Royal College of Obstetricians & Gynaecologists

Antenatal corticosteroids to reduce neonatal morbidity and mortality

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Antenatal corticosteroids to reduce neonatal morbidity and mortality

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This guideline will supplement NICE guideline [NG25] Preterm labour and birth (November 2015, updated 2019) and the archived RCOG Green-top Guideline No. 7 *Antenatal corticosteroids to reduce neonatal morbidity and mortality* (October 2010).

1. Key recommendations

- A course of antenatal corticosteroids given within the seven days prior to preterm birth reduces perinatal and neonatal death and respiratory distress syndrome. [Grade A]
- For women undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks an informed discussion should take place with the woman about the potential risks and benefits of a course of antenatal corticosteroids. Although antenatal corticosteroids may reduce admission to the neonatal unit for respiratory morbidity, it is uncertain if there is any reduction in respiratory distress syndrome, transient tachypnoea of the newborn or neonatal unit admission overall, and antenatal corticosteroids may result in harm to the neonate which includes hypoglycaemia and potential developmental delay. [Grade B]
- Corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks' gestation in whom imminent preterm birth is anticipated (either due to established preterm labour, preterm prelabour rupture of membranes [PPROM] or planned preterm birth). [Grade A]
- Women with twins and triplets should be offered targeted antenatal corticosteroids for early birth in line with recommendations for singletons. [Grade D]
- Birth should not be delayed for antenatal corticosteroids if the indication for birth is impacting the health of the woman or her baby. [Grade GPP]
- Antenatal corticosteroids should be offered to women with PPROM, who are at increased risk of preterm birth. [Grade A]
- Antenatal corticosteroid use reduces neonatal death when the first dose is given within the 48 hours prior to birth. [Grade D]
- Benefits are also seen when the first dose is given within 24 hours of birth and antenatal corticosteroids should still be given if birth is expected within this time. [Grade D]

2. Background and scope

Maternal administration of antenatal corticosteroids before anticipated preterm birth is one of the most important interventions to improve neonatal outcomes.[1] They are effective in reducing neonatal respiratory morbidity and other complications of prematurity. The aim of this guideline is to provide evidence-based recommendations on the use of antenatal corticosteroids in women at risk of preterm birth or undergoing caesarean birth at term.

This guideline replaces the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guideline No. 7, *Antenatal corticosteroids to reduce neonatal morbidity and mortality* (published October 2010 and archived in 2016) and supplements NICE guideline [NG25], *Preterm labour and birth* (published November 2015, updated 2019).[2] Relevant recommendations can also be found in:

- RCOG Green-top Guideline No. 73, *Care of women presenting with suspected preterm, prelabour rupture of membranes from 24^{+0} weeks of gestation*[3]
- RCOG Green-top Guideline No. 31, *Investigation and management of the small-for-gestational-age fetus*[4]
- RCOG Green-top Guideline No. 27a, *Placenta Praevia and Placenta Accreta: diagnosis and management*[5]
- NICE NG133, *Hypertension in pregnancy: diagnosis and management*[6]
- NICE NG137, *Twin and triplet pregnancy*.[7]

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only people who identify as women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

3. Identification and assessment of evidence

The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched looking for the following terms in the title or abstract 'corticosteroids', 'glucocorticoids', 'pregnancy', 'obstetrics', 'antenatal' and 'fetal'. The search was restricted to articles published until January 2021. The full search strategy is available to view online as supporting information (Appendix S1 and S2).

This guideline was developed using the standard methodology for developing Green-top Guidelines. The recommendations have been graded according to the SIGN hierarchy of evidence.[8]

4. The benefits of antenatal corticosteroids

4.1. What are the benefits of corticosteroids in preterm labour and birth?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
A course of antenatal corticosteroids given within the seven days prior to preterm birth reduces perinatal and	**1++**	**A**	Corticosteroids recommended by a Cochrane systematic review of randomised

(Continued)

Recommendation	Evidence quality	Strength	Rationale for the recommendation
neonatal death and respiratory distress syndrome			controlled trials and supported by NICE NG25.[2]

A Cochrane systematic review (including 27 studies with 11 272 women and 11 925 babies) investigating the effects of corticosteroids administered prior to anticipated preterm birth found high certainty of the benefit of antenatal corticosteroids for the neonate.[9] These benefits include reductions in perinatal death (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.77–0.93), neonatal death (RR 0.78, 95% CI 0.70–0.87) and respiratory distress syndrome (RDS) (RR 0.71, 95% CI 0.65–0.78). There was moderate certainty evidence that antenatal corticosteroids reduce intraventricular haemorrhage (IVH) (RR 0.58, 95% CI 0.45–0.75), and reduce developmental delay in childhood (RR 0.51, 95% CI 0.27–0.97)

Evidence level 1++

No studies were identified that showed direct beneficial effects of antenatal corticosteroids for the woman.

4.2. *What are the benefits of corticosteroids in planned caesarean birth at term?*

Recommendation	Evidence quality	Strength	Rationale for the recommendation
NICE CG132 recommends that planned caesarean birth should not routinely be carried out before 39^{+0} weeks' gestation	**4**	**D**	Recommended by NICE CG132.[10]
For women undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks an informed discussion should take place with the woman (and her family members or carers as appropriate) about the potential risks and benefits of a course of antenatal corticosteroids. Although antenatal corticosteroids may reduce admission to the neonatal unit (NNU) for respiratory morbidity, it is uncertain if there is any reduction in RDS, transient tachypnoea of the newborn (TTN) or NNU admission overall, and antenatal corticosteroids may result in harm to the neonate which includes hypoglycaemia and potential developmental delay (see table 1)	**2+**	**B**	Supported by a Cochrane systematic review that found that steroids may reduce admission to the neonatal unit for respiratory morbidity, but the quality of evidence was low to moderate and came from a single trial

Compared with vaginal birth, infants born by caesarean birth are at greater risk of RDS, TTN, and admission to the neonatal intensive care unit (NICU).[11] The risk of respiratory morbidity at term is low (~5%) and decreases with advancing gestational age.[12] Ideally, planned caesarean births should be undertaken at or after 39^{+0} weeks' gestation.[10]

Evidence level 4

When a planned caesarean birth is being undertaken before 39^{+0} weeks' gestation, corticosteroids may be considered to reduce the risk of neonatal respiratory morbidity. A Cochrane systematic review has assessed the effects of antenatal corticosteroid administration given before planned caesarean birth at term (at or after 37^{+0} weeks' gestation).[13] A previous version of this review[14] included data from four trials, but in the updated version data from three trials were removed as trials did not meet pre-specifed trustworthiness criteria.[13] The updated review includes only one multicentre randomised controlled trial of 998 women and infants, of whom 943 were analysed. As the trial was not placebo controlled and so both participants and personnel knew whether or not antenatal corticosteroids were given, the trial was classified as having high risk of performance and detection bias. There was uncertainty if antenatal corticosteroid administration decreased the risk of RDS (RR 0.34 95% CI 0.07–1.65; low certainty evidence) or TTN, (RR 0.52, 95% CI 0.25–1.11; low certainty evidence). Antenatal corticosteroids probably reduced admission to NNU or NICU for respiratory morbidity (all levels of care; RR 0.45, 95% CI 0.22–0.90) with an absolute reduction of NNU admission for respiratory morbidity from 5.1 to 2.3% (moderate certainty evidence). However, it was uncertain if overall admissions to NNU were reduced (RR 0.81, 95% CI 0.49–1.33). The authors of this Cochrane review concluded that there is currently insufficient evidence to draw any definite conclusions and that further studies of higher quality and larger sample sizes are required. There are several ongoing trials of antenatal corticosteroids that may inform future guidelines.

Evidence level 2–

There is a paucity of evidence on the balance of benefits versus harms when corticosteroids are administered in late pregnancy. Antenatal corticosteroids may increase the risk of neonatal hypoglycaemia in term neonates (extrapolating data from trials of corticosteroids in the late preterm period[15] and observational data[16,17]) and there is some evidence that they may be associated with developmental delay (based on limited and incomplete trial follow-up[18] and observational studies;[19] see section 9.2). As the risk of respiratory distress at term is low (~5%), and it is usually mild and transient, and there is low certainty of benefit, clinicians should discuss these factors with the woman when considering the administration of corticosteroids prior to caesarean birth at term (See Table 1).

5. At what gestation should antenatal corticosteroids be discussed and offered?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Corticosteroid administration has benefits when administered to women in whom imminent preterm birth is anticipated (either due to established preterm labour, PPROM or planned preterm birth) before 24^{+0} weeks' gestation. The obstetric and neonatal team should discuss the administration of corticosteroids at these early gestations with the woman in the context of her individual circumstances and preferences	2+	B	The benefits of corticosteroids at the threshold of viability are supported by a systematic review and meta-analysis of observational studies, and recommended by guidance from the British Association of Perinatal Medicine.[20]
Corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks' gestation in whom imminent preterm birth is anticipated (either due to established preterm labour, PPROM or planned preterm birth)	1++	A	Corticosteroids recommended by a Cochrane systematic review of randomised controlled trials and supported by NICE NG25.[2]

Table 1. Risks and benefits of antenatal corticosteroids to inform discussions with the woman (and her family members or carers as appropriate)

	Benefits	Harms	Uncertainties
22^{+0}* to 34^{+6} weeks *(*when the woman, in discussion with the perinatal care team, has made an informed decision that active care for the baby is appropriate)*	**Highly likely** to reduce: • **perinatal mortality** (RR 0.85, 95% CI 0.77–0.93; 2.3% fewer, 95% CI 1.1%–3.6% fewer).[9] ***NNT 43.5 (95% CI 27.8–100)*** • **neonatal death** (RR 0.78, 95% CI 0.70–0.87; 2.6% fewer, 95% CI 1.5%–3.6% fewer).[9] ***NNT 38.5 (95% CI 27.8–62.5)*** • **neonatal respiratory distress** (RR 0.71, 95% CI 0.65–0.78; 4.3% fewer, 95% CI 3.2%–5.2% fewer).[9] ***NNT 23.3 (95% CI 19.2–30.3)*** **Likely** to reduce: • **intraventricular haemorrhage** (RR 0.58, 95% CI 0.45–0.75; 1.4% fewer, 95% CI 0.8%–1.8% fewer).[9] ***NNT 71.4 (95% CI 55.6–125)*** • **developmental delay in childhood** (RR 0.51, 95% CI 0.27–0.97; 95% CI 0.2%–5.7% fewer).[9] ***NNT 27 (95% CI 17.9–500)*** Reductions in the above conditions are most likely to be seen if birth is **24–48 hours** after starting treatment.[1] A reduction in **respiratory morbidity** (but *not* mortality or interventricular haemorrhage) likely to be seen if birth is within **7 days** of starting treatment.[1]	**Likely** to affect maternal glucose tolerance for up to 5 days after administration (with higher risk in diabetic women).[28] **Likely** to reduce birthweight if birth more than 7 days after steroids (MD −147.01 g, 95% CI −291.97 to −2.05).[1] No benefits are likely to be seen if birth is more than 7 days after starting treatment.[1] **May** increase psychiatric and behavioural diagnoses if children born at term ***NNH 38.8 (95% CI 30–52.4)***[19]	There is less evidence for women with multiple pregnancy.[9] Effects of unnecessary antenatal corticosteroids (i.e. if birth more than 7 days after steroids) are not well described. While no long term harms have been proven, large scale observational studies necessary for pharmacovigilance are lacking

Table 1. (Continued)

	Benefits	Harms	Uncertainties
35^{+0} to 36^{+6} weeks	**Likely** to reduce: • respiratory support (reduction from 146/1000 to 116/1000, RR 0.80 [0.66–0.97])*.[15] ***NNT 33.3 (95% CI 21.5–76.9)***	**Likely** to increase neonatal hypoglycaemia (150/1000 to 240/1000, RR 1.60 [1.37–1.87])**.[15] ***NNH 11.1 (95% CI 8.8–14.7)*** **May** increase psychiatric and behavioural diagnoses if children born at term. ***NNH 38.8 (95% CI 30.5–52.4)***[19]	While no long term harms have been proven, large scale observational studies necessary for pharmacovigilance are lacking. Benefits seem unlikely if birth is more than 7 days after starting treatment, but this has not been studied in women at this gestation
Before planned caesarean birth at term 37–39 weeks	**May** decrease: • admission to NNU with respiratory morbidity (reduction from 51 per 1000 to 23 per 1000 RR 0.45 [0.22 to 0.90]).[13] ***NNT 35.7 (95% CI 25.1–196.1)***	**May** reduce educational attainment at school age (increase in the proportion of children ranked by teachers as being in lower quartile of academic ability from 9 to 18%; and reduction in proportion of children obtaining English proficiency from 13 to 7%).[18]	There is uncertainty as to whether there is any reduction in RDS, TTN or NNU admission overall. Risk of bias in the single centre study means there is low certainty around estimates. Short term complications such as hypoglycaemia have not been rigorously studied, but are likely to also apply at these gestational ages[16] as well as at late preterm gestations. Benefits seem unlikely if birth is more than 7 days after starting treatment, but this has not been studied in women at this gestation. While no long term harms have been proven, large scale observational studies necessary for pharmacovigilance are lacking
Rescue Course if treatment more than 7 days ago	**Likely** to reduce need for respiratory support (reduction from 395 per 1000 to 311 per 1000 RR 0.91 [0.85–0.97]). ***NNT 11.9 (95% CI 9.9–14.9)***[64]	**Likely** to reduce birthweight (mean difference 80g), head circumference and length, and neonatal blood pressure.[64]	Dose effects are seen for harms

NNH, number needed to harm; NNT, Number needed to treat; MD, mean difference.
*Figures include women 34–36^{+5} weeks' gestation.
**Figures include women 34–36^{+5} weeks' gestation. 'Highly likely' indicates high certainty evidence; 'Likely' indicates moderate certainty evidence and 'May' indicates low certainty evidence. Certainty of evidence was aligned to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.[75]

(Continued)

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Clinicians and women should consider the balance of risks and benefits of corticosteroids in women in whom imminent preterm birth is anticipated from 35^{+0} to 36^{+6} weeks' gestation	4	D	In late preterm birth, steroids have short term respiratory benefits for the neonate but increase the likelihood of neonatal hypoglycaemia. This is addressed in the Cochrane systematic review and in NICE NG25.[2]

The gestational age range at which antenatal corticosteroids provide benefit and should therefore be considered or offered, remains controversial.[21] NICE NG25 addresses the administration of corticosteroids to women at risk of preterm birth, recommending that when offering or considering corticosteroids a discussion should take place with the woman about how steroids may help and the potential risks associated with their administration.[2]

Evidence level 4

There is evidence that corticosteroid administration has benefits when given prior to birth at the threshold of viability (before 24^{+0} weeks' gestation).[22–24] A systematic review and meta-analysis investigating corticosteroid administration before 25^{+0} weeks' gestation, (nine observational studies and a total of 13 443 neonates) found that compared with controls, corticosteroid administration was associated with reduced mortality (odds ratio [OR] 0.48, 95% CI 0.42–0.55), and reduced IVH/periventricular leukomalacia (PVL) (OR 0.70, 95% CI 0.63–0.79).[25] In this study, antenatal corticosteroids were associated with significantly reduced neonatal mortality at 22, 23 and 24 weeks; the benefit for severe IVH/PVL was significant only at 23 and 24 weeks.

Evidence level 2+

The British Association of Perinatal Medicine recommends that neonatal stabilisation and resuscitation may be considered for babies born from 22^{+0} weeks' gestation.[20] When a woman has made an informed decision, that active care for the baby is appropriate, then active obstetric management, including the administration of corticosteroids, is important.

Evidence level 4

The 2020 Cochrane systematic review looked at outcomes in two gestational age subgroups at trial entry: up to 35 weeks^{+0} days and from 34 weeks^{+0} days.[9] No differences between subgroups for the outcomes of perinatal death, neonatal death, fetal death, RDS, IVH, birthweight or chorioamnionitis were seen.

Evidence level 1++

The subgroup analysis of antenatal corticosteroids from 34^{+0} weeks gestation included in the Cochrane review[9] was dominated by a single trial which assessed the effects of corticosteroids in 2831 woman at risk of late preterm birth (34^{+0} until 36^{+5} weeks' gestation).[15] In this trial the administration of corticosteroids significantly reduced the requirement for respiratory support in the first 72 hours of life (11.6% versus 14.4%; RR 0.80, 95% CI 0.66–0.97). Neonatal hypoglycaemia was more common in the betamethasone group than in the placebo group (24.0 versus 15.0%; RR 1.6, 95% CI 1.37–1.87).

Evidence level 1+

There are currently insufficient data to assess on long-term effects of late preterm antenatal corticosteroids for the child.[9]

In very late preterm gestation women (from 35^{+0} weeks') the use of antenatal corticosteroids should be considered in light of the balance of risks and benefits. Evidence level 4

6. In what particular circumstances should antenatal corticosteroids be discussed with and offered to women?

6.1. *Multiple pregnancy*

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with twins and triplets should be offered targeted antenatal corticosteroids for early birth in line with recommendations for singletons	**3**	**D**	There is little direct evidence of benefit in twins, but no indication that the effects of corticosteroids are different in multiple pregnancies than in singletons in a Cochrane systematic review of randomised controlled trials
Uncertainties around the benefits and risks of antenatal corticosteroids in twins and triplets should be discussed with women	**4**	**GPP**	This is regarded as good practice
Single or multiple untargeted (routine) courses of corticosteroids should not be used in twin or triplet pregnancy. Women should be informed that there is no evidence of benefit in using untargeted administration of corticosteroids	**4**	**D**	Recommendation from NICE NG137 on basis of no evidence of benefit.[7]

The majority of antenatal corticosteroid trials has excluded women with multiple pregnancy so there is little evidence regarding use in twins or higher order multiple pregnancies. Eleven trials included in the Cochrane Systematic Review of Antenatal Corticosteroids for lung maturity included some women with multiple pregnancies, but outcomes were only reported separately for twins in four included studies.[9] In a prespecified subgroup analysis of these studies there were no statistically significant differences in the maternal or perinatal outcomes of multiple pregnancies that received antenatal corticosteroids compared to those that did not. However, the analyses included a limited number of cases so these findings should be interpreted with caution. Evidence Level 3

A secondary analysis of data from a trial of progesterone to prevent preterm birth in multiple pregnancy suggested there may be harm associated with antenatal corticosteroid use (432 women; 850 neonates). Babies of women who received antenatal corticosteroid treatment were more likely to be admitted to a neonatal intensive care unit (235 [78%] versus 322 [59%]) and receive mechanical ventilation (70 [23%] Evidence level 2–

versus 66 [12%]) with no apparent improvement in RDS or neonatal morbidity compared with babies of women who did not receive treatment.[26]

NICE guideline NG137 recommends the targeted use of antenatal corticosteroids in women with multiple pregnancy based on a presumption of similar effects in multiple pregnancies as in singletons.[7] Evidence level 4

NICE guideline NG137 recommends against the use of single or repeat doses of untargeted steroids due to limited, low quality evidence.[7] Evidence level 4

6.2. *Women with diabetes mellitus*

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Diabetes should not be considered an absolute contraindication to antenatal corticosteroids for fetal lung maturation	**4**	**D**	NICE NG3 addresses the use of antenatal corticosteroids in women with diabetes.[27]
In women with diabetes who are receiving corticosteroids, additional insulin should be given according to an agreed protocol and close monitoring should be undertaken	**4**	**D**	NICE NG3 addresses the use of antenatal corticosteroids in women with diabetes.[27]
For women with diabetes undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks an informed discussion should take place with the woman (and her family members or carers as appropriate) about the potential risk and benefits of a course of corticosteroids. Corticosteroid administration is associated with increased rates of neonatal hypoglycaemia	**2+**	**C**	The administration of corticosteroids has been shown to increase rates of neonatal hypoglycaemia in retrospective cohort studies

Women with diabetes mellitus have been excluded from most randomised controlled trials of antenatal corticosteroids because of concerns about their potential effects on glycaemic control. Maternal blood glucose levels rise shortly after administration of corticosteroids and can remain elevated for up to 5 days.[28,29] One systematic review and meta-analysis identified no eligible studies on preterm birth outcomes following corticosteroid therapy in pregnancies complicated by diabetes.[30]

Guidance from NICE recommends that diabetes should not be considered a contraindication to antenatal corticosteroids for fetal lung maturation.[27] Evidence level 4

In view of the effects of corticosteroids on glycaemic control, NICE recommends that in women with insulin-treated diabetes who are receiving steroids for fetal lung maturation, additional insulin should be given according to an agreed protocol and the women should be monitored closely. Guidelines on the management of glycaemic control in pregnant women with diabetes during antenatal steroid administration have been produced by the Joint British Diabetes Societies for Inpatient Care.[31]

Evidence level 4

Retrospective cohort studies have shown that the administration of corticosteroids prior to caesarean section at term (after 37^{+0} weeks' gestation) in women with diabetes (gestational and pre-existing), is associated with increased rates of neonatal hypoglycaemia.[32]

Evidence level 2+

Ideally the risks and benefits of corticosteroids, and the potential adverse effects of a variable rate intravenous insulin infusion if required, should be discussed with the woman (and her family members or carers as appropriate) prior to the administration of steroids.

6.3. *Pregnancies complicated by fetal growth restriction, pre-eclampsia or antepartum haemorrhage*

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Birth should not be delayed for antenatal corticosteroids if the indication for birth is impacting the health of the woman or her baby	**4**	**GPP**	This is considered good practice
NICE guidance NG25 recommends a course of antenatal corticosteroids should be offered if planned early birth is necessary for hypertension in pregnancy	**1+**	**B**	There is limited direct evidence of benefit in women with hypertensive syndromes. The use of antenatal corticosteroids and is endorsed by NICE NG25.[2]
If imminent preterm birth is likely, a course of antenatal corticosteroids should be offered to women whose babies are thought to be either small-for-gestational-age (SGA) or to have fetal growth restriction, but women should be counselled about the lack of evidence to guide care	**2++**	**C**	There is little direct evidence of benefit in SGA babies, but equally there is little evidence that antenatal corticosteroids perform differently in babies with growth restriction compared to the overall preterm population. The use of corticosteroids in this situation is recommended by RCOG Green-top Guideline No. 31.[4]

Trials of antenatal corticosteroids include a diverse number of sub-populations of women whose response to corticosteroids may vary. However, in general sub-group analyses have been underpowered to provide precise estimates of the benefits and risks of antenatal corticosteroids for specific indications. NICE NG25 recommendations for antenatal corticosteroid administration were thus made regardless of any specific indication for preterm birth.[2]

In the Cochrane Systematic Review of antenatal corticosteroids prespecified subgroup analyses were performed in women with hypertension syndromes.[9] There were no differences in corticosteroid effects on perinatal mortality, neonatal mortality and fetal death seen between women with and without hypertension syndromes. Heterogeneity of effects were seen for RDS in the subgroup analyses, with potentially a larger reduction in RDS seen in hypertensive mothers than other groups, but there is considerable uncertainty around these estimates. There were insufficient data to perform subgroup analyses for many other outcomes. NICE guidance recommends that a course of antenatal corticosteroids is offered if planned early birth is necessary for hypertension in pregnancy.[2,6]

Evidence level 1+

A systematic review identified no randomised controlled trials of antenatal corticosteroids in pregnancies complicated by fetal growth restriction.[30] A meta-analysis of eight observational studies of women with SGA or fetal growth restricted babies (2846 women and babies) found no statistically significant benefits associated with antenatal corticosteroids. No differences in neonatal mortality were associated with antenatal corticosteroid administration in babies that were SGA (pooled OR 0.78, 95% CI 0.58–1.04; six studies, 958 infants) or those that had fetal growth restriction (pooled OR 0.81, 95% CI 0.58–1.14; four studies, 504 infants). Antenatal corticosteroids were not associated with any statistically significant reductions in morbidities either. One small study included in the meta-analysis found significantly higher rates of survival without disability at two years' corrected age in infants born with fetal growth restriction who were exposed to antenatal corticosteroids compared to those that were not exposed (115 infant; OR 2.55, 95% CI 1.11–5.87], 82 versus 65%).[33] A subsequent systematic review of 13 observational, cohort and case-control studies including 6387 preterm SGA infants found that neonatal mortality was significantly lower among infants whose mothers had received antenatal corticosteroids than those who had not (12 studies: 12.8 versus 15.1%; pooled OR 0.63; 95% CI 0.46–0.86). There was no apparent effect on neonatal morbidity.[34]

Evidence level 2++

Children who are born preterm and growth restricted are at increased risk of adverse long-term neurodevelopmental outcomes. However, a secondary analysis of data from the multicentre Australasian Collaborative Trial of Repeated Doses of Corticosteroids (ACTORDS), found that repeated antenatal betamethsone treatment compared with placebo was not associated with adverse effects on neurocognitive function at 6–8 years of age, even in the presence of fetal growth restriction.[35]

Evidence level 1–

There is however, little evidence to suggest that steroids will perform differently in babies with growth restriction compared to the overall preterm population.[1] RCOG guidance on SGA babies recommends that women with a SGA baby should receive antenatal corticosteroids to accelerate fetal lung maturation and reduce neonatal death and morbidity in a similar way to those with a SGA baby.[4]

Evidence level 4

Additional recommendations on antenatal corticosteroids for women with Placenta Praevia and Placenta Accreta are given in RCOG Green-top Guideline No. 27a.[5]

Evidence level 4

7.4. *Preterm, prelabour rupture of the membranes (PPROM)*

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Antenatal corticosteroids should be offered to women with PPROM who are at increased risk of preterm birth	**1++**	**A**	A meta-analysis of randomised controlled trials supports the use of antenatal corticosteroids in this situation
There is currently limited evidence to recommend repeat courses of antenatal corticosteroids if a woman remains at imminent risk of preterm birth seven days after administration of antenatal corticosteroids. However, a further course may reduce the need for neonatal respiratory support	**1+**	**B**	The administration of one or more repeat courses of corticosteroids is addressed in section 10.

The role of antenatal corticosteroids in women presenting with suspected PPROM from 24^{+0} weeks' gestation is addressed in RCOG Green-top Guideline no. 73 and in NICE NG25.[2,3] The World Health Organization recommends that corticosteroids are appropriate for women with PPROM who have no clinical signs of infection.[1]

Evidence level 4

PPROM complicates up to 3% of pregnancies and is associated with 30–40% of preterm births.[36] The median latency after PPROM is seven days and tends to shorten as the gestational age at PPROM advances.[37,38] A meta-analysis of 17 randomised controlled trials has demonstrated that the administration of corticosteroids to women with PPROM reduces the risks of RDS (RR 0.81, 95% CI 0.67–0.98) and IVH (RR 0.49, 95% CI 0.25–0.96). No difference was observed between steroid and control groups concerning the risk for necrotising enterocolitis, neonatal sepsis and Apgar score of less than 7 at 5 minutes. Perinatal mortality was similar between steroid and control groups.[39]

Evidence level 1++

The administration of a repeat course of corticosteroids is addressed in section 10. In women with PPROM, concerns have been raised that multiple courses of corticosteroids may increase the risk of chorioamnionitis and neonatal sepsis.[40–42]

A secondary analysis of the Beneficial Effects of Antenatal Magnesium (BEAM) randomised controlled trial[43] investigated 1641 women with PPROM who received either one or two courses of antenatal corticosteroids.[44] The rate of neonatal sepsis was similar whether the woman had received one compared with two courses of steroids (16.2 versus 17.2%).[44] A further secondary analysis of the BEAM dataset found no increased risk of chorioamnionitis between the groups (single course incidence 12.3% and repeat course, 11.0%).[45]

Evidence level 2+

7. What is the optimum dose and route of administration for a course of antenatal corticosteroids?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
In the UK it is recommended that 24mg dexamethasone phosphate is given intramuscularly in two divided doses of 12 mg 24 hours apart or four divided doses of 6 mg 12 hours apart	**2+**	**B**	A Cochrane systematic review, found that dexamethasone, compared with betamethasone, reduced the risk of intraventricular haemorrhage
An alternative is 24 mg betamethasone sodium phosphate/acetate mix given intramuscularly in two divided doses of 12 mg 24 hours apart	**2++**	**B**	Betamethasone acetate/phosphate is the formulation of betamethasone which is most trialled. Compared to dexamethasone, betamethasone sodium phosphate/acetate may reduce the risk of chorioamnionitis
Clinicians should be aware that betamethasone phosphate, the preparation widely available in the United Kingdom, has different pharmacokinetics from betamethasone sodium phosphate/acetate mix and there is little evidence to guide the effective dosage regimen for this formulation		**GPP**	This is considered good practice
Oral or transplacental administration is not recommended	**2++**	**B**	There is insufficient evidence to support administration by these routes

Antenatal corticosteroids are designed to cross the placenta. They are given at high doses that have been unchanged since Liggins' and Howie's original experiments in the 1970s and have not been optimised for human pregnancy.[46] Two types of antenatal corticosteroid have been widely tested and used in clinical practice – betamethasone and dexamethasone. These are synthetic fluorinated corticosteroids, with similar activities.[46]

Betamethasone

Betamethasone is available in two formulations. Betamethasone sodium phosphate is soluble with a short half-life, while betamethasone sodium acetate is insoluble and has a long half-life.[47] In many countries the two preparations are available in a 50:50 mixture (as a generic preparation or under the trade name Celestone Chronodose®). This mixed soluble/insoluble preparation is similar to one used in the original studies performed by Liggins and Howie and has been most widely used in trials of antenatal corticosteroids for fetal lung maturity.[46,47] This formulation is used in North America, Australia and most of Europe. It is an opaque white liquid that requires refrigeration. The most commonly trialled and recommended dosage regimen is two 12 mg boluses given intramuscularly 24 hours apart (total 24 mg).

Evidence level 2++

Betamethasone sodium phosphate, the soluble form of betamethasone, is used in some countries, including the United Kingdom, where the mixed formulation is not widely available. This is a clear liquid, has a short half-life and has been less widely tested in clinical trials. The difference between the two formulations of betamethasone and their very different pharmacokinetics has not been widely recognised and many trial publications do not specify the formulation used. The optimum dosage strategy for betamethasone sodium phosphate is not clear; however, given the short half-life a similar dosage schedule to dexamethasone may be pragmatic.

Evidence level 4

Dexamethasone

Dexamethasone phosphate is a soluble preparation, which is slightly cheaper than betamethasone sodium phosphate/acetate mix and does not require refrigeration. Dexamethasone is included in the World Health Organisation *Essential Medicine List*, the World Health Organisation *Managing complications in pregnancy and childbirth: a guide for midwives and doctors* and is more commonly used in low and middle income countries.[48,49] The most commonly used dosage schedule in trials is four doses of 6 mg given intramuscularly 12 hours apart (total 24 mg).

Evidence level 2+

In the Cochrane Systematic review on antenatal corticosteroids for fetal lung maturity a prespecified subgroup analysis was performed comparing the formulation of antenatal corticosteroid used.[9] Sixteen trials used 'betamethasone', and eight used dexamethasone. No distinction was made between betamethasone sodium phosphate/acetate mix or betamethasone phosphate in the review, but the majority of betamethasone studies were carried out in countries where betamethasone sodium phosphate/acetate mix is recommended. In this analysis betamethasone resulted in less maternal chorioamnionitis than dexamethasone, although there was uncertainty regarding these estimates. Little difference between formulations was seen in other outcomes.

Evidence level 2+

Another Cochrane systematic review assessed the use of different corticosteroids and regimens for accelerating fetal lung maturation and included a total of 12 trials (1557 women and 1661 infants).[50] No distinction was made in the review between betamethasone sodium phosphate/acetate mix or betamethasone phosphate. Six of the included trials had a primary outcome of a fetal biophysical parameter or maternal blood parameter rather than a morbidity outcome. On analysis of the remaining trials, no differences were seen in respiratory distress syndrome (five trials, 753 babies) or perinatal death (four trials, 596 babies) between the two formulations. Dexamethasone resulted in a lower risk of interventricular haemorrhage (four trials, 549 babies).

Evidence level 2+

More recently, a randomised control trial (1346 women, 1509 babies, 79 with follow up to two years) found no differences in the incidence of death or neurosensory disability at two years between dexamethasone and betamethasone phosphate/acetate mix (198 [33%] of 603 infants receiving dexamethasone versus 192 [32%] of 591 infants receiving betamethasone phosphate/acetate mix; adjusted relative risk [adjRR] 0.97, 95% CI 0.83–1.13; $P = 0.66$). Both drugs were given in two divided doses 24 hours apart. Side effects of the two preparations were similar, although more women experienced discomfort at the injection site with betamethasone phosphate/acetate mix.[51]

Evidence level 1+

There is insufficient evidence to recommend use of other antenatal corticosteroids that may cross the placenta (including hydrocortisone), the use of oral preparations or direct fetal administration.[50,52]

Evidence level 2++

8. How long after administration is a course of antenatal corticosteroids most effective?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Antenatal corticosteroid use reduces neonatal death when the first dose is given within the 48 hours prior to birth	**4**	**D**	Discussed in WHO guidance, that cites an archived Cochrane review of randomised controlled trials.[1]
Benefits are also seen when the first dose is given within 24 hours of birth and antenatal corticosteroids should still be given if birth is expected within this time	**4**	**D**	Discussed in WHO guidance that cites an archived Cochrane review of randomised controlled trials.[1]
Antenatal corticosteroids are most effective in reducing RDS in pregnancies that birth between 24 hours and 7 days of administration of the second dose of antenatal corticosteroids	**4**	**D**	Discussed in WHO guidance, that cites an archived Cochrane review of randomised controlled trials.[1]

The WHO recommendations on interventions to improve preterm birth outcomes cites the (now archived) 2006 Cochrane review where subgroup analyses were performed according to the interval between corticosteroid administration and preterm birth.[1,53] There was a significant reduction in cases of RDS among babies born before 48 hours (RR 0.67, 95% CI 0.49–0.93; three studies, 374 infants) and between one and seven days (RR 0.46, 95% CI 0.35–0.60; nine studies, 1110 infants), but not among those born before 24 hours (RR 0.87, 95% CI 0.66–1.15; nine studies, 517 infants) or those born more than seven days after the first dose of antenatal corticosteroids (RR 0.82, 95% CI 0.53–1.28; eight studies, 988 infants). Significant reductions were also observed in cases of cerebroventricular haemorrhage among infants born within 48 hours of the first dose of steroids (RR 0.26, 95% CI 0.09–0.75; one study, 339 infants) but not in any of the other subgroups.

Evidence level 4

There was a significant reduction in fetal and neonatal death for birth within 24 hours of administration (RR 0.60, 95% CI 0.39–0.94; three studies 293 infants) and within 48 hours (RR 0.59, 95% CI 0.41–0.86; one study, 373 infants) but not those born between one and seven days (RR 0.81, 95% CI 0.60–1.09; three studies, 606 infants) or those born after seven days (RR 1.42, 95% CI 0.91–2.23; three studies, 598 infants). This difference was due to reduction in neonatal but not fetal deaths.

Evidence level 4

However, caution should be exercised in the interpretation of the data due to the limitations and potential bias of the subgroup analyses in the original 2006 review. The question as to whether the effects of antenatal corticosteroids change with time to delivery would require re-analysis of individual patient data to clarify whether the association is real.[54] This re-analysis was not undertaken in the 2017 or 2020 updates of the Cochrane review and therefore the need for caution remains.[9,55]

Accumulation of data from population based cohort studies including large numbers of infants supports the early effects of antenatal corticosteroids. The EPICE group demonstrated that any antenatal corticosteroid was associated with reduced mortality with the largest effect 24 hours to seven days after first injection (adjRR 0.5; 95% CI 0.4–0.6).[56] Further analysis demonstrated a significant risk reduction in mortality of 50% with a time of administration to birth interval of 18–36 hours (4594 infants 24–31 weeks, 11 countries) compared with no antenatal steroids, though the significant reduction in severe brain injury was associated with longer administration to birth intervals (more than 48 hours). All outcomes had an increased risk after the interval had increased beyond seven days.

Evidence Level 2+

A population based cohort study in Sweden of infants born at 22–26 completed weeks' gestation, demonstrated that survival was lower in infants not exposed to antenatal corticosteroids (Hazard ratio [HR] 0.26; 95% CI 0.15–0.43), in infants born less than 24 hours [HR 0.53 (0.33–0.87)] and more than 7 days after steroid administration [HR 0.56 (0.32–0.97)], but not in infants born 24–47 hours after steroids [HR 1.60 (0.73–3.50)], as compared with infants born 48 hours to seven days after administration.[57]

Evidence Level 2+

A Canadian retrospective cohort study of 6870 infants born at 24–33 weeks' gestation concluded antenatal corticosteroids had maximal effect when given between one and seven days before birth. The odds of the composite adverse outcome were significantly higher in all groups compared with neonates who received antenatal corticosteroids one to seven days before birth (no antenatal corticosteroids: adjusted OR 2.12, 95% CI 1.69–2.65; partial antenatal corticosteroids: adjusted OR 1.48, 95% CI 1.22–1.80; and antenatal corticosteroids at greater than seven days: adjusted OR 1.46, 95% CI 1.20–1.77). Similar findings were observed with respect to neonatal mortality (no antenatal corticosteroids: adjusted OR 2.56, 95% CI 1.83–3.59; partial antenatal corticosteroids: adjusted OR 1.59, 95% CI 1.16–2.18; and antenatal corticosteroids at greater than seven days: adjusted OR 1.40, 95% CI 1.00–1.97).[58]

Evidence Level 2+

A secondary analysis of two prospective studies including 2259 babies found that neonates exposed to antenatal corticosteroids between two and up to seven days prior to birth had the lowest risk of respiratory distress syndrome (51.3%), when compared to babies who received antenatal corticosteroids before two days, seven to before 14 days, and from 14 days prior to birth (62.7%, 55.9, and 57.6%, respectively, $P < 0.001$). There odds of respiratory distress syndrome with antenatal corticosteroids before two days and from 14 days prior to birth was increased when compared to antenatal corticosteroids given between two and up to seven days before birth (aOR 2.07, 95%CI 1.61–2.66 up to 2 days and aOR 1.40, 95% CI 1.07–1.83 for from 14 days). Babies exposed to antenatal corticosteroids from 14 days prior to birth were at increased odds for severe neonatal morbidity (aOR 1.57, 95% CI 1.12–2.19) and early childhood morbidity (aOR 1.74, 95% CI 1.02–2.95), compared to those exposed between two and up to seven days before birth.[59]

Evidence Level 2+

9. What are the risks associated with the administration of antenatal corticosteroids?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women should be counselled regarding the risks and uncertainties surrounding the evidence of antenatal corticosteroid treatment		**GPP**	This is considered good practice
Institutions should use standard guidelines for the assessment and management of neonatal hypoglycemia in late preterm or early term newborns who have received recent antenatal corticosteroids		**GPP**	This is considered good practice. In a large RCT, antenatal corticosteroids increased the risk of hypoglycaemia in babies born late preterm

9.1. What are the risks to the woman?

In the Cochrane systematic review on antenatal corticosteroids for fetal lung maturity there was no evidence that antenatal corticosteroids increased rates of maternal infection.[9] Although the majority of data within the meta-analysis was from high income settings, the meta-analysis did include data from a large randomised control trial of 2852 women at risk of early preterm birth (26^{+0} to 33^{+6} weeks' gestation) at sites with maternal and neonatal hospital services meeting the WHO criteria for antenatal corticosteroid treatment in five low and middle income countries.[60]

Evidence level 1+

As described above corticosteroids are known to increase maternal blood glucose levels.[29] One trial included in the Cochrane systematic review on antenatal corticosteroids for fetal lung maturity reported effects on glucose tolerance.[9] In this small trial women treated with antenatal corticosteroids were more likely to have an abnormal glucose tolerance test (performed from 72 hours after steroid administration) compared to controls (123 women; RR 2.71, 95% CI 1.14–6.46).[61]

Evidence level 1–

9.2. What are the risks to the baby?

Antenatal corticosteroid administration affects fetal growth. Babies who receive antenatal corticosteroids have a lower birth weight than those that received placebo.[1,62,63] A dose response is seen, and babies that receive multiple courses of antenatal corticosteroids are most affected with reductions in weight, head circumference and length.[64]

Evidence level 1+

As discussed above, late preterm babies who receive antenatal corticosteroids have higher rates of neonatal hypoglycaemia.[15] A retrospective cohort study including 99 neonates whose mother had received antenatal corticosteroids, found that the occurrence of neonatal hypoglycaemia was independent from the

Evidence level 2+

time interval between steroid administration and birth.[17] Neonatal hypoglycaemia has also been demonstrated in women with diabetes who have received steroids prior to caesarean birth at term.[32]

The long-term metabolic and neurological consequences of neonatal hypoglycaemia are uncertain; a follow-up cohort (at 4.5 years) from the Children With Hypoglycemia and Their Later Development (CHYLD) Study found that neonatal hypoglycaemia was associated with a dose-dependent increased risk of poor executive function and visual motor function and may therefore impact on later learning.[65]

Evidence level 2+

Concerns have been raised that antenatal corticosteroids may have long lasting effects on the cardiovascular system and metabolic profile. A 30-year follow up of 534 surviving participants of a randomised controlled trial of antenatal corticosteroids, found no statistically significant differences in growth, blood pressure, blood lipids, plasma cortisol, prevalence of diabetes, or history of cardiovascular disease in the group exposed to antenatal corticosteroids compared to placebo.[66] However, participants exposed to antenatal corticosteroids were more insulin resistant and had higher plasma insulin concentrations in response to a glucose tolerance test than those exposed to placebo (60.5 versus 52.0 mIU/L; $P = 0.02$). Cohort studies have shown young adults (23–28 years) who were exposed to antenatal corticosteroids had decreased aortic distensibility and altered glucose metabolism compared to controls[67] and 14-year-olds exposed to antenatal corticosteroids had higher blood pressure than unexposed children.[68]

Evidence level 2+

Another concern is that antenatal corticosteroids may have effects on brain development. An individual patient data meta-analysis of the effects of repeat antenatal corticosteroids is reassuring in that no differences were seen on death or neurodevelopment in follow up studies (six trials; 4557 children).[64]

Evidence level 1+

However, emerging evidence suggested that there may be detrimental effects on long term development particularly in term born infants who were exposed to antenatal corticosteroids. A population cohort study of nearly 70 000 school age children in Finland found antenatal corticosteroid exposure, compared with non-exposure, was associated with higher risk of psychiatric and behavioural disorders (12.01% versus 6.45%; adjusted hazard ratio [aHR], 1.33 [95% CI 1.26–1.41]) especially in term-born children (8.89 versus 6.31%; HR, 1.47 [95% CI, 1.36–1.69]; NNH 38.8 [95% CI 30.5–52.4]).[19]

Evidence level 2+

A Canadian population cohort study found a similar association among term born infants exposed to antenatal corticosteroids during pregnancy with healthcare utilisation during childhood related to suspected neurocognitive and neurosensory disorders (audiometry testing, visual testing or physician service claim with a diagnosis code related to a suspected neurocognitive disorder; 61.7% in corticosteroid exposed children (3346/5423) compared to 57.8% (302 520/523 782) in non-steroid exposed children; aHR 1.12, 95% CI 1.08–1.16; $P < 0.001$; NNH 25 (95% CI 19–38).[69]

Evidence level 2–

A cohort study has shown an increased cortisol response to psychological stress in term born 6–11 year old girls and term born 14–18 year olds exposed to antenatal corticosteroids preterm, compared to non-exposed children.[70,71] Further analysis of this cohort found effects on the development of fronto-parietal brain functions during adolescence, affecting multiple facets of adaptive cognitive and behavioural control associated with antenatal corticosteroid exposure.[72]

Evidence level 2+

Follow up of 407 of the original 998 participants of a trial of antenatal corticosteroids prior to term planned caesarean birth at 8–15 years of age found that children exposed to antenatal betamethasone prior to planned caesarean birth were more likely to be in the lower quartile of academic ability (8.5 versus 17.7%; $P = 0.03$); although no other differences in outcome were detected.[18] These findings must be interpreted with caution due to the low follow-up rates. In a cohort of 179 surviving adults, 29–36 years old, who were born at extremely low birthweight (below 1 kg), exposure to antenatal corticosteroid was associated with clinically significant anxiety (OR 3.34 [95% CI 1.03–10.81]).[73]

Evidence level 2–

WHO recommend antenatal corticosteroids should only be offered when a minimum standard of maternal and neonatal hospital services are available.[1] In a cluster randomised control trial in low- and middle-income settings of a strategy to scale up use of antenatal corticosteroids,[74] there was a very unexpected increase in neonatal mortality (RR 1.12, 1.02–1.22) and stillbirth (RR 1.11, 1.02–1.22) in clusters with increased antenatal corticosteroid use. Only 16% of the women who received antenatal corticosteroids gave birth to a less-than-fifth-percentile newborn (which was used as a surrogate for preterm birth, due to difficulties in establishing gestation) suggesting significant over diagnosis of imminent preterm birth and overtreatment with antenatal corticosteroids. The increased mortality was driven by increases in infants above the 25th percentile for birthweight (i.e. likely term born). Reassuringly however, a subsequent large randomised control trial of 2852 women at risk of early preterm birth (26^{+0} to 33^{+6} weeks' gestation) attending sites with maternal and neonatal hospital services meeting the WHO criteria for antenatal corticosteroid treatment in five low and middle income countries, found that, compared to placebo, dexamethasone phosphate reduced neonatal death (RR 0.84; 95% CI 0.72–0.97; $P = 0.03$) and perinatal mortality (RR 0.88; 95% CI 0.78–0.99; $P = 0.04$) without increasing maternal infection (RR, 0.76; 95% CI 0.56–1.03).[60]

Evidence level 1–

10. What are the contraindications to the use of antenatal corticosteroids?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Birth should not be delayed to administer antenatal corticosteroids when there are serious concerns about maternal or fetal condition that will be alleviated by expedited birth	**4**	**GPP**	This is considered good practice
In the presence of systemic infection, the potential beneficial effects of antenatal corticosteroids intended for the baby are balanced against the effect of exacerbating the severity of systemic infection both for the woman and her baby	**4**	**D**	Addressed in guidance from the WHO. Corticosteroids cause immune suppression, so there is a potential risk of worsening systemic infection

Corticosteroids suppress the immune system, so there is a risk that their use may activate latent infections or exacerbate fungal infections. In a woman with systemic infection, it may theoretically suppress the immune response to infection. There is no evidence to suggest that a single course of corticosteroids increase infections or antibiotic use but caution should be exercised when there is systemic infection.[1,9]

Evidence level 4

11. In what circumstances should an antenatal course of corticosteroids be repeated?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women should be informed that no reduction in serious morbidity or long-term benefits have been seen with repeat corticosteroids but babies who receive repeat doses of antenatal corticosteroids are smaller (lower birthweight and reduced length)	**1+**	**B**	These are the findings from an individual participant data meta-analysis of RCTs
There is currently limited evidence to recommend repeat courses of antenatal corticosteroids if a woman remains at imminent risk of preterm birth seven days after administration of antenatal corticosteroids. However, a further course may reduce the need for neonatal respiratory support	**1+**	**B**	These are the findings from an individual participant data meta-analysis of RCTs
The maximum number of corticosteroid courses given in any one pregnancy should not exceed three	**4**	**GPP**	Authors expert opinion from an individual participant data meta-analysis of RCTs

An individual participant data meta-analysis included data from 11 randomised trials of repeat doses of corticosteroids (4857 women; 5915 babies; 4557 children) compared to single dose.[64] There was a statistically significant reduction in the use of respiratory support in babies who had repeat antenatal corticosteroids compared with infants who received a single dose (RR 0.91, 95% CI 0.85–0.97). However, there was no effect of repeat corticosteroids on serious morbidity or mortality outcomes for the baby. No differences were seen in childhood outcomes of death, neurosensory impairment or disability or respiratory disease. Babies exposed to repeat antenatal corticosteroids had a lower birth weight than those exposed to a single course and a dose response was seen. Children who received repeat doses of antenatal corticosteroids had lower systolic, diastolic, and mean arterial blood pressures. The clinical relevance of this is unclear. The authors concluded that total dose of repeat antenatal corticosteroids to reduce the need for neonatal respiratory support should be limited to 24–48 mg and a maximum of three courses to minimise side effects.

Evidence level 1+

The World Health Organisation systematic review and guidance recommends a single rescue course of antenatal corticosteroids if women remain at high risk of preterm birth and more than seven days has elapsed since previous treatment.[1]

Evidence level 4

12. Recommendations for future research

- Studies are required to determine whether antenatal corticosteroids are effective in reducing neonatal morbidity when administered prior to elective caesarean birth at term.
- The gestational age range at which antenatal corticosteroids provide benefit and should therefore be considered or offered, remains controversial and requires further investigation.
- The safety and effectiveness of steroids in multiple pregnancy, women with diabetes and in women with chorioamnionitis requires further investigation.
- Research is needed to investigate the effectiveness of lower doses of corticosteroids, compared with current regimens, and the potential off-target effects of different formulations and dosing schedules of antenatal corticosteroids.
- Follow up studies are required to determine the long term effects of antenatal corticosteroids including on cardiovascular function and neurodevelopment.
- Research is needed to investigate sexual dimorphism in response to antenatal corticosteroids.

13. Auditable topics

- Proportion of women undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks' who have a documented discussion about the risks and benefits of a course of corticosteroids. (ideally 100%)
- Proportion of women who are considered to be at high risk of imminent preterm birth between 24^{+0} and 34^{+6} weeks' who are offered corticosteroids. (ideally 100%)
- Proportion of women with twin or triplet pregnancy who receive single or multiple untargeted (routine) courses of corticosteroids. (0%)
- Proportion of women who were deemed to be at high risk of imminent preterm birth, who give birth eight days or more after administration of antenatal corticosteroids. (ideally 0%)
- Proportion of women who receive antenatal corticosteroids unnecessarily – women who birth at term after preterm administration of steroids. (ideally 0%)

14. Useful links and support groups

- RCOG Information for you https://www.rcog.org.uk/en/patients/patient-leaflets/corticosteroids-in-pregnancy-to-reduce-complications-from-being-born-prematurely/
- Bliss https://www.bliss.org.uk
- Little Heartbeats https://www.little-heartbeats.org.uk
- Tommy's Premature birth – information and support https://www.tommys.org/pregnancy-information/pregnancy-complications/premature-birth-information-and-support
- RCOG Information for you – When your waters break prematurely https://www.rcog.org.uk/en/patients/patient-leaflets/when-your-waters-break-prematurely/
- NICE NG25, Preterm labour and birth http://www.nice.org.uk/guidance/ng25
- SANDS http://www.sands.org.uk/
- Birthrights Maternal request caesarean https://www.birthrights.org.uk/campaigns-research/maternal-request-caesarean/

- Better Births Improving outcomes in maternity services in England https://www.england.nhs.uk/wp-content/uploads/2016/02/national-maternity-review-report.pdf
- Caesarean Birth - Your Baby, Your Body, Your Life, Your Choice https://caesareanbirth.org/

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Corticosteroids literature search strategy.

Appendix S2. Corticosteroids search strategy top up.

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