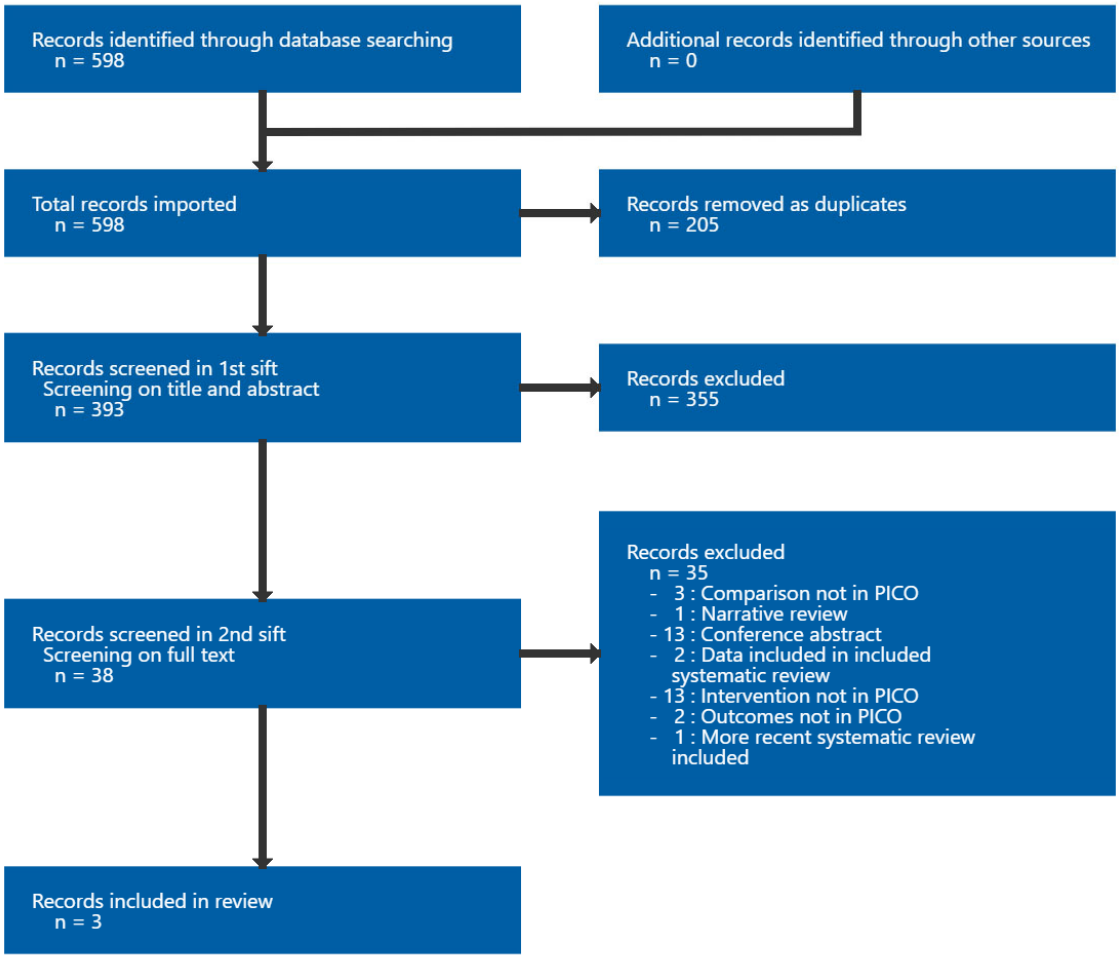
Date of last search: 11/10/2021

#	Searches
	All: "Respiratory Distress Syndrome, Newborn"[mh]
	OR All: "respiratory distress" or "respiratory complication" or "respiratory morbidity"
	OR All: "Fetal Organ Maturity"[mh]
	OR All: "lung maturity" or "lung development" or "pulmonary maturity" or "pulmonary development"

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Table 4: Evidence tables

Atarod, 2014

Bibliographic Reference	Atarod Z; Taghipour M; Roohanizadeh H; Fadavi S; Taghavipour M; Effects of single course and multicourse betamethasone prior to birth in the prognosis of the preterm neonates: A randomized, double-blind placebo-control clinical trial study.; Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences; 2014; vol. 19 (no. 8)

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	not reported
Inclusion criteria	• Women with risk of preterm labour and birth (gestational age 28-35 weeks, painful or painless uterine contractions, lower abdominal pain and cervical dilatation <3cm) or preterm birth history • Women with placenta previa, or chronic detachment and cerclage history • Women who had received a single course of betamethasone IM (2x 12mg, every 24 hours) 10 days previously
Exclusion criteria	• Premature rupture of membranes before entering the trial • Major fetal anomalies • Intrauterine growth restriction • Insulin-dependent diabetes • Chorioamnionitis • Taking systemic corticosteroids during pregnancy
Patient	• Gestational age at intervention: (at randomisation), mean ± SD: not reported (range: 28- 35 weeks)

characteristics	• Gestational age at birth: mean ± SD: experimental = not reported (range: 28- 35 weeks) • Term deliveries (≥ 37 weeks): only women with preterm deliveries included in analysis • Interval between corticosteroid administration and delivery, mean ± SD: not reported • Completed repeat course(s): one course, n = 316; two courses, n=138; three courses, n= 149
Intervention(s)/control	**Repeat courses group** • n= 674 (n= 271 women who had preterm birth were analysed in this study) • 2x 12mg betamethasone IM, every 24 hours, repeated every 10 days for up to 2 additional courses **Single course group** • n= 674 (n= 316 women who had preterm birth were analysed in this study) • 2 x placebo IM, every 24 hours, repeated every 10 days for up to 2 additional courses
Sources of funding	Not reported
Sample size	N= 1348
Other information	The study analysed only the women who had preterm births n=138 women received 2 courses and n=149 women received 3 courses of betamethasone in the intervention group

Study arms

Single course (N = 674)

Multiple course (N = 674)

Outcomes

Perinatal mortality

Outcome	Single course, , N = 316	Multiple course, , N = 271
Perinatal mortality (overall) No of events	n = 89 ; % = 28.1	n = 62 ; % = 22.9
Birthweight (grams) Mean (SD)	2015.9 (421.7)	1938 (428.8)

Perinatal mortality (overall) - Polarity - Lower values are better

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High Only participants who delivered preterm were included in the analysis.
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the	Risk-of-bias judgement for	Low

Section	Question	Answer
reported result	selection of the reported result	
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Direct
Overall bias and Directness	Risk of bias variation across outcomes	The participants may have been aware of the group they were in if they experienced side effects they knew to be specific to the intervention. The HCPs may have been aware of the groups that the participants were assigned to if they recognised that side effects caused by the intervention were present in the participant The participants were contacted on a weekly basis up until delivery where they could have reported side effects that may have led them to be aware of the group that they were in. The HCPs did contact the participants on a weekly basis up until where they could have reported side effects that may have led them to be aware of the group that they were in

Crowther, 2019

Bibliographic Reference Crowther, Caroline A.; Middleton, Philippa F.; Voysey, Merryn; Askie, Lisa; Zhang, Sasha; Martlow, Tanya K.; Aghajafari, Fariba; Asztalos, Elizabeth V.; Brocklehurst, Peter; Dutta, Sourabh; Garite, Thomas J.; Guinn, Debra A.; Hallman, Mikko; Hardy, Pollyanna; Lee, Men-Jean; Maurel, Kimberley; Mazumder, Premasish; McEvoy, Cindy; Murphy, Kellie E.; Peltoniemi, Outi M.; Thom, Elizabeth A.; Wapner, Ronald J.; Doyle, Lex W.; Group, Precise; Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: An individual participant data meta-analysis; PLoS medicine; 2019; vol. 16 (no. 4); e1002771

Study details

Country/ies where study was carried out	United States, Canada, Australia, New Zealand, Finland, India, United Kingdom
Study dates	Date of last full search: 20 January 2015 (and updated in 22 January 2019)
Inclusion criteria	Randomised controlled trials (published, unpublished or ongoing) comparing repeat course(s) of prenatal corticosteroids

with a single course of corticosteroid in women at risk of preterm birth. Trials were eligible if women had received an initial single course 7 or more days previously.

Aghajafari 2002

- women at 24-30 weeks gestation at continued increased risk of preterm birth who remained undelivered 7 or more days following a single course of antenatal corticosteroids (12 mg/dose betamethasone IM, two doses at 12- or 24-h apart or 5-6mg betamethasone IM, four doses at 12-h apart)

Crowther 2006

- women with singleton or multiple pregnancy < 32 weeks gestation who had received an initial treatment of corticosteroid 7 or more days previously and were judged to be at continued risk of preterm birth

Garite 2009

- women with singleton or twin pregnancy, > 25 weeks and < 33 weeks who had received a course of betamethasone ≥ 14 days previously and who were judged to have recurrent or continued risk of preterm birth

Guinn 2001

- women between 24 and 33 weeks' gestation at high risk of preterm birth who remained undelivered 1 week following an initial course of antenatal corticosteroids

Mazumder 2008

- women between 26 and 33 weeks' gestation at risk of preterm birth who had received a course of betamethasone 7 or more days previously

McEvoy 2002

- women between 25 and 33 weeks' gestation who were at increased risk of preterm birth and remained undelivered 1 week after a single course of antenatal corticosteroids

	McEvoy 2010 • women between 26 and 34 weeks' gestation who had received one course of antenatal corticosteroids at least 14 days previously and were at continued risk of preterm birth **Murphy 2008** • women with single, twin or triplet pregnancy between 25 and 32 weeks' gestation who had received an initial course of antenatal corticosteroids (either betamethasone or dexamethasone) 14 -21 days previously and who remained undelivered and at continued high risk of preterm birth **Peltoniemi 2007** • women at < 34 weeks' gestation who had received a single course of betamethasone > 7 days previously and were to have elective delivery within 48h or were at very high risk of spontaneous preterm birth within 48h (cervical opening ≥ 3cm and regular contractions at 5 to 10 min intervals) **TEAMS** • women who have already received one course of antenatal steroids to improve foetal maturity and gestational age is less than 32 weeks **Wapner 2006** women with intact membranes between 23+0 weeks and 31+6 weeks who had received a single full course of betamethasone or dexamethasone between 7 and 10 days previously and were at high risk of preterm birth, or had the placenta praevia or chronic abruptionStudies included in this evidence report but not included in Crowther 2019: • Atarod 2014: not identified in database search • Ernawati 2016: not eligible as participants received repeat courses 48 hours after an initial course
Exclusion criteria	• Quasi-randomised and crossover trials • Trials where the fetus received corticosteroids directly

Aghajafari 2002

- chronic doses of corticosteroids secondary to medical conditions, contraindication to corticosteroids, clinical evidence of chorioaminonitis, known lethal congenital anomaly

Crowther 2006

- contraindication to corticosteroids, in second stage of labour, chorioamnionitis needing urgent delivery, further corticosteroid therapy was judged to be essential

Garite 2009

- major fetal anomaly, cervical dilatation 5cm or more, triplet or higher order multiples, ruptured membranes, clinical chorioamnionitis, documented lung maturity, receiving corticosteroids for other indications, HIV or active tuberculosis

Guinn 2001

- requiring immediate delivery, fetal anomalies incompatible with life, documented fetal lung maturity, maternal active tuberculosis, HIV

Mazumder 2008

- unreliable gestational age, frank chorioamnionitis, major fetal malformation

McEvoy 2002

- insulin-dependent diabetes, drug addiction, known lethal congenital anomaly

McEvoy 2010

- insulin-dependent diabetes, major fetal or chromosomal abnormality, multiple pregnancy greater than twins, clinical chorioamnionitis, first course of corticosteroids given < 24 weeks' gestation, chronic steroid use during pregnancy for clinical care

	Murphy 2008 • contraindication to corticosteroid use, need for chronic doses of corticosteroids, evidence of chorioamnionitis, known lethal congenital abnormality, initial course of corticosteroids before 23 weeks' gestation, previously participated in the MACS study, women with a multiple pregnancy with fetal death after 13 weeks' gestation **Peltoniemi 2007** • long-term maternal corticosteroid use, clinical chorioamnionitis, lethal disease of the fetus **TEAMS** • Not reported **Wapner 2006** pPROM, confirmed fetal lung maturity, chorioamnionitis, major fetal anomaly, non -reassuring fetal status, systemic corticosteroid use during current pregnancy, insulin -dependent diabetes
Patient characteristics	**Aghajafari 2002** • Gestational age at intervention: not reported • Gestational age at birth, mean ± SD: experimental = 31 ± 4 weeks; control = 35 ± 5 weeks • Interval between corticosteroid administration and delivery, median (IQR): experimental = 23 (5,96) days; control = 57 (1,89) days • Completed repeat course(s): one course = 4/12 (33%); two course = 3/12 (25%); more than two courses = 5/12 (42%) **Crowther 2006** • Gestational age at intervention, median (IQR(: experimental = 26.7 weeks (24.7 to 28.7); control = 26.7 weeks (24.7 to 28.7) • Gestational age at birth, mean ± SD: experimental = 32.5 weeks ± 3.9; control = 32.4 weeks ± 3.9 • Term deliveries (≥ 37 weeks): experimental = 109/567 (19%); control = 94/577 (16%) • Interval between corticosteroid administration and delivery: not reported • Completed repeat course(s): one course = 408/982 (42%), two courses = 227/982 (23%), three courses = 117/982

(12%), four or more courses = 215/982 (22%)

Garite 2009

- Gestational age at intervention, mean± SD : experimental = 29.5 ± 2.2; control = 29.4 ± 1.9
- Gestational age at birth, mean± SD : experimental = 33.1 ± 3.1; control = 33.04 ± 3.1
- Term deliveries: not reported
- Interval between corticosteroid administration and delivery, mean ± SD: experimental = 24.5 days, SD not reported; control = 25.1 days, SD not reported
- Completed repeat course(s): all women in intervention arm received one repeat course of corticosteroids

Guinn 2001

- Gestational age at intervention (at randomisation), mean ± SD: experimental = 29.2 weeks ± 2.7; control = 28.8 weeks ± 2.7
- Gestational age at birth: mean ± SD: experimental=33.1 weeks ± 4.0; control=33.5 weeks ± 4.0
- Term deliveries: not reported
- Interval between corticosteroid administration and delivery: mean ± SD: experimental = 5.0 weeks ± 3.7; control = 5.8 weeks ± 3.8
- Completed repeat course(s): two courses = 88/256, three courses = 55/256, four courses = 34/256, five courses = 20/256, six or more courses = 48/256

Mazumder 2008

- Gestational age at intervention (at baseline): mean ± SD: experimental = 30.2 weeks ± 4.0; control =30.0 weeks ± 1.7
- Gestational age at birth: not reported
- Term deliveries: not reported
- Interval between corticosteroid administration and delivery: *not reported
- Completed repeat course(s): one course = 3/38, two courses = 15/38, three courses = 7/38, four courses = 8/38, five courses = 3/38, six courses = 2/38

McEvoy 2002

- Gestational age at intervention (at randomisation) mean ± SD: experimental = 29.8 weeks ± 2.9; control = 30.2

weeks ± 2.1
- Gestational age at birth: mean ± SD: experimental = 32.2 weeks ± 3.3; control = 32.8 weeks ± 2.7
- Term deliveries (>36 weeks) experimental = 1/18; control = 1/19
- Interval between corticosteroid administration and delivery, mean (range): experimental = not reported; control = 24 days (7.5 to 55 days)
- Completed repeat course(s): two courses = 8/18, three courses = 5/18, four courses = 4/18, 5 courses = 1/18

McEvoy 2010

- Gestational age at intervention: both groups received first course of corticosteroids at about 27 weeks and study dose at 30 weeks
- Gestational age at birth: 83/113 (73.5%) were delivered at ≤34 weeks
- Term deliveries: not reported
- Interval between corticosteroid administration and delivery: not reported
- Completed repeat course(s): all women in intervention arm received the one repeat course of corticosteroids

Murphy 2008

- Gestational age at intervention: (at randomisation) mean ± SD: experimental = 29.3 weeks ±2.0; control = 29.4 weeks ± 2.0
- Gestational age at birth, mean ± SD: experimental = 34.5 weeks ±3.6; control = 34.9 weeks ± 3.6
- Term deliveries (≥ 37weeks): experimental = 278/935 (30%); control = 318/918 (35%)
- Interval between corticosteroid administration and delivery (time of delivery after repeated drug exposures): <48h = 183/1853 (10%); 48h to < 7 days = 284/1853 (15%); ≥ 7 days = 1374/1853 (75%)
- Completed repeat course(s): "number of courses of study drug": zero courses = 10/1853 (0.5%), one course = 750/1853 (40.5%), two courses = 578/1853 (31%), three courses = 319/1853 (17%), four courses = 194/1853 (10.5%)

Peltoniemi 2007

- Gestational age at intervention, mean ± SD: experimental 30.3 weeks ± 2.6, control = 30.7 weeks ± 2.5
- Gestational age at birth: 24-27 weeks = 51/326 (16%), 28-30 weeks = 89/326 (27%), 31-34 weeks = 159/326 (49%), ≥34 weeks = 27/326 (8%)
- Term deliveries: not reported (see above line for reported gestational age categories)
- Interval between corticosteroid administration and delivery, median (IQR): experimental = 9 hours (3 to 23), control

	= 7 hours (3 to 23) • Completed repeat course(s): all women in intervention arm received one repeat course of corticosteroids **TEAMS** • Gestational age at intervention: (at randomisation), mean ± SD: 28.6 weeks ± 6 • Gestational age at birth: mean ± SD: experimental = 28.8 weeks ± 1.9 • Term deliveries (≥ 37 weeks): not reported • Interval between corticosteroid administration and delivery, mean ± SD: not reported • Completed repeat course(s): not reported **Wapner 2006** • Gestational age at intervention: (at randomisation), mean ± SD: experimental = 28.0 weeks ± 2.4; control = 28.1 weeks ± 2.3 • Gestational age at birth: *Mean ± SD: experimental = 34.8 weeks ± 3.8; control = 34.8 weeks ± 3.9 • Term deliveries (≥ 37 weeks): experimental = 93/157; control = 85/157 • Interval between corticosteroid administration and delivery, mean ± SD: experimental = 47.4 days ± 28.9; control = 47.0 days ± 27.1 • Completed repeat course(s): 63.4% of women received 4 or more study courses of corticosteroids
Intervention(s)/control	Intervention: corticosteroids (intravenously, intramuscularly, or orally) in women who have already received a single course of prenatal corticosteroid ≥ 7 days previously Control: placebo or no placebo **Aghajafari 2002** • Intervention: weekly course of 12 mg betamethasone IM, two doses 24h apart, until 33 weeks or delivery if the woman remained at increased risk of preterm birth • Control: weekly course of placebo, normal saline IM, two doses 24h apart, until 33 weeks or delivery if the woman remained at increased risk of preterm birth

Crowther 2006

- Intervention: weekly course of 11.4 mg Celestone Chronodose (7.8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) if woman remained undelivered at risk of preterm birth and < 32 weeks gestation
- Control: weekly saline IM

Garite 2009

- Intervention: single course of 12 mg betamethasone IM, two doses 24h apart (women had received a course of betamethsone ≥ 14 days previously). In some centres betamethasone became unavailable and was replaced with dexamethasone 6 mg IM, 4 doses, every 12h
- Control: weekly saline IM

Guinn 2001

- Intervention: weekly course of 12 mg betamethasone IM, two doses 24 h apart, until 34 weeks or birth, whichever came first
- Control: similarly administered placebo

Mazumder 2008

- Intervention: weekly course of 12 mg betamethasone IM, two doses 24 h apart, until delivery or end of 33rd week of gestation
- Control: no intervention

McEvoy 2002

- Intervention: weekly course of 12 mg betamethasone IM, two doses, timing not reported, until delivery or 34 weeks' gestation
- Control: weekly doses of IM placebo until delivery or 34 weeks's gestatiom

McEvoy 2010

- Intervention: one course of 12 mg betamethasone IM, 2 doses 24h apart

	• Control: one course of 25 mg cortisone acetate (inactive steroid - 2 doses 24h apart) **Murphy 2008** • Intervention: 12 mg betamethasone IM (Celestone, 6 mg betamethasone sodium phopshate and 6mg betamethasone acetate), two doses 24h apart, repeated fortnightly until 33 weeks' gestation or birth, whichever happened first. For women with PROM the recommendation was to stop the study medication at 32 weeks' gestation • Control: similarly appearing IM injection of dilute concentration of aluminium monostearate **Peltoniemi 2007** • Intervention: single dose of 12mg betamethasone IM given before 34 weeks of pregnancy, ≥7 days after a full treatment course of betamethasone • Control: isotonic saline IM **TEAMS** • Intervention: 12 mg betamethasone, 2 doses 12 or 24 hours apart, usually repeated every 7 days but could be 10–14 days depending on unit's protocol • Control: placebo **Wapner 2006** • Intervention: 12 mg betamethasone IM, 2 doses 24h apart, repeated weekly until 33+6 weeks or birth, whichever came first. After 67 women had been recruited the number of courses (including the qualifying course) was limited to 4 because of difficulty in recruitment and interim analysis showed a tendency towards decreased birthweight in the experimental group • Control: "matching" placebo
Sources of funding	Australian National Health and Medical Research Council

	Individual studies: • Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia • Liggins Institute, University of Auckland, New Zealand • Australian Department of Health and Ageing, Australia • National Institute for Health Research, UK • Action Medical Research, UK
Sample size	K= 11 studies N = 4857 women N = 5915 babies **Aghajafari 2002** • N = 12 women • N= 16 babies **Crowther 2006** • N = 982 women • N = 1147 babies **Garite 2009** • N = 437 women • N = 577 babies **Guinn 2001** • N = 502 women

- N= 496 babies

Mazumder 2008

- N = 76 women
- N = 76 babies

McEvoy 2002

- N = 37 women
- N= 37 babies

McEvoy 2010

- N = 85 women
- N = 113 babies

Murphy 2008

- N = 1858 women
- N = 2318 babies

Peltoniemi 2007

- N = 249 women
- N = 326 babies

TEAMS

- N= 156 women
- N= 182 babies

Wapner 2006

- N = 495 women

	• N = 594 babies
Other information	

Study arms

Outcomes

Aghajafari 2002

Outcome	Multiple courses, , N = 9	Single course, , N = 7
Perinatal mortality No of events	n = 0 ; % = 0	n = 0 ; % = 0
Intraventricular hemorrhage Grade 3 or 4 No of events	n = 0 ; % = 0	n = 1 ; % = 14
Bronchopulmonary dysplasia Need for oxygen at 36 weeks) No of events	n = 1 ; % = 11	n = 2 ; % = 29

Perinatal mortality - Polarity - Lower values are better
Intraventricular hemorrhage - Polarity - Lower values are better
Bronchopulmonary dysplasia - Polarity - Lower values are better
n= number of babies

Crowther 2006

Outcome	Multiple courses, , N = 567	Single course, , N = 577
Perinatal mortality	n = 27 ; % = 4.8	n = 29 ; % = 5

Outcome	Multiple courses, , N = 567	Single course, , N = 577
Death before hospital discharge No of events		
Neonatal admission No of events	n = 407 ; % = 72	n = 399 ; % = 69
Intraventricular haemorrhage (all grades) No of events	n = 34 ; % = 6	n = 39 ; % = 7
Grade 3-4 No of events	n = 5 ; % = 1	n = 8 ; % = 1
Chronic lung disease Need for oxygen at 36 weeks post conception No of events	n = 76 ; % = 13	n = 82 ; % = 14
Birthweight (grams) Mean (SD)	1867 (824)	1877 (816)
Growth at 2 years - weight (kg) Repeat course n= 524; single course n=536 Mean (SD)	12.6 (1.9)	12.6 (1.9)
Growth at 2 years (head circumference) (cm) Mean (SD)	48.9 (1.7)	48.9 (1.8)
Neurodevelopmental delay at 2 years - severe (MDI score > 3 SD below the mean) repeat course n=495; single course n=504	n = 23 ; % = 4.6	n = 29 ; % = 5.8

Outcome	Multiple courses, , N = 567	Single course, , N = 577
No of events		
Neurodevelopmental delay at 2 years - moderate (MDI score, > 2 SD to 3 SD below the mean) repeat course n=495; single course n=504 No of events	n = 30 ; % = 6.1	n = 41 ; % = 8.1
Birthweight (z-scores) repeat course n=569; single course n=578 Mean (SE)	-0.13 (0.04)	-0.04 (0.04)

Perinatal mortality - Polarity - Lower values are better
Neonatal admission - Polarity - Lower values are better
Intraventricular haemorrhage (all grades) - Polarity - Lower values are better
Chronic lung disease - Polarity - Lower values are better
Growth at 2 years (head circumference) - Polarity - Lower values are better
n= no. of babies; 2-year follow-up outcomes from Crowther 2007

Garite 2009

Outcome	Multiple courses, , N = 276	Single course, , N = 282
Intraventricular haemorrhage (all babies) repeat courses n=272; single course n=274 No of events	n = 19 ; % = 7	n = 25 ; % = 9.1
Grade 3-4 (all babies) repeat courses n=272; single course n=274 No of events	n = 6 ; % = 2.2	n = 4 ; % = 1.5
Bronchopulmonary dysplasia (all babies)	n = 27 ; % = 9.9	n = 20 ; % = 7.2

Outcome	Multiple courses, , N = 276	Single course, , N = 282
repeat courses n=273; single course n=278 No of events		
Birthweight (grams) Mean (SD)	1905 (738)	1920 (667)
Birthweight (z-scores) Mean (SE)	-0.09 (0.07)	-0.09 (0.06)

Intraventricular haemorrhage (all babies) - Polarity - Lower values are better
Bronchopulmonary dysplasia (all babies) - Polarity - Lower values are better
n= number of babies

Guinn 2001

Outcome	Multiple courses, , N = 256	Single course, , N = 246
Perinatal mortality No of events	n = 5 ; % = 2	n = 9 ; % = 3.8
Bronchopulmonary dysplasia No of events	n = 28 ; % = 11.3	n = 26 ; % = 11
Intraventricular haemorrhage No of events	n = 30 ; % = 25.2	n = 25 ; % = 24.5
Grade 3-4 No of events	n = 9 ; % = 7.6	n = 2 ; % = 2
Birthweight (z-scores)	-0.05 (0.06)	0.12 (0.07)

Outcome	Multiple courses, , N = 256	Single course, , N = 246
repeat course n=291; single course n= 277 Mean (SE)		
Birthweight (grams) Mean (SD)	2009.1 (858.7)	2138.8 (875.8)

Perinatal mortality - Polarity - Lower values are better
Bronchopulmonary dysplasia - Polarity - Lower values are better
Intraventricular haemorrhage - Polarity - Lower values are better
n= no. of babies

Mazumder 2008

Outcome	Multiple courses, , N = 37	Single course, , N = 38
Perinatal mortality Death within 28 days No of events	n = 4 ; % = 11	n = 7 ; % = 18
Bronchopulmonary dysplasia No of events	n = 0 ; % = 0	n = 0 ; % = 0
Birthweight (grams) Mean (SD)	1553.4 (441.4)	1645.6 (627)
Birthweight (z-scores) repeat courses n=37; single course n=36 Mean (SE)	-1.24 (0.16)	-0.93 (0.18)

Perinatal mortality - Polarity - Lower values are better
Bronchopulmonary dysplasia - Polarity - Lower values are better

McEvoy 2010

Outcome	Multiple courses, , N = 56	Single course, , N = 56
Perinatal mortality No of events	n = 1 ; % = 2	n = 0 ; % = 0
Birthweight (grams) Mean (SD)	1806 (778)	1830 (657)
Birthweight (z-scores) Mean (SE)	0.14 (0.13)	0.12 (0.15)

Perinatal mortality - Polarity - Lower values are better
n= number of babies

McEvoy 2002

Outcome	Multiple courses, , N = 18	Single course, , N = 19
Birthweight (grams) Mean (SD)	1767 (659)	1975 (740)
Birthweight (z-scores) Mean (SE)	-0.31 (0.27)	-0.04 (0.28)

n= no. of babies

Murphy 2008

Outcome	Multiple courses, , N = 1164	Single course, , N = 1140
Perinatal mortality Stillbirth or neonatal death ≤28 days after birth or before discharge, whichever happened	n = 43 ; % = 4	n = 40 ; % = 4

Outcome	Multiple courses, , N = 1164	Single course, , N = 1140
later No of events		
Neonatal admission No of events	n = 465 ; % = 42	n = 464 ; % = 42
Intraventricular haemorrhage Grade 3-4 No of events	n = 6 ; % = 0.52	n = 9 ; % = 0.79
Bronchopulmonary dysplasia No of events	n = 19 ; % = 2	n = 11 ; % = 1
Birthweight (grams) Mean (SD)	2216 (28.3)	2330 (28.7)
Birthweight (z-scores) repeat courses n=1158; single course n=1137 Mean (SE)	-0.12 (0.13)	0.12 (0.15)

Perinatal mortality - Polarity - Lower values are better
Neonatal admission - Polarity - Lower values are better
Intraventricular haemorrhage - Polarity - Lower values are better
Bronchopulmonary dysplasia - Polarity - Lower values are better
n= number of babies

Wapner 2006

Outcome	Multiple courses, , N = 296	Single course, , N = 294

Outcome	Multiple courses, , N = 296	Single course, , N = 294
Perinatal mortality No of events	n = 3 ; % = 1.2	n = 6 ; % = 2.5
Intraventricular haemorrhage Multiple courses n= 230; single course n= 230 No of events	n = 15 ; % = 6.5	n = 18 ; % = 7.8
Intraventricular haemorrhage: Grade 3-4 No of events	n = 0 ; % = 0	n = 2 ; % = 0.87
Bronchopulmonary dysplasia Multiple courses n= 250; single course n= 242 No of events	n = 16 ; % = 6.4	n = 26 ; % = 10.7
Birthweight (grams) Unit of analysis is the number of babies; multiple courses n = 296; single course n= 294 Mean (SD)	2194.3 (762.3)	2289.6 (791.8)
Neurodevelopmental delay: severe Bayley PDI score: < 70 No of events	n = 26 ; % = 12.4	n = 23 ; % = 11.8
Neurodevelopmental delay: moderate Bayley PDI score: 70-84 No of events	n = 26 ; % = 12.5	n = 32 ; % = 16.7
Neurodevelopmental delay: severe Bayley MDI score: < 70	n = 39 ; % = 18.7	n = 31 ; % = 16

Outcome	Multiple courses, , N = 296	Single course, , N = 294
No of events		
Neurodevelopmental delay: moderate Bayley MDI score: 70-84 No of events	n = 50 ; % = 24.3	n = 56 ; % = 28.9
Growth at 2 years - weight (Kilograms) multiple course n=206; single course n=195 Mean (SD)	13.5 (2.7)	13.7 (2.6)
Growth at 2 years- head circumference (cm) Mean (SD)	49 (1.9)	49.1 (1.8)
Birthweight (z-scores) repeat courses n= 296; single course n=294 Mean (SE)	-0.21 (0.06)	-0.04 (0.06)

Perinatal mortality - Polarity - Lower values are better
Intraventricular haemorrhage - Polarity - Lower values are better
Bronchopulmonary dysplasia - Polarity - Lower values are better
Neurodevelopmental delay at 2 years - Polarity - Lower values are better
2-year follow-up outcomes from Wapner 2007; n= no. of women (for perinatal mortality, IVH and BPD); n= no. of babies (for birthweight and growth outcomes)

Peltoniemi 2007

Outcome	Multiple courses, , N = 159	Single course, , N = 167
Perinatal mortality Death during hospitalisation No of events	n = 8 ; % = 5	n = 3 ; % = 2

Outcome	Multiple courses, , N = 159	Single course, , N = 167
Intraventricular haemorrhage No of events	n = 31 ; % = 20	n = 27 ; % = 17
Grade 3-4 No of events	n = 6 ; % = 4	n = 4 ; % = 3
Bronchopulmonary dysplasia No of events	n = 15 ; % = 10	n = 14 ; % = 9
Birthweight (grams) Mean (SD)	1460 (500)	1558 (487)
Growth at 2 years - weight (Kilograms) Repeat courses n= 115; single course n = 128 Mean (SD)	12.1 (1.4)	12.1 (1.6)
Growth at 2 years - head circumference (Kilograms) repeat courses n= 115; single course n = 128 Mean (SD)	49.1 (2)	49.3 (1.5)
Birthweight (z-scores) repeat course n= 160; single course n=165 Mean (SE)	-0.16 (0.09)	-0.06 (0.08)

Perinatal mortality - Polarity - Lower values are better
Intraventricular haemorrhage - Polarity - Lower values are better
Bronchopulmonary dysplasia - Polarity - Lower values are better
n= number of babies ; 2-year follow-up outcomes from Peltoniemi 2009

Crowther 2019

Outcome	
Perinatal mortality: GA at 1st dose < 26 weeks Relative risk/95% CI	0.96 (0.57 to 1.6)
Perinatal mortality: GA at 1st dose 26 to < 28 Relative risk/95% CI	0.93 (0.61 to 1.43)
Perinatal mortality: GA at 1st dose 28 to < 30 Relative risk/95% CI	1.17 (0.69 to 1.98)
Perinatal mortality: GA at 1st dose 30 to < 32 Relative risk/95% CI	1.05 (0.52 to 2.15)
Perinatal mortality: GA at 1st dose 32 to < 34 Relative risk/95% CI	0.69 (0.18 to 2.6)
Perinatal mortality: Interval between courses: single course Relative risk/95% CI	1.28 (0.9 to 1.84)
Perinatal mortality: Interval between courses ≤7 days Relative risk/95% CI	0.66 (0.35 to 1.24)
Perinatal mortality: Interval between courses ≥8 days Relative risk/95% CI	0.52 (0.26 to 1.03)
Perinatal mortality: Reason the woman was considered to be at risk of PTLB: cervical incompetence Relative risk/95% CI	1.48 (0.71 to 3.09)
Perinatal mortality: Reason the woman was considered to be at	1.01 (0.68 to 1.51)

Outcome	
risk of PTLB: preterm premature rupture of membranes Relative risk/95% CI	
Perinatal mortality: Reason the woman was considered to be at risk of PTLB: preterm labour Relative risk/95% CI	1.28 (0.86 to 1.9)
Perinatal mortality: Reason the woman was considered to be at risk of PTLB: multi-fetal pregnancy Relative risk/95% CI	1.38 (0.79 to 2.41)
Perinatal mortality: Dose per treatment: ≤12 mg Relative risk/95% CI	1.85 (0.99 to 3.46)
Perinatal mortality: Dose per treatment: >12-24 mg Relative risk/95% CI	0.88 (0.6 to 1.29)
Perinatal mortality: Dose per treatment: >24-48 mg Relative risk/95% CI	0.33 (0.15 to 0.72)
Perinatal mortality: Dose per treatment: > 48 mg Relative risk/95% CI	2.11 (0.87 to 5.11)
Chronic lung disease: GA at 1st dose <26 Relative risk/95% CI	1.01 (0.76 to 1.36)
Chronic lung disease: GA at 1st dose 26 to < 28 Relative risk/95% CI	1.18 (0.88 to 1.59)

Outcome	
Chronic lung disease: GA at 1st dose 28 to <30 Relative risk/95% CI	0.87 (0.53 to 1.41)
Chronic lung disease: GA at 1st dose 30 to <32 Relative risk/95% CI	0.69 (0.29 to 1.64)
Chronic lung disease: GA at 1st dose 32 to < 34 Relative risk/95% CI	0.55 (0.04 to 7.73)
Chronic lung disease: No. of repeat courses = 1 Relative risk/95% CI	1.01 (0.79 to 1.28)
Chronic lung disease: No. of repeat courses = 2 to 3 Relative risk/95% CI	1.08 (0.74 to 1.58)
Chronic lung disease: No. of repeat courses = 4 to 5 Relative risk/95% CI	0.56 (0.27 to 1.18)
Chronic lung disease: No. of repeat courses = 6 or more Relative risk/95% CI	1.73 (0.45 to 6.67)
Chronic lung disease: Reason the woman was considered to be at risk of PTLB: cervical incompetence Relative risk/95% CI	0.72 (0.38 to 1.36)
Chronic lung disease: Reason the woman was considered to be at risk of PTLB: preterm premature rupture of membranes Relative risk/95% CI	1.01 (0.68 to 1.51)

Outcome	
Chronic lung disease: Reason the woman was considered to be at risk of PTLB: preterm labour Relative risk/95% CI	1.28 (0.86 to 1.9)
Chronic lung disease: Reason the woman was considered to be at risk of PTLB: multi-fetal pregnancy Relative risk/95% CI	1.38 (0.79 to 2.41)
Chronic lung disease: Dose per treatment: ≤12 mg Relative risk/95% CI	1.05 (0.74 to 1.48)
Chronic lung disease: Dose per treatment: >12-24 mg Relative risk/95% CI	0.92 (0.68 to 1.26)
Chronic lung disease: Dose per treatment: >24-48 mg Relative risk/95% CI	1.09 (0.71 to 1.68)
Chronic lung disease: Dose per treatment: >48 mg Relative risk/95% CI	0.8 (0.42 to 1.52)
Birthweight (z-score): GA at 1st dose <26 Mean Difference (95% CI)	-0.31 (-0.49 to -0.12)
Birthweight (z-score): GA at 1st dose 26 to < 28 Mean Difference (95% CI)	-0.21 (-0.32 to -0.09)
Birthweight (z-score): GA at 1st dose 28 to <30 Mean Difference (95% CI)	-0.13 (-0.24 to -0.02)

Outcome	
Birthweight (z-score): GA at 1st dose 30 to <32 Mean Difference (95% CI)	-0.03 (-0.14 to 0.07)
Birthweight (z-score): GA at 1st dose 32 to <34 Mean Difference (95% CI)	-0.02 (-0.19 to 0.16)
Birthweight (z-score): No. of repeat courses = 1 Mean Difference (95% CI)	-0.09 (-0.18 to -0.01)
Birthweight (z-score): No. of repeat courses = 2 to 3 Mean Difference (95% CI)	-0.03 (-0.13 to 0.08)
Birthweight (z-score): No. of repeat courses = 4 to 5 Mean Difference (95% CI)	-0.26 (-0.4 to -0.11)
Birthweight (z-score): No. of repeat courses = 6 or more Mean Difference (95% CI)	-0.57 (-0.83 to -0.32)
Birthweight (z-score): Interval between courses: single course Mean Difference (95% CI)	-0.14 (-0.24 to -0.04)
Birthweight (z-score): Interval between courses ≤7 days Mean Difference (95% CI)	-0.21 (-0.33 to -0.09)
Birthweight (z-score): Interval between courses ≥8 days Mean Difference (95% CI)	-0.24 (-0.37 to -0.1)
Birthweight (grams): Reason the woman was considered to be	-122 (-215 to -28)

Outcome	
at risk of PTLB: cervical incompetence Mean Difference (95% CI)	
Birthweight (grams): Reason the woman was considered to be at risk of PTLB: preterm premature rupture of membranes Standardised Mean (95% CI)	-100 (-178 to -22)
Birthweight (grams): Reason the woman was considered to be at risk of PTLB: preterm labour Mean Difference (95% CI)	-134 (-194 to -73)
Birthweight (grams): Reason the woman was considered to be at risk of PTLB: multi-fetal pregnancy Mean Difference (95% CI)	-100 (-171 to -30)
Birthweight (z-score): Dose per treatment: ≤12 mg Mean Difference (95% CI)	-0.1 (-0.24 to 0.04)
Birthweight (z-score): Dose per treatment: >12-24 mg Mean Difference (95% CI)	-0.05 (-0.14 to 0.05)
Chronic lung disease: Dose per treatment: >24-48 mg Standardised Mean (95% CI)	-0.19 (-0.32 to -0.05)
Chronic lung disease: Dose per treatment: >48 mg Standardised Mean (95% CI)	-0.16 (-0.27 to -0.05)

Perinatal mortality - Polarity - Lower values are better
Chronic lung disease - Polarity - Lower values are better
Additional subgroup analysis using data unreported in the original articles

TEAMS

Outcome	**Multiple courses, , N = 91**	**Single course, , N = 91**
Birthweight (z-scores) Mean (SE)	-0.38 (0.11)	-0.07 (0.14)

Critical appraisal

Quality of the Cochrane Systematic review assessed using CheckMAP tool	
Crowther 2019	**Answer** 1. Was the IPD meta-analysis done within a systematic review framework? Yes 2. Were all of the methods pre-specified in a publicly available protocol? Yes 3. Did it have a clear research question qualified by explicit eligibility criteria for trials and participants? Yes 4. Did it use a systematic and comprehensive search to identify trials? Yes 5. Was the approach to data collection consistent and thorough? Yes 6. Were IPD obtained for most trials of the eligible trials and their participants? Yes 7. Was the quality of the IPD checked for each trial? Yes 8. Was the risk of bias assessed for each trial and informed by checks of the associated IPD? Yes 9. Were the methods of meta-analysis appropriate? Unclear: the meta-analysis of IPD effect estimates did not include information on sample size and standard deviation 10. Did the project's report cover the items described in PRISMA-IPD or explain why they were not relevant? Yes
Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool	

Aghajafari 2002	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: some concerns Blinding of outcome assessment: low
Crowther 2006	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low
Garite 2009	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low

Guinn 2001	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low
Mazumder	Random sequence generation: low Allocation concealment: low Incomplete outcome data: some concerns Selective reporting: some concerns Other bias: some concerns Blinding of participants and personnel: high Blinding of outcome assessment: some concerns
McEvoy 2010	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: low

	Blinding of outcome assessment: low
McEvoy 2008	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low
Murphy 2008	Random sequence generation: low Allocation concealment: low Incomplete outcome data: low Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low
Peltoniemi 2007	Random sequence generation: low Allocation concealment: low Incomplete outcome data: some concerns Selective reporting: low

	Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low
TEAMS 1999	Random sequence generation: low Allocation concealment: low Incomplete outcome data: some concerns Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low
Wapner 2006	Random sequence generation: low Allocation concealment: low Incomplete outcome data: some concerns Selective reporting: low Other bias: low Blinding of participants and personnel: low Blinding of outcome assessment: low

Ernawati, 2016

Bibliographic Reference	Ernawati; Gumilar, Erry; Kuntoro; Soeroso, Joewono; Dekker, Gus; Expectant management of preterm preeclampsia in Indonesia and the role of steroids; The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; 2016; vol. 29 (no. 11); 1736-40

Study details

Country/ies where study was carried out	Indonesia
Study type	Randomised controlled trial (RCT)
Study dates	August 2013 - January 2016
Inclusion criteria	• Women with a gestational age of 30-34 weeks with preterm preeclampsia • Women who had received 4 x 6 mg dexamethasone IM every 12 hours for fetal lung maturation
Exclusion criteria	• Women in whom maternal and/or fetal condition required immediate delivery and presence of major coexisting maternal disorders (severe chronic hypertension, preexisting renal disease, pre-existing diabetes mellitus, known infectious diseases – in particular tuberculosis)
Patient characteristics	• Gestational age at intervention: (at randomisation), mean (days) ± SD: multiple courses group, 224.90 ± 8.20; single course group, 224.14 ± 8.44 • Gestational age at birth: mean (days) ± SD: multiple courses group, 238.77 ± 8.94; single course group, 237.54 ± 12.97 • Term deliveries (≥ 37 weeks): not reported • Interval between corticosteroid administration and delivery (reported as time between study entry and delivery), mean (days): multiple courses group, 13.7; single course group, 13.8 (no sig. dif.) • Completed repeat course(s): not reported
Intervention(s)/control	48 hours after receiving a single course of corticosteroids, participants were randomized to receive either methylprednisolone or placebo as follows:

	• 25 mg methylprednisolone IV or placebo IV for 7 days, followed by 12.5 mg methylprednisolone IV or placebo IV until birth • Postpartum antenatal IV dose of methylprednisolone or placebo was continued for 48 h • 4 day oral tapering protocol of 25, 10 and 5 mg of methylprednisolone or placebo, respectively
Duration of follow-up	6 months
Sources of funding	n/a
Sample size	N= 48 women were randomised (44 included in analysis) Methylprednisolone group, n= 22 (22 included in analysis) Placebo group, n= 22 (22 included in analysis) 1 participant in the MP group had 6 days of trial medication, self-discharged for unknown reasons but came back 3 weeks later to give birth (participant included in analysis).

Study arms

Placebo (PL) (N = 22)

Methylprednisolone (MP) (N = 22)

Outcomes

Primary Outcomes

Outcome	**Placebo (PL), , N = 22**	**Methylprednisolone (MP), , N = 22**

Outcome	Placebo (PL), , N = 22	Methylprednisolone (MP), , N = 22
Perinatal mortality (number) No of events	n = 3 ; % = 13.64	n = 5 ; % = 22.73
Intraventricular haemorrhage (number) All grades No of events	n = 0 ; % = 0	n = 0 ; % = 0
Grade 3-4 No of events	n = 0 ; % = 0	n = 0 ; % = 0
Birthweight (grams) Mean (SD)	1954.17 (617.84)	1924.09 (558.45)

Perinatal mortality - Polarity - Lower values are better
Intraventricular haemorrhage - Polarity - Lower values are better
Birthweight - Polarity - Higher values are better

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the	Risk of bias judgement for deviations from the	Low

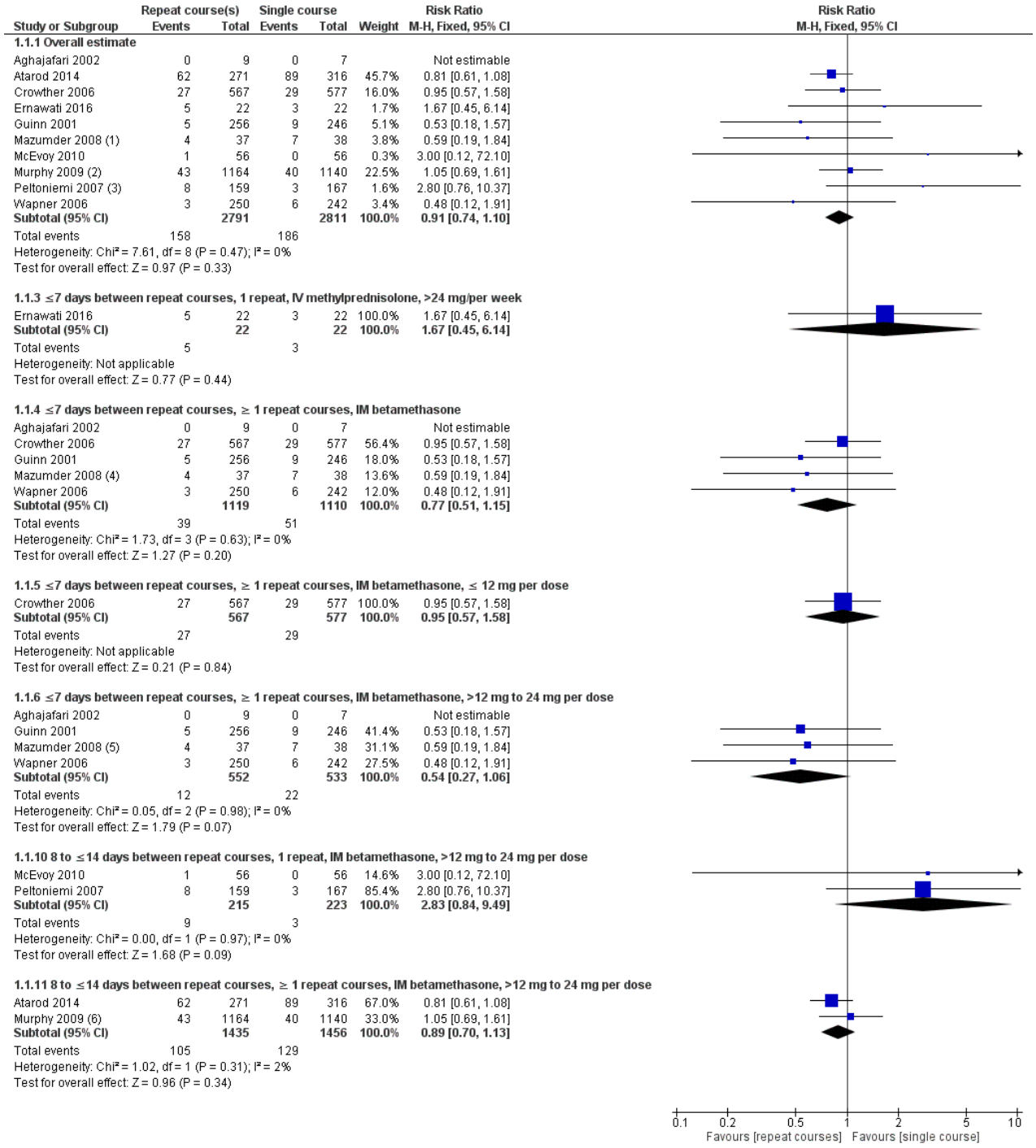
Section	Question	Answer
intended interventions (effect of adhering to intervention)	intended interventions (effect of adhering to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Pre-specified analysis intentions not available in sufficient detail)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Direct
Overall bias and Directness	Risk of bias variation across outcomes	n/a

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

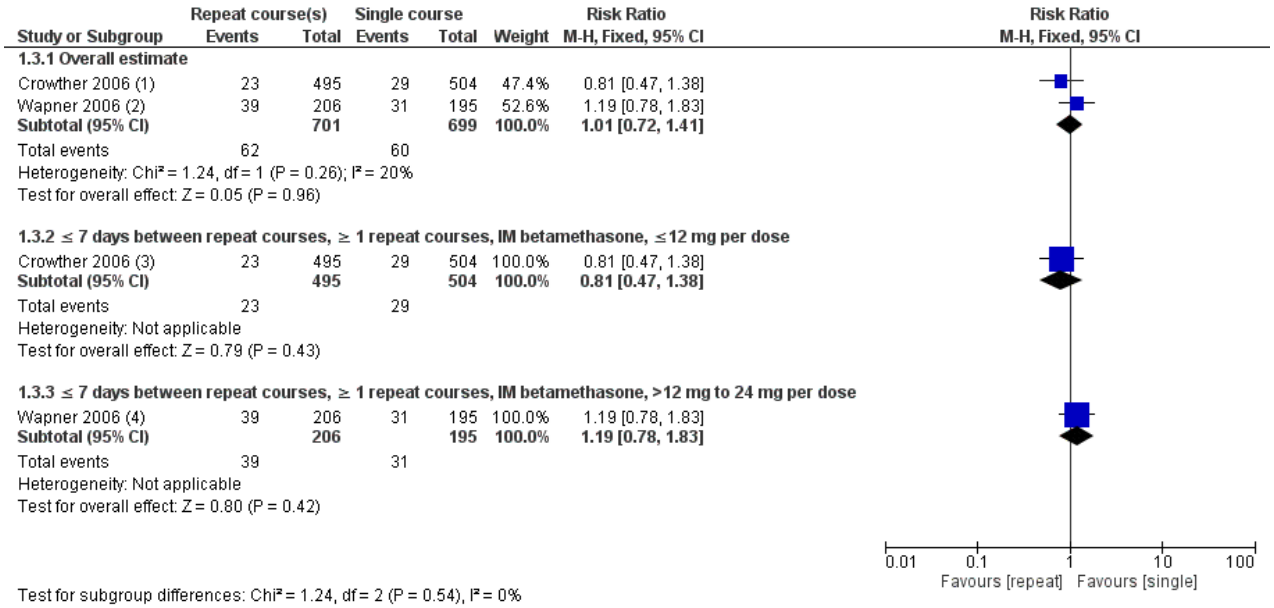
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies or reported as part of the IPD meta-analysis are not presented here, unless these were calculated as part of a stratified analysis; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Perinatal mortality



Footnotes
(1) Death within 28 days
(2) Stillbirth or death ≤28 days after birth or before discharge, whichever happened later
(3) Death before discharge
(4) Death within 28 days
(5) Death within 28 days
(6) Stillbirth or death ≤28 days after birth or before discharge, whichever happened later

Figure 3: Neurodevelopmental delay at 2 years – severe



Test for subgroup differences: Chi² = 1.24, df = 2 (P = 0.54), I² = 0%

Footnotes

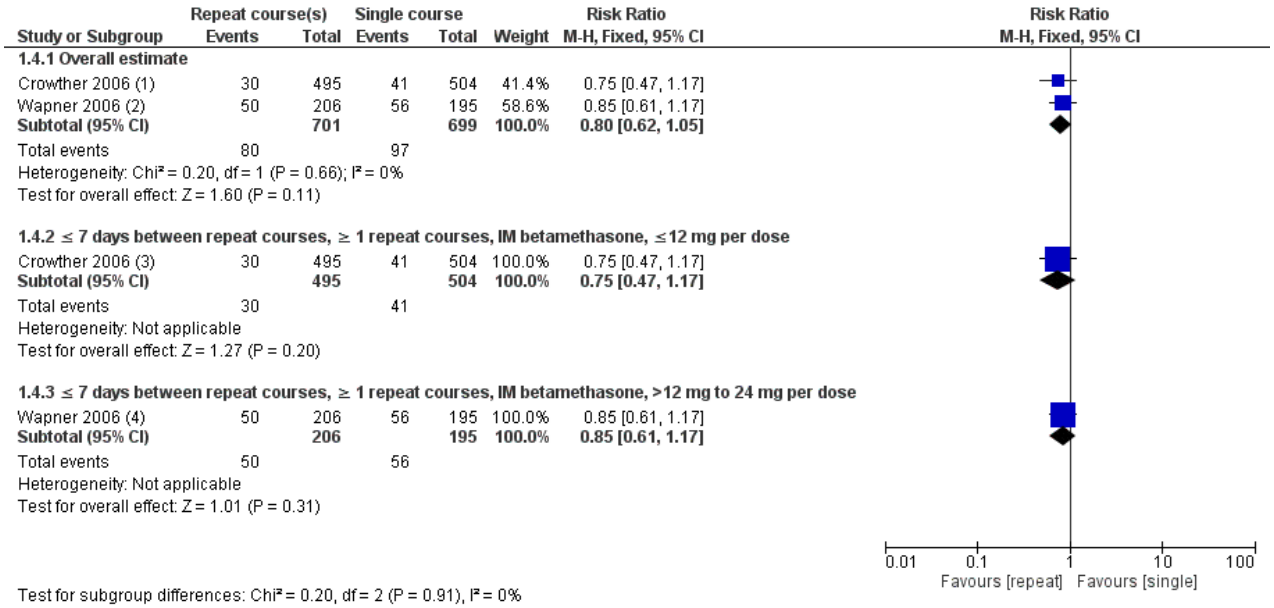
(1) *MDI score > 3 SD below the mean*

(2) MDI score < 70

(3) *MDI score > 3 SD below the mean*

(4) MDI score < 70

Figure 4: Neurodevelopmental delay at 2 years – moderate



Test for subgroup differences: Chi² = 0.20, df = 2 (P = 0.91), I² = 0%

Footnotes

(1) *MDI score > 2 SD to 3 SD below the mean*

(2) *MDI score 70-84*

(3) *MDI score > 2 SD to 3 SD below the mean*

(4) *MDI score 70-84*

Figure 5: Neonatal admission

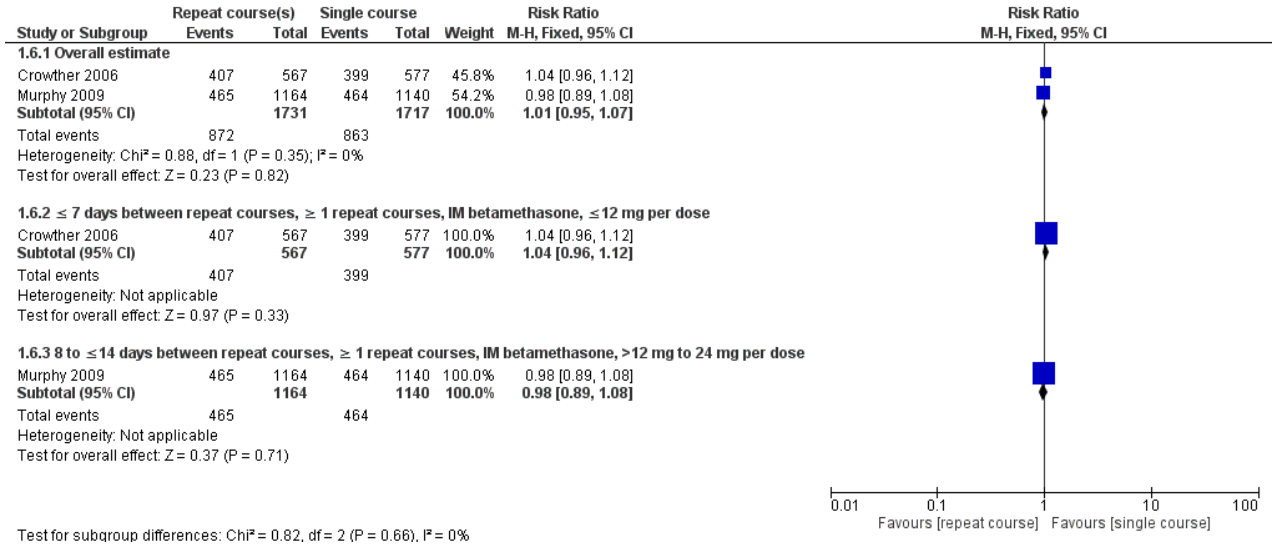


Figure 6: Intraventricular haemorrhage (all grades)

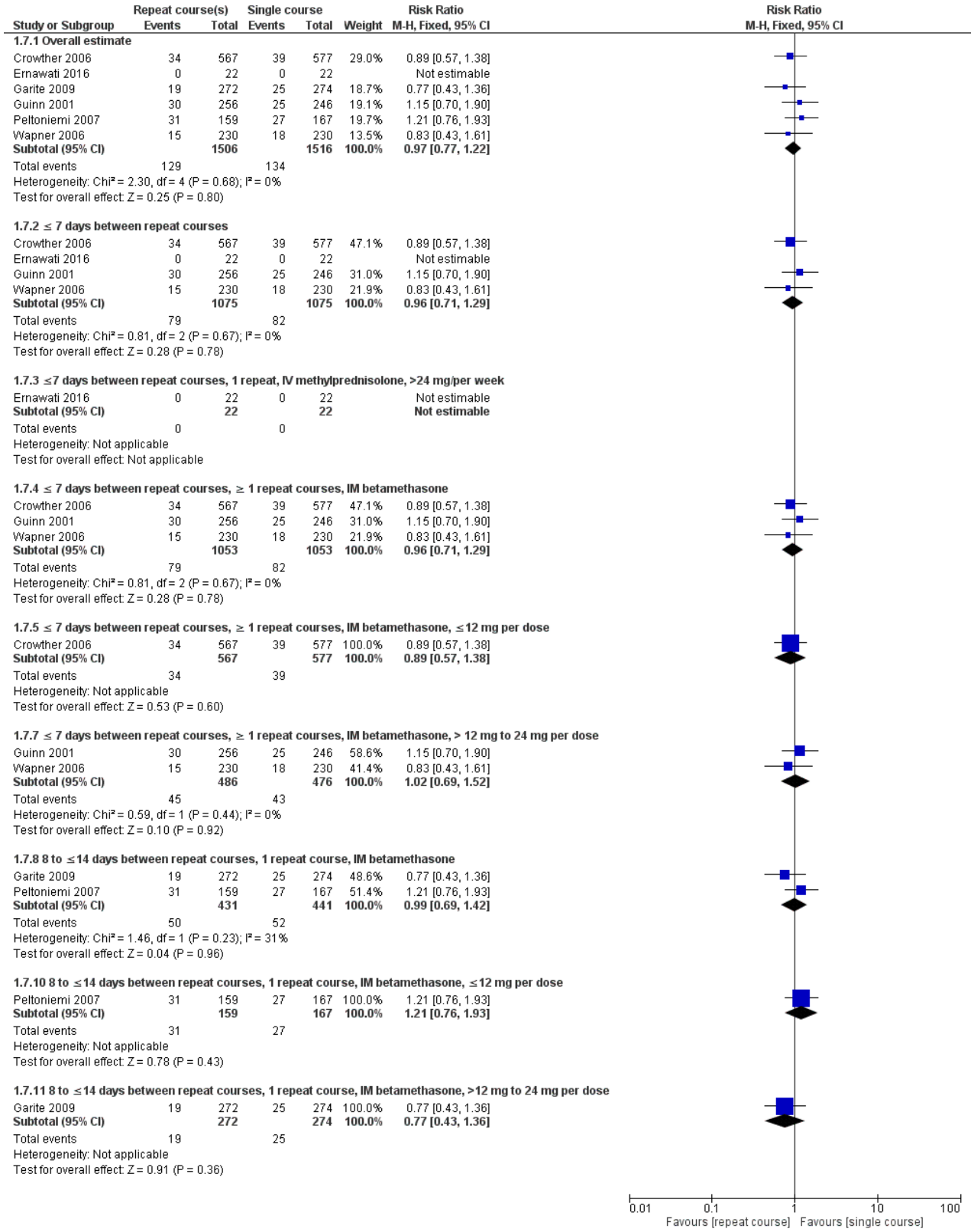


Figure 7: Intraventricular haemorrhage (grades III-IV)

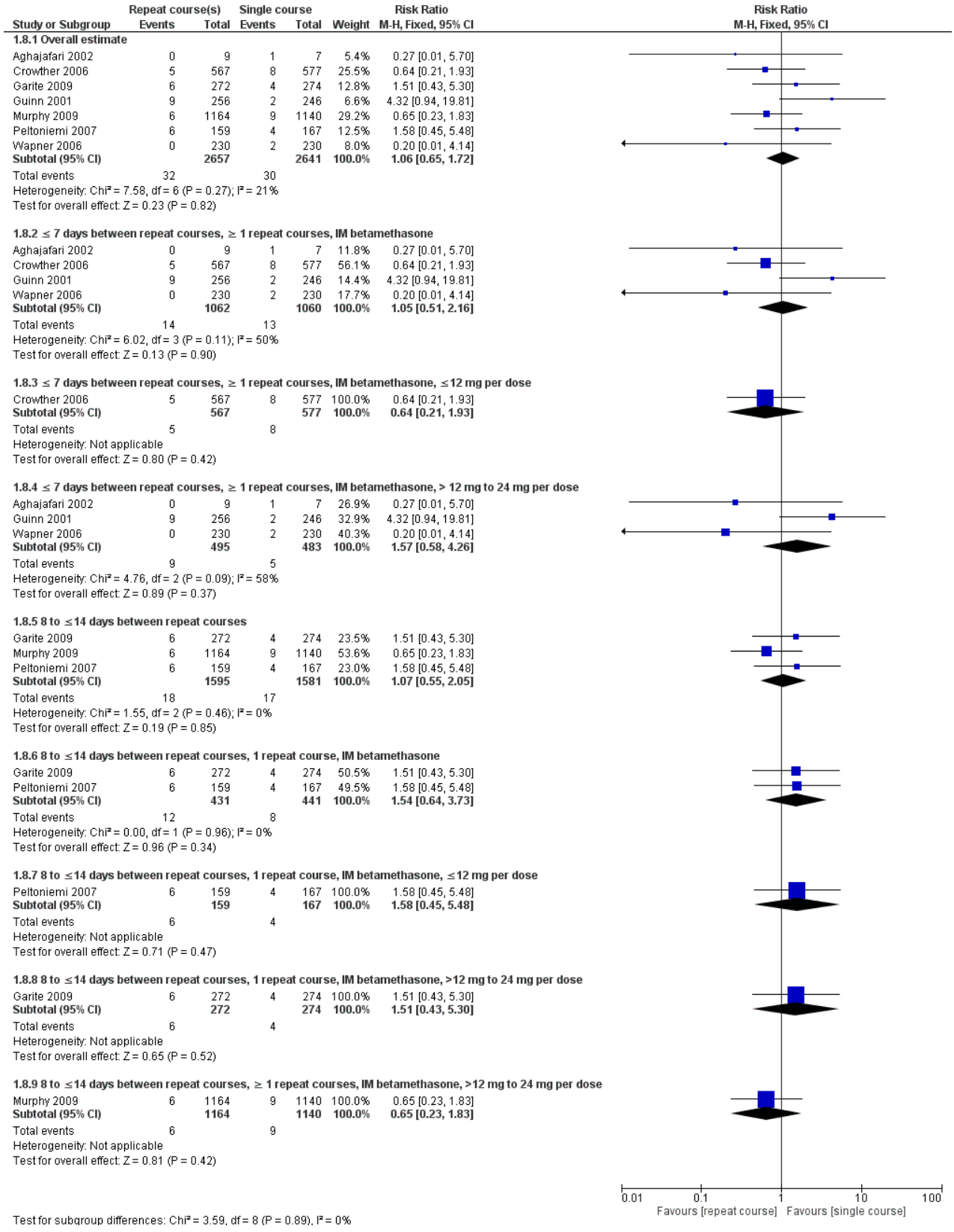


Figure 8: Chronic lung disease

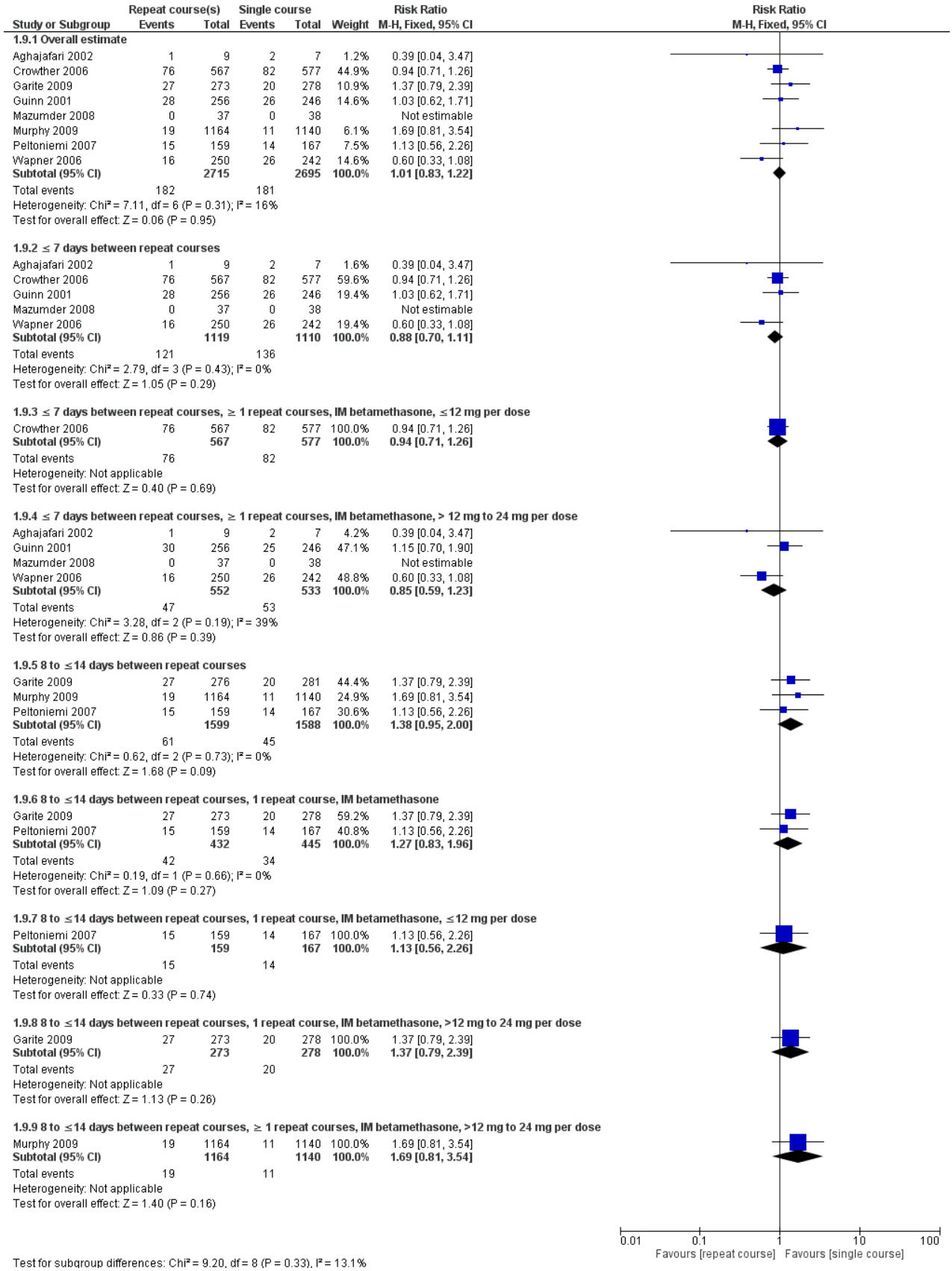


Figure 9: Birthweight (grams)

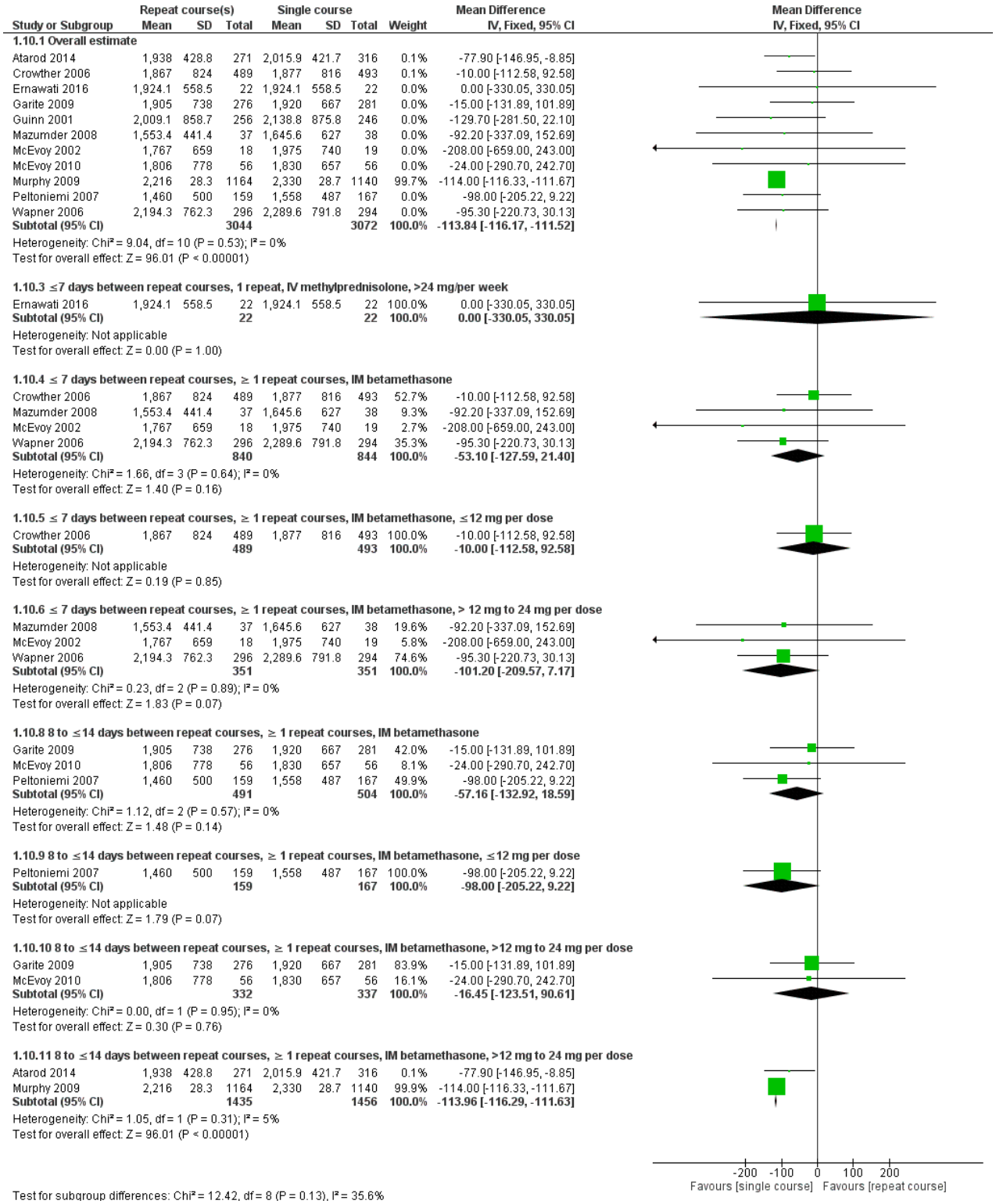


Figure 10: Growth at 2 years - weight (kilograms)

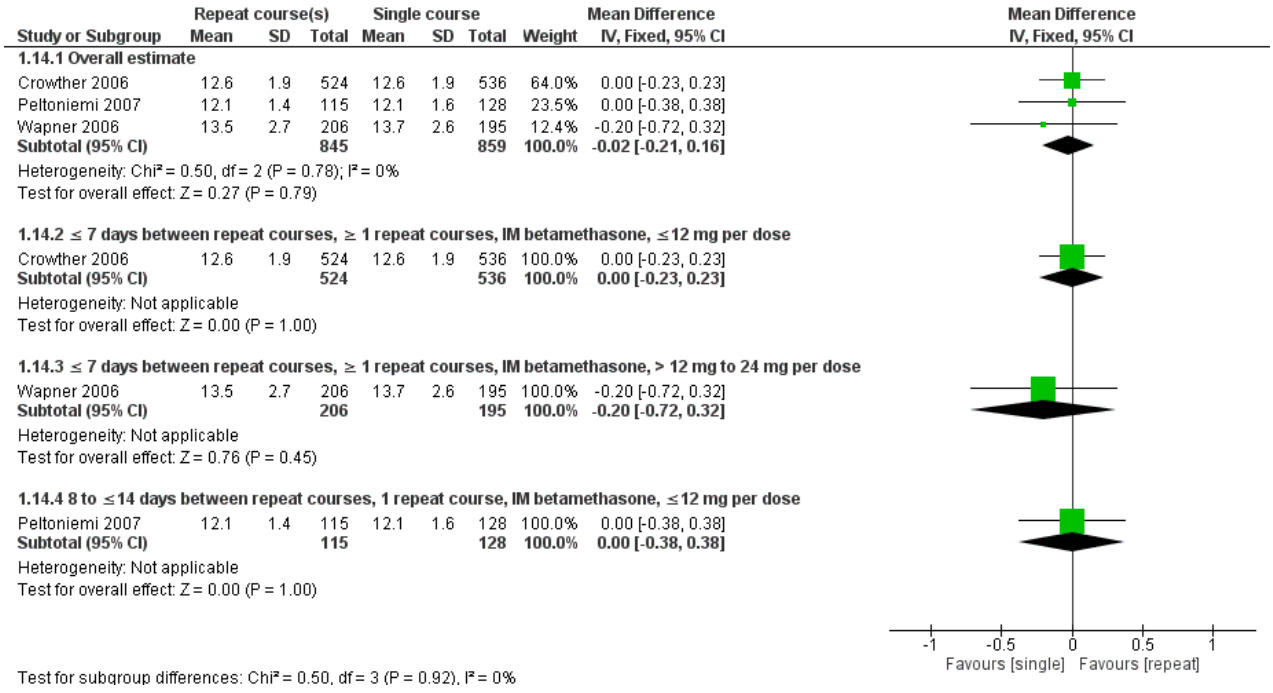
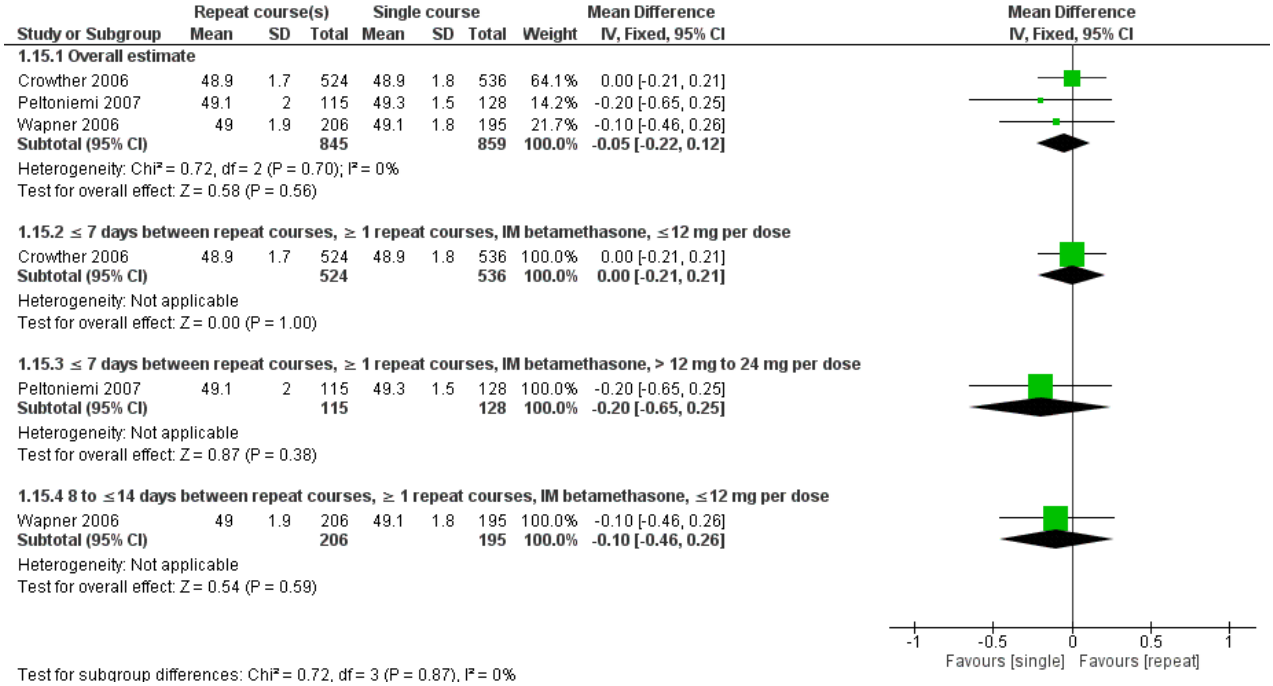


Figure 11: Growth at 2 years - head circumference (cm)



Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Table 5: Evidence profile for comparison between repeat course(s) of corticosteroids to single course of corticosteroids (data extracted from individual studies)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
Perinatal mortality, overall estimate												
10 (Aghajafari 2002, Atarod 2014, Crowther 2006, Ernawati 2016, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	158/2791 (5.7%)	186/2811 (6.6%)	RR 0.91 (0.74 to 1.1)	7 fewer per 1000 (from 17 fewer to 7 more)	MODERATE	CRITICAL
Perinatal mortality, ≤7 days between repeat courses, 1 repeat, IV methylprednisolone, 25 mg for 7 days, followed by 12.5 mg until birth												
1 (Ernawati 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/22 (22.7%)	3/22 (13.6%)	RR 1.67 (0.45 to 6.14)	91 more per 1000 (from 75 fewer to 701 more)	VERY LOW	CRITICAL
Perinatal mortality, ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone												
5 (Aghajafari 2002, Crowther 2006, Guinn 2001, Mazumder 2008, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	39/1119 (3.5%)	51/1110 (4.6%)	RR 0.77 (0.51 to 1.15)	11 fewer per 1000 (from 23 fewer to 7 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
Perinatal mortality, ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27/567 (4.8%)	29/577 (5%)	RR 0.95 (0.57 to 1.58)	3 fewer per 1000 (from 22 fewer to 29 more)	MODERATE	CRITICAL
Perinatal mortality, ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
4 (Aghajafari 2002, Guinn 2001, Mazumder 2008, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/552 (2.2%)	22/533 (4.1%)	RR 0.54 (0.27 to 1.06)	19 fewer per 1000 (from 30 fewer to 2 more)	MODERATE	CRITICAL
Perinatal mortality, 8 to ≤14 days between repeat courses, 1 repeat, IM betamethasone, >12 mg to 24 mg per course												
2 (McEvoy 2010, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	9/215 (4.2%)	3/223 (1.3%)	RR 2.93 (0.84 to 9.49)	25 more per 1000 (from 2 fewer to 114 more)	LOW	CRITICAL
Perinatal mortality, 8 to ≤14 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
2 (Atarod 2014, Murphy 2008)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	105/1435 (7.3%)	129/1456 (8.9%)	RR 0.89 (0.7 to 1.13)	10 fewer per 1000 (from 27 fewer to 12 more)	LOW	CRITICAL
Neurodevelopmental delay (severe), overall estimate (follow-up 2 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
2 (Crowther 2006, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	62/701 (8.8%)	60/699 (8.6%)	RR 1.01 (0.72 to 1.41)	1 more per 1000 (from 24 fewer to 35 more)	LOW	CRITICAL
Neurodevelopmental delay (severe), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course (follow-up 2 years)												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	23/495 (4.6%)	29/504 (5.8%)	RR 0.81 (0.47 to 1.38)	11 fewer per 1000 (from 30 fewer to 22 more)	LOW	CRITICAL
Neurodevelopmental delay (severe), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course (follow-up 2 years)												
1 (Wapner 2006)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	39/206 (18.9%)	31/195 (15.9%)	RR 1.19 (0.78 to 1.83)	30 more per 1000 (from 35 fewer to 132 more)	VERY LOW	CRITICAL
Neurodevelopmental delay (moderate), overall estimate (follow-up 2 years)												
2 (Crowther 2006, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	80/701 (11.4%)	97/699 (13.9%)	RR 0.8 (0.62 to 1.05)	28 fewer per 1000 (from 53 fewer to 7 more)	MODERATE	CRITICAL
Neurodevelopmental delay (moderate), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course (follow-up 2 years)												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	30/495 (6.1%)	41/504 (8.1%)	RR 0.75 (0.47 to 1.17)	20 fewer per 1000 (from 43 fewer to 14 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
Neurodevelopmental delay (moderate), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course (follow-up 2 years)												
1 (Wapner 2006)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	56/206 (24.3%)	56/195 (28.7%)	RR 0.85 (0.61 to 1.17)	43 fewer per 1000 (from 112 fewer to 49 more)	LOW	CRITICAL
Neonatal admission, overall estimate												
2 (Crowther 2006, Murphy 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	872/1731 (50.4%)	863/1717 (50.3%)	RR 1.01 (0.95 to 1.07)	5 more per 1000 (from 25 fewer to 35 more)	HIGH	CRITICAL
Neonatal admission, ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	407/567 (71.8%)	399/577 (69.2%)	RR 1.04 (0.96 to 1.12)	28 more per 1000 (from 28 fewer to 83 more)	HIGH	CRITICAL
Neonatal admission, 8 to ≤14 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
1 (Murphy 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	465/1140 (39.9%)	464/1140 (40.7%)	RR 0.98 (0.89 to 1.08)	8 fewer per 1000 (from 45 fewer to 33 more)	HIGH	CRITICAL
Intraventricular haemorrhage (all grades*), overall estimate												
6 (Crowther 2006, Ernawati 2016, Garite 2009, Guinn 2001, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	129/1506 (8.6%)	134/1516 (8.8%)	RR 0.97 (0.77 to 1.22)	3 fewer per 1000 (from 20 fewer to 19 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
Intraventricular haemorrhage (all grades*), ≤7 days between repeat courses												
4 (Crowther 2006, Ernawati 2016, Guinn 2001, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	79/1075 (7.3%)	82/1075 (7.6%)	RR 0.96 (0.71 to 1.29)	3 fewer per 1000 (from 22 fewer to 22 more)	LOW	IMPORTANT
Intraventricular haemorrhage (all grades*), ≤7 days between repeat courses, 1 repeat, IV methylprednisolone, 25 mg for 7 days, followed by 12.5 mg until birth												
1 (Ernawati 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/22 (0%)	0/22 (0%)	RD 0.00 (-0.07, 0.07)	0 fewer per 1000 (from 7 fewer to 7 more)	VERY LOW	IMPORTANT
Intraventricular haemorrhage (all grades*), ≤7 days between repeat courses, ≥ 1 repeat courses, IM betamethasone												
3 (Crowther 2006, Guinn 2001, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	79/1053 (7.5%)	82/1053 (7.8%)	RR 0.93 (0.69 to 1.26)	5 fewer per 1000 (from 24 fewer to 20 more)	LOW	IMPORTANT
Intraventricular haemorrhage (all grades*), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	34/567 (6%)	39/577 (6.8%)	RR 0.89 (0.57 to 1.38)	7 fewer per 1000 (from 29 fewer to 26 more)	LOW	IMPORTANT
Intraventricular haemorrhage (all grades*), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
2 (Guinn 2001, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	43/486 (8.8%)	43/476 (9%)	RR 0.97 (0.65 to 1.46)	3 fewer per 1000 (from 32 fewer to 42 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
Intraventricular haemorrhage (all grades*), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone												
2 (Garite 2009, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	50/431 (11.6%)	52/441 (11.8%)	RR 0.99 (0.69 to 1.42)	1 fewer per 1000 (from 37 fewer to 50 more)	LOW	IMPORTANT
Intraventricular haemorrhage (all grades*), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, ≤12 mg per course												
1 (Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	31/159 (19.5%)	27/167 (16.2%)	RR 1.21 (0.76 to 1.93)	34 more per 1000 (from 39 fewer to 150 more)	LOW	IMPORTANT
Intraventricular haemorrhage (all grades*), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, >12 mg to 24 mg per course												
1 (Garite 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	19/272 (7%)	25/274 (9.1%)	RR 0.77 (0.43 to 1.36)	21 fewer per 1000 (from 52 fewer to 33 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), overall estimate												
7 (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Murphy 2009, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	32/2657 (1.2%)	30/2641 (1.1%)	RR 1.06 (0.65 to 1.72)	1 more per 1000 (from 4 fewer to 8 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
4 (Aghajafari 2002, Crowther 2006, Guinn 2001, Wapner 2006)	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	very serious[4]	none	14/1062 (1.3%)	13/1060 (1.2%)	RR 1.05 (0.51 to 2.16)	1 more per 1000 (from 6 fewer to 14 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	5/567 (0.88%)	8/577 (1.4%)	RR 0.64 (0.21 to 1.93)	5 fewer per 1000 (from 11 fewer to 13 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
3 (Aghajafari 2002, Guinn 2001, Wapner 2006)	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	very serious[4]	none	9/495 (1.8%)	5/483 (1%)	RR 1.57 (0.58 to 4.26)	6 more per 1000 (from 4 fewer to 34 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), 8 to ≤14 days between repeat courses												
3 (Garite 2009, Murphy 2009, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	18/1595 (1.1%)	17/1581 (1.1%)	RR 1.07 (0.55 to 2.05)	1 more per 1000 (from 5 fewer to 11 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone												
2 (Garite 2009, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	12/431 (2.8%)	8/441 (1.8%)	RR 1.54 (0.64 to 3.73)	10 more per 1000 (from 7 fewer to 50 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, ≤12 mg per course												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
1 (Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/159 (3.8%)	4/167 (2.4%)	RR 1.58 (0.45 to 5.48)	14 more per 1000 (from 13 fewer to 107 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, >12 mg to 24 mg per course												
1 (Garite 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/272 (2.2%)	4/274 (1.5%)	RR 1.51 (0.43 to 5.3)	7 more per 1000 (from 8 fewer to 63 more)	LOW	IMPORTANT
Intraventricular haemorrhage (grades III-IV), 8 to ≤14 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
1 (Murphy 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/1164 (0.52%)	9/1140 (0.79%)	RR 0.65 (0.23 to 1.83)	3 fewer per 1000 (from 6 fewer to 7 more)	LOW	IMPORTANT
Chronic lung disease, overall estimate												
8 (Aghajafari 2002, Crowther 2006, Garite 2009, Guinn 2001, Mazumder 2008, Murphy 2008, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	182/2715 (6.7%)	181/2695 (6.7%)	RR 1.01 (0.83 to 1.22)	1 fewer per 1000 (from 11 fewer to 15 more)	HIGH	IMPORTANT
Chronic lung disease, ≤7 days between repeat courses												
5 (Aghajafari 2002, Crowther 2006, Guinn 2001, Mazumder 2008, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	121/1119 (10.7%)	136/1110 (12.3%)	RR 0.88 (0.7 to 1.11)	15 fewer per 1000 (from 37 fewer to 12 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
Chronic lung disease, ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	76/567 (13.4%)	82/577 (14.2%)	RR 0.94 (0.71 to 1.26)	9 fewer per 1000 (from 41 fewer to 37 more)	LOW	IMPORTANT
Chronic lung disease, ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
4 (Aghajafari 2002, Guinn 2001, Mazumder 2008, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	47/532 (8.5%)	53/521 (9.9%)	RR 0.85 (0.59 to 1.23)	15 fewer per 1000 (from 41 fewer to 23 more)	MODERATE	IMPORTANT
Chronic lung disease, 8 to ≤14 days between repeat courses												
3 (Garite 2009, Murphy 2008, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	61/1599 (3.8%)	45/1588 (2.8%)	RR 1.38 (0.95 to 2)	11 more per 1000 (from 1 fewer to 28 more)	MODERATE	IMPORTANT
Chronic lung disease, 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone												
2 (Garite 2009, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	42/432 (9.7%)	34/445 (7.6%)	RR 1.27 (0.83 to 1.96)	21 more per 1000 (from 13 fewer to 73 more)	MODERATE	IMPORTANT
Chronic lung disease, 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, ≤12 mg per course												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
1 (Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	15/159 (9.4%)	14/167 (8.4%)	RR 1.13 (0.56 to 2.26)	11 more per 1000 (from 37 fewer to 106 more)	LOW	IMPORTANT
Chronic lung disease, 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, >12 mg to 24 mg per course												
1 (Garite 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	27/273 (9.9%)	20/278 (7.2%)	RR 1.37 (0.79 to 2.39)	27 more per 1000 (from 15 fewer to 100 more)	LOW	IMPORTANT
Chronic lung disease, 8 to ≤14 days between repeat courses, ≥ 1 repeat courses, IM betamethasone, >12 mg to 24 mg per course												
1 (Murphy 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	19/1164 (1.6%)	11/1140 (0.96%)	RR 1.69 (0.81 to 3.54)	7 more per 1000 (from 2 fewer to 25 more)	MODERATE	IMPORTANT
Birthweight, overall estimate; measured with: grams												
11 (Atarod 2014, Crowther 2006, Ernawati 2016, Garite 2009, Guinn 2001, Mazumder 2008, McEvoy 2002, McEvoy 2010, Murphy 2008, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3044	3072	-	MD 113.84 lower (116.17 to 111.52 lower)	HIGH	IMPORTANT
Birthweight, ≤7 days between repeat courses, 1 repeat, IV methylprednisolone, 25 mg for 7 days, followed by 12.5 mg until birth; measured with: grams												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
1 (Ernawati 2016)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[8]	none	22	22	-	MD 0 higher (330.05 lower to 330.05 higher)	VERY LOW	IMPORTANT
Birthweight, ≤7 days between repeat courses, ≥ 1 repeat courses, IM betamethasone; measured with: grams												
4 (Crowther 2006, Mazumder 2008, McEvoy 2002, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	840	844	-	MD 53.1 lower (127.59 lower to 21.4 higher)	HIGH	IMPORTANT
Birthweight, ≤7 days between repeat courses, ≥ 1 repeat courses, IM betamethasone, ≤12 mg per course; measured with: grams												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	489	493	-	MD 10 lower (112.58 lower to 92.58 higher)	HIGH	IMPORTANT
Birthweight, ≤7 days between repeat courses, ≥ 1 repeat courses, IM betamethasone, >12 mg to 24 mg per course; measured with: grams												
3 (Mazumder 2008, McEvoy 2002, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	351	351	-	MD 101.2 lower (209.57 lower to 7.17 higher)	HIGH	IMPORTANT
Birthweight, 8 to ≤14 days between repeat courses, 1 repeat courses, IM betamethasone; measured with: grams												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
3 (Garite 2009, McEvoy 2010, Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	491	504	-	MD 57.16 lower (132.92 lower to 18.59 higher)	HIGH	IMPORTANT
Birthweight, 8 to ≤14 days between repeat courses, 1 repeat courses, IM betamethasone, ≤12 mg per course; measured with: grams												
1 (Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	159	167	-	MD 98 lower (205.22 lower to 9.22 higher)	HIGH	IMPORTANT
Birthweight, 8 to ≤14 days between repeat courses, 1 repeat courses, IM betamethasone, >12 mg to 24 mg per course; measured with: grams												
2 (Garite 2009, McEvoy 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	332	337	-	MD 16.45 lower (123.51 lower to 90.61 higher)	HIGH	IMPORTANT
Birthweight, 8 to ≤14 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course; measured with: grams												
2 (Atarod 2014, Murphy 2008)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1435	1456	-	MD 113.96 lower (116.29 to 111.63 lower)	MODERATE	IMPORTANT
Growth (weight), overall estimate (follow-up 2 years; measured with: kilograms)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
3 (Crowther 2006, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	845	859	-	MD 0.02 lower (0.21 lower to 0.16 higher)	HIGH	IMPORTANT
Growth (weight), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course (follow-up 2 years; measured with: kilograms)												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	524	536	-	MD 0 higher (0.23 lower to 0.23 higher)	HIGH	IMPORTANT
Growth (weight), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course (follow-up 2 years; measured with: kilograms)												
1 (Wapner 2006)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	206	195	-	MD 0.2 lower (0.72 lower to 0.32 higher)	MODERATE	IMPORTANT
Growth (weight), 8 to ≤14 days between repeat courses, 1 repeat course, IM betamethasone, ≤12 mg per course (follow-up 2 years; measured with: kilograms)												
1 (Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	128	-	MD 0 higher (0.38 lower to 0.38 higher)	HIGH	IMPORTANT
Growth (head circumference), overall estimate (follow-up 2 years; measured with: cm)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Repeat courses	Single course)	Relative (95% CI)	Absolute		
3 (Crowther 2006, Peltoniemi 2007, Wapner 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	845	859	-	MD 0.05 lower (0.22 lower to 0.12 higher)	HIGH	IMPORTANT
Growth (head circumference), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, ≤12 mg per course (follow-up 2 years; measured with: cm)												
1 (Crowther 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	524	536	-	MD 0 higher (0.21 lower to 0.21 higher)	HIGH	IMPORTANT
Growth (head circumference), ≤7 days between repeat courses, ≥1 repeat courses, IM betamethasone, >12 mg to 24 mg per course (follow-up 2 years; measured with: cm)												
1 (Wapner 2006)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	128	-	MD 0.2 lower (0.65 lower to 0.25 higher)	MODERATE	IMPORTANT
Growth (head circumference), 8 to ≤14 days between repeat courses, 1 repeat courses, IM betamethasone, ≤12 mg per course (follow-up 2 years; measured with: cm)												
1 (Peltoniemi 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	206	195	-	MD 0.1 lower (0.46 lower to 0.26 higher)	HIGH	IMPORTANT

** IVH reported by study authors either without specifying grades or where grades III-IV was reported separately*
MD: mean difference; POR: peto odds ratio; RD: risk difference; RR: risk ratio; SD: standard deviation
1 95% CI crosses the line of no effect
2 Serious concerns of risk of bias in the evidence contributing to the outcomes as per RoB 2.0
3 95% CI crosses the line of no effect and is subjectively wide
4 95% CI crosses 2 MIDs

5 95% CI crosses 1 MID
6 Sample size <200
7 Serious heterogeneity
8 95% CI crosses 2 MIDs (+/-0.5x control group SD, for 'birthweight, ≤ 7 days between repeat courses, 1 repeat IV methylprednisolone, > 24 mg/ week' = +/-279.25)

Table 7: Evidence profile for comparison between repeat course(s) of corticosteroids to single course of corticosteroids (IPD subgroup effect estimates from Crowther 2019)

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
Perinatal mortality, GA at 1st course < 26 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 0.96 (0.57 to 1.60)	-	LOW	CRITICAL
Perinatal mortality, GA at 1st course 26 to < 28 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 0.93 (0.61 to 1.43)	-	LOW	CRITICAL
Perinatal mortality, GA at 1st course 28 to < 30 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 1.17 (0.69 to 1.98)	-	LOW	CRITICAL
Perinatal mortality, GA at 1st course 30 to < 32 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 1.05 (0.52 to 2.15)	-	LOW	CRITICAL
Perinatal mortality, GA at 1st course 32 to < 34 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 0.69 (0.18 to 2.60)	-	LOW	CRITICAL

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
Perinatal mortality, Interval between courses: single repeat course												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 1.28 (0.90 to 1.84)	-	LOW	CRITICAL
Perinatal mortality, ≤7 days between repeat courses												
1 (Crowther 2019)	randomised trial	no serious risk of bias	N/A	serious indirectness[3]	very serious[5]	none	-	-	RR 1.48 (0.71 to 3.09)	-	VERY LOW	CRITICAL
Perinatal mortality, 8 to ≤14 days between repeat courses												
1 (Crowther 2019)	randomised trial	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 0.52 (0.26 to 1.03)	-	LOW	CRITICAL
Perinatal mortality, Reason the woman was considered to be at risk of PTLB: cervical incompetence												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	very serious[5]	none	-	-	RR 1.48 (0.71 to 3.09)	-	VERY LOW	CRITICAL
Perinatal mortality, Reason the woman was considered to be at risk of PTLB: preterm premature rupture of membranes												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 1.01 (0.68 to 1.51)	-	LOW	CRITICAL
Perinatal mortality, Reason the woman was considered to be at risk of PTLB: preterm labour												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 1.28 (0.86 to 1.9)	-	LOW	CRITICAL
Perinatal mortality, Reason the woman was considered to be at risk of PTLB: multi-fetal pregnancy												
1	randomised	no serious	N/A	serious	serious[4]	none	-	-	RR 1.38 (0.79 to 2.41)	-	LOW	CRITICAL

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
(Crowther 2019)	trials	risk of bias		indirectness[3]								
Perinatal mortality, Overall total dose of repeat courses ≤12 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	very serious[5]	none	-	-	RR 1.85 (0.99 to 3.46)	-	VERY LOW	CRITICAL
Perinatal mortality, Overall total dose of repeat courses >12-24 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	serious[4]	none	-	-	RR 0.88 (0.60 to 1.29)	-	LOW	CRITICAL
Perinatal mortality, Overall total dose of repeat courses >24-48 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	no serious imprecision	none	-	-	RR 0.33 (0.15 to 0.72)	-	MODERATE	CRITICAL
Perinatal mortality, Overall total dose of repeat courses > 48 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	serious indirectness[3]	very serious[5]	none	-	-	RR 2.11 (0.87 to 5.11)	-	VERY LOW	CRITICAL
Chronic lung disease, GA at 1st course <26 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.01 (0.76 to 1.36)	-	MODERATE	IMPORTANT
Chronic lung disease, GA at 1st course 26 to <28 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.18 (0.88 to 1.59)	-	MODERATE	IMPORTANT
Chronic lung disease, GA at 1st course 28 to <30 weeks												

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 0.87 (0.53 to 1.4)	-	MODERATE	IMPORTANT
Chronic lung disease, GA at 1st course 30 to <32 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	0.69 (0.29 to 1.64)	-	MODERATE	IMPORTANT
Chronic lung disease, GA at 1st course 32 to <34 weeks												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[5]	none	-	-	RR 0.55 (0.04 to 7.73)	-	LOW	IMPORTANT
Chronic lung disease, No. of repeat courses =1												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.01 (0.79 to 1.28)	-	MODERATE	IMPORTANT
Chronic lung disease, No. of repeat courses =2 to 3												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.08 (0.74 to 1.58)	-	MODERATE	IMPORTANT
Chronic lung disease, No. of repeat courses =4 to 5												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 0.56 (0.27 to 1.18)	-	MODERATE	IMPORTANT
Chronic lung disease, No. of repeat courses =6 or more												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[5]	none	-	-	RR 1.73 (0.45 to 6.67)	-	LOW	IMPORTANT

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
Chronic lung disease, Reason the woman was considered to be at risk of PTLB: cervical incompetence												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 0.72 (0.38 to 1.36)	-	MODERATE	IMPORTANT
Chronic lung disease, Reason the woman was considered to be at risk of PTLB: preterm premature rupture of membranes												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 0.94 (0.70 to 1.27)	-	MODERATE	IMPORTANT
Chronic lung disease, Reason the woman was considered to be at risk of PTLB: preterm labour												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.26 (0.77 to 2.06)	-	MODERATE	IMPORTANT
Chronic lung disease, Reason the woman was considered to be at risk of PTLB: multi-fetal pregnancy												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.09 (0.70 to 1.68)	-	MODERATE	IMPORTANT
Chronic lung disease, Overall total dose of repeat courses ≤12 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 1.05 (0.74 to 1.48)	-	MODERATE	IMPORTANT
Chronic lung disease, Overall total dose of repeat courses >12-24 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 0.92 (0.68 to 1.26)	-	MODERATE	IMPORTANT
Chronic lung disease, Overall total dose of repeat courses >24-48 mg												
1	randomised	no serious	N/A	no serious	serious[4]	none	-	-	RR 1.09 (0.71 to 1.68)	-	MODERATE	IMPORTANT

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
(Crowther 2019)	trials	risk of bias		indirectness								
Chronic lung disease, Overall total dose of repeat courses >48 mg												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-	-	RR 0.80 (0.42 to 1.52)	-	MODERATE	IMPORTANT
Birthweight, GA at 1st course <26; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.31 lower (0.49 lower to 0.12 lower)	HIGH	IMPORTANT
Birthweight, GA at 1st course 26 to <28; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.21 lower (0.32 lower to 0.09 lower)	HIGH	IMPORTANT
Birthweight, GA at 1st course 28 to <30; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.13 lower (0.24 lower to 0.02 lower)	HIGH	IMPORTANT
Birthweight, GA at 1st course 30 to <32; measured with: z-scores												
1	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.03 lower	HIGH	IMPORTANT

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
(Crowther 2019)										(0.14 lower to 0.07 higher)		
Birthweight, GA at 1st course 32 to <34; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.02 lower (0.19 lower to 0.16 higher)	HIGH	IMPORTANT
Birthweight, No. of repeat courses =1; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.09 lower (0.18 lower to 0.01 lower)	HIGH	IMPORTANT
Birthweight, No. of repeat courses =2 to 3; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.03 lower (0.13 lower to 0.08 lower)	HIGH	IMPORTANT
Birthweight, No. of repeat courses =4 to 5; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.26 lower (0.40 lower to 0.11 lower)	HIGH	IMPORTANT

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
Birthweight, No. of repeat courses =6 or more; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.57 lower (0.83 lower to 0.32 lower)	HIGH	IMPORTANT
Birthweight, Interval between courses: single course; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.14 lower (0.24 lower to 0.04 lower)	HIGH	IMPORTANT
Birthweight, Interval between courses ≤7 days; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.18 lower 0.29 lower to 0.07 lower)	HIGH	IMPORTANT
Birthweight, Interval between courses ≥8 days; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.08 lower (0.20 lower to 0.03 higher)	HIGH	IMPORTANT
Birthweight (grams), Reason the woman was considered to be at risk of PTLB: cervical incompetence; measured with: grams												
1	randomised	no serious	N/A	no serious	no serious	none	-	-	--	MD 122	HIGH	IMPORTANT

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
(Crowther 2019)	trials	risk of bias		indirectness	imprecision					lower (215 lower to 28 lower)		
Birthweight (grams), Reason the woman was considered to be at risk of PTLB: preterm premature rupture of membranes; measured with: grams												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-		MD 100 lower (178 lower to 22 lower)	HIGH	IMPORTANT
Birthweight (grams), Reason the woman was considered to be at risk of PTLB: preterm labour; measured with: grams												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 134 lower (195 lower to 73 lower)	HIGH	IMPORTANT
Birthweight(grams), Reason the woman was considered to be at risk of PTLB: multi-fetal pregnancy; measured with: grams												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 100 lower (171 lower to 30 lower)	HIGH	IMPORTANT
Birthweight, Overall total dose of repeat courses ≤12 mg; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.10 lower (0.24 lower to 0.04 higher)	HIGH	IMPORTANT
Birthweight, Overall total dose of repeat courses >12-24 mg; measured with: z-scores												

Quality assessment							No of patients[1]	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency[2]	Indirectness	Imprecision	Other considerations	Repeat courses	Single course	Relative (95% CI)	Absolute		
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.05 lower (0.14 lower to 0.05 higher)	HIGH	IMPORTANT
Birthweight, Overall total dose of repeat courses >24-48 mg; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.19 lower (0.32 lower to 0.05 lower)	HIGH	IMPORTANT
Birthweight, Overall total dose of repeat courses >48 mg; measured with: z-scores												
1 (Crowther 2019)	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	-	-	-	MD 0.16 lower (0.27 lower to 0.05 lower)	HIGH	IMPORTANT

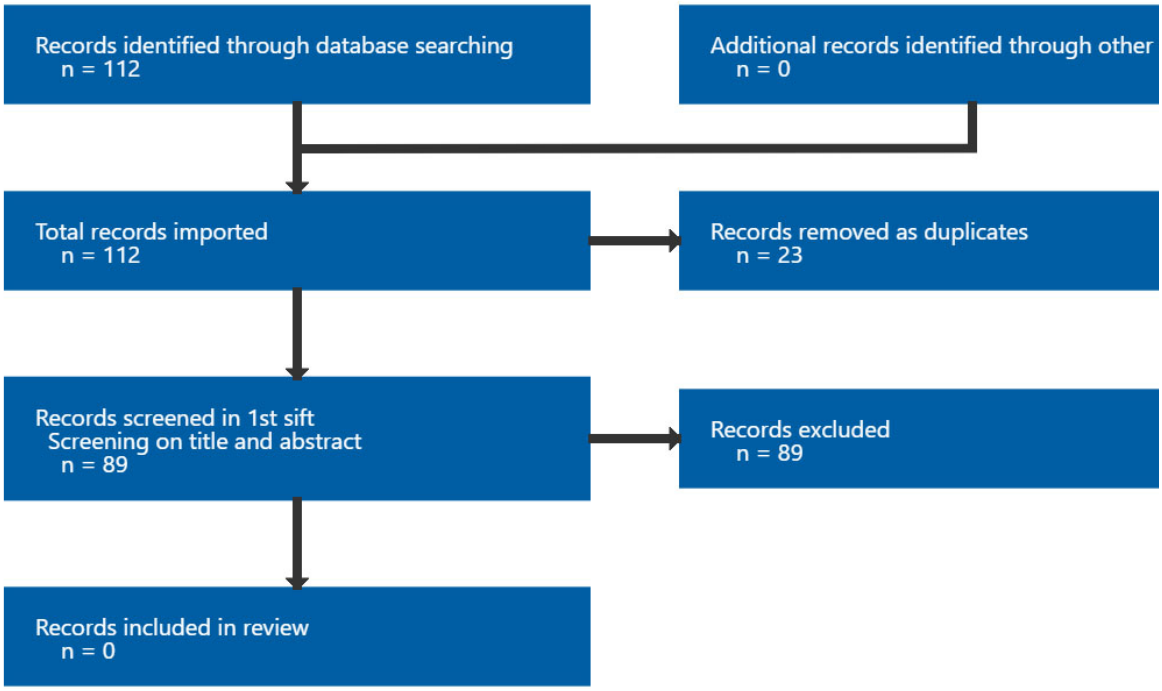
MD: mean difference; RR: risk ratio
1 Number of participants not reported by authors. Effect estimates and 95% CIs reported only
2 Inconsistency could not be assessed
3 Indirectness due to outcome reported as 'Death at any time'
4 95% CI crosses the line of no effect
5 95% CI crosses the line of no effect and is subjectively wide

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

No economic evidence was identified which was applicable to this review question.

Figure 3: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Abbasalizadeh, Fatemeh, Pouya, Khadijeh, Zakeri, Raana et al. (2020) Prenatal Administration of Betamethasone and Neonatal Respiratory Distress Syndrome in Multifetal Pregnancies: A Randomized Controlled Trial. Current clinical pharmacology 15(2): 164-169	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Asztalos EV, Murphy KE, Willan AR et al. (2013) Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5). JAMA pediatrics 167(12): 1102-1110	- Outcomes not in PICO *Study presents 5 year follow-up outcomes of a study included in Crowther 2019 (Murphy 2008)*
Cartwright, R., Crowther, C., Harding, J. et al. (2019) Influence of fetal growth restriction on neurocognitive function after repeat antenatal betamethasone: Secondary analysis of a randomised trial. Journal of Paediatrics and Child Health 55(supplement1): 12-13	- Conference abstract
Deshmukh, M. and Patole, S. (2020) Antenatal corticosteroids for impending late preterm (34-36+6 weeks) deliveries-current evidence from RCTS. Journal of Paediatrics and Child Health 56(suppl1): 73-74	- Conference abstract
Deshmukh, Mangesh and Patole, Sanjay (2021) Antenatal corticosteroids for impending late preterm (34-36+6 weeks) deliveries-A systematic review and meta-analysis of RCTs. PLoS ONE 16(3march): e0248774	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Dorairajan, G., Ontella, V., Bhat, V. et al. (2018) Effect of antenatal dexamethasone on respiratory morbidity of late preterm newborns: A randomized controlled trial. BJOG: An International Journal of Obstetrics and Gynaecology 125(supplement1): 67-68	- Conference abstract

Study	Code [Reason]
Dresang, Lee and Hooper-Lane, Christopher (2018) Clinical Inquiries: What are the benefits/risks of giving betamethasone to women at risk of late preterm labor?. The Journal of family practice 67(7): 448-449	- Narrative review
Gubert, Palma, Murphy, Kellie E., Ryu, Michelle et al. (2020) Rescue steroids after administration remote from delivery: A systematic review of the literature. Journal of Obstetrics and Gynaecology Canada 42(5): 676	- Conference abstract
Gupta, P.; Sharma, S.; Kumar, V. (2019) A Randomised Controlled Trial of 12 Hours vs 24 Hours Betamethasone Dosing Interval in Preterm Premature Rupture of Membranes for Prevention of Respiratory Distress Syndrome (RDS) in Neonates. Journal of medical science and clinical research 7(8): 669-674	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Hofer, Olivia J., McKinlay, Christopher J. D., Tran, Thach et al. (2021) Antenatal corticosteroids, maternal body mass index and infant morbidity within the ASTEROID trial. The Australian & New Zealand journal of obstetrics & gynaecology 61(3): 380-385	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Kashanian, Maryam, Eshraghi, Nooshin, Sheikhansari, Narges et al. (2018) Comparison between two doses of betamethasone administration with 12 hours vs. 24 hours intervals on prevention of respiratory distress syndrome: a randomised trial. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 38(6): 770-776	- Intervention not in PICO *Intervention is a single course of corticosteroids*
McEvoy, Cindy, Schilling, Diane, Spitale, Patricia et al. (2017) Pulmonary function and outcomes in babies randomized to a rescue course of antenatal steroids. Pediatric pulmonology 52(9): 1171-1178	- Outcomes not in PICO
McKinlay, C., Crowther, C. A., Hofer, O. J. et al. (2020) Effect of maternal body mass index on neonatal health following the administration of antenatal corticosteroids. Journal of Paediatrics and Child Health 56(suppl1): 21	- Conference abstract
McKinlay, Christopher J. D., Harding, Jane E., Crowther, Caroline A. et al. (2015) Repeat doses of prenatal corticosteroids for women at risk of	- Systematic review *More recent systematic review included*

Study	Code [Reason]
preterm birth for improving neonatal health outcomes. Cochrane Database of Systematic Reviews 2015(7): cd003935	
Mendez-Figueroa, Hector, Abramovici, Adi, O'Neil, Amy E. et al. (2015) Chorioamnionitis without and with neonatal sepsis: Newborn and infant outcomes. American Journal of Obstetrics and Gynecology 212(1suppl1): S318-S319	- Conference abstract
Mirzamoradi, Masoomeh, Joshaghani, Zahra, Hasani Nejhad, Fatemeh et al. (2020) Evaluation of the effect of antenatal betamethasone on neonatal respiratory morbidity in early-term elective cesarean. Journal of Maternal-Fetal and Neonatal Medicine 33(12): 1994-1999	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Mirzamoradi, Masoumeh, Hasani Nejhad, Fatemeh, Jamali, Razyeh et al. (2020) Evaluation of the effect of antenatal betamethasone on neonatal respiratory morbidities in late preterm deliveries (34-37 weeks). Journal of Maternal-Fetal and Neonatal Medicine 33(15): 2533-2540	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Mwita, Stanley, Jande, Mary, Katabalo, Deogratias et al. (2021) Reducing neonatal mortality and respiratory distress syndrome associated with preterm birth: a scoping review on the impact of antenatal corticosteroids in low- and middle-income countries. World journal of pediatrics : WJP 17(2): 131-140	- Comparison not in PICO *Participants in control arms in included studies received placebo and did not receive a single course of corticosteroids prior to being randomized*
Ninan, Kiran, Morfaw, Frederick, Murphy, Kellie E. et al. (2021) Neonatal and Maternal Outcomes of Lower Versus Standard Doses of Antenatal Corticosteroids for Women at Risk of Preterm Delivery: A Systematic Review of Randomized Controlled Trials. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 43(1): 74-81	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Ontela, Vijaya, Dorairajan, Gowri, Bhat, Vishnu B. et al. (2018) Effect of Antenatal Steroids on Respiratory Morbidity of Late Preterm Newborns: A Randomized Controlled Trial. Journal of tropical pediatrics 64(6): 531-538	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Pasquier, Jean-Charles, Claris, Olivier, Rabilloud, Muriel et al. (2019) Intentional early delivery versus expectant management for preterm premature rupture of membranes at 28-32 weeks' gestation: A multicentre randomized controlled	- Intervention not in PICO *Intervention is a single course of corticosteroids*

Study	Code [Reason]
trial (MICADO STUDY). European Journal of Obstetrics and Gynecology and Reproductive Biology 233: 30-37	
Rasool, A., Farooq, U., Nazir, Q. U. et al. (2017) Efficacy of two regimens of dexamethasone for Management of preterm labour: pilot study. Journal of Ayub Medical College, Abbottabad 29(3): 393-397	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Rezaie, M., Soofizadeh, N., Saymari, F. et al. (2016) Comparison of the effect of single versus double doses of Betamethasone on the outcome of preterm neonates: a Clinical trial study. Research journal of pharmaceutical, biological and chemical sciences 7(6): 874-879	- Intervention not in PICO *Intervention is a single course of corticosteroids*
Rohwer, A. C.; Oladapo, O. T.; Hofmeyr, G. J. (2020) Strategies for optimising antenatal corticosteroid administration for women with anticipated preterm birth. Cochrane Database of Systematic Reviews	- Intervention not in PICO *Systematic review- included studies evaluate strategies to promote the use of corticosteroids*
Schmitz, T. (2016) Prevention of preterm birth complications by antenatal corticosteroid administration. Journal de Gynecologie Obstetrique et Biologie de la Reproduction 45(10): 1399-1417	- Conference abstract
Schmitz, T., Doret, M., Sentilhes, L. et al. (2021) Dose reduction of antenatal betamethasone in women at risk of very preterm delivery (BETADOSE trial). American journal of obstetrics and gynecology 224(2): S723-S724	- Conference abstract
Sela, Hen Y. and Gyamfi-Bannerman, Cynthia (2015) Impact of a 'second course' of antenatal corticosteroids on neonatal outcomes. Reproductive Sciences 22(suppl1): 155a	- Conference abstract
Shaughnessy, Allen F. (2017) Steroids at 34 to 36 Weeks' and Before Term Cesarean Decrease Respiratory Distress Syndrome. American family physician 95(4): 257	- Conference abstract
Shittu, K., Rabiu, K., Ahmed, S. et al. (2021) Does antenatal corticosteroids reduce respiratory morbidity in late preterm babies?. BJOG: An International Journal of Obstetrics and Gynaecology 128(suppl2): 51-52	- Conference abstract

Study	Code [Reason]
Uggioni, Maria Laura Rodrigues, Colonetti, Tamy, Grande, Antonio Jose et al. (2021) Corticosteroids in Pregnancy for Preventing RDS: Overview of Systematic Reviews. Reproductive sciences (Thousand Oaks, Calif.)	- Comparison not in PICO *Participants in control arms in included studies received placebo and did not receive a single course of corticosteroids prior to being randomized*
Viteri, Oscar A., Blackwell, Sean C., Chauhan, Suneet P. et al. (2016) Antenatal Corticosteroids for the Prevention of Respiratory Distress Syndrome in Premature Twins. Obstetrics and gynecology 128(3): 583-91	- Comparison not in PICO *Participants in control arm did not received placebo and did not receive a single course of corticosteroids prior to randomization*
Viteri, Oscar A., Doty, Morgen S., Alrais, Mesk A. et al. (2019) 471: Intended administration of antenatal late preterm steroids: Is a single dose enough?. American Journal of Obstetrics and Gynecology 220(1supplement): 315	- Conference abstract
Yahya, A., Sulayman, H., Abdulkadir, I. et al. (2021) Effect of antenatal corticosteroids in late preterm delivery: A randomised controlled trial. BJOG: An International Journal of Obstetrics and Gynaecology 128(suppl2): 104-105	- Conference abstract

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of repeat courses of maternal corticosteroids for fetal lung maturation in improving preterm neonatal outcomes?

K.1.1 Research recommendation

Is a single repeat dose or a single repeat course (2 doses) of maternal corticosteroids more effective than a single course for preterm neonatal outcomes and longer term outcomes for babies and children, and what is the optimal time interval between completing the initial course (2 doses) and the repeat dose or course?

K.1.2 Why this is important

There is evidence for the benefit of maternal corticosteroids on lung maturation in babies born preterm. Some evidence comparing a single course to repeat courses was identified and there is still a lack of clarity over the long-term benefits or harms of a single repeat course. It is also not known if a repeat single dose of corticosteroids would be as effective as a repeat course (2 doses), and the optimal time interval between doses, which may depend on gestational age.

K.1.3 Rationale for research recommendation

Table 7: Research recommendation rationale

Importance to 'patients' or the population	Maternal corticosteroids are part of standard antenatal management in women considered to be at high risk of giving birth prematurely and it is important they are used in the most effective way to optimise outcomes for women and babies.
Relevance to NICE guidance	The preterm labour and birth guideline (NG25) needs to be updated to provide clear advice to clinicians on when and how to administer repeat doses or courses of maternal corticosteroids.
Relevance to the NHS	The outcome would affect the short and long term health implications of preterm babies
National priorities	High – saving babies lives includes interventions to improve care in cases of preterm birth
Current evidence base	The current evidence does not provide enough information to define the most effective dose (for example, is a single dose sufficient or is a repeat course required) or timing of repeat maternal corticosteroids.
Equality considerations	None known

K.1.4 Modified PICO table

Table 8: Research recommendation modified PICO table

Population	Women between 24 and 34 weeks who have received a course of corticosteroids more than 7 days ago and are at risk of preterm birth within the next 48 hours.
Intervention	• Single repeat dose of corticosteroids • Single repeat course (2 doses) of corticosteroids
Comparator	• No further corticosteroids
Outcome	• Perinatal mortality

	• Acute respiratory distress (for example, need for oxygen or non-invasive/invasive ventilation) • Neurodevelopmental outcomes up to 10 years • Neonatal admission • Intraventricular haemorrhage • Chronic lung disease (for example, BPD, oxygen dependency at 36 weeks) • Birthweight • Growth outcomes up to 10 years
Study design	Cross-sectional study design
Timeframe	Long-term follow (ideally up to 10 years)
Additional information	Stratify results by gestational age and interval between initial course and repeat dose or course

BPD: bronchopulmonary dysplasia