Multiple courses of antenatal corticosteroids: a systematic review and meta-analysis
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Authors' objectives
To assess the effects of multiple courses of antenatal corticosteroids (ACS) on perinatal and neonatal death and neonatal, infant and maternal disease.

Searching
MEDLINE (from 1966 to 1999) and EMBASE (from 1980 to 1999) were searched. MEDLINE was searched using the terms 'adrenal cortex hormones', 'glucocorticoids', 'betamethasone' and 'dexamethasone' combined with the terms 'lung', 'fetal organ maturity' and 'respiratory distress syndrome'. These terms were also used with 'pregnancy' and 'pregnancy complications' in two separate searches. A similar strategy was used in EMBASE. The references from included articles and personal files were also searched for additional articles. Only full articles published in English were included in the review.

Study selection
Study designs of evaluations included in the review
Both prospective and retrospective observational studies were eligible for inclusion. When data were collected prospectively but as part of another study or as part of normal care, and not specifically to answer the research question posed in this review, it was classified as a retrospective cohort study. All of the included studies were retrospective. Studies that did not control for differences in gestational age at birth were excluded.

Specific interventions included in the review
Studies that compared multiple courses of ACS versus a single course were included. The specific interventions assessed were betamethasone (5 studies), dexamethasone (1 study), and either betamethasone or dexamethasone (2 studies). The specific dosages of corticosteroids used in the studies were not reported. The number of courses, where reported, was two to twelve.

Participants included in the review
Studies that assessed women at increased risk for pre-term birth were included. The studies included women who had foetuses delivered in the gestational age range of 20 to 36 weeks (5 studies). One study defined participants as neonates weighing less than 1,750 g. One study was conducted in women who had experienced pre-term pre-labour rupture of the membranes before 32 weeks' gestation.

Outcomes assessed in the review
Studies that reported perinatal, neonatal, infant or maternal outcomes were included. The specific neonatal outcomes assessed were respiratory distress syndrome (RDS), mortality, intraventricular haemorrhage, bronchopulmonary dysplasia, sepsis, patent ductus arteriosus, necrotising enterocolitis and birth weight. The maternal outcomes assessed were chorioamnionitis, endometritis and infection.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors assessed the validity of the studies according to whether they were prospective or retrospective in the association between ACS and the outcomes of interest; whether the use of multiple versus single courses of corticosteroids was part of routine hospital policy, or varied among clinicians; and whether the potential confounding variables of gestational age at first course, time from last course to delivery, pre-term pre-labour rupture of membranes, pre-eclampsia or hypertension, and multiple pregnancy had been controlled for in the analysis. The authors stated that they assessed each paper for methodological quality. However, it was unclear how many reviewers...
were involved in this process, or how any disagreements were resolved.

**Data extraction**
Two reviewers independently extracted the data and resolved any discrepancies by consensus. The extracted data were author and year, participant characteristics, the type and number of corticosteroids courses, and how potential confounders for size at birth and clinical outcomes were handled.

**Methods of synthesis**
How were the studies combined?
The baseline information was analysed descriptively. When the gestational age at delivery was documented to be similar between groups in a study, or when the results were presented by gestational age subgroup, the data were combined in a meta-analysis using a random-effects model. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P-value of less than 0.05 was considered statistically significant. Publication bias was not assessed.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared test. A P-value of less than 0.05 was considered statistically significant.

**Results of the review**
Eight retrospective studies (n=2,798) were included in the review: 1,682 foetuses were exposed to a single course of ACS, while 1,116 foetuses were exposed to multiple courses of ACS.

Seven studies were included in the meta-analysis to determine the effect of multiple courses of ACS on RDS. Multiple courses of ACS were associated with significantly decreased odds of RDS (OR 0.79, 95% CI: 0.64, 0.98), a trend toward an increased odds of bronchopulmonary dysplasia (OR 1.30, 95% CI: 0.96, 1.78), and a significantly decreased odds of patent ductus arteriosus (OR 0.56, 95% CI: 0.35, 0.90). The odds of intraventricular haemorrhage, necrotising enterocolitis, sepsis and neonatal death were not significantly different between multiple and single courses of ACS.

Four studies also reported on maternal outcomes. In the meta-analysis, although the rate of chorioamnionitis was not significantly increased (OR 1.46, 95% CI: 0.47, 4.59), the odds of postpartum endometritis was increased with the use of multiple courses versus a single course of ACS (OR 3.22, 95% CI: 1.90, 5.45).

There was no significant heterogeneity in any of the meta-analyses, except for that assessing the effects of multiple versus single courses of ACS for neonatal sepsis and chorioamnionitis.

**Authors’ conclusions**
The authors concluded that it was not possible to establish the true effects of multiple courses of ACS by a review of the results of observational studies, because of the effect of confounding variables.

**CRD commentary**
The authors addressed a clear review question in terms of the interventions, participants, study designs and outcome measures that were to be assessed. The literature search was fair, but only English language articles published in full were included. This means that language bias and publication bias could have influenced the findings, and that other relevant studies could have been missed. It was not reported how the studies were screened for inclusion in the review, or whether the quality of the included studies was assessed. This could have introduced bias and errors into the review process. The data extraction process was undertaken in an appropriate manner, and there are unlikely to be mistakes in this process that would have influenced the results of the review.

Adequate details of the characteristics of the primary studies were tabulated, which allow the reader to assess whether
the authors’ results and conclusions are consistent with the evidence base reviewed. The statistical methods used were appropriate, and heterogeneity between the studies was assessed. The authors also provided a thorough discussion of clinical heterogeneity and potential confounding factors that might have influenced the results of the review. Overall, this was a reasonably well-conducted review. The authors’ results and conclusion appear to be consistent with the evidence base reviewed.

Implications of the review for practice and research
Practice: The authors stated that it is clear that a single course of ACS has very substantial immediate benefits for pre-term infants, but the evidence from studies that addressed multiple courses of ACS and their long-term effects causes concern. The authors therefore recommended that until the results from a number of multicentre randomised trials are available, the practice of providing repeated courses of ACS (including rescue therapy) should be reserved for patients enrolled in such clinical trials.

Research: The authors stated that the practice of repeating courses of ACS should be addressed in large multicentre randomised trials, with an emphasis on assessing long-term effects on growth and neurodevelopment. They also pointed out that several such trials are presently underway.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.