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Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

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Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

This is the fourth edition of this guideline, which was previously published in April 1996, December 1999 and February 2004. The previous guideline was entitled *Antenatal Corticosteroids to Prevent Respiratory Distress Syndrome*.

1. Purpose and scope

The aim of this guideline is to provide up-to-date information on the appropriate use of antenatal corticosteroid therapy in women whose babies are at risk of complications owing to either preterm birth or elective caesarean section at term.

This guideline does not assess the effectiveness of tests in the prediction of preterm delivery (e.g. ultrasound scanning for cervical length, cervical fibronectin measurement) or other interventions that may prevent preterm labour (e.g. tocolysis).

2. Background

There is evidence to suggest that antenatal corticosteroids are effective not only in reducing respiratory distress syndrome (RDS) but also in reducing other complications of prematurity such as intraventricular haemorrhage (IVH). The title of this guideline has been changed to *Antenatal Corticosteroids to Prevent Neonatal Morbidity and Mortality* to include all groups of women and all outcomes.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews), DARE, Embase, TRIP, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses and cohort studies. The search was restricted to articles published between 2002 to July 2008. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'steroids', 'premature labour', 'premature fetus' and 'membrane rupture', and the search was limited to humans and to the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

4. What are the benefits of antenatal corticosteroids?

Antenatal steroids are associated with a significant reduction in rates of neonatal death, RDS and intraventricular haemorrhage and are safe for the mother.

> **A**

Antenatal corticosteroids have no known benefits for the mother.

> **A**

A Cochrane review of 21 studies (3885 women and 4269 infants) showed that treatment of women at risk of preterm birth with a single course of antenatal corticosteroids reduced the risk of neonatal death by 31% (95% CI 19–42%), RDS by 44% (95% CI 31–57%) and intraventricular haemorrhage by 46% (95% CI 31%–67%).[1] Antenatal corticosteroid use is also associated with a reduction in necrotising enterocolitis, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life compared with no treatment or treatment with placebo.[1]

> *Evidence level 1++*

5. At what gestation should antenatal steroids be used?

Clinicians should offer a single course of antenatal corticosteroids to women between 24^{+0} and 34^{+6} weeks of gestation who are at risk of preterm birth.

> A

Antenatal corticosteroids can be considered for women between 23^{+0} and 23^{+6} weeks of gestation who are at risk of preterm birth.

> C

The decision to administer corticosteroids at gestations less than 24^{+0} weeks should be made at a senior level taking all clinical aspects into consideration.

> ✓

The data are strongest for gestations between 26^{+0} and 34^{+6} weeks. The data for pregnancies between 24^{+0} and 26^{+0} weeks of gestation are scarce, with only one trial (49 infants) contributing data to the Cochrane review.[1]

> Evidence level 1++

The conclusion of the authors of the Cochrane review[1] and the American Congress of Obstetricians and Gynecologists (ACOG) Committee opinion (2008)[2] is that, despite the paucity of data at earlier gestations, the reduction in outcomes other than RDS at 26^{+0} weeks of gestation would suggest that there is some benefit in corticosteroid prophylaxis at earlier gestations between 24^{+0} and 26^{+0} weeks.

> Evidence level 4

In a prospective cohort of 4446 infants between 22^{+0} and 25^{+0} weeks of gestation, multivariable analyses showed that those who received intensive care, were exposed to antenatal corticosteroids, were of female sex, were from singleton pregnancies, and of higher birth weight (per each 100g increment) had a reduced risk of death. Among survivors, the risk of death, or profound or any neurodevelopmental impairment at 18–22 months corrected age, was reduced.[3] These reductions were similar to those associated with a 1-week increase in gestational age.

> Evidence level 2+

A retrospective cohort study on 181 infants born at 23 weeks of gestation revealed that those exposed to antenatal corticosteroids had decreased odds of death (OR 0.32, 95% CI 0.12–0.84), with no significant differences in the occurrence of necrotising enterocolitis among survivors (15.4% compared with 28.6%, P=0.59) or severe intraventricular hemorrhage (23.1% compared with 57.1%, P=0.17). Only a complete course of corticosteroids was associated with a decreased odds of death (OR 0.18, 95% CI 0.06–0.54).[4] The study concluded that neonates at 23 weeks of gestation whose mothers completed a course of antenatal corticosteroids had an associated 82% reduction in odds of death.

> Evidence level 2-

Evidence from the EPICure study, a prospective cohort study, showed that of 283 babies born at less than 26^{+0} weeks of gestation assessed at 2.5 years and 241 assessed at 6 years, antenatal corticosteroids was associated with an increased mental development index.[5]

> Evidence level 2+

Trial data are scanty for pregnancies at the extreme of prematurity. Obstetricians currently have the discretion to administer steroids before the 24th week of pregnancy, but the whole clinical picture needs to be taken into account with respect to intact survival data as well as the chance of any survival based on antenatal assessment of viability at these extremes (e.g. by estimation of fetal weight). In this context, we have advised caution and discussion at senior level prior to considering antenatal corticosteroid administration at 23^{+0} to 23^{+6} weeks of gestation.

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

Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids.

> A

Antenatal corticosteroid use reduces neonatal death within the first 24 hours and therefore should still be given even if delivery is expected within this time. A.

<div style="float:right">**A**</div>

Reduction in RDS is seen in infants born up to 7 days after the first dose (RR 0.46, 95% CI 0.35–0.60, nine studies, 1110 infants).[1] No reduction in neonatal death, RDS or cerebro-ventricular haemorrhage is seen in infants delivered more than 7 days after treatment with antenatal corticosteroids.[1]

<div style="float:right">*Evidence level 1+*</div>

Antenatal corticosteroid use reduces neonatal death even when infants are born less than 24 hours after the first dose has been given (RR 0.53, 95% CI 0.29–0.96, four studies, 295 infants).[1]

However, caution should be exercised in the interpretation of the data. The question as to whether the effects of antenatal corticosteroids change with time to delivery cannot be answered by existing analyses, the main reason being that the time periods chosen for subgroup analysis were arbitrary. All the babies born at term were in one subgroup. Analyses based on subgroups defined by outcomes not known at randomisation are subject to considerable bias. This question would require re-analysis of individual patient data to clarify whether the association is real.[6]

7. How safe is the use of antenatal corticosteroids?

Women may be advised that the use of a single course of antenatal corticosteroids does not appear to be associated with any significant short-term maternal or fetal adverse effects.

<div style="float:right">**A**</div>

Evidence on the longer-term benefits and risks of a single course of antenatal corticosteroids shows no clear difference in adverse neurological or cognitive effects. There is still insufficient evidence on the longer-term benefits and risks of multiple courses of antenatal corticosteroids.

<div style="float:right">**A**</div>

Studies in the sheep model have shown that injections with glucocorticoids enhance fetal lung maturation but are associated with developmental and other functional alterations that are of concern. Weekly doses to the sheep mother are associated with restricted fetal growth, delayed myelination of the central nervous system, altered blood pressure soon after birth and increased insulin response to glucose challenge in early adulthood. There have therefore been concerns about whether steroid administration may have adverse effects on the long-term outcomes of children exposed in the antenatal period. Multivariate analyses in humans have shown that increasing the number of glucocorticoid exposures, for the purpose of enhancing lung maturation prior to preterm birth, is associated with reduced birth weight and behavioural disorders at 3 years of age.[7]

The Cochrane review and other studies have shown that a single course of corticosteroid therapy for preterm birth results in benefit without causing significant adverse effects such as neonatal or maternal sepsis.[1,8,9] The Cochrane review revealed that no statistically significant differences were seen for chorioamnionitis (RR 0.91, 95% CI 0.70–1.18, 12 studies, 2485 women) or puerperal sepsis (RR 1.35, 95% CI 0.93–1.95, eight studies, 1003 women). There were no maternal deaths, but the randomised controlled trials were underpowered to detect such a difference (RR 0.98, 95% CI 0.06–15.50, three studies, 365 women).[1]

Long-term follow-up of survivors from randomised trials of antenatal corticosteroid therapy through childhood to adulthood (up to 20 years of age) shows no clear adverse neurological or cognitive effects.[10,11]

<div style="float:right">*Evidence level 1-*</div>

A randomised controlled trial showed that children who had been exposed to repeat as compared with single courses of antenatal corticosteroids did not differ significantly in physical or neuro-cognitive measures. However, there was a nonsignificant higher risk of cerebral palsy among children who had been exposed to repeat doses of corticosteroids (RR 5.7, 95% CI 0.7–46.7, *P*=0.12). The number of children with cerebral palsy was small. This was, however, felt to be of concern and warranting further study.[12]

<div style="float:right">*Evidence level 1++*</div>

Furthermore, studies on long-term cardiovascular risks, cognitive functioning, working memory and attention, psychiatric morbidity, handedness or health-related quality of life on the survivors of the first and largest double-blind, placebo-controlled, randomised trial of a single course of antenatal betamethasone for the prevention of neonatal RDS at age 31 found no differences between groups exposed to betamethasone and placebo.[13,14]

<div style="text-align: right;">Evidence level 1+</div>

8. Are there any contraindications to the use of antenatal corticosteroids?

Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis or sepsis.

☑

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 would have a profound effect in women with systemic infection, but caution should be exercised in its use.

Senior opinion should be sought when contemplating delaying delivery for steroid prophylaxis in cases of overt chorioamnionitis.

☑

A large meta-analysis of observational studies reports that clinical chorioamnionitis is significantly associated with both cystic periventricular leucomalacia (RR 2.6, 95% CI 1.7–3.9) and cerebral palsy (RR, 1.9, 95% CI 1.5–2.5).[15,16] This would suggest that with chorioamnionitis, a course of antenatal corticosteroids may be started, but should not delay delivery if indicated by maternal or fetal condition.

9. Who should receive antenatal corticosteroids?

Antenatal corticosteroids should be given to all women at risk of iatrogenic or spontaneous preterm birth up to 34^{+6} weeks of gestation.

A

Antenatal corticosteroids should be given to all women for whom an elective caesarean section is planned prior to 38^{+6} weeks of gestation.

A

There is no evidence to support a practice of prophylactic steroids in women with a previous history of preterm delivery or multiple pregnancy who show no signs of being at risk of iatrogenic or spontaneous preterm birth.

There is evidence of benefit in all major subgroups of preterm babies, such as women with premature rupture of membranes and pregnancy-related hypertension syndromes as well as the subgroups discussed below.[1] This benefit is irrespective of race or gender. A single course of antenatal corticosteroids should be considered routine for preterm delivery with few exceptions.

<div style="text-align: right;">Evidence level 1++</div>

9.1 In multifetal pregnancy

Clinicians should continue to offer a single course of antenatal corticosteroid treatment to women with multiple pregnancy at risk of imminent iatrogenic or spontaneous preterm delivery between 24^{+0} and 34^{+6} weeks of gestation.

C

In the Cochrane review, no statistically significant differences in women with multiple pregnancies were seen for chorioamnionitis (RR 0.48, 95% CI 0.04–4.49, one study, 74 women), fetal death (RR 0.53, 95% CI 0.20–1.40, two studies, 252 infants), neonatal death (RR 0.79, 95% CI 0.39–0.61, two studies, 236 infants), RDS (RR 0.85, 95% CI 0.60–1.20, four studies, 320 infants), cerebro-ventricular haemorrhage (RR 0.39, 95% CI 0.07–2.06, one study, 137 infants) or birth weight (fixed weighted mean difference 82.36 g, 95% CI –146.23 to 310.95 g, one study, 150 infants). However, only two studies contributed data for multiple pregnancy (252 infants).[1]

The optimal dose and pharmacokinetics in multiple pregnancies is not clearly understood. Evidence suggests that multiple pregnancy attenuates the beneficial effect of antenatal steroids.[17] Although there are limited data to support the use of antenatal corticosteroids in multiple pregnancy, the overall improvement in outcomes in singleton fetuses would suggest that steroids could be beneficial in multiple pregnancy.

Evidence level 4

A retrospective cohort study of 1038 twin babies delivered between 1990 and 1996 demonstrated that a prophylactic approach of administering antenatal corticosteroids every two weeks from 24 to 32 weeks of gestation was not associated with a significant reduction in RDS (adjusted OR 0.7, 95% CI 0.2–2.0).[18] Mean birth weight was reduced in term babies by 129 g (95% CI –218 to –33, P=0.008).

Evidence level 2-

9.2   In women with diabetes mellitus

Diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation.

D

Women with impaired glucose tolerance or diabetes who are receiving fetal steroids should have additional insulin according to an agreed protocol and be closely monitored.

D

Women with either insulin-dependent diabetes or gestational diabetes were not entered into randomised controlled trials of antenatal corticosteroid therapy. There is therefore no evidence from randomised controlled trials that antenatal corticosteroid therapy is either safe or effective in these circumstances. Maternal hyperglycaemia can adversely affect fetal lung maturity. It is possible that any benefit of corticosteroids could be offset by corticosteroid-induced hyperglycaemia.[19] However, the National Institute of Health and Clinical Excellence (NICE) has published a clinical guideline for diabetes in pregnancy that states that 'diabetes should not be considered a contra-indication to antenatal corticosteroids'.[20] The NICE guideline recommends that diabetic women receiving steroids should have additional insulin according to an agreed protocol.[20]

Evidence level 4

9.3   In women undergoing elective caesarean section

Elective lower segment caesarean section should normally be performed at or after 39^{+0} weeks of gestation to reduce respiratory morbidity.

C

Corticosteroids should be given to reduce the risk of respiratory morbidity in all babies delivered by elective caesarean section prior to 38^{+6} weeks of gestation.

A

Studies have shown that delivery by elective caesarean section at less than 39^{+0} weeks of gestation can lead to respiratory morbidity in neonates, requiring admission to the neonatal intensive care unit (NICU).[21-24] A recent retrospective cohort study showed that, compared with elective caesarean section births at 39^{+0} weeks of gestation, births at 37^{+0} weeks of gestation and at 38^{+0} weeks of gestation were associated with an increased risk of a composite outcome of neonatal death and/or respiratory complications, treated hypoglycaemia, newborn sepsis and admission to the NICU (adjusted OR for births at 37 weeks of gestation 2.1, 95% CI 1.7–2.5; adjusted OR for births at 38 weeks of gestation 1.5; 95% CI 1.3–1.7; P for trend <0.001).[21] The rates of adverse respiratory outcomes, mechanical ventilation, newborn sepsis, hypoglycaemia, admission to the NICU and hospitalisation for 5 days or more were increased by a factor of 1.8–4.2 for births at 37 weeks of gestation and 1.3–2.1 for births at 38 weeks of gestation. A further study in Denmark[23] showed the risk of respiratory morbidity for infants delivered by elective caesarean section decreased by gestation compared with vaginal birth (37 weeks of gestation OR 3.9, 95% CI 2.4–6.5; 38 weeks of gestation OR 3.0, 95% CI 2.1–4.3; and 39 weeks of gestation OR 1.9, 95% CI 1.2–3.0).

Evidence level 2-

Treatment with antenatal corticosteroids prior to delivery by elective caesarean section has been shown to reduce the need for admission to the NICU up to 38^{+6} weeks of gestation compared with controls. A randomised controlled trial showed that the relative risk of admission with RDS in babies treated with antenatal corticosteroids prior to elective caesarean section at term was 0.46 (95% CI 0.23–0.93, P=0.02). The relative risk of transient tachypnoea of the newborn was 0.040 in the control group and 0.021 in the treatment group (RR 0.54, 95% CI 0.26–1.12). The relative risk of RDS was 0.011 in the control group and 0.002 in the treatment group (RR 0.21, 95% CI 0.03–1.32). The predicted probability of admission to NICU at 37 weeks of gestation was 11.4% in the control group and 5.2% in the treatment group, at 38 weeks it was 6.2% and 2.8%, respectively, and at 39 weeks it was 1.5% and 0.6%, respectively.[25]

Evidence level 1+

There is an absence of evidence available for the safety of antenatal corticosteroids in babies born after 36^{+0} weeks of gestation. Elective lower segment caesarean section should not normally be performed until 39^{+0} weeks of gestation, rather than the administration of antenatal corticosteroids.

9.4 In pregnancies with fetal growth restriction

Pregnancies affected by fetal growth restriction between 24^{+0} and 35^{+6} weeks of gestation at risk of delivery should receive a single course of antenatal corticosteroids.

C

There is evidence to suggest that antenatal corticosteroids have an effect on cerebral blood flow in growth-restricted fetuses that is different from that in normally grown fetuses.[26,27] This has led to speculation as to whether corticosteroids should be used in such pregnancies.

In a well-designed case–control study of 124 preterm infants between 26 and 32 weeks of gestation with growth restriction secondary to placental insufficiency,[28] survival without disability or handicap at 2 years of age was better in the corticosteroid group than in the matched group of growth-restricted babies who did not receive corticosteroids. Although there were more children with physical growth problems in the corticosteroid group, there was no difference detected in behaviour. The benefits from antenatal corticosteroids for early preterm growth-restricted infants appear to outweigh the possible adverse effects.

Evidence level 2+

10. What is the best dose and route of administration for a course of antenatal corticosteroids?

Betamethasone 12 mg given intramuscularly in two doses or dexamethasone 6 mg given intramuscularly in four doses are the steroids of choice to enhance lung maturation.

A

The most extensively studied regimens of corticosteroid treatment for the prevention of RDS are two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart. Evidence for other dosing regimens such as the commonly used two doses of betamethasone 12 mg given 12 hours apart is sparse (two trials, 92 women),[29,30] but it would seem reasonable that as long as 24 mg of either drug is given within a 24–48-hour period, any dosing regimen can be used.

A large nonrandomised retrospective study has suggested that infants exposed to antenatal betamethasone have less neonatal cystic periventricular leukomalacia than infants exposed to antenatal dexamethasone.[31] Another historical cohort study used multivariate logistic regression analysis to compare the two steroid-treated groups with each other. It showed the risk of neonatal death was lower with betamethasone than with dexamethasone (OR 0.44 for betamethasone versus 0.73 with dexamethasone, P<0.05).[32]

Evidence level 2-

The Cochrane review on antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth suggests that betamethasone treatment causes a larger reduction in RDS

Evidence level 1++

than dexamethasone.[1] Since then, in a Cochrane review on different corticosteroid regimes (ten trials, 1089 women and 1161 infants), dexamethasone decreased the incidence of intraventricular haemorrhage compared with betamethasone (RR 0.44, 95% CI 0.21–0.92, four trials, 549 infants).[33] This review advised caution in suggesting benefit of dexamethasone over betamethasone. A randomised controlled trial looking at long-term outcomes in children treated with dexamethasone would be required as this form of corticosteroid has not been studied in the long term. For current practice, the use of either corticosteroid is acceptable.

<div align="right">Evidence level 1++</div>

Comparison of oral versus intramuscular administration of dexamethasone (one trial, 183 infants) suggests that oral administration increased the incidence of neonatal sepsis (RR 8.48, 95% CI 1.11 –64.93) in one trial of 183 infants. No statistically significant differences were seen for other outcomes reported. The authors suggest that very few conclusions about the optimum regimens can be made.[34]

11. When should an antenatal course of corticosteroids be repeated?

Weekly repeat courses of antenatal corticosteroids reduce the occurrence and severity of neonatal respiratory disease, but the short-term benefits are associated with a reduction in weight and head circumference. Weekly repeat courses are not recommended.

<div align="right">[A]</div>

A single rescue course may be considered with caution in pregnancies where the initial course was given at less than 26+0 weeks of gestation. Senior opinion should be sought if a rescue course is to be considered.

<div align="right">[✓]</div>

Animal studies and observational studies in humans have suggested that multiple courses of steroids may lead to possible harmful effects including growth delay, brain developmental delay, lung development problems, necrotising enterocolitis, maternal and neonatal sepsis, adrenal gland insufficiency and placental infarction.[35–41] A systematic review of 19 randomised controlled trials of repeat doses of antenatal corticosteroids in animals concluded that there might be beneficial effects in terms of lung function but adverse effects on brain function and fetal growth.[40]

<div align="right">Evidence level 1+</div>

The effect of repeat courses of antenatal corticosteroids in humans is the subject of a Cochrane review by Crowther et al.[42] The review suggests that although repeat courses reduce the occurrence and severity of neonatal lung disease (RR 0.60, 95% CI 0.48–0.75, three trials, 2139 infants) and the risk of serious health problems in the first few weeks of life (RR 0.79, 95% CI 0.67–0.93, four trials, 2157 infants), they are associated with a reduction in some measures of weight (Z-score [weighted mean difference] –0.13, 95% CI –26 to 0.00, one trial, 1144 infants) and with being small for gestational age at birth (RR 1.63, 95% CI 1.12–2.37, two trials, 602 infants). There is still insufficient evidence on the longer-term benefits and risks to be able to recommend the routine use of repeat courses.

<div align="right">Evidence level 1++</div>

The Cochrane review did not include the results of several continuing trials, two of which have been completed since its publication.[43,44] The results of TEAMS (Trial of early and multiple steroids) are awaited.[43] In the MACS (Multiple Courses of Antenatal Corticosteroids for Preterm Birth) trial of 1858 women at 25–32 weeks of gestation, multiple courses of antenatal corticosteroids (n=937) or placebo (n=921) every 14 days until week 33 or delivery (whichever came first) found that although infants exposed to multiple courses of antenatal corticosteroids had similar morbidity and mortality to those exposed to placebo (12.9% versus 12.5%), those receiving multiple doses of corticosteroids weighed less at birth (2216 g versus 2330 g, P=0.0026), were shorter (44.5 cm versus 45.4 cm, P<0.001), and had a smaller head circumference (31.1 cm versus 31.7 cm, P<0.001). A regime of repeat doses should not be recommended.[44]

<div align="right">Evidence level 1+</div>

In 2000, a National Institutes of Health consensus statement concluded that 'repeat courses of corticosteroids should not be used routinely and should be reserved for women enrolled in randomised controlled trials'.[45] A recent randomised controlled trial recruited 437 patients with singleton or twin pregnancies at less than 33^{+0} weeks of gestation who had completed a single course of corticosteroids before 30^{+0} weeks of gestation and randomised them to a single rescue course of betamethasone (two 12 mg doses 24 hours apart) or placebo. There was a significant reduction in the primary outcome of composite neonatal morbidity at less than 34 weeks of gestation in the rescue steroid group than in the placebo group (43.9% versus 63.6%, OR 0.45, 95% CI 0.27–0.75, P=0.002) and significantly decreased RDS, ventilator support and surfactant use. Perinatal mortality and other morbidities were similar in each group. No long-term outcomes were reported for this study.[46]

<div style="text-align:right">Evidence level 1+</div>

Peltoniemi *et al.* looked at whether a single additional dose of 12 mg betamethasone given when preterm birth is imminent before 34^{+0} weeks of gestation and at least a week after the full treatment course would lower the risk of RDS and severe (grade 3 or 4) intraventricular haemorrhage compared with placebo. This study showed that more infants in the steroid group required surfactant therapy. Post hoc analysis of data on 206 infants who were delivered within 1 to 24 hours indicated that the additional steroid dose tended to increase the risk of RDS and reduce the rate of intact survival. No differences were found between the steroid and placebo groups in mortality rates or rates of severe intraventricular haemorrhage. The results of this study would suggest that rescue doses may alter respiratory adaptation.[47] A subanalysis within the MACS study also showed no benefit from a rescue dose.[44]

<div style="text-align:right">Evidence level 1- and level 1+</div>

A rescue course of two doses of 12 mg betamethasone or four doses of 6 mg dexamethasone should only be considered with caution in those pregnancies where the first course was given at less than 26^{+0} weeks of gestation and another obstetric indication arises later in pregnancy.

<div style="text-align:right">✓</div>

In the absence of evidence, a rescue course of two doses of 12 mg betamethasone or four doses of 6 mg dexamethasone should only be considered with caution in those pregnancies where the first course was given at less than 26^{+0} weeks of gestation and another obstetric indication arises later in pregnancy. This would be justified by the paucity of data on the efficacy of the current dosing regimens on babies less than 26^{+0} weeks of gestation.

12. Auditable standards

- The proportion of babies delivered before 36^{+0} weeks of gestation and exposed to antenatal corticosteroids (i.e. did all babies who could have received corticosteroids receive them?).
- The proportion of all babies delivered before 36^{+0} weeks of gestation exposed to more than one course of antenatal corticosteroids.
- The proportion of babies delivered after 36^{+0} weeks of gestation exposed to steroids at any time during the pregnancy (false positive for preterm delivery).
- The proportion of babies delivered by elective caesarean section at less than 39^{+0} weeks of gestation exposed to antenatal corticosteroids.
- The proportion of babies with intrauterine growth restriction requiring preterm delivery exposed to antenatal corticosteroids.
- The proportion of babies born who were exposed to less than 24 hours of antenatal steroids as a function of when a diagnosis of risk of preterm labour was made.
- The diabetic management of women with diabetes who are given antenatal corticosteroids.

References

1. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006;(3):CD004454. DOI:0.1002/14651858.CD004454.pub2.

2. American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion No. 402: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2008;111:805–7.

3. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity – moving beyond gestational age. *N Engl J Med* 2008;358:1672–81.

4. Hayes EJ, Paul DA, Stahl GE, Seibel-Seamon J, Dysart K, Leiby BE, *et al*. Effect of antenatal corticosteroids on survival for neonates born at 23 weeks of gestation. *Obstet Gynecol* 2008;111:921–6.

5. Costeloe K; EPICure Study Group. EPICure: facts and figures: why preterm labour should be treated. *BJOG* 2006;113 Suppl 3:10–2.

6. Gates S, Brocklehurst P. Decline in effectiveness of antenatal corticosteroids with time to birth: real or artefact? *BMJ* 2007;335:77–9.

7. Newnham JP. Is prenatal glucocorticoid administration another origin of adult disease? *Clin Exp Pharmacol Physiol* 2001;28:957–61.

8. Goldenberg RL, Andrews WW, Faye-Petersen OM, Cliver SP, Goepfert AR, Hauth JC. The Alabama preterm birth study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various markers of intrauterine infection. *Am J Obstet Gynecol* 2006;195:1020–4.

9. Smrcek JM, Schwartau N, Kohl M, Berg C, Geipel A, Krapp M, *et al*. Antenatal corticosteroid therapy in premature infants. *Arch Gynecol Obstet* 2005;271:26–32.

10. Smolders-de Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10- to 12-year follow-up. *Pediatrics* 1990;86:65–70.

11. Dessens AB, Haas HS, Koppe JG. Twenty-year follow-up of antenatal corticosteroid treatment. *Pediatrics* 2000;105:E77.

12. Wapner RJ, Sorokin Y, Mele L, Johnson F, Dudley DJ, Spong CY, *et al*. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007;357:1190–8.

13. Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, *et al*. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 2005;365:1856–62.

14. Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, *et al*. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. *BMJ* 2005;331:665.

15. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. *JAMA* 2000;284:1417–24.

16. Wu YW. Systematic review of chorioamnionitis and cerebral palsy. *Ment Retard Dev Disabil Res Rev* 2002;8:25–9.

17. Quist-Therson EC, Myhr TL, Ohlsson A. Antenatal steroids to prevent respiratory distress syndrome: multiple gestation as an effect modifier. Acta Obstet Gynecol Scand 1999;78:388–92.

18. Murphy DJ, Caukwell S, Joels LA, Wardle P. Cohort study of the neonatal outcome of twin pregnancies that were treated with prophylactic or rescue antenatal corticosteroids. *Am J Obstet Gynecol* 2002;187:483–8.

19. Carlson KS, Smith BT, Post M. Insulin acts on the fibroblast to inhibit glucocorticoid stimulation of lung maturation. *J Appl Physiol* 1984;57:1577–9.

20. National Institute for Health and Clinical Excellence. NICE Clinical Guideline 63: *Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period*. London: NICE; 2008.

21. Tita AT, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW, *et al*.; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med* 2009;360:111–20.

22. Yee W, Amin H, Wood S. Elective cesarean delivery, neonatal intensive care unit admission, and neonatal respiratory distress. *Obstet Gynecol* 2008;111:823–8.

23. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ* 2008;336:85–7.

24. Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynecol* 1995;102:101–6.

25. Stutchfield P, Whitaker R, Russell I; Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. *BMJ* 2005;331:662.

26. Miller SL, Chai M, Loose J, Castillo-Meléndez M, Walker DW, Jenkin G, *et al*. The effects of maternal betamethasone administration on the intrauterine growth-restricted fetus. *Endocrinology* 2007;148:1288–95.

27. Simchen MJ, Alkazaleh F, Adamson SL, Windrim R, Telford J, Beyene J, *et al*. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. *Am J Obstet Gynecol* 2004;190:296–304.

28. Schaap AH, Wolf H, Bruinse HW, Smolders-De Haas H, Van Ertbruggen I, Treffers PE. Effects of antenatal corticosteroid administration on mortality and long-term morbidity in early preterm, growth-restricted infants. *Obstet Gynecol* 2001;97:954–60.

29. Magee LA, Dawes GS, Moulden M, Redman CW. A randomised controlled comparison of betamethasone with dexamethasone: effects on the antenatal fetal heart rate. *Br J Obstet Gynaecol* 1997;104:1233–8.

30. Mushkat Y, Ascher-Landsberg J, Keidar R, Carmon E, Pauzner D, David MP. The effects of betamethasone versus dexamethasone on fetal biophysical parameters. *Eur J Obstet Gynecol Reprod Biol* 2001;97:50–2.

31. Baud O, Foix-L'Helias L, Kaminski M, Audibert F, Jarreau PH, Papiernik E, *et al*. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *N Engl J Med* 1999;341:1190–6.

32. Lee BH, Stoll BJ, McDonald SA, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Adverse neonatal outcomes associated with antenatal dexamethasone versus antenatal betamethasone. *Obstet Gynecol Surv* 2006;61:568–69.

33. Brownfoot FC, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2008;(4):CD006764. DOI: 10.1002/14651858.CD006764.pub2.

34. Egerman RS, Mercer BM, Doss JL, Sibai BM. A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. *Am J Obstet Gynecol* 1998;179:1120–3.

35. Jobe AH, Wada N, Berry LM, Ikegami M, Ervin MG. Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep. *Am J Obstet Gynecol* 1998;178:880–5.

36. Walfisch A, Hallak M, Mazor M. Multiple courses of antenatal steroids: risks and benefits. *Obstet Gynecol* 2001;98:491–7.

37. Kay HH, Bird IM, Coe CL, Dudley DJ. Antenatal steroid treatment and adverse fetal effects: what is the evidence? *J Soc Gynecol Investig* 2000;7:69–78.

38. Goldenberg RL, Wright LL. Repeated courses of antenatal corticosteroids. *Obstet Gynecol* 2001;97:316–7.

39. Vermillion ST, Soper DE, Newman RB. Neonatal sepsis and death after multiple courses of antenatal betamethasone therapy. *Am J Obstet Gynecol* 2000;183:810–4.

40. Aghajafari F, Murphy K, Matthews S, Ohlsson A, Amankwah K, Hannah M. Repeated doses of antenatal corticosteroids in animals: a systematic review. *Am J Obstet Gynecol* 2002;186:843–9.

41. Aghajafari F, Murphy K, Willan A, Ohlsson A, Amankwah K, Matthews S, *et al*. Multiple courses of antenatal corticosteroids: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2001;185:1073–80.

42. Crowther CA, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. *Cochrane Database Syst Rev* 2007;(3):CD003935. DOI: 10.1002/14651858.CD003935.pub2.

43. TEAMS Trial of early and multiple steroids.

44. Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, *et al*.; MACS Collaborative Group. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. *Lancet* 2008;372:2143–51.

45. National Institutes of Health Consensus Development Panel. Antenatal corticosteroids revisited: repeat courses – National Institutes of Health Consensus Development Conference Statement, August 17–18, 2000. *Obstet Gynecol* 2001;98:144–50.

46. Garite TJ, Kurtzman J, Maurel K, Clark R; Obstetrix Collaborative Research Network. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol* 2009;200:248.e1–9.

47. Peltoniemi OM, Kari M, Tammela O, Lehtonen L, Marttila R, Halmesmäki E, *et al*.; The Repeat Antenatal Betamethasone Study Group. Randomized trial of a single repeat dose of prenatal betamethasone treatment in imminent preterm birth. *Obstet Gynecol Surv* 2007;62:368–70.

APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at **http://www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes**). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated. The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels	Grades of recommendations
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	**A** At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	
1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	**B** A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	
2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	**C** A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	**D** Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
3 Non-analytical studies, e.g. case reports, case series	**Good practice point**
4 Expert opinion	✓ Recommended best practice based on the clinical experience of the guideline development group

This Guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by **Dr D Roberts MRCOG, Liverpool**.

It was peer-reviewed by the British Association of Perinatal Medicine; British Maternal and Fetal Medicine Society; RCOG Consumers' Forum; Royal College of Midwives; Professor P Brocklehurst FRCOG, Oxford; Professor LMM Duley FRCOG, Leeds; Mr KW Murphy FRCOG, London; Dr SR Sheehan MRCOG, Ireland.

The Guidelines Committee Lead reviewer was Mrs C Overton FRCOG.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The Guidelines review process will commence in 2013 unless evidence requires earlier review.