Outcomes at 2 Years of Age after Repeat Doses of Antenatal Corticosteroids

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ABSTRACT

BACKGROUND

We previously reported the results of a randomized, controlled trial showing that repeat doses of antenatal corticosteroids reduced the risk of respiratory distress syndrome and serious neonatal morbidity. However, data have not been available regarding longer-term effects of this treatment.

METHODS

Women who had received an initial course of corticosteroid treatment 7 or more days previously were randomly assigned to receive an intramuscular injection of corticosteroid (11.4 mg of betamethasone) or saline placebo; the dose was repeated weekly if the mother was still considered to be at risk for preterm delivery and the duration of gestation was less than 32 weeks. We assessed survival free of major neurosensory disability and body size of the children at 2 years of corrected age.

RESULTS

Of the 1085 children who were alive at 2 years of age, 1047 (96.5%) were seen for assessment (521 exposed to repeat-corticosteroid treatment and 526 exposed to placebo). The rate of survival free of major disability was similar in the repeat-corticosteroid and placebo groups (84.4% and 81.0%, respectively; adjusted relative risk, 1.04, 95% confidence interval, 0.98 to 1.10; adjusted $P=0.20$). There were no significant differences between the groups in body size, blood pressure, use of health services, respiratory morbidity, or child behavior scores, although children exposed to repeat doses of corticosteroids were more likely than those exposed to placebo to warrant assessment for attention problems ($P=0.04$).

CONCLUSIONS

Administration of repeat doses of antenatal corticosteroids reduces neonatal morbidity without changing either survival free of major neurosensory disability or body size at 2 years of age. (Current Controlled Trials number, ISRCTN48656428.)

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PRETERM BIRTH IS A MAJOR RISK FACTOR for neurosensory impairments and disabilities, including cerebral palsy.[1,2] A single course of antenatal corticosteroids given to women at risk for preterm delivery substantially reduces the risk of neonatal mortality and morbidity and reduces the risk of long-term neurologic sequelae.[3] However, in comparison with unexposed infants, infants born more than 7 days after exposure to a single course of antenatal corticosteroids have lower birth weight[3] and increased perinatal mortality.[4] It therefore became common clinical practice to repeat the dose of antenatal corticosteroids after 7 or more days, despite a lack of evidence to support this practice.[5] However, current guidelines do not support the use of repeat doses of antenatal corticosteroids outside of clinical trials.[6]

Lambs exposed to repeat doses of antenatal corticosteroids have higher blood pressure,[7] reduced skeletal growth,[7] delayed neuronal myelination,[8] and lower brain weight in later life[9] than lambs exposed to a single dose. In observational studies in humans, exposure to repeat courses of corticosteroids has been associated with poorer infant growth,[10] abnormal childhood behavior,[11] and delayed psychomotor development[12] as compared with exposure to a single course. However, not all observational studies have shown an increased incidence of neurosensory disability in childhood after repeat doses of corticosteroids,[10,13] and one study suggested a reduction in the incidence of cerebral palsy.[11]

We previously reported short-term results of the Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS), in which babies of women randomly assigned to repeat doses of corticosteroids as compared with babies of women assigned to a single course, were much less likely to have respiratory distress syndrome (33% vs. 41%, P=0.01), severe neonatal lung disease (12% vs. 20%, P<0.001), and serious neonatal morbidity (20% vs. 26%, P=0.02).[14] However, z scores for weight and head circumference were lower at birth in the repeat-dose group, although there were no significant differences by the time of hospital discharge.

A meta-analysis of the currently available evidence from randomized, controlled trials of women given repeat doses of antenatal corticosteroids similarly showed a reduction in the risk of neonatal respiratory distress syndrome as compared with those given a single course (26% vs. 32%; relative risk, 0.82; 95% confidence interval [CI], 0.72 to 0.93; four trials, 2155 women).[15] We are unaware of any reports from randomized clinical trials on developmental and health outcomes in later childhood after exposure to repeat doses of antenatal corticosteroids.

We assessed outcomes at 2 years of corrected age of surviving children whose mothers took part in the ACTORDS trial. We aimed to determine whether exposure to repeat doses of antenatal corticosteroids affected the rate of survival free of major neurosensory disability (caused by impairments such as cerebral palsy, blindness, deafness, or developmental delay); body size; general health, including respiratory health; blood pressure; or behavior.

METHODS

DESIGN AND STUDY POPULATION

Eligible children were born to women recruited into the ACTORDS trial and were discharged home alive. As previously reported,[14] women were eligible for the trial if they were considered by their obstetricians to be at risk for preterm delivery at less than 32 weeks of gestation with a single, twin, or triplet pregnancy and had received an initial course of a corticosteroid 7 or more days earlier. The research and ethics committees at the 23 collaborating hospitals approved the protocol.

INTERVENTION

Women who gave written informed consent that included follow-up of their children through 2 years of corrected age were randomly assigned to the repeat-corticosteroid group or the placebo group and given an intramuscular injection of either betamethasone (11.4 mg of Celestone Chronodose, Schering-Plough) or saline placebo; the dose was repeated weekly if the woman remained at risk for preterm delivery before 32 weeks of gestation. Randomization was performed by a central telephone randomization service with stratification according to center, gestational age, and number of fetuses.[14]

TWO-YEAR FOLLOW-UP

Contact with mothers of infants discharged home alive was maintained at 6, 12, and 18 months

after birth. Surviving children were assessed at 2 years of corrected age by a developmental pediatrician and a psychologist, with staff and families unaware of treatment-group assignment. The pediatric assessment included measurement of weight, height, head circumference, and blood pressure; assessment of vision and hearing; and a neurologic examination. Body-size measurements were converted to z scores (standard-deviation scores) specific for age and sex.[16] Blood pressure was measured according to local practice, and measurements were converted to z scores specific for age, height, and sex, with hypertension defined as systolic or diastolic blood pressure above the 95th percentile.[17] Children were considered blind if vision in both eyes was worse than 6/60. Children were considered deaf if they required hearing aids. The criteria for cerebral palsy included abnormalities of muscle tone as well as loss of motor function.[18]

The psychological assessment included the Psychomotor Developmental Index and the Mental Developmental Index of the Bayley Scales of Infant Development[19] or an equivalent psychological test. Both indexes of the Bayley Scales have a mean (±SD) score of 100±15, and higher scores indicate better performance. Children unable to complete the Psychomotor Developmental Index or the Mental Developmental Index because of severe psychomotor or developmental delay were assigned scores of 49.

Severe neurosensory disability was defined as severe cerebral palsy (the child was considered permanently nonambulant), severe developmental delay (Mental Developmental Index score, >3 SD below the mean), or blindness. Moderate disability was defined as moderate cerebral palsy (the child was nonambulant at 2 years of age but was likely to walk), moderate developmental delay (Mental Developmental Index score, >2 SD to 3 SD below the mean), or deafness. Mild disability was defined as either mild cerebral palsy (the child was able to walk by 2 years of age) or mild developmental delay (Mental Developmental Index score, >1 SD to 2 SD below the mean).

Each child's parent or caregiver completed a questionnaire on the child's history of illness, including respiratory illness, and the use of health services since the primary hospitalization. Each parent or caregiver also completed the Child Behavior Checklist, a rating scale that screens for behavioral and emotional problems.[20]

OUTCOME VARIABLES

Primary Outcomes

The primary prespecified outcome was survival at the corrected age of 2 years free of major neurosensory disability, defined as survival free of moderate or severe disability. The other primary
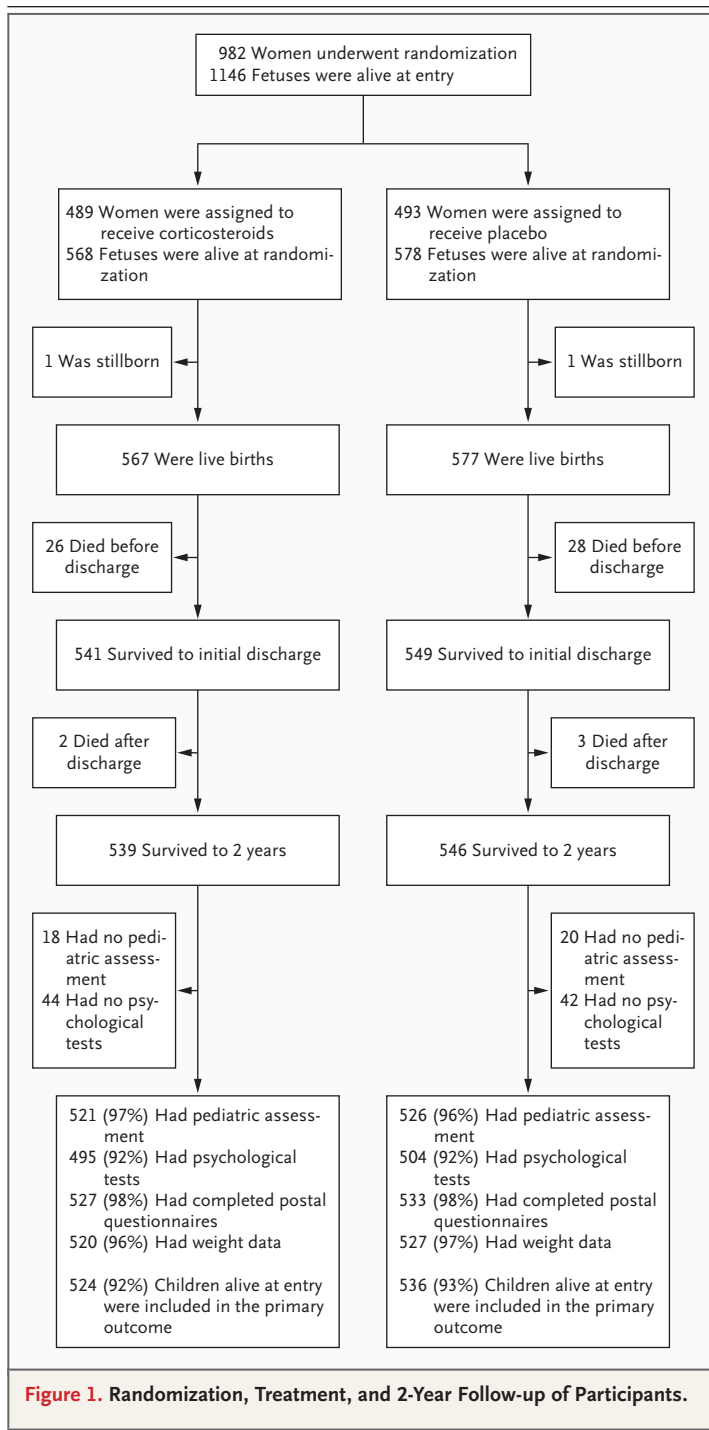

Figure 1. Randomization, Treatment, and 2-Year Follow-up of Participants.

Table 1. Characteristics of the Women and Their Infants.*

Characteristic	Repeat-Corticosteroid Group (N=464)	Placebo Group (N=460)	P Value
Maternal age — yr	30.0±6.0	29.9±5.9	0.84
Parity — no. (%)			0.69
0	146 (31.5)	146 (31.7)	
1, 2, or 3	275 (59.3)	264 (57.4)	
≥4	43 (9.3)	50 (10.9)	
Smoking during pregnancy — no. (%)	153 (33.0)	152 (33.0)	0.98
Gestational age at study entry — wk			0.71
Median	28.6	28.6	
Interquartile range	26.4–30.3	26.4–30.1	
Gestational age at initial dose of corticosteroids — wk			0.85
Median	26.8	26.9	
Interquartile range	24.7–28.7	24.9–28.7	
Multiple pregnancy — no. (%)†	72 (15.5)	76 (16.5)	0.68
Previous preterm delivery <32 wk — no. (%)	47 (10.1)	47 (10.2)	0.96
Previous perinatal death ≥20 wk — no. (%)	40 (8.6)	41 (8.9)	0.88
Main reason for risk of preterm delivery — no. (%)			
Antepartum hemorrhage	150 (32.3)	123 (26.7)	0.06
Preterm prelabor rupture of membranes	138 (29.7)	162 (35.2)	0.08
Preterm labor	126 (27.2)	117 (25.4)	0.55
Cervical incompetence	56 (12.1)	42 (9.1)	0.15
Preeclampsia or eclampsia	46 (9.9)	47 (10.2)	0.88
Severe growth restriction	35 (7.5)	29 (6.3)	0.46
Multiple pregnancy†	31 (6.7)	23 (5.0)	0.28
Other	36 (7.8)	48 (10.4)	0.16
Highest level of maternal education — no./total no. (%)			0.86
Secondary	247/460 (53.7)	241/456 (52.9)	
Tertiary	216/460 (47.0)	206/456 (45.2)	
No. of doses of treatment given — no. (%)			0.10
0	4 (0.9)	7 (1.5)	
1	185 (39.9)	195 (42.4)	
2 or 3	155 (33.4)	169 (36.7)	
≥4	120 (25.9)	89 (19.3)	
Sex of child — no. (%)‡			0.61
Male	295 (55.6)	289 (53.8)	
Female	236 (44.4)	248 (46.2)	
Gestational age at birth — wk‡	32.8±3.9	32.6±3.8	0.58
Birth weight — g‡	1911±823	1915±803	0.97

* Plus–minus values are means ±SD.
† Multiple pregnancies are twins or triplets.
‡ Data are based on 531 infants in the repeat-corticosteroid group and 537 in the placebo group.

Table 2. Primary Outcomes, Assessed at 2 Years of Corrected Age.*

Outcome	Repeat-Corticosteroid Group (N = 524)	Placebo Group (N = 536)	Adjusted Relative Risk (95% CI)†	Adjusted P Value
Survival free of major neurosensory disability — no. (%)‡	442 (84.4)	434 (81.0)	1.04 (0.98 to 1.10)	0.20
			Adjusted Mean Difference (95% CI)	
Body-size measurements§				
Weight — kg	12.6±1.9	12.6±1.9	−0.1 (−0.3 to 0.2)	0.62
Height — cm	87.6±4.6	87.7±4.7	−0.2 (−0.8 to 0.4)	0.45
Head circumference — cm	48.9±1.7	48.9±1.8	0.03 (−0.19 to 0.26)	0.78
z score				
Weight	−0.04±1.30	−0.01±1.29	−0.04 (−0.20 to 0.12)	0.62
Height	0.01±1.17	0.08±1.24	−0.08 (−0.23 to 0.08)	0.33
Head circumference	−0.74±1.26	−0.76±1.33	0.002 (−0.162 to 0.167)	0.98

* Plus–minus values are means ±SD.
† Relative risks and mean differences were adjusted for gestational age, antepartum hemorrhage requiring hospitalization, and preterm prelabor rupture of the membranes at trial entry. Analyses of data for children are adjusted for clustering effects due to multiple gestations.
‡ This outcome is defined as being ambulant by 2 years of age and not having blindness, deafness, a developmental index score of more than 2 SD below the mean, or cerebral palsy.[1]
§ Body-size measurements are based on 520 children in the repeat-corticosteroid group and 527 in the placebo group.

outcome was body size (weight, height, and head circumference).

Secondary Outcomes

The secondary outcomes were general health, including the use of health services since primary discharge; hospital readmission; respiratory morbidity, defined as the need for hospital admission for respiratory illness and the rate of asthma (determined on the basis of parental report of recurrent cough and wheeze requiring treatment with a bronchodilator); blood-pressure z scores and proportions in the hypertensive range; child behavior assessed by the Child Behavior Checklist[20]; incidence of neurosensory impairments and disabilities; total number of deaths by 2 years of corrected age, including stillbirths, neonatal deaths, and deaths after hospital discharge; and the combined adverse outcome of death or any neurosensory disability at 2 years of corrected age.

STATISTICAL ANALYSIS

We originally estimated that 918 children who were alive at 2 years of corrected age would be available for assessment. A trial with 524 babies in the re-

peat-corticosteroid group and 536 babies in the placebo group, on the assumption of a design effect of 1.2 to account for the clustering effect due to multiple gestations, has an 80% power to detect a significant difference at an alpha level of 0.05 (two-tailed) if survival free of major disability changed from 81% up to 88% or down to 73%. For measures of body size, this sample size would detect a change in z score of 0.2 SD with 80% power.

Statistical analyses were performed on an intention-to-treat basis with SAS software, version 9.1. All analyses were adjusted for gestational age at trial entry, antepartum hemorrhage, and preterm prelabor rupture of the membranes.[14] Binary outcomes are presented as relative risks with 95% confidence intervals. Relative risks were calculated with the use of log binomial regression.[21] Continuous variables, if normally distributed, were analyzed by analysis of variance, with transformation of skewed data to normality before analysis. Robust variance estimation was used to account for clustering effects due to multiple gestations. A P value of less than 0.05 was considered to indicate statistical significance. All P values were two-sided.

Table 3. Secondary Outcomes, Assessed at 2 Years of Corrected Age.*

Outcome	Repeat-Corticosteroid Group (N = 568)	Placebo Group (N = 578)	Adjusted Relative Risk (95% CI)†	Adjusted Mean Difference (95% CI)	Adjusted P Value
Death — no. (%)	29 (5.1)	32 (5.5)	0.91 (0.55 to 1.53)		0.73
Death or any neurosensory disability — no./total no. (%)	204/524 (38.9)	214/536 (39.9)	1.00 (0.85 to 1.17)		1.00
Death or moderate-to-severe disability	82/524 (15.6)	102/536 (19.0)	0.85 (0.64 to 1.12)		0.25
Death or severe disability	52/524 (9.9)	61/536 (11.4)	0.89 (0.62 to 1.29)		0.54
Cerebral palsy — no./total no. (%)					
Any	22/521 (4.2)	25/526 (4.8)	0.91 (0.51 to 1.63)		0.74
None	499/521 (95.8)	501/526 (95.2)	1.00 (0.98 to 1.03)		0.73
Severity‡					0.89
Mild	9/521 (1.7)	10/526 (1.9)	0.91 (0.38 to 2.22)		0.84
Moderate	7/521 (1.3)	10/526 (1.9)	0.71 (0.27 to 1.85)		0.48
Severe	6/521 (1.2)	5/526 (1.0)	1.24 (0.36 to 4.21)		0.73
Blindness — no./total no. (%)	3/521 (0.6)	1/526 (0.2)	2.94 (0.26 to 33.57)		0.39
Deafness — no./total no. (%)	4/521 (0.8)	5/526 (1.0)	0.77 (0.19 to 3.06)		0.71
Bayley PDI score§	92.5±17.3	92.1±16.7		0.2 (−2.0 to 2.5)	0.83
Bayley MDI score¶	91.1±17.1	90.5±17.7		0.1 (−2.2 to 2.4)	0.90
Delayed development — no./total no. (%)‖					0.49
None	327/495 (66.1)	329/504 (65.3)	1.00 (0.91 to 1.11)		0.93
Mild	120/495 (24.2)	110/504 (21.8)	1.12 (0.88 to 1.42)		0.37
Moderate	25/495 (5.1)	36/504 (7.1)	0.72 (0.43 to 1.21)		0.21
Severe	23/495 (4.6)	29/504 (5.8)	0.84 (0.47 to 1.50)		0.56
Neurosensory disability — no./total no. (%)**					0.50
None	320/495 (64.6)	322/504 (63.9)	1.00 (0.91 to 1.11)		0.97
Mild	122/495 (24.6)	112/504 (22.2)	1.12 (0.89 to 1.43)		0.33
Moderate	30/495 (6.1)	41/504 (8.1)	0.75 (0.47 to 1.20)		0.23
Severe	23/495 (4.6)	29/504 (5.8)	0.84 (0.47 to 1.50)		0.56
Use of health services since discharge — no./total no. (%)					
Hospital readmission	266/527 (50.5)	261/533 (49.0)	1.04 (0.92 to 1.18)		0.50
Physical therapy	28/521 (5.4)	21/526 (4.0)	1.35 (0.78 to 2.34)		0.29
Organized play group††	32/521 (6.1)	43/526 (8.2)	0.73 (0.45 to 1.20)		0.21
Admission for respiratory illness	174/527 (33.0)	177/533 (33.2)	1.01 (0.84 to 1.20)		0.95
Asthma — no./total no. (%)	122/527 (23.1)	142/533 (26.6)	0.88 (0.71 to 1.09)		0.24
Systolic blood pressure — z score‡‡	0.2±1.2	0.3±1.2		−0.1 (−0.2 to 0.1)	0.56
Diastolic blood pressure — z score§§	1.1±0.9	1.0±1.0		0.01 (−0.15 to 0.16)	0.93
Hypertension — no./total no. (%)¶¶	92/301 (30.6)	103/327 (31.5)	0.98 (0.77 to 1.25)		0.85
Weight — no./total no. (%)‖‖					
<10th percentile	68/520 (13.1)	81/527 (15.4)	0.86 (0.63 to 1.18)		0.35
>90th percentile	70/520 (13.5)	70/527 (13.3)	1.01 (0.73 to 1.39)		0.97

Table 3. (Continued.)

Outcome	Repeat-Corticosteroid Group (N = 568)	Placebo Group (N = 578)	Adjusted Relative Risk (95% CI)†	Adjusted Mean Difference (95% CI)	Adjusted P Value
Height <10th percentile — no./total no. (%)‖‖	60/520 (11.5)	68/520 (13.1)	0.92 (0.65 to 1.29)		0.62
Head circumference <10th percentile — no./total no. (%)‖‖	160/519 (30.8)	167/522 (32.0)	0.98 (0.81 to 1.18)		0.81

* Plus–minus values are means ±SD.
† Relative risks and mean differences were adjusted for gestational age, antepartum hemorrhage requiring hospitalization, and preterm prelabor rupture of the membranes at trial entry. Analyses of data for children are adjusted for clustering effects due to multiple gestations.
‡ The P value for the linear treatment effect is 0.85.
§ The values are based on 472 children in the repeat-corticosteroid group and 486 in the placebo group. PDI denotes Psychomotor Developmental Index.
¶ The values are based on 474 children in the repeat-corticosteroid group and 493 in the placebo group. MDI denotes Mental Developmental Index.
‖ A few children assessed with alternative psychometric tests are included. The P value for the linear treatment effect is 0.33.
** Severe neurosensory disability was defined as severe cerebral palsy (child considered permanently nonambulant), severe developmental delay (MDI score, >3 SD below the mean), or blindness. Moderate disability was defined as moderate cerebral palsy (child nonambulant at 2 years but likely to walk), moderate developmental delay (MDI score, >2 SD to 3 SD below the mean), or deafness. Mild disability was defined as either mild cerebral palsy (walking at 2 years) or mild developmental delay (MDI score, >1 SD to 2 SD below the mean). Children with no disability had no neurosensory impairment. The P value for the linear treatment effect is 0.35.
†† An organized play group is defined as a supervised group in which play is treatment oriented.
‡‡ The values are based on 327 children in the repeat-corticosteroid group and 345 in the placebo group.
§§ The values are based on 301 children in the repeat-corticosteroid group and 327 in the placebo group.
¶¶ Hypertension is defined as either systolic hypertension (systolic blood pressure >95th percentile) or diastolic hypertension (diastolic blood pressure >95th percentile).[17]
‖‖ Percentiles for weight, height, and head circumference are taken from a standard chart.[16]

RESULTS

Of the 982 women enrolled, 489 were assigned to the repeat-corticosteroid group and 493 to the placebo group (Fig. 1). Clinical outcomes up to the time of discharge after the primary hospitalization have been reported previously for all 982 women who underwent randomization and their 1146 fetuses who were alive at randomization.[14]

Of the 1090 infants discharged home alive, 5 had died by 2 years of corrected age (2 in the repeat-corticosteroid group and 3 in the placebo group). Of the 1085 survivors, 1047 (96%) were assessed at 2 years of corrected age and 38 had no pediatric assessment (18 in the repeat-corticosteroid group and 20 in the placebo group) (Fig. 1). The maternal characteristics and the reasons for the risk of preterm delivery were similar in the two treatment groups (Table 1).

PRIMARY OUTCOMES

The rates of survival free of major disability did not differ significantly between the repeat-corticosteroid and placebo groups (84.4% and 81.0%, respectively; adjusted relative risk, 1.04; 95% CI, 0.98 to 1.10; adjusted P=0.20) (Table 2). There were also no significant differences between the groups in measurements or z scores for weight, height, or head circumference (Table 2). In a prespecified analysis according to the number of repeat trial treatments given (one, two or three, or four or more treatments), there were no significant interactions with the treatment effect for survival free of major disability or for measures of body size (unadjusted and adjusted P>0.25).

SECONDARY OUTCOMES

There were no significant differences between the groups in the use of health service resources. The overall rates of readmission to the hospital were similar, as were the rates of asthma and admission to the hospital with a respiratory illness. There were no significant differences between the groups in mean systolic or diastolic blood pressures or in the proportions of children with blood pressure in the hypertensive range (Table 3). Children exposed to one or more repeat doses of antenatal corticosteroids were not more likely to be small for their age in weight, height, or head circumference than children not exposed (Table 3).

There were 61 deaths (5.3%): 29 (5.1%) in the repeat-corticosteroid group and 32 (5.5%) in the placebo group (Table 3). There were no significant differences between the treatment groups in the distribution of the severity of neurosensory disability, in any of the individual neurosensory impairments (cerebral palsy, blindness, deafness, and developmental delay), or in the combined outcome of death or any neurosensory disability (Table 3). The mean Psychomotor Developmental and Mental Developmental Index scores did not significantly differ between treatment groups (Table 3).

For the Child Behavior Checklist, there were no significant differences between the groups in the total or individual mean scores for internalizing, externalizing, emotional reactivity, anxiety or depression, somatic complaints, withdrawal, sleep problems, attention problems, or aggressive behavior (Table 4). Similarly, there were no significant differences in the proportions of children with scores within the clinical range (the top 2.5th percentile, indicating further assessment is warranted)[20] in any of these behavioral domains, with the exception of attention problems, for which there were more children in the clinical

Table 4. Child Behavior Checklist Scores at 2 Years of Corrected Age.*

Outcome	Repeat-Corticosteroid Group (N = 519)	Placebo Group (N = 526)	Adjusted Mean Difference (95% CI)†	Adjusted P Value
Child Behavior Checklist domain scores				
Total	35.6±21.3	35.0±20.2	0.8 (−1.9 to 3.4)	0.56
Internalizing	8.3±6.4	8.0±6.5	0.3 (−0.6 to 1.1)	0.55
Externalizing	13.9±8.6	13.6±8.0	0.4 (−0.7 to 1.4)	0.51
Emotionally reactive	2.3±2.2	2.3±2.3	0.1 (−0.2 to 0.4)	0.65
Anxious or depressed	2.7±2.2	2.6±2.2	0.1 (−0.2 to 0.4)	0.51
Somatic complaints	1.8±2.1	1.8±2.0	0.1 (−0.2 to 0.3)	0.71
Withdrawn	1.5±1.8	1.4±1.8	0.1 (−0.2 to 0.3)	0.60
Sleep problems	2.9±2.8	3.1±2.8	−0.1 (−0.4 to 0.3)	0.66
Attention problems	2.6±2.1	2.4±1.9	0.2 (−0.1 to 0.4)	0.18
Aggressive behavior	11.3±7.0	11.2±6.8	0.2 (−0.7 to 1.1)	0.69
			Adjusted Relative Risk (95% CI)†	
Scores within clinical range — no. (%)‡				
Total	68 (13.1)	63 (12.0)	1.11 (0.79 to 1.57)	0.54
Internalizing	46 (8.9)	51 (9.7)	0.94 (0.63 to 1.39)	0.76
Externalizing	57 (11.0)	51 (9.7)	1.18 (0.81 to 1.72)	0.40
Emotionally reactive	8 (1.5)	8 (1.5)	1.02 (0.40 to 2.63)	0.96
Anxious or depressed	7 (1.3)	9 (1.7)	0.82 (0.31 to 2.14)	0.68
Somatic complaints	23 (4.4)	21 (4.0)	1.12 (0.62 to 2.00)	0.71
Withdrawn	23 (4.4)	28 (5.3)	0.87 (0.50 to 1.50)	0.61
Sleep problems	25 (4.8)	29 (5.5)	0.87 (0.52 to 1.46)	0.59
Attention problems	31 (6.0)	17 (3.2)	1.87 (1.03 to 3.42)	0.04
Aggressive behavior	21 (4.0)	21 (4.0)	1.06 (0.57 to 1.98)	0.85

* Plus–minus values are means ±SD.
† Mean differences and relative risks were adjusted for gestational age, antepartum hemorrhage requiring hospitalization, and preterm prelabor rupture of the membranes at trial entry. Analyses of data for children are adjusted for clustering effects due to multiple gestations.
‡ Scores in the clinical range are those in the top 2.5th percentile, indicating that further assessment of the child is warranted.

range in the repeat-corticosteroid than in the placebo group (6.0% vs. 3.2%; adjusted relative risk, 1.87; 95% CI, 1.03 to 3.42; P=0.04) (Table 4). In post hoc analyses, there were no significant interactions between sex and treatment effect on child behavior (unadjusted and adjusted P>0.18).

DISCUSSION

In this follow-up study of offspring of women at risk for preterm delivery who were assigned to repeat doses of betamethasone or placebo, exposure to repeat doses of corticosteroids had no significant effects on survival free of major neurosensory disability or on childhood growth to 2 years of corrected age. The study used central randomization, the outcome assessors were unaware of treatment-group assignment, the follow-up rate achieved was very high, and the sample size was sufficiently large to detect important but small differences between treatment groups.

These results may be viewed as reassuring, given previous reports of adverse effects of repeat doses of corticosteroids on neuronal myelination[8] and brain weight in sheep,[9] as well as the increased rate of neurosensory disability in childhood reported in some observational studies of children whose mothers received repeat corticosteroid doses.[12] The differences between the findings in sheep and humans may be related to the much greater effects of repeat corticosteroids on fetal growth in sheep,[7] perhaps due to the higher doses used, as well as differences in the timing of brain growth and myelination in the two species.[22] Our results are robust, in that they show a similar distribution of developmental outcomes in the corticosteroid and placebo groups across a range of different measures of neurosensory disability. However, since neurosensory abilities at 2 years of age are of limited predictive value, particularly for more subtle problems, follow-up of these children is warranted later in childhood, when other important cognitive outcomes, such as executive function, can be determined more completely.

We also found no differences between treatment groups in body-size measurements at 2 years. This is consistent with our earlier finding that there were no differences between the groups in body size at initial discharge from the hospital. The mean size at birth also did not differ significantly between the groups, although the z scores

for weight and head circumference at birth were slightly lower in infants who were exposed to repeat doses of corticosteroids.[14] Together these findings suggest that any effects of repeat doses of corticosteroids on growth before birth are unlikely to have any clinically important effect on size in later life. The reason for the difference between our findings and those of many studies in animals showing long-term impairment of growth after antenatal corticosteroids is not clear, but it may in part be related to the longer period of administration and larger doses of corticosteroids used in the studies in animals.[7]

Almost one third of the children in our study had blood pressures above the 95th percentile. Preterm birth is itself associated with increased blood pressure in adulthood[23,24] and with a doubling of the risk of hypertension by 30 years of age.[25] However, we found no apparent effect of exposure to repeat corticosteroids on blood pressure at 2 years of age. This is consistent with the findings of previous randomized trials that exposure to a single course of antenatal corticosteroids has no effect on blood pressure in later childhood[26] and early adulthood,[27,28] but not with findings of observational studies[23,29] and studies in animals suggesting that antenatal corticosteroid exposure increases blood pressure in both fetal[30] and postnatal[7,31] life. These differences may be related in part to the lack of effects on growth in our study, since in rats, exposure to antenatal corticosteroids does not alter blood pressure unless growth is also affected.[32] The differences may also be related to the timing of corticosteroid exposure, since fetuses exposed to repeat doses of corticosteroids, as was the case in our study, often are exposed to their first dose earlier in gestation than those exposed to a single dose.[33]

Some studies in animals have suggested that the effects of antenatal corticosteroid exposure on blood pressure may increase with increasing postnatal age.[34] Therefore, long-term follow-up of this and similar randomized trials will be important to determine whether repeat doses of antenatal corticosteroids have adverse effects on later cardiovascular health beyond those associated with preterm birth.

Overall child behavior was similar between the treatment groups. We did not find an increase in aggressive behavior in children who had been exposed to repeat doses of corticosteroids, as was

reported in an earlier observational study.[11] The higher proportion of children exposed to repeat doses of corticosteroids who reached the clinical range of scores for attention problems may have been a chance finding, since it represents a difference in the sum of 5 items in a 100-item standardized test. However, further follow-up is warranted, given the reported changes in neurotransmitter systems and associated increases in hyperactivity and anxiety-like behavior in animals after antenatal exposure to repeat doses of corticosteroids.[35,36]

Our results should not be generalized to other treatment regimens or inclusion criteria. A trial using a single rescue or booster dose of corticosteroid when preterm birth was imminent (within 48 hours) did not show benefit in the neonatal period.[37] The 2-to-3-year follow-up of children in the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network trial[38] reported in this issue of the *Journal*[39] showed no significant differences in physical or neurocognitive measures between children who had been exposed to repeat courses of antenatal corticosteroids and those who had been exposed to single courses. Another trial of repeat antenatal corticosteroids has completed recruitment, and the results are awaited.[40]

Exposure to one or more repeat doses of antenatal betamethasone has previously been shown to reduce the risk of respiratory distress syndrome and overall serious neonatal morbidity.[14,15] The current report shows that this treatment does not change survival free of major neurosensory disability or growth to 2 years of age. On the basis of this evidence, clinicians may wish to consider the use of a single injection of Celestone Chronodose, or equivalent, repeated weekly if the woman remains at risk for very preterm delivery, 7 or more days after an initial course of antenatal corticosteroids.

APPENDIX

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