Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial

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Summary

Background **The efficacy and safety of repeat doses of prenatal corticosteroids remains uncertain. Our aim was to establish whether repeat prenatal corticosteroids given to women at risk of preterm birth can reduce neonatal morbidity without harm.**

Methods **In this hospital-based study, 982 women who remained at risk of preterm birth at less than 32 weeks' gestation, 7 or more days after receiving a first course of prenatal corticosteroids, were randomly assigned to receive a repeat intramuscular dose of either 11·4 mg betamethasone (as Celestone Chronodose), or saline placebo. This was repeated every week the woman remained undelivered, at less than 32 weeks' gestation, and at risk of preterm birth. Primary outcomes were occurrence and severity of neonatal respiratory distress syndrome, use and duration of oxygen and mechanical ventilation, and weight, length, and head circumference at birth and hospital discharge. Statistical analyses were on an intention to treat basis. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN48656428.**

Findings **Fewer babies exposed to repeat corticosteroids had respiratory distress syndrome (33% *vs* 41%; relative risk 0·82, 95% CI 0·71–0·95, p=0·01) and fewer had severe lung disease (12% *vs* 20%; relative risk 0·60, 95% CI 0·46–0·79, p=0·0003) than those in the placebo group. In keeping with these benefits, babies exposed to repeat corticosteroids needed less oxygen therapy (p=0·03), and shorter duration of mechanical ventilation (p=0·01). Mean weight, length, and head circumference at birth and hospital discharge did not differ between treatment groups. Z-scores for weight (p=0·04) and head circumference (p=0·03) at birth were lower in the babies who received repeat corticosteroids although at the time of hospital discharge Z-scores did not differ between treatment groups (p=0·29 for weight, p=0·48 for head circumference).**

Interpretation **Exposure to repeat doses of antenatal corticosteroids reduces neonatal morbidity. Pending long-term outcome results, the short-term benefits for the babies in our study support the use of repeat doses of corticosteroids in women who remain at risk of very preterm birth 7 or more days after an initial course.**

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Introduction

Babies born preterm are at high risk of neonatal lung disease and its sequelae. Respiratory distress syndrome, as a result of immature lung development, is the main cause of early neonatal mortality. It causes substantial immediate[1] and long-term morbidity in some survivors. A single course of prenatal corticosteroids given to the mother remains the most effective known prenatal strategy for reducing the adverse results of preterm birth.[2] Single-course prenatal corticosteroids given to women at risk of preterm birth have not been effective in babies born more than 7 days after initial treatment,[2] and perinatal death is increased.[3]

The suggestion of a possible benefit in repeating the prenatal corticosteroids in women who remain at risk of preterm birth 7 or more days after their initial course[4] has led to such treatment being introduced into clinical practice[5] without assessment by randomised trials. Although repeat doses of prenatal corticosteroids were thought to be a simple and inexpensive way to reduce the respiratory morbidity associated with immaturity, clinical practice recommendations do not endorse the use of repeat doses of prenatal corticosteroids outside clinical trials.[6]

In animals, repeat doses of prenatal betamethasone have a dose-dependent benefit for lung function,[7] but adverse effects on lung development,[8] skeletal growth,[7] hypothalamic-pituitary-adrenal function,[7] and neuronal myelination.[9]

In man, there has been concern that prenatal corticosteroids raise the risk of maternal infection after preterm prelabour rupture of the membranes.[2] For the infant, some non-randomised studies of repeat corticosteroids have reported adverse effects on measures of growth at birth,[10] heightened risk of neonatal infection, suppression of the fetal hypothalamic-pituitary-adrenal axis, adverse effects on childhood behaviour,[11] and abnormal neurodevelopment.[12] However, other observational studies have not shown adverse effects on neurosensory disability,[10,13,14] and one report suggests protection against cerebral palsy.[11] The efficacy and safety of repeat doses of prenatal steroids is therefore uncertain, and there have been repeated calls for randomised controlled trials.[2,6,15,16]

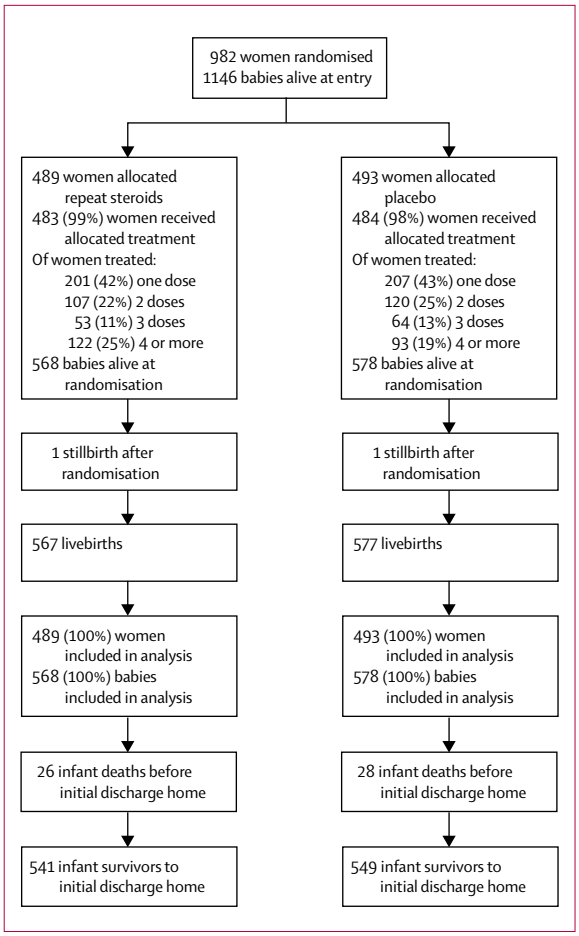

***Figure*: Trial profile**

Our aim was to establish whether repeat prenatal corticosteroids given to women at risk of preterm birth can reduce neonatal morbidity without harm.

Methods

Participants

Women were eligible with a single, twin, or triplet pregnancy at less than 32 weeks' gestational age if they had received an initial treatment of corticosteroid 7 or more days previously, and their responsible clinician regarded them to be at continued risk of preterm birth and there was no contraindication to further corticosteroid therapy. Women were excluded if they were in the second stage of labour, had chorioamnionitis needing urgent delivery, had mature lung development, or if further corticosteroid therapy was judged to be essential.

The study protocol was approved by the ethics committees at each of the 23 collaborating hospitals—16 in Australia and seven in New Zealand. Women were given written information about the trial, which was reviewed with them by a member of the study team. Of the eligible women asked to take part, 982 (44·1%) consented and an estimated 1245 (55·9%) declined.

Procedures

Women who gave written informed consent were randomly assigned to the repeat dose of steroid group or the placebo group by the central telephone randomisation service and were given a study number corresponding to a treatment pack. The study randomisation numbers were generated by computer with variable block sizes, and stratification by centre, gestational age (two groups <28 weeks' gestation and ≥28 weeks'), and number of fetuses (three groups—singleton, twin, or triplet). Every study number correlated with a masked treatment pack held at the participating centres ready for use.

Each treatment pack looked identical and contained an opaque study-labelled syringe of either Celestone Chronodose with 7·8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate (Schering-Plough, Sydney, Australia) or saline placebo. Women were given the contents of the syringe by intramuscular injection. Every week, if the woman remained undelivered and less than 32 weeks' gestation, and the responsible clinician regarded her as at continued risk of preterm birth, a further treatment pack from the same treatment group was allocated by the telephone randomisation service and

	Repeat steroid n=489	Placebo n=493
Maternal age, years*	29·9 (6·1)	29·8 (5·9)
Parity		
0	155 (32%)	156 (32%)
1–3	288 (59%)	283 (57%)
≥4	46 (9%)	54 (11%)
Smoking at first antenatal visit	164 (34%)	169 (34%)
Gestational age at entry (weeks)†	28·4 (26·4–30·3)	28·6 (26·3–30·1)
Gestational age at initial steroids (weeks)†	26·7 (24·7–28·7)	26·7 (24·7–28·7)
Multiple pregnancy (twin or triplet)	75 (15%)	80 (16%)
Previous preterm birth <32 weeks	49 (15%)	49 (15%)
Previous perinatal death ≥20 weeks	42 (13%)	41 (12%)
Main reasons why at risk of preterm birth		
Antepartum haemorrhage	156 (32%)	130 (26%)
Preterm prelabour rupture of the membranes	153 (31%)	181 (37%)
Preterm labour	131 (27%)	127 (26%)
Cervical incompetence	56 (12%)	44 (9%)
Pre-eclampsia/eclampsia	49 (10%)	48 (10%)
Severe growth restriction	40 (8%)	30 (6%)
Multiple pregnancy	34 (7%)	25 (5%)
Other	33 (7%)	47 (10%)

Data are numbers (%) unless otherwise indicated. *mean (SD), †median (interquartile range).

***Table 1*: Baseline characteristics of women in repeat steroid and placebo groups at trial entry**

given to the woman. The date, time, main reason for risk of preterm birth, and any side-effects of the injection or injections were recorded.

The care given to women and babies was otherwise according to standard practice at each centre. All women and perinatal staff were masked as to treatment-group allocation. Women and their children were followed up until first discharge from hospital. The pregnancy and delivery data (including details of clinical chorioamnionitis requiring intrapartum antibiotics and maternal postpartum pyrexia) and neonatal data (including details of neonatal respiratory disease and treatment, measures of growth at birth, and hospital discharge) were obtained from case notes by a research coordinator who was unaware of the treatment-group allocation.

The primary outcomes were frequency and severity of respiratory distress syndrome (defined as clinical signs of respiratory distress and a ground-glass appearance on chest radiograph) and the severity of any respiratory disease present (defined as: mild, maximum appropriate mean airway pressure [MAP] <7 cm H_2O, or maximum appropriate fractional inspired oxygen [FiO_2] <0·40; moderate, MAP 7– <10 cm H_2O or FiO_2 0·40–0·79; severe, MAP ≥10 cm H_2O or FiO_2 ≥0·80, with need for ventilation); need for and duration of oxygen therapy; need for and duration of mechanical ventilation via an endotracheal tube (including high frequency ventilation); and weight, length, and head circumference at birth and at discharge from hospital. Secondary clinical outcomes were clinical chorioamnionitis requiring intrapartum antibiotics, maternal postpartum pyrexia 38·0°C or greater, and any side-effects of the injection for the mother, and other measures of neonatal morbidity for the infant.

Statistical analysis

Statistical analyses were on an intention-to-treat basis. We prespecified that analyses would be adjusted for gestational age and for prognostic variables with imbalance. We adjusted all analyses for gestational age at trial entry, antepartum haemorrhage, and preterm prelabour rupture of the membranes. We presented binary outcomes as relative risks with 95% CI, and number needed to treat to benefit (NNTB) and number needed to treat to harm presented for primary outcomes. We calculated relative risks using log binomial regression.[17] We analysed continuous variables using analysis of variance if normally distributed and by non-parametric tests if not. We used robust variance estimation to account for clustering of babies within mothers. Level of significance was 0·05 and all p values were two-sided. We used SAS Version 9.1 software. We calculated Z-scores for weight, head circumference, and length using data relative to standard growth references.[18,19] For a normally grown infant, the expected value for a Z-score is zero; larger than normal infants have negative Z-scores. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN48656428.

A sample size of 980 women was needed to detect a 25% reduction in the risk of respiratory distress syndrome (the main endpoint of the trial) from 30%[20] to 22·5% with 80% power (β=0·20) at a two-sided significance level of 5% (α=0·05). Data were reviewed twice by the independent data monitoring committee who were not aware of treatment-group allocation. The first review was done in March, 2000, after release of the Guinn trial results[21] when 201 women had been recruited, and the second, prompted by safety concerns raised by other reports, was done in September, 2002, after the recruitment of 675 women.

	Repeat steroids n=567	Placebo n=577	Adjusted treatment effect (95% CI)	p value
Respiratory distress syndrome	186 (33%)	239 (41%)	0·82 (0·71–0·95)	0·01
Severity of lung disease				0·0004
No lung disease	229 (40%)	191 (33%)	1·23 (1·05–1·44)	0·01
Mild lung disease	181 (32%)	169 (29%)	1·09 (0·91–1·31)	0·34
Moderate lung disease	92 (16%)	103 (18%)	0·91 (0·70–1·19)	0·49
Severe lung disease	65 (12%)	114 (20%)	0·60 (0·46–0·79)	0·0003
Use of oxygen therapy	317 (56%)	361 (63%)	0·90 (0·81–0·99)	0·03
Duration of oxygen therapy*(days)	1 (0–7)	1 (0–8)	..	0·24
Use of mechanical ventilation	167 (30%)	204 (35%)	0·87 (0·75–1·01)	0·08
Duration of mechanical ventilation*(days)	0·0 (0–1)	0·0 (0–2)	..	0·01

Data are number (%) unless otherwise indicated. Relative risk is treatment effect, or *median (interquartile range). Analyses are adjusted for gestational age at entry, preterm prelabour rupture of the membranes, and antepartum haemorrhage necessitating admission to hospital. Infant analyses are adjusted for clustering within mother.

Table 2: **Primary clinical outcomes for liveborn infants, assessed before hospital discharge**

	Repeat steroids	Placebo	Treatment effect (adjusted 95% CI)	p value
At birth	n=567	n=577		
Weight (g)	1867 (824)	1877 (816)	−36 (−130 to 57)	0·44
Length (cm)	42·1 (5·9)	42·1 (5·6)	−0·1 (−0·8 to 0·6)	0·75
Head circumference (cm)	29·6 (3·7)	29·7 (3·6)	−0·1 (−0·6 to 0·3)	0·50
Birth *Z* scores				
Weight (g)	−0·40 (1·05)	−0·27 (1·14)	−0·13 (−0·26 to −0·004)	0·04
Length (cm)	−0·53 (1·31)	−0·48 (1·22)	−0·07 (−0·22 to 0·09)	0·38
Head circumference (cm)	−0·30 (1·22)	−0·14 (1·28)	−0·17 (−0·32 to −0·02)	0·03
At hospital discharge*	n=541	n=549		
Weight (g)	2692 (726)	2693 (542)	−18 (−95 to 58)	0·64
Length (cm)	47·4 (4·3)	47·4 (4·0)	−0·1 (−0·6 to 0·4)	0·66
Head circumference (cm)	33·7 (2·1)	33·6 (1·9)	−0·0 (−0·3 to 0·2)	0·94
Discharge *Z*-scores				
Weight	−1·07 (0·98)	−1·02 (0·93)	−0·06 (−0·18 to 0·05)	0·29
Length	−1·11 (1·47)	−1·08 (1·55)	−0·06 (−0·25 to 0·12)	0·50
Head circumference	−0·19 (1·12)	−0·15 (1·06)	−0·05 (−0·18 to 0·09)	0·48

Values are mean (SD). Analyses are adjusted for gestational age at entry, preterm prelabour rupture of the membranes, and antepartum haemorrhage necessitating admission to hospital. *Babies discharged alive. Infant analyses are adjusted for clustering within mother.

Table 3: **Measures of infant growth for liveborns at birth and at discharge from hospital**

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The figure shows the trial profile. Recruitment started in April, 1998, and was completed in July, 2004. Table 1 shows baseline variables. 7 or more days before trial entry, most women (882, 90%) received two doses 24 h apart of betamethasone (as Celestone Chronodose). The remainder (100, 11%) received dexamethasone (24 mg in 24 h). Clinical outcomes were recorded up to the time of hospital discharge for all 982 women and their 1146 babies alive at the time of randomisation.

	Repeat steroid n=567	Placebo n=577	Treatment effect (95% CI)	Significance p-value
Gestational age at birth, weeks*	32·5 (3·9)	32·4 (3·9)	0·06 (−0·4 to 0·5)	0·79
Gestational age at birth	..	..	..	0·74
<28 weeks	74 (13%)	71 (12%)	..	..
28–33^{6} weeks	288 (51%)	302 (52%)	..	..
34–36^{6} weeks	96 (17%)	110 (19%)	..	..
≥37 weeks	109 (19%)	94 (16%)	..	..
Highest appropriate FiO_2 value, %†	22 (21–35)	28 (21–50)	..	< 0·0001
Use of surfactant	138 (24%)	186 (32%)	0·81 (0·68–0·97)	0·02
Patent ductus arteriosus	40 (7%)	67 (12%)	0·59 (0·40–0·87)	0·01
Maximum peak pressure, cm H_2O†	16 (6–21)	18 (6–24)	..	0·08
Use of nitric oxide for respiratory support	12 (2%)	21 (4%)	0·60 (0·30–1·20)	0·15
Use of inotropic support	64 (11%)	87 (15%)	0·75 (0·55–1·03)	0·07
Air leak syndrome	19 (3%)	18 (3%)	1·10 (0·59–2·05)	0·77
Need for oxygen at 36 weeks post conception	76 (13%)	82 (14%)	0·95 (0·72–1·25)	0·70
Use of steroids postnatally	43 (8%)	31 (5%)	1·39 (0·89–2·18)	0·15
Admission to neonatal intensive-care unit	407 (72%)	399 (69%)	1·05 (0·99–1·12)	0·08
Length of hospital stay, days†	29 (9–56)	32 (11–57)	..	0·66
Apgar score <7				
At 1 minute	182 (32%)	195 (34%)	0·96 (0·81–1·13)	0·64
At 5 minutes	34 (6%)	38 (7%)	0·92 (0·58–1·47)	0·73
Intraventricular haemorrhage	34 (6%)	39 (7%)	0·86 (0·55–1·35)	0·51
Grade 3–4 intraventricular haemorrhage	5 (1%)	8 (1%)	0·64 (0·21–2·02)	0·45
Periventricular leucomalacia	4 (1%)	9 (2%)	0·53 (0·16–1·79)	0·30
Proven necrotising enterocolitis	5 (1%)	11 (2%)	0·47 (0.16–1·35)	0·16
Retinopathy of prematurity	40 (7%)	43 (8%)	0·94 (0·60–1·46)	0·77
Systemic infection				
Suspected <48 h after birth	173 (31%)	188 (33%)	1·00 (0·83–1·19)	0·98
Confirmed <48 h after birth	10 (2%)	10 (2%)	0·98 (0·41–2·36)	0·96
Any proven infection	70 (12%)	72 (13%)	0·98 (0·72–1·33)	0·89
Other serious neonatal morbidity‡	114 (20%)	150 (26%)	0·79 (0·65–0·97)	0·02

Data are number (%) except where *mean (SD), or †median (interquartile range). Relative risk as treatment effect or mean difference as treatment effect with 95% CI. Analyses are adjusted for gestational age at entry, preterm prelabour rupture of the membranes, and antepartum haemorrhage necessitating admission to hospital. Infant analyses are adjusted for clustering within mother. ‡Defined as one of air leak syndrome, patent ductus arteriosus, need for oxygen at 36 weeks, postmenstrual age, severe intraventricular haemorrhage (grade 3 or 4), periventricular leucomalacia, proven necrotising enterocolitis, or retinopathy of prematurity.

Table 4: **Neonatal morbidity for liveborn babies in the first hospital stay**

Almost all women received their allocated trial medication with the largest proportion of participants receiving only one dose of trial medication (figure). 11 (2%) women in the repeat steroid group and 12 (2%) in the placebo group received open-label repeat prenatal corticosteroids for clinical reasons after enrolment.

Fewer babies exposed to repeat corticosteroids had respiratory distress syndrome than did those in the placebo group (table 2; NNTB 14, 95% CI 8–50). Fewer babies in the corticosteroid group had severe lung disease (NNTB 14, 95% CI 9–29) than did those in the placebo group. In keeping with these benefits, babies exposed to repeat doses of corticosteroids needed less oxygen therapy (15, 8–190) and a shorter duration of mechanical ventilation (p=0·01) than did those in the placebo group. The number of babies who needed mechanical ventilation did not differ significantly between the treatment groups, nor did the duration of oxygen therapy.

At birth, infant weight, length, and head circumference did not differ between groups (table 3). Similarly, at hospital discharge no significant differences were seen.

At birth, the Z-scores were lower for babies exposed to repeat corticosteroids than for those in the placebo group for weight-adjusted mean difference and head circumference, but not for length. At hospital discharge, there was no statistically significant difference in measures of growth Z-scores between treatment groups for head circumference (table 3).

There were 56 (5%) infant deaths before hospital discharge—1 stillbirth and 26 deaths of liveborn infants in the repeat steroid group, and 1 stillbirth and 28 deaths of liveborn infants in the placebo group. The main causes of death were much the same between the two groups (data not shown).

Average gestational age at birth was similar at just over 32 weeks in both groups as was the proportion who were born preterm (table 4). In keeping with the findings that babies exposed to repeat doses of steroids had less neonatal lung disease than those in the placebo group, these babies had significantly lower maximum appropriate fractional inspired oxygen values 12 h after birth and fewer babies in this group needed surfactant or had a patent ductus arteriosus requiring treatment. No significant differences were seen between treatment groups for other respiratory outcomes of maximum peak ventilatory pressure reached within 12 h of birth, use of nitric oxide for respiratory support, use of inotropic support, air leak syndrome, need for oxygen at 36 weeks' postmenstrual age, or in the postnatal use of corticosteroids.

There were no significant differences between groups for rates of admission to neonatal intensive care, length of hospital stay, or other measures of neonatal morbidity including Apgar scores, intraventricular haemorrhage, severe intraventricular haemorrhage (grade 3 and 4), periventricular leucomalacia, proven necrotising enterocolitis, or retinopathy of prematurity. Of note, there were no statistically or clinically significant differences

between groups in the outcomes that assessed neonatal infection (systemic infection suspected or confirmed in first 48 h of life, or any proven infection) (table 4). Fewer babies exposed to repeat corticosteroids than those given placebo had other serious neonatal morbidity—a posthoc, composite outcome.

The number of women who developed clinical chorioamnionitis requiring intrapartum antibiotics or postpartum pyrexia of 38·0°C or greater was closely similar between the treatment groups (table 5). More women in the repeat steroid group than in the placebo group had a caesarean birth. Minor maternal side-effects at the time of trial injection were two-fold greater than in those in the repeat steroid group than in the placebo group.

	Repeat steroid n=489	Placebo n=493	Adjusted relative risk (95% CI)	Adjusted p value
Maternal outcomes				
Chorioamnionitis requiring antibiotics	44 (9%)	41 (8%)	1·21 (0·83–1·77)	0·32
Postpartum pyrexia ≥ 38°C	32 (7%)	37 (8%)	0·85 (0·54–1·35)	0·49
Postnatal blood pressure ≥ 140/90 mm Hg	62 (13%)	67 (14%)	0·96 (0·71–1·30)	0·78
Caesarean section	326 (67%)	287 (58%)	1·13 (1·02–1·24)	0·01
Any side-effects	47 (10%)	24 (5%)	2·04 (1·27–3·29)	0·003
Pain/discomfort	20 (4%)	10 (2%)	2·01 (0·95–4·26)	0·07
Maternal distress	14 (3%)	12 (2%)	1·26 (0·59–2·71)	0·55
Haematoma	6 (1%)	3 (1%)	2·02 (0·51–8·04)	0·32
Rash	2 (0%)	1 (0%)	2·02 (0·18–22·2)	0·62
Sleeplessness	3 (1%)	0 (0%)	..	0·12
Lethargy	1 (0%)	0 (0%)	..	0·50
Other	5 (1%)	2 (0%)	2·56 (0·50–13·12)	0·26

Data are number (%). Analyses are adjusted for gestational age at entry, preterm prelabour rupture of the membranes, and antepartum haemorrhage necessitating admission to hospital.

Table 5: **Side-effects at time of trial injection and maternal outcomes**

Discussion

In our randomised controlled trial of repeat doses of prenatal corticosteroids given to women who remained at risk of birth before 32 weeks' gestation, 7 or more days after an initial course of corticosteroids, fewer babies exposed to repeat corticosteroids developed respiratory distress syndrome, and fewer had severe lung disease than those in the placebo group. These significant reductions in neonatal morbidity are clinically important, with NNTB of only 14 babies. In addition to this reduction in neonatal respiratory distress syndrome, there were other respiratory benefits, with less need for oxygen therapy, shorter periods of mechanical ventilation, lower maximum inspired oxygen concentrations, less use of surfactant therapy, and less need for treatment for patent ductus arteriosus. Overall, serious neonatal morbidity was reduced. We recorded no evidence of an increased risk of infection for the infants or women exposed to repeat doses of corticosteroids. Reassuringly, there were no differences in measures of infant growth at hospital discharge.

The respiratory protective effect of repeat corticosteroids might be attributable to improved lung maturation. The initial trial of antenatal cortiocosteroids[4] did not show benefit after 7 days, suggesting that the maturity induced by steroids is reversible. For a beneficial clinical effect, sustained exposure or repeat doses of corticosteroids might be needed to alter biochemical pathways, enhance surfactant turnover, and produce the necessary structural changes to lung tissue. These short-term benefits for the babies in our study provide strong evidence for recommendation of the use of repeat doses of corticosteroids in women who remain at risk of very preterm birth 7 or more days after an initial course using the protocol for inclusion and exclusion specified in our trial.

Whether repeated courses of prenatal corticosteroids have any long-term effects of clinical significance for height, weight, lung function, neurodevelopment, and general health in these babies will require longer follow-up. As yet, there are no data from randomised controlled trials that have reported for disability at childhood follow-up,[16] and the inconsistencies raised by observational studies remain.[10–14] We will assess the presence and severity of any neurosensory impairment, including cerebral palsy, blindness, deafness, and developmental delay at 2 years' corrected-age for children in our trial.

Programming of cardiovascular settings in the fetus by glucocorticoid exposure has been described as the link with subsequent adult cardiovascular disease,[22] although not evident at 30 years after brief exposure in late gestation to a single antenatal course of betamethasone.[23] Insulin resistance was, however, raised in the patients exposed to a single course of antenatal corticosteroids.[23] When repeat courses of antenatal corticosteroids are used, the first course is often needed earlier in gestation than when a single course is used,[24] and with potential exposure for several weeks of gestation the effect of repeat doses of antenatal corticosteroids on the risk of diabetes and cardiovascular disease in later life should be assessed.

The reduction in risk of respiratory distress syndrome in our trial was not shown in a meta-analysis[16] that has been reported since our study began, which included three randomised trials of 551 women.[25–27] The one trial in the meta-analysis that was able to provide data, showed a similar reduction in risk of neonatal severe respiratory disease (15·3% *vs* 24·1%; relative risk 0·63, 95% CI 0·44–0·93), for infants exposed to repeat corticosteroids.[25] We are aware of three other randomised trials of repeat antenatal corticosteroids; two have so far been reported only in abstract form[28,29] and the other, the Canadian multiple antenatal corticosteroids study, is assessing repeat corticosteroids given at intervals of 14 days.[30]

In our study, caesarean section rates were high in both treatment groups. The higher rate in the repeat dose group is unexplained. We doubt that this difference affected these results, since there was no evidence of differences in low

Apgar scores between treatment groups, and caesarean births would have been expected to increase, rather than reduce, the risk of respiratory disease. Maternal side-effects from repeat prenatal corticosteroids have not been previously well-reported. The higher rates of minor side-effects in women given repeat doses of corticosteroids in our study were not surprising. We did not detect any obvious short-term harmful effects of repeat corticosteroids for the fetuses or infants. However, much larger trials would be needed to exclude smaller differences in health outcomes. Entry into our trial was over a wide range of gestational ages and varying treatment doses were given, as per the trial protocol. The results are not generalisable beyond the gestational ages and doses used in the trial. Further studies are needed to examine the effects of different number of doses of corticosteroids at different gestational ages.

Thus, the clinically important improvement in neonatal respiratory outcomes from repeat prenatal corticosteroids given to women at continuing risk of very preterm birth 7 or more days after an initial course, reduced the inherent respiratory complications of immaturity and so improved the health outcomes of preterm infants without increasing maternal morbidity. These benefits come at the expense of slightly reduced weight and head circumference at birth for gestational age, although there were no differences in measures of growth adjusted for gestational age at hospital discharge. This trial has produced clear evidence of short-term benefit of repeat doses of antenatal corticosteroids to women who remain at risk of preterm birth 7 or more days after an initial course of corticosteroids in reducing neonatal lung disease. Whether there are effects on health that continue into childhood and beyond must await later assessment.

Contributors

Study concept and design: C A Crowther, R R Haslam, J E Hiller, L W Doyle, J S Robinson; *Acquisition of data:* C A Crowther, L W Doyle, R R Haslam; *Analysis and interpretation of data:* C A Crowther, R R Haslam, J E Hiller, L W Doyle, J S Robinson; *Drafting of the manuscript:* C A Crowther; *Revision of the manuscript:* C A Crowther, R R Haslam, J E Hiller, L W Doyle, J S Robinson; *Statistical expertise:* J E Hiller, L W Doyle; *Obtained funding:* C A Crowther, R R Haslam, J S Robinson; *Administrative, technical, or material support:* C A Crowther, R R Haslam, J E Hiller, L W Doyle, J S Robinson; *Study supervision:* C A Crowther, R R Haslam, J E Hiller

Conflict of interest statement

We declare that we have no conflict of interest.

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Collaboration by hospital (total number of women recruited)

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