A Literature Review on Multiple Courses of Antenatal Steroids to Prevent Neonatal Respiratory Distress Syndrome

Corresponding Author:
Ms. Farah Saeed,
Medical Student, University of Liverpool - United Kingdom

Submitting Author:
Mr. Muhammed R Siddiqui,
Registrar, Mayday Hospital, 23 Malvern Road, TN24 8HX - United Kingdom

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A Literature Review on Multiple Courses of Antenatal Steroids to Prevent Neonatal Respiratory Distress Syndrome

Author(s): Saeed F, Siddiqui M R

Abstract

Introduction: Repeat antenatal corticosteroids may reduce respiratory distress syndrome however there is conflicting evidence suggesting it may be unnecessary or harmful. This article reviews the literature to examine the role of multiple courses of antenatal steroids to prevent neonatal respiratory distress syndrome.

Methods: Electronic databases were searched online.

Results: Four randomised controlled trials were identified according to our inclusion criteria.

Conclusions: There is evidence that courses of ACS improve pulmonary outcomes in the neonate, preventing RDS. There is evidence suggesting potential harm, and the lack of long term safety data, caution and careful patient selection is required when instituting this intervention.

Introduction

There are approximately 500,000 preterm deaths per year worldwide1 and is a significant proportion of neonatal mortality. Premature infants are at a high risk of medical complications such as intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP) and sepsis. However the main cause of early death in premature infants is still respiratory distress syndrome (RDS).2

RDS often occurs in babies born before 32 weeks of gestation; the risk depends on earlier birth. Endogenous corticosteroids interact with other hormones in the foetus to control tissue maturation. Babies born preterm have immature lungs and an insufficient amount of surfactant in the lungs which may cause RDS.3 The most important and most effective known prevention of RDS in preterm infants is a course of antenatal corticosteroids (ACS) given to the mother.4

ACS speeds up foetal lung development by mimicking the effect of endogenous corticosteroids5. This is achieved by inducing surfactant components and important lipogenic enzymes and stimulating pneumonocytes that normally appear in the foetal lung at about 24-28 weeks gestation.6 The production of endogenous surfactant is increased and improves lung compliance, thereby reducing the incidence of RDS. A relatively brief exposure of a foetus to corticosteroids may accelerate the normal developmental process in the lung and other tissues.

The discovery that ACS treatment improves foetal maturation and decreases the risk of RDS was made by Professor Liggins about four decades ago. While working on research on labour initiation, Liggins noticed that preterm lambs exposed to corticosteroids in the womb were “viable at an earlier gestational age, had less severe respiratory distress, and had structurally more mature lungs than would be anticipated”. This observation was then confirmed in humans in 1972 in a controlled trial where incidence of RDS was significantly reduced (4.3% vs 24%) in infants under 37 weeks gestation after corticosteroid treatment. This finding has been supported by other investigators.

The scientific basis for this relationship between lung maturation, steroids, and RDS is convincing. For example, glucocorticoids administered to foetal rabbits stimulated development of many types of lung cells, including type II alveolar cell which is the site of surfactant synthesis. Many other studies in animal species have confirmed this, and experiments have shown organ maturation is delayed when there is a deficiency of endogenous corticosteroid. It is thus that administering repeat courses of corticosteroids to mothers at risk of preterm birth became commonplace, despite a paucity of data confirming safety and efficacy of additional exposures of ACS.

Current UK practice

Most obstetric units in the UK administer two doses of betamethasone or dexamethasone over 24 hours as a single course.10 However the time between administration of steroids and delivery alters their effectiveness, and it was suggested that treatment was most effective in babies born 1-7 days after administration.11 This belief that steroids lasted only 7 days caused the trend of weekly repeat ACS for women not delivering within 7-10 days of receiving it.
causing prolonged exposure of babies to corticosteroids. This routine began when there was almost no data from randomised controlled trials (RCT’s) to confirm that the benefits outweighed the risks. EURAIL (Europe against the immature lung) conducted a survey10 which showed a high rate of prescribing of repeated courses. One study showed that more than 50% of perinatologists were willing to give 6 or more courses of ACS12. Furthermore, in 1999 a survey in the UK revealed that of the 75% obstetric units that responded, 98% prescribed repeated courses13.

Recently, concerns have been raised about the unnecessary treatment of many patients who did not deliver prematurely. In addition, a worrying amount of evidence regarding the potential harm of ACS began to accumulate, raising concerns about adverse effects of exposure to corticosteroids, which has led to a decline in use of multiple doses.

Findings from animal studies

Some studies examining the impact of repeat steroids in rabbits14, sheep15 and monkeys16 showed decreased birth weight, brain weight and liver weight. For example, it was shown that repeat ACS treatment has noticeable effects on optic nerve myelination of sheep17. Repeat steroids also inhibited myelination in the corpus callosum, and the effect stayed until term. This finding did not recover by adulthood. However the question is whether impairment of brain development impairs later neurologic function. Long term effects of ACS on brain development and growth are unclear however one study18 showed that adult sheep exposed as foetuses to repeat ACS “showed no differences in growth parameters from control animals”.

Findings from human studies

In the late 1990’s French et al19 found an increase in the rate of growth restriction in foetuses exposed to multiple courses (33%) versus single courses (15%) ACS. Also, an Australian nonrandomised cohort study of 477 neonates born before 33 weeks’ gestation showed growth restriction as high as 9%20. Retrospective observational studies showed different effects on mother and infant. Concerns about adverse effects, especially long term effects on growth and development led to cautious obstetric use.

National Institutes of Health (NIH) Consensus Conferences

The NIH held a consensus conference in 1994 that reviewed all evidence on the safety of ACS21. The panel used results from a meta-analysis of 15 RCT’s, concluding that ACS use significantly reduces neonatal mortality and RDS with little risk to the infant. They recommended ACS administration “whenever the birth of an infant between 24-34 weeks gestation is likely and the mother is likely to deliver within 7 days”. Subsequent to this, the use of antenatal corticosteroids increased dramatically. Within 3 years of these recommendations, 70-90% of women who delivered babies under 34 weeks gestation had received at least 1 course of ACS22.

As more studies reported complications, the NIH Consensus panel reconvened in 2000 and concluded that these studies of repeat ACS are indicative of possible benefits, especially in reducing RDS, however due to design weaknesses caution must be used23. Cohort studies cannot be relied upon for changing current recommendations, therefore recommendations remained as previously stated and use of multiple courses was warned against (apart from in research trials). Despite this, wide variations in clinical practice continue to exist. Repeat ACS may be unnecessary and even harmful, yet withholding further treatment may jeopardize infants delivering prematurely. This article reviews the literature to examine the role of multiple courses of antenatal steroids to prevent neonatal respiratory distress syndrome.

Methods

Electronic databases were searched online; OVID (Medline), PubMed (Medline), Scopus and Science Direct. The following search terms were used “respiratory distress syndrome”, “betamethasone or glucocorticoids or steroids” and “antenatal”. The bibliographies of articles were also searched. Inclusion criteria were human studies, under 33 weeks gestation, 1-4 ACS courses given as re-treatment, randomised controlled trials, free full text and the article must examine effects of repeated courses of ACS as a prevention for RDS.

Results

Evidence of the impact of multiple courses of ACS on neonatal birth weight, head circumference, brain growth and neurodevelopmental outcome should be performed using human studies, as results from animal studies may reflect a “species-dependent timing of exposure”24.

Guinn et al, 2001

In 2001 the first major (human) RCT to evaluate the effectiveness of single versus weekly courses of ACS was published by Guinn et al25. It was conducted in 13 academic centres in the USA between February
1996 and April 2000. Pregnant women at high risk of preterm delivery between 24-32 gestational weeks were eligible. The trial was stopped after 500 patients were enrolled due to safety concerns emerging in new literature.

No difference was observed in the primary outcome between the groups. For example, mean birth weights were 856 grams (g) and 876g in the treated and placebo groups respectively a non-statistically significant difference. The head circumferences were not significantly different either. A secondary analysis showed that infants most likely to benefit from repeat ACS were born between 24-27 weeks. It was concluded that the data suggested “a possible benefit of repeated ACS in terms of morbidity at early gestational ages and a reduction in severe RDS, accompanied by a possibly harmful but small effect on growth”.

Wapner et al, 2006

This RCT was conducted at 18 centres in 2006-2008. Eligible women were randomized to weekly injections of ACS or placebo until delivery or until 33 weeks and six days gestation. Number of courses were reduced to only four after the first 67 patients were enrolled, in view of safety concerns. After an interim analysis, babies in the repeated ACS group were shown to have decreased birth weight with no benefit to neonatal outcome hence the study was aborted. Altogether a total of 495 patients were enrolled out of an anticipated 2400. There were no differences between the two groups in morbidity. However surfactant administration, use of mechanical ventilation, and occurrence of pneumothorax were significantly less in the repeat ACS group but a 95g significant reduction in birth weight was also found. There were significantly more infants in the repeated ACS group with birth weights less than the 10th and 5th percentiles.

Physical and neurological examinations were carried out on 486 of the infants at 2-3 years of age. Both repeat ACS and placebo groups were similar in physical dimensions and general health measures. Six children in the repeat ACS group, and one in the placebo group had cerebral palsy. The authors concluded that weekly repetition of ACS to all women is not significantly different either. A secondary analysis showed that infants most likely to benefit from repeat ACS were born between 24-27 weeks. It was concluded that the data suggested “a possible benefit of repeated ACS in terms of morbidity at early gestational ages and a reduction in severe RDS, accompanied by a possibly harmful but small effect on growth”.

Crowther et al, 2006

The largest clinical trial so far was conducted in 16 Australian and 7 New Zealand hospitals and published in the Lancet27. Recruitment took six years and three months and resulted in a sample size of 982 women and 1146 babies. 42% of women received one additional dose, 22% received two additional doses and 36% received three or more additional doses. Repeated ACS treatments decreased not only rates of RDS, but duration of mechanical ventilation, the need for oxygen therapy and the need for surfactant therapy. Neonatal weight and head circumference were reduced at birth but were normal by the time of hospital discharge.

96.5% of the children were followed up at two years of age and no differences were found between the repeated ACS and placebo groups in body size, disability, lung disease or ‘general health measures’. Both groups of children scored similarly on the Child Behaviour Checklist, with the exception of attention problems- children in the repeated ACS group were “significantly more likely to need further assessment”. Garite et al, 2009

Garite and colleagues’ RCT was conducted between May 2003 and February 2008 in 18 private and university medical centres28. Patients were randomized to receive one additional rescue course of ACS or placebo. Composite morbidity, RDS and use of surfactant in the ACS group was significantly reduced compared with the placebo group, but there was no reduction in the need for ventilator therapy. Rates of perinatal death, birth weights and head circumference were similar. No trend was found in reduced body or head growth in the ACS group.

Discussion

Studies found either a small effect of ACS on foetal growth or no difference, and concluded that there may be harm in repeat ACS, recommending limiting the number of courses administered. However are their findings conclusive? All studies described good methods in allocation of patients into the groups and ensured participants and staff were blind to the study groups, which limited participant and observer bias, making results more valid. They have also attempted to limit potentially confounding variables by strictly defining the study population to a limited gestational age, and not including women who experienced premature rupture of membranes. However there are various methodological problems with these studies. The evidence in both Guinn and Wapner’s RCT’s sounds encouraging; however, by not completing the RCT as originally planned, conclusions made about efficacy may be invalid. The study may not have been large enough to answer the question. Because of the smaller than planned sample size, the study lacks statistical power to determine the effect of repeat courses of ACS or to detect slight differences between the groups. This renders the findings of this trial
inconclusive. Furthermore Guinn’s trial shows data from the cohort of 308 patients from the interim analysis and the patients subsequently enrolled. Clearly, there was higher morbidity in the weekly ACS group in the second cohort than the first. If the authors calculated the ‘probability of showing a benefit’ for repeated ACS at the time of ending recruitment (502 patients), a more than 75% chance of demonstrating efficacy at 1000 patients would have been found (if the trend had persisted). It is true the trend could have changed in the next 500 patients, but this shows how halting RCT’s based on beliefs of what may or may not occur may lead to unclear conclusions.

Moreover, all trials with the exception of Garites trial did not provide data comparing the baseline characteristics of women of the time to delivery subgroups. Women who deliver more than seven days after randomisation may differ from the others in age, number of previous pregnancies, gestational age, reasons for the preterm birth, as well as other factors. Any differences between subgroups may therefore be caused by differences in the subgroups and not the effectiveness of repeat courses of ACS. The likelihood of bias cannot therefore be assessed. The trials recruited women with a gestational age of fewer than 36 weeks. Almost all babies born at term, i.e. over 37 weeks, were therefore in the subgroup of babies delivered seven or more days after randomisation. Because death and RDS are rare in babies delivered at term; fewer outcomes would be seen in this subgroup, so a statistically significant difference would be less likely to be found. Therefore, not finding a difference may simply be because of the lower occurrence of outcomes in babies born at term. (In a 2006 review, incidence of RDS in three subgroups is consistent with this argument: 27.5% in the

As reduction in head circumferences seen at birth are relatively small, the concern is the effects on brain growth. In studies that did suggest a damaging effect, minimal or no effects were seen until 3 or more courses of ACS were administered. Even though associations were shown in these studies, causation has not been confirmed; therefore it is difficult to interpret these findings.

Further trials addressing this question are needed, especially since the trials of Guinn et al and Wapner et al could have demonstrated a beneficial effect of repetitive courses with minimal risks. Arising from this are several implications for education and practice and implications for further research.

Conclusion

There is evidence that courses of ACS improve pulmonary outcomes in the neonate, preventing RDS. There is evidence suggesting potential harm, and the lack of long term safety data, caution and careful patient selection is required when instituting this intervention.

References

11. Howie RN, Liggins GC, Anderson ABM, Beard RW,
Brudenell JM, Dunn PM. Clinical trial of antepartum betamethasonetherapy for prevention of respiratory distress in pre-term infants. Pre-term labour. 1977;281-9


Illustrations

Illustration 1

Tables

Table 1 shows the search results and table 2 shows the selected four articles.

Table 1

<table>
<thead>
<tr>
<th>OVID</th>
<th>PubMed</th>
<th>Scopus</th>
<th>Science Direct</th>
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<tr>
<td>Respiratory distress syndrome</td>
<td>13895</td>
<td>14344</td>
<td>38,721 682</td>
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<td>Betamethasone or Glucocorticoids or Steroids</td>
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<td>666355</td>
<td>558,004 555</td>
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<td>Antenatal</td>
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<td>16920</td>
<td>20,051 380</td>
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Table 2- Selected articles

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
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<tbody>
<tr>
<td>‘Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery’</td>
<td>Guinn et al, 2001</td>
</tr>
<tr>
<td>‘Single vs weekly courses of antenatal corticosteroids: Evaluation of safety and efficacy’</td>
<td>Wapner et al, 2006</td>
</tr>
<tr>
<td>‘Neonatal Respiratory Distress Syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial’</td>
<td>Crowther et al, 2006</td>
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</tbody>
</table>
### Illustration 2

#### Tables

<table>
<thead>
<tr>
<th>Trial</th>
<th>Gestational age (weeks)</th>
<th>Initial treatment</th>
<th>No of pts in weekly ACS grp</th>
<th>Mean no of additional courses (ACS)</th>
<th>Primary outcome</th>
<th>Sample size</th>
<th>Power analysis</th>
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<tbody>
<tr>
<td>Guinn et al</td>
<td>24-32</td>
<td>Single dose betamethasone/dexamethasone 7 days earlier</td>
<td>256</td>
<td>2.8</td>
<td>Composite neonatal morbidity, severe RDS, severe IVH, NEC, sepsis, perinatal death</td>
<td>500</td>
<td>1000 patients needed for 90% power to detect a 33% reduction in morbidity</td>
</tr>
<tr>
<td>Wapner et al</td>
<td>23-31</td>
<td>Single dose betamethasone/dexamethasone 7-10 days earlier</td>
<td>252</td>
<td>4</td>
<td>Composite neonatal morbidity, severe RDS, severe IVH, chronic lung disease, perinatal death</td>
<td>495</td>
<td>2400 required for 80% power to detect a 30% reduction in morbidity</td>
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<tr>
<td>Crowther et al</td>
<td>&lt;32</td>
<td>Single dose betamethasone/dexamethasone 7+ days earlier</td>
<td>570</td>
<td>3.5</td>
<td>Frequency of RDS</td>
<td>982</td>
<td>980 required for 80% power to detect a 25% reduction in morbidity</td>
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</table>
### Garite et al

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Composite morbidity</th>
<th>Severe RDS</th>
<th>Mean birth weights (g)</th>
<th>Mean head circumferences (cm)</th>
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<tr>
<td>&lt;33</td>
<td>Placebo</td>
<td>28%</td>
<td>24.5%</td>
<td>876</td>
<td>29.4</td>
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<td></td>
<td>ACS</td>
<td>22.5%</td>
<td>15.3%</td>
<td>856</td>
<td>29.1</td>
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<tr>
<td></td>
<td>Comments</td>
<td>Non sig*</td>
<td>P=0.01, significant</td>
<td>Non sig*</td>
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### Guinn et al

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Composite morbidity</th>
<th>Severe RDS</th>
<th>Mean birth weights (g)</th>
<th>Mean head circumferences (cm)</th>
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<tr>
<td></td>
<td>Placebo</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>9.1%</td>
<td>(reduced)</td>
<td>Reduced by 95</td>
<td>(not affected)</td>
</tr>
<tr>
<td></td>
<td>Comments</td>
<td></td>
<td></td>
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### Wapner et al

<table>
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<th>Study</th>
<th>Treatment</th>
<th>Composite morbidity</th>
<th>Severe RDS</th>
<th>Mean birth weights (g)</th>
<th>Mean head circumferences (cm)</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>63.6%</td>
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<tr>
<td></td>
<td>ACS</td>
<td>43.9%</td>
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<td></td>
<td>Comments</td>
<td></td>
<td></td>
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### Crowther et al

<table>
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<th>Study</th>
<th>Treatment</th>
<th>Composite morbidity</th>
<th>Severe RDS</th>
<th>Mean birth weights (g)</th>
<th>Mean head circumferences (cm)</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>41%</td>
<td>(reduced)</td>
<td>(reduced)</td>
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</table>

217 required for 80% power to detect a 40% reduction in morbidity.
<table>
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<th></th>
<th>Composite morbidity</th>
<th>Severe RDS</th>
<th>Birth weight</th>
<th>Head circumference</th>
<th>Long term concerns</th>
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<tbody>
<tr>
<td>Guinn et al</td>
<td>reduced</td>
<td>reduced</td>
<td>Small effect</td>
<td>Small effect</td>
<td></td>
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<tr>
<td>Wapner et al</td>
<td>No difference</td>
<td>(better pulmonary outcomes)</td>
<td>reduced</td>
<td>reduced</td>
<td>Age 2-3: concerns over cerebral palsy</td>
</tr>
<tr>
<td>Crowther et al</td>
<td>-</td>
<td>(better pulmonary outcomes)</td>
<td>Reduced (short term)</td>
<td>Reduced (short term)</td>
<td>Age 2: concerns over attention problems</td>
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<tr>
<td>Garite et al</td>
<td>Reduced</td>
<td>reduced</td>
<td>No difference</td>
<td>No difference</td>
<td>-</td>
</tr>
</tbody>
</table>
### Considerations for Education & Practice

Limit the number of absolute courses of ACS given.

Only treat babies most likely to deliver at a gestational age where they would benefit mostly from ACS treatment.

Best approach is a ‘rescue course’: initial course of ACS administered when preterm birth is likely.

If the patient does not deliver over the next 7 or more days, a repeat ACS course can be given up to 32 weeks’ gestation.

### Considerations for further research

Although a great deal of research exists, there is still a need for RCT’s to determine the best possible number of courses of ACS to reduce neonatal RDS without adversely affecting other neonatal outcomes. Searching for the best dosage and timing, and the risk-benefit ratio can only be accomplished through continued research.

Well structured RCT’s that evaluate single and multiple courses are needed to answer important questions such as:

Do repeat ACS doses maintain the production of surfactant in the foetal lung?
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