CRD summary
The authors concluded that administration of multiple courses of antenatal corticosteroids in women at high risk of preterm birth did not add further benefits in terms of composite neonatal morbidity, even if it was associated with some short-term benefits. The review had some methodological problems, but the authors’ conclusions were suitably cautious and appear appropriate.

Authors’ objectives
To determine the risks and benefits of multiple courses of antenatal corticosteroids.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched between 1999 and 2007 for articles in English. Search terms were reported. The related articles feature in PubMed was used. Reference lists of included articles were searched.

Study selection
Published full-text randomised controlled trials (RCTs) in women at high risk of preterm birth who had received a seven-day course of corticosteroids and who subsequently received multiple courses of antenatal corticosteroids compared with placebo/no placebo were eligible for inclusion. Multiple courses were considered to be two or more courses of antenatal corticosteroids. Placebo was allowed to include a single booster dose of antenatal corticosteroids prior to delivery. Relevant outcomes were perinatal, neonatal, infant and maternal outcomes.

The included RCTs compared weekly or two-weekly betamethasone (two doses of 12mg/dose intramuscularly) with weekly or two-weekly courses of placebo in women between 23 and 33 weeks gestation at high risk of pre-term birth. Reported outcomes included perinatal death, respiratory distress syndrome, birth weight, head circumference, maternal side-effects and composite neonatal morbidity.

The authors did not state how many reviewers undertook the selection process.

Assessment of study quality
Quality assessment was undertaken using the Cochrane Collaboration Issue 4 tool for RCTs, which assessed six quality factors including blinding, drop-outs and randomisation. Only articles that scored at least 6 points were included.

The authors did not state how many reviewers undertook quality assessment.

Data extraction
The authors did not state how data were extracted.

Methods of synthesis
Pooled relative risks (RR) or weighted mean differences (WMD), together with 95% CIs, were calculated using a random-effects meta-analysis. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$ statistics.

Results of the review
Eleven RCTs were included in the review (n=4,390 women and 5,227 babies). Sample sizes of included trials ranged from 12 to 1,858 women. Study quality of the RCTs ranged from 6 to 8 out of 8.

Compared with a single course, multiple courses of antenatal corticosteroids were associated with a statistically significant decrease in respiratory distress syndrome (RR 0.80, 95% CI 0.71 to 0.89, $I^2=0\%$; six studies, n=2,785), patent ductus arteriosus (RR 0.74, 95% CI 0.57 to 0.95, $I^2=24\%$; five studies, n=4,031), ventilator support (RR 0.84, 95% CI 0.75 to 0.94, $I^2=4\%$; eight studies, n=3,585), and composite neonatal morbidity (RR 0.79, 95% CI 0.71 to 0.87, $I^2=14\%$; eight studies, n=3,585).
95% CI 0.77 to 0.91, I²=47%; four studies, n=4,480), surfactant use (RR 0.75, 95% CI 0.67 to 0.84, I²=0%; six studies, n=5,032) and any maternal side-effects (RR 0.79, 95% CI 0.66 to 0.96, I²=94%; three studies, n=3,327).

Compared with a single course, multiple courses of antenatal corticosteroids were associated with a statistically significant decrease in birth weight (WMD -83, 95% CI -124.47 to -42.55, I²=0%; seven studies, n=5,372) and head circumference (WMD -0.35, 95% CI -0.52 to -0.17, I²=43%; seven studies, n=5,089).

There was no statistical difference between single course and multiple course antenatal corticosteroids for 15 other outcomes, which included composite neonatal mortality, perinatal death, endometritis and severe respiratory distress syndrome.

Authors’ conclusions
Administration of multiple courses of antenatal corticosteroids in women at high risk of preterm birth did not add further benefits in terms of composite neonatal morbidity, even if it was associated with some short-term benefits.

CRD commentary
Inclusion criteria for the review were clearly defined. Two relevant databases were searched. There was potential for language and publication biases as the search was restricted to published English-language studies; publication bias was not assessed. The authors did not state how many reviewers performed study selection, data extraction and quality assessment, which may have been due to poor reporting or indicated a methodological weakness with the review. Study quality was used as an inclusion criteria, which ensured high-quality included studies. The trials seemed comparable in terms of patient populations. Trials were combined using a random-effects meta-analysis and statistical heterogeneity was estimated, which were appropriate.

The review had some methodological problems, but the authors’ conclusions were suitably cautious and appear appropriate.

Implications of the review for practice and research
Practice: The authors stated that obstetricians should be cautious in administering repeat injections of antenatal corticosteroids.

Research: The authors stated that further evaluations (with particular attention to the long-term outcomes of children and to the timing and dose regimens) were required before multiple courses of antenatal corticosteroids could be recommended.

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