Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Guideline No. 7
Revised February 2004

ANTENATAL CORTICOSTEROIDS TO PREVENT RESPIRATORY DISTRESS SYNDROME

This is the third edition of this guideline, which was previously published in April 1996 and December 1999.

1. Purpose and scope

Preterm delivery rates vary from 6% to 15% of all deliveries, with the rate increasing in recent years.[1] Respiratory distress syndrome (RDS) causes significant mortality and morbidity in these babies. RDS is known to affect 40–50% of babies born before 32 weeks.[2] Evidence has been available since 1972 that the antenatal administration of corticosteroids prior to preterm delivery reduces the incidence of RDS.[3]

The aim of this guideline is to provide up to date information on the appropriate use of antenatal corticosteroid therapy prior to preterm delivery for the reduction of neonatal mortality and morbidity. Other therapeutic interventions that may increase or decrease the effects of corticosteroids are also discussed (i.e. tocolytics and thyrotrophin-releasing hormone).

This guideline does not address measures designed to predict preterm delivery (i.e. ultrasound scanning for cervical length, cervical fibronectin measurement or bacterial screening of mothers), nor does it address other interventions that may reduce the mortality and morbidity from preterm labour (i.e. antibiotics for preterm prelabour rupture of membranes, PPROM).

2. Identification and assessment of evidence

The Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register Issue 4, 2002, were searched for relevant RCTs, systematic reviews and meta-analyses. The electronic databases Medline (1996–2002) and Embase (1996–2002) were searched for further studies published since the last revision of the guideline in December 1999. The principle MeSH terms used were 'steroids,' 'premature labour,' 'premature fetus' and 'membrane rupture'.

The internet databases, National Guidelines Clearing House, National Electronic Library for Health, OMNI, e-guidelines, TRIP database and Health Evidence Bulletins Wales, were searched for national and international guidelines.

The definitions of types of evidence used in this guideline originate from the US Agency for Health Care Research and Quality. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'Good practice points'.

3. Effectiveness of antenatal corticosteroid therapy

Clinicians should offer antenatal corticosteroid treatment to women at risk of preterm delivery because antenatal corticosteroids are associated with a significant reduction in rates of RDS, neonatal death and intraventricular haemorrhage. **A**

A Cochrane meta-analysis of 18 randomised trials indicates that antenatal corticosteroid therapy reduces the incidence of RDS, neonatal death and intraventricular haemorrhage.[4] The efficacy of neonatal surfactant therapy is enhanced by antenatal exposure to corticosteroids.[5,6] There is evidence of benefit in all major subgroups of preterm babies, irrespective of race or gender.

A review[7] and a case series[8] question the value of steroid therapy for those cases where preterm delivery is preceded by PPROM, especially in babies weighing ≤ 1000 g. However, Crowley's original meta-analysis showed clear benefit for the use of antenatal corticosteroids after PPROM in reducing RDS.[9] Further studies, including a meta-analysis of randomised controlled trials, have shown that a single course of corticosteroid therapy results in benefit without causing significant adverse effects such as neonatal sepsis.[10–14]

Evidence level Ia

Crowley's Cochrane review showed a statistically significant reduction in RDS in preterm babies born before 34 weeks of gestation (OR 0.36, 95% CI 0.27–0.48). RDS reduction in babies born after 34 weeks did not reach statistical significance, although the trend was towards benefit (OR 0.65, 95% CI 0.33–1.29). A similar finding was found for preterm birth at less than 28 weeks, although total numbers at this gestation were small (OR 0.64, 95% CI 0.16–2.50). An analysis of 'the number needed to treat' suggests that after 34 weeks 94 women will need to be treated to prevent one case of RDS, while before 31 weeks one case of RDS is prevented for every five women treated.[15]

Healthcare organisations and services should have policies and protocols in place for antenatal steroid treatment because the cost and duration of neonatal intensive care is reduced following corticosteroid therapy. **B**

The cost and duration of neonatal intensive care is reduced following corticosteroid therapy. However, the overall economic effect of antenatal corticosteroids will be influenced by the potential increase in survival of very-low-birthweight babies and by the use of surfactant. Simpson calculated that an increase in use from 15% to 60% in babies of less than 2000 grams born in the USA would result in an annual saving of US$157 million (equivalent to £94.2 million at October 2003 currency exchange rates).[16] Mugford *et al.*[17] predicted a more modest saving to the NHS, although the costs of treating low-birthweight infants remain considerable.[18,19]

Evidence level III

The optimal treatment–delivery interval for administration of antenatal corticosteroids is more than 24 hours but fewer than seven days after the start of treatment. **A**

The effect of treatment is optimal if the baby is delivered more than 24 hours and less than seven days after the start of treatment.[4] However, there is a trend towards benefit in babies delivered before and after the optimal treatment interval has elapsed.

Evidence level Ia

The use of antenatal corticosteroids in multiple pregnancies is recommended, but a significant reduction in rates of RDS has not been demonstrated. ✓

Conflicting evidence is available from retrospective studies of the outcome of steroid use in multiple pregnancies. Some studies report no difference in risks for death or major morbidity between corticosteroid-exposed singleton and multiple infants.[20] Other studies report that antenatal steroid therapy does not

significantly reduce the incidence of RDS in multiple gestations. Meta-analysis of randomised controlled trials involving multiple pregnancies suggests a trend towards a reduction in incidence of RDS, although this did not reach statistical significance (OR 0.72, 95% CI 0.35–1.68).[4] It is not known whether this is due to small numbers included in the meta-analysis or to sub-therapeutic drug levels, perhaps secondary to plasma volume expansion or to altered pharmacokinetics of corticosteroids in twin pregnancies.[21] In support of the latter, retrospective studies suggest that multiple pregnancy attenuates the beneficial effect of antenatal steroids.[22] Future placebo controlled trials are unlikely to be forthcoming and would require very large numbers of preterm twins to demonstrate a statistically significant reduction in perinatal morbidity.

There is no evidence to support a practice of prophylactic steroids in multiple pregnancy. 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 was not associated with a significant reduction in RDS (adjusted OR 0.7, 95% CI 0.2–2.0).[23] Mean birth weight was reduced in term babies by 129 g (95% CI –218 to –33, $P = 0.008$).

In preterm labour it is reasonable not to use tocolytic drugs, as there is no clear evidence that they improve outcome. However, clinicians should consider the use of short-term tocolysis if the few days gained can be put to good use, such as completing a course of corticosteroids, or *in utero* transfer. **A**

If a tocolytic drug is used, ritodrine no longer seems to be the best choice. Atosiban or nifedipine appear to be preferable, as they have fewer adverse effects and seem to have comparable effectiveness. Atosiban is licensed for this usage in the UK but nifedipine is not. **A**

The RCOG clinical Guideline No. 1(B) addresses tocolytic drugs for women in preterm labour.[24] The recommendation for the class of tocolytic drug to be used is reproduced here. Evidence level Ia

4. Safety

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

Long-term follow up of survivors from randomised trials of antenatal corticosteroid therapy through childhood to adulthood (up to 20 years) shows no adverse neurological or cognitive effects.[25–29] Evidence level Ib

Corticosteroid use does not appear to increase the risk of either fetal or maternal infection, regardless of whether the membranes are ruptured or not at the time of treatment.

The use of antenatal corticosteroids in pregnancies complicated by maternal diabetes mellitus is recommended, but a significant reduction in rates of RDS has not been demonstrated. If commenced, inpatient supervision by an experienced diabetic/obstetric team is essential to regulate diabetic control. ✓

Maternal diabetes mellitus is a recognised risk factor for neonatal RDS.[30] Strict glycaemic control prior to conception and during pregnancy has been shown to reduce the incidence of neonatal RDS to that of matched controls.[31,32]

Women with either insulin-dependent diabetes or gestational diabetes were not entered into randomised controlled trials of antenatal corticosteroid therapy, so there is no evidence that antenatal corticosteroid therapy is either safe or effective in these circumstances. In view of the adverse effects of maternal hyperglycaemia on fetal lung maturity it is possible that any benefit of corticosteroids could be offset by corticosteroid-induced hyperglycaemia.[33] However, the Scottish Intercollegiate Guideline Network (SIGN)

has published a national clinical guideline for the management of diabetes which states that 'women with diabetes in pregnancy who are at risk of preterm delivery should receive antenatal corticosteroids in line with local protocols'.[34] The SIGN guideline recommends that 'inpatient supervision by an experienced team is essential to regulate diabetic control'.

5. Indications for antenatal corticosteroid therapy

Every effort should be made to initiate antenatal corticosteroid therapy in women between 24 and 34 weeks of gestation with any of the following:

A

- **threatened preterm labour**
- **antepartum haemorrhage**
- **preterm rupture of membranes**
- **any condition requiring elective preterm delivery.**

Evidence level Ia

Between 35 to 36 weeks obstetricians might want to consider antenatal steroid use in any of the above conditions although the numbers needed to treat will increase significantly.

As gestation advances, the number of women who will have to be treated with corticosteroids in order to prevent a single case of RDS increases,[15] i.e. the potential benefit reduces and there is a rise in potential short- and long-term risks.

Antenatal education programmes or patient information leaflets should be considered to encourage early recognition of these conditions, in an effort to ensure early presentation and commencement of treatment. Maternity services should consider multidisciplinary staff training in providing information, including risk ratios, to women.

6. Contraindications and precautions

Corticosteroid therapy is contraindicated if a woman suffers from systemic infection including tuberculosis. Caution is advised if suspected chorioamnionitis is diagnosed.

✓

The *British National Formulary* advises that corticosteroid therapy is contraindicated with systemic infection.[35] A large meta-analysis reports that clinical chorioamnionitis is significantly associated with both periventricular leucomalacia and cerebral palsy.[36] Caution is advised in the use of corticosteroids in women with clinical chorioamnionitis because delaying delivery to allow their use may be detrimental to the fetus and there is a theoretical risk that steroids could worsen chorioamnionitis.

7. Dose and route of administration

Betamethasone is the steroid of choice to enhance lung maturation. Recommended therapy involves two doses of betamethasone 12 mg, given intramuscularly 24 hours apart.

B

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 and four doses of dexamthasone 6 mg, given intramuscularly 12 hours apart. Neither corticosteroid is licensed in the UK for this indication and so responsibility for use lies with the prescribing doctor.

Evidence level III

Within Crowley's meta-analysis, betamethasone and dexamethasone were found to be equally effective in preventing RDS.[9] However, a large observational study suggested that antenatal exposure to betamethasone, but not dexamethasone, is associated with a decreased risk of cystic

periventricular leucomalacia among premature infants born at 24–31 weeks of gestation.[37] The RCOG Scientific Advisory Committee recommends that betamethasone is the steroid of choice to enhance lung maturation.[38]

The pharmokinetics of the steroid regimens suggest that betamethasone 12 mg binds to glucocorticoid receptors with an affinity more than five times higher than cortisol and provides >75% receptor occupancy 'which should provide a near maximal induction of glucocorticoid-regulated genes in fetal target tissues'.[39] The half-life in the fetal circulation is reportedly around 12 hours. This review concluded that 'the corticosteroid preparation and administration regimen chosen by Liggins in his initial clinical study appears to be optimal with regard to efficacy'. The US National Institutes for Health (NIH) consensus statement concluded that 'higher or more frequent doses do not increase the benefits of antenatal corticosteroid therapy and may increase the likelihood of adverse effects'.[6]

Evidence level III

Comparison of oral versus intramuscular administration of dexamethasone suggests no difference in the frequency of RDS between the two modes of drug delivery but neonatal sepsis and intraventricular haemorrhage were significantly higher in the neonates of women receiving oral dexamethasone.[40] Consequently, oral administration of steroids cannot be recommended for routine clinical use at present.

8. Repeated doses

If repeat courses of antenatal corticosteroids are contemplated then senior opinion should be sought as, at present, there is a lack of evidence to show significant benefit. **A**

Obstetricians should consider enrolling their patients in randomised controlled trials if repeat corticosteroid therapy is contemplated. **A**

A survey of UK obstetricians conducted in 1997 reported that 98% of responders prescribed repeated courses of antenatal corticosteroids.[41] The NIH has prepared a consensus statement concerning repeat courses of corticosteroids and concluded that 'because of insufficient scientific data from randomised clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely. In general it should be reserved for patients enrolled in randomised controlled trials'.[42] 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.[43–47] 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.[48]

Evidence level III

One randomised trial of single versus weekly courses of corticosteroids involving 502 pregnant women between 24 and 32 weeks of gestation concluded that weekly courses of antenatal corticosteroids did not reduce composite neonatal morbidity compared with a single course of treatment.[49] This trial was stopped early before reaching its planned sample and thus lacks power for finding clinically important reductions in adverse perinatal outcomes. Despite its early closure, planned subgroup analyses showed significant decreases in composite morbidity among neonates delivered prior to 28 weeks and in severe RDS. A meta-analysis of eight observational studies of multiple courses of antenatal corticosteroids found a decreased risk of RDS and patent ductus arteriosus with an increased risk of endometritis.[50] However, all studies reviewed in this meta-analysis suffered from selection bias and the authors concluded that 'it is not possible to establish

the true effects of multiple courses of antenatal corticosteroids by a review of the results of observational studies because of the effect of confounding variables'.

Evidence level Ib

At least four large multicentre randomised controlled trials are either proposed or continuing. Clinicians may want to consider recruiting women into one of these trials. In the UK, the National Perinatal Epidemiology Unit in Oxford proposed the TEAMS trial (Trial of the Effects of Antenatal Multiple courses of Steroids versus a single course) but closed recruitment to their pilot study at the beginning of 2003.

A Canadian-led trial, coordinated through the University of Toronto, is conducting MACS (Multiple Courses of Antenatal Corticosteroids for preterm birth Study) and has over 40 active participating centres in at least 12 countries, with planned recruitment of 1900 women over the next two years. MACS would welcome contact with UK clinicians in recruiting woomen and contact details are supplied at the end of this guideline.

9. Effectiveness of thyrotrophin-releasing hormone

The use of thyrotrophin-releasing hormone is not recommended in combination with antenatal corticosteroids. **A**

A meta-analysis within the Cochrane Database, by Crowther *et al.*, reviewed 11 trials involving over 4500 women.[51] Use of antenatal thyrotrophin-releasing hormone, in addition to corticosteroids, did not reduce the risk of RDS (RR 1.06, 95% CI 0.97–1.16), need for oxygen therapy at ≥ 28 days (RR 1.01, 95% CI 0.85–1.19) or death before discharge (RR 1.05, 95% CI 0.86–1.27). This meta-analysis found an increased risk of mechanical ventilation (RR 1.16, 95% CI 1.03–1.29) and low Apgar scores at five minutes (RR 1.48, 95% CI 1.14–1.92) in infants who were exposed to antenatal thyrotrophin-releasing hormone. All maternal adverse effects were more likely to occur in the group receiving thyrotrophin-releasing hormone. On the basis of amalgamated results from these trials, a large UK trial which had a proposed sample size of 3600 women was terminated after 225 women had been recruited.[52,53] The Cochrane reviewers concluded that 'thyrotrophin-releasing hormone, in addition to corticosteroids, given to women at risk of very preterm birth, cannot be recommended for clinical practice'.

Evidence level Ia

10. Audit

Auditable standards for antenatal corticosteroid therapy include:

- the proportion of women delivering between 24 and 34 weeks receiving a full course of corticosteroid therapy
- the proportion of women delivering between 24 and 34 weeks receiving at least one injection of steroids
- the proportion of women with PPROM who receive a full course of corticosteroid therapy.

11. Contact details for MACS

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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: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). 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

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	vidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

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

The guideline review process will commence in February 2008
unless evidence requires earlier review