Mid-Childhood Outcomes of Repeat Antenatal Corticosteroids: A Randomized Controlled Trial

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abstract

OBJECTIVE: To assess if exposure to repeat dose(s) of antenatal corticosteroids has beneficial effects on neurodevelopment and general health in mid-childhood, at 6 to 8 years' corrected age.

METHODS: Women at risk for very preterm birth, who had received a course of corticosteroids ≥7 days previously, were randomized to intramuscular betamethasone (11.4 mg Celestone Chronodose) or saline placebo, repeated weekly if risk of very preterm birth remained. Mid-childhood assessments included neurocognitive function, behavior, growth, lung function, blood pressure, health-related quality of life, and health service utilization. The primary outcome was survival free of neurosensory disability.

RESULTS: Of the 1059 eligible long-term survivors, 963 (91%) were included in the primary outcome; 479 (91%) in the repeat corticosteroid group and 484 (91%) in the placebo group. The rate of survival free of neurosensory disability was similar in both groups (78.3% repeat versus 77.3% placebo; risk ratio 1.00, 95% confidence interval, 0.94–1.08). Neurodevelopment, including cognitive function, and behavior, body size, blood pressure, spirometry, and health-related quality of life were similar in both groups, as was the use of health services.

CONCLUSIONS: Treatment with repeat dose(s) of antenatal corticosteroids was associated with neither benefit nor harm in mid-childhood. Our finding of long-term safety supports the use of repeat dose(s) of antenatal corticosteroids, in view of the related neonatal benefits. For women at risk for preterm birth before 32 weeks' gestation, ≥7 days after an initial course of antenatal corticosteroids, clinicians could consider using a single injection of betamethasone, repeated weekly if risk remains.

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WHAT'S KNOWN ON THIS SUBJECT: Repeat dose(s) of corticosteroids before very preterm birth reduces neonatal respiratory morbidity and serious outcomes in the newborn period, without evidence of harm at preschool age. The effect on health and neurodevelopment in later childhood is unknown.

WHAT THIS STUDY ADDS: Use of repeat dose(s) of antenatal betamethasone when indicated reduces neonatal morbidity without beneficial or adverse effects on survival free of neurosensory disability in mid-childhood, or evidence of any other effects.

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Repeat doses of corticosteroids before very preterm birth reduce neonatal respiratory morbidity and serious outcomes in the newborn period.[1] Systematic review of 4 trials[2–5] that have reported on health outcomes in early childhood after repeat dose(s) of antenatal corticosteroids found no differences between exposed or unexposed children.[1] However, the efficacy and safety effects on health in later childhood are unknown.

In animals, repeat doses of antenatal corticosteroids have been associated with long-term adverse effects on blood pressure and brain mass,[6,7] and a human observational study has reported behavioral problems.[8]

The Australasian Collaborative Trial of Repeat Doses of Corticosteroids for the Prevention of Neonatal Respiratory Disease (ACTORDS) reported clear evidence of neonatal benefit up to the time of hospital discharge, including reduced neonatal respiratory and serious morbidity.[2] Although *z*-scores at birth for weight and head circumference were reduced in infants randomly assigned to repeat corticosteroids compared with placebo, by hospital discharge, no significant differences were seen between groups.[2] Early childhood follow-up found no differences in survival free of major neurosensory disability between groups.[9]

Despite evidence of neonatal benefit and reassuring findings at early childhood follow-up, repeat corticosteroids are not commonly prescribed partly because of concerns about possible longer-term adverse effects on the child.

Therefore, we reassessed surviving children whose mothers participated in the ACTORDS at 6- to 8-years' corrected age. We hypothesized that exposure to repeat dose(s) of antenatal corticosteroids would have beneficial effects on the rate of survival free of any neurosensory disability, cognitive function, behavior, educational achievement, body size, blood pressure, general health including respiratory health, and health-related quality of life.

METHODS

Design and Study Population

Eligible children were born to women recruited into the ACTORDS. As previously described,[2] women were eligible for the trial if at risk for preterm birth at <32 weeks' gestation with a singleton, twin, or triplet pregnancy, and they had received an initial course of antenatal corticosteroids ≥7 days prior.

Intervention

Women were randomized to either the repeat corticosteroid group (one 2-mL dose Celestone Chronodose, which contains 11.4 mg betamethasone, comprising 7·8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) or the saline placebo group. If the woman remained at risk for preterm birth, the allocated study treatment could be repeated weekly, up to 32 weeks' gestation.

Six- to 8-Year Follow-up

This mid-childhood follow-up of participating children was not part of the original protocol developed in 1997. Contact with families of surviving children was maintained both at the time of notification of the initial study results,[2] and the early childhood follow-up at 2 years of age.[9] Parents gave written informed consent for their child to participate. The protocol for the school-age follow-up received human research ethics approval and is available in the supplemental material.

Surviving children were assessed at 6- to 8-years' corrected age by a pediatrician and a psychologist who were unaware of the child's randomized group. The pediatric assessment included a history of health and health service use; physical and neurologic examination; measurement of weight, height, and head circumference; blood pressure; lung function; assessment of vision and hearing; and assessment of gross and fine motor function by using the Movement Assessment Battery for Children, Second Edition.[10] Some children were assessed with an earlier edition of the Movement Assessment Battery for Children. Cerebral palsy included nonprogressive loss of motor function with disordered muscle tone or tendon reflexes.[11] The severity of gross motor function in children with cerebral palsy was assessed by using criteria of Palisano et al[12] and graded into mild (grade 1), moderate (grades 2–3), and severe (grades 4–5). Blindness comprised vision worse than 6/60 in the better eye. Deafness comprised hearing loss requiring hearing aids, or worse. Lung function was measured by portable flow spirometry (EasyOne 2001; NDD Technologies, Zurich, Switzerland) by using forced expiratory maneuvers. Spirogram quality was determined by 2 independent examiners, and children with at least 2 adequate and reproducible spirograms were included in the analysis.[13]

The psychological assessment included the Wechsler Abbreviated Scale of Intelligence.[14] Full-scale IQ was derived from 4 subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. Verbal and Performance IQ were also generated. Scores are age standardized (mean [M] = 100, SD = 15). Children unable to complete the Wechsler Abbreviated Scale of Intelligence because of severe intellectual impairment were assigned a score of 40. Intellectual impairment was classified as mild (IQ from –2 SD to <–1 SD), moderate (–3 SD to <–2 SD), or severe (<–3 SD).

Neurosensory disability comprised any of cerebral palsy, IQ <–1 SD, blindness or deafness, and was

graded as mild (mild cerebral palsy or mild intellectual impairment), moderate (deafness, moderate cerebral palsy, or moderate intellectual impairment), or severe (blindness, severe cerebral palsy, or severe intellectual impairment).

Academic skills were assessed by the word reading, spelling, and math computation subtests of the Wide Range Achievement Test.[15] Each scale is age standardized (M = 100, SD = 15). Attention was assessed using subtests from the Test of Everyday Attention for Children.[16]

Selective visual attention was assessed with the Sky Search subtest, sustained attention with the Score! subtest, shifting attention with the Creature Counting subtest, and divided attention with the Sky Search Dual Task subtest. For the Sky Search, Score!, and Creature Counting subtests, performance was judged by age-standardized scores of accuracy (M = 10, SD = 3). For the Sky Search Dual Task, performance was determined by the average of (proportion of visual targets correctly identified plus proportion of correct auditory counting games) × 100.[16] Although there are no published norms for this scoring procedure, the range of possible values is 0 to 100, and in a study of 173 control children at 8 years of age the mean (SD) score was 80.3 (16.5).[17]

Attention-deficit/hyperactivity disorder (ADHD) symptoms were evaluated with parent and teacher versions of the Conners' ADHD/DSM-IV Scales (CADS; Psychological Corporation), which have age/sex *t*-scores (M = 50, SD = 10; higher scores indicate more problems).[18]

Executive function was assessed with the Rey Complex Figure,[19] the Fruit Stroop Task,[20] and the Behavior Rating Inventory of Executive Function (BRIEF).[21] The Rey Complex Figure assesses spatial organization. Children's copying of a complex geometrical figure was scored for accuracy (maximum score 36),[22] and strategic organization.[23] The Fruit Stroop Task assesses impulse control, with performance judged by the number of correct responses in 45 seconds. The BRIEF is completed by parents and teachers and assesses behavioral manifestations of inattention and executive function. Performance was judged by the General Executive Composite, and the Metacognition and Behavioral Regulation Indices (M = 50, SD = 10; higher scores indicate more problems).

Memory and learning was assessed with the Rey Auditory Verbal Learning Test.[24] The Rey Auditory Verbal Learning Test comprises 5 trials in which the child recalls a single list of 15 words. Performance was assessed by the number of correct words recalled in trial 1, and over all 5 trials.

Visual perception was assessed by the Visual Discrimination, Figure Ground, and Visual closure subtests of the Test of Visual-Perceptual Skills.[25] Each subtest has age-standardized scores (M = 10, SD = 3).

General behavior was assessed using the Total Difficulties score from parent and teacher reports of the Strengths and Difficulties Questionnaire (SDQ), with possible scores ranging from 0 to 40: normal 0 to 13, borderline 14 to 16, and abnormal ≥17.[26]

Health-related quality of life was measured by the parent-completed Multiattribute Health Status classification system.[27] A Health Utility Index is obtained, ranging from 1 for perfect health to 0 for death. The parent-completed Australian Authorized Adaptation of the Child Health Questionnaire[28] provided assessments of the child's psychosocial health (score 0–600) and physical health (score 0–400), with higher scores indicating better health.

The primary outcomes were survival free of any neurosensory disability, and the categorization of neurosensory disability as none, mild, moderate, or severe. Secondary outcomes were mortality; cerebral palsy; blindness or deafness; *z*-scores for height, weight, BMI, and head circumference; expiratory flows on lung function; blood pressure *z*-scores and proportions in the abnormal ranges; IQ; attention and executive function; memory and learning; visual perception; academic achievement; behavior; health service utilization and reason for use; general health; and health-related quality of life.

Statistical Analysis

Data were analyzed by using SAS software, version 9.3 (SAS Institute, Inc, Cary, NC). Normative data were used to calculate age- and sex-adjusted *z*-scores for body size[29] and blood pressure,[30] and sex- and height-adjusted *z*-scores for spirometry.[31] Primary analyses compared primary and secondary outcomes between children with and without exposure to repeat betamethasone by using generalized linear models, adjusted for potential confounders (gestational age at trial entry, antepartum hemorrhage, and preterm prelabor rupture of membranes), and clustering of children from multiple pregnancy by using generalized estimating equations. Treatment effects are presented as risk ratio (RR) for binary and mean difference for continuous outcomes, with 95% confidence intervals (CIs). Two-tailed $\alpha < 0.05$ was considered statistically significant, with no adjustment for multiple comparisons. Estimates of study power are included in the study protocol (supplemental material).

RESULTS

Participant flow is outlined in Fig 1. Of the 1146 fetuses known to be alive at randomization, the mortality rate to mid-childhood was similar between groups; repeat corticosteroids (5.5%; 31/568) compared with the placebo group (6.1%; 35/578) (RR 0.90, 95% CI 0.55 to 1.46, *P* = .67, Fig 1). Of the

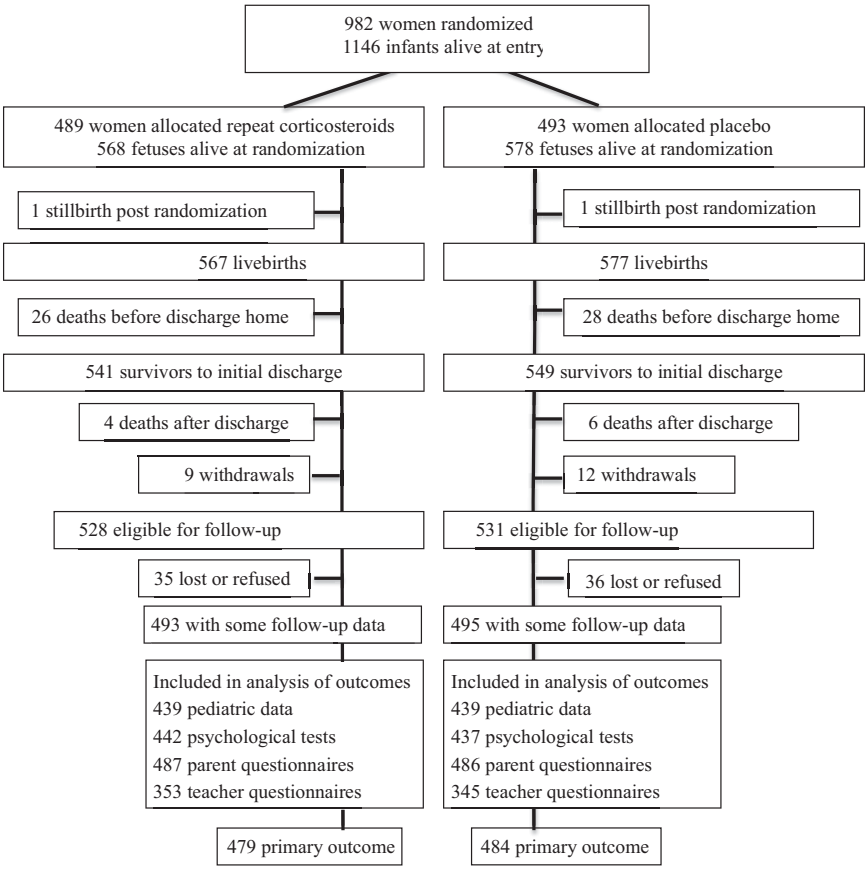

FIGURE 1
Flowchart of randomization, treatment, and mid-childhood follow-up of participants.

survivors, 21 had withdrawn from the study before this follow-up, leaving 528 in the repeat corticosteroids group, and 531 in the placebo group, about whom some data were available for 93% (n = 493) of the repeat corticosteroids group and 93% (n = 495) of the placebo group at mid-childhood. There were no substantial differences in the children eligible for follow-up between those with some data and those without any data (see the Supplemental Table 5). Of the 988 children followed, parental questionnaires were received for 98%, pediatric and psychological assessments for 89%, and teacher questionnaires for 71%, with assessment or response rates similar in the repeat corticosteroids and placebo groups.

The treatment groups were well balanced for important perinatal and sociodemographic variables (Table 1), with exceptions of higher rates of antepartum hemorrhage and lower rates of preterm prelabor rupture of the membranes in the repeat corticosteroids group compared with the placebo group. Gestational ages at initial dose of corticosteroids, at trial entry, and at birth, and ages of the children when assessed were similar for both groups (Table 1).

Primary Outcomes

The rates of survival free of neurosensory disability at 6 to 8 years did not differ significantly in repeat corticosteroid and placebo groups (78% vs 77%, RR 1.00, 95% CI 0.94 to 1.08, P = .89) (Table 2). There were no significant differences between the groups in the distribution of the severity of the neurosensory disabilities, or in any of the individual components; intellectual impairment, blindness, deafness, or cerebral palsy (Table 2). There were 66 deaths after randomization, 31 in the repeat corticosteroid group and 35 in the placebo group. The rates of combined outcomes of death or moderate disability and of death or severe disability were similar in both groups (Table 2).

Secondary Outcomes

Health Outcomes

There were no differences between the groups for body size, either as mean differences or proportions with measurements <10th percentile (Table 3).

The rates of asthma were equally high in both groups, as were the rates of requiring medication for asthma. Only 27% (185/691) of children tested could produce satisfactory expiratory flows. In those with valid data, there were no differences in expiratory flow rates between the groups (Table 3).

Mean systolic and diastolic blood pressure z-scores were not different between treatment groups, neither were the proportions of children with blood pressure in the prehypertensive range (Table 3). The rates of use of health services were also similar, with no differences in the need for readmission to hospital overall or for respiratory illnesses, or in the use of medical services (Table 3).

Functional Outcomes

There were no differences between groups in the rates of parent-assessed exercise tolerance (Table 3). Utilities and scores for the Child Health Questionnaire were similar between the treatment groups (Table 3).

Psychological Outcomes

There were no differences between the groups in Full-scale, Verbal, or Performance IQ (Table 4), or in scores for tests of attention and executive function, visual perception, or academic skills (Table 4). A small group difference (<0.2 SD) in favor of the placebo group was observed for the immediate recall of a list of 15 words, but no differences in recalling the words over 5 trials.

TABLE 1 Perinatal and Demographic Characteristics of Mothers and Children With Any Follow-up at Mid-Childhood

Variables	Repeat Steroids	Placebo
Mothers, *n*	430	426
Age at entry, y, mean (SD)	30.2 (6.0)	30.1 (5.8)
Gestation at first corticosteroids, median (25th–75th percentiles)	26.5 (24.5–28.5)	26.6 (24.6–28.5)
Gestation at entry, median (25th–75th percentiles)	28.4 (26.2–30.2)	28.4 (26.3–30.1)
Primiparous	32 (139)	32 (135)
Multiple pregnancy	16 (69)	16 (70)
Previous perinatal death	8 (35)	9 (37)
Previous preterm birth	13 (58)	16 (68)
Days from randomization to delivery, median (25th–75th percentiles)	25.5 (7.4–52.1)	23.0 (7.9–49.0)
Major reason for preterm birth		
Antepartum hemorrhage	33 (141)	26 (112)
Prelabor, preterm rupture of membranes	29 (125)	36 (152)
Preterm labor	27 (114)	24 (104)
Speak only English at home	87 (374)	87 (370)
Intact family	61 (263)	64 (274)
Socioeconomic status		
Home duties only	31 (132)	30 (129)
Lower	38 (162)	33 (142)
Higher	33 (142)	34 (144)
Doses of treatment given		
0	1 (4)	2 (7)
1	39 (169)	42 (178)
2–3	33 (143)	37 (158)
4	27 (114)	19 (83)
Infants, *n*	493	495
Gestational age at birth, completed wk, mean (SD)	32.5 (3.6)	32.4 (3.6)
Birth weight, g, mean (SD)	1917 (831)	1910 (808)
Boys	56 (275)	54 (268)
Mid-childhood follow-up		
Corrected age when assessed, y, mean (SD)	7.7 (1.1)	7.8 (1.2)

Data are % (*n*), unless otherwise specified.

TABLE 2 Primary Outcomes and Their Components at Mid-childhood

Outcomes	Repeat Steroids, *n* = 493	Placebo, *n* = 495	RR (95% CI)[a]	*P*[a]
Survival free of disability	78% (375/479)	77% (374/484)	1.00 (0.94 to 1.08)	.89
Death, *n*	31	35		
Neurosensory disability, *n*	448	449		.83[b]
Nil	84 (375)	83 (374)		
Mild	12 (54)	12 (54)		
Moderate	2 (8)	2 (9)		
Severe	2 (11)	3 (12)		
IQ, mean (SD), *n*	99.9 (16.2), 444	99.7 (15.8), 445	0.0 (–2.2 to 2.3)	.99
IQ 70 to <85	11 (48)	11 (47)	1.04 (0.69 to 1.57)	.85
IQ 55 to <70	1 (5)	0.2 (1)	5.34 (0.64 to 44.5)	.12
IQ <55	2 (7)	2 (8)	0.89 (0.33 to 2.41)	.81
Blind	0.4 (2)	0.6 (3)	0.65 (0.11 to 3.91)	.64
Deaf	1.4 (7)	1.0 (5)	1.38 (0.43 to 4.41)	.59
Cerebral palsy	4 (19/493)	4 (20/494)	0.99 (0.54 to 1.82)	.97
Death or moderate/severe disability	10 (50/479)	12 (56/484)	0.92 (0.63 to 1.33)	.64
Death or severe disability	9 (42/479)	10 (47/484)	0.91 (0.61 to 1.39)	.67

Data are % (*n*), unless otherwise specified.

[a] Adjusted for gestational age at entry, antepartum hemorrhage, prelabor, preterm rupture of membranes, and for clustering within mother.

[b] From test for linear trend over all categories.

On the parent-rated perceptions of their child's behavior, there were no differences in scores on the BRIEF or Conners Scales, or in the SDQ raw scores (Table 4). Similarly, teacher rated perceptions of behavior did not differ between groups (Table 4).

DISCUSSION

In our study, repeat corticosteroids in women at risk for very preterm birth ≥7 days after an initial course reduced serious neonatal morbidity and respiratory disease[2] without adverse effects on survival free of neurosensory disability, or on any other health or functional outcomes in mid-childhood. Given this evidence of longer-term safety, we consider that eligible women should receive repeat corticosteroids in view

TABLE 3 Health Outcomes at Mid-childhood.

Outcomes	Repeat Steroids, *n* = 493	Placebo, *n* = 495	Mean Difference/RR (95% CI)[a]	*P*[a]
Auxology				
Weight *z*-score	0.12 (1.27) 475	0.18 (1.36) 465	−0.06 (−0.24 to 0.12)	.52
Height *z*-score	0.15 (1.14) 461	0.13 (1.20) 451	0.02 (−0.15 to 0.18)	.85
BMI *z*-score	0.07 (1.27) 461	0.20 (1.29) 449	−0.14 (−0.32 to 0.04)	.14
Head circumference *z*-score	−0.49 (1.33) 442	−0.45 (1.36) 443	−0.04 (−0.24 to 0.14)	.62
Weight <10th percentile	12.2% (58/475)	13.0% (60/465)	0.96 (0.67 to 1.39)	.83
Height <10th percentile	10.6% (49/461)	11.3% (51/451)	0.94 (0.64 to 1.40)	.78
Head circumference <10th percentile	26.9% (118/442)	24.2% (107/443)	1.12 (0.89 to 1.41)	.34
Lung function				
FVC *z*-score	−0.04 (0.94) 98	0.02 (1.01) 87	−0.07 (−0.35 to 0.21)	.62
FEV_1 *z*-score	−0.92 (1.10) 98	−0.74 (1.04) 87	−0.16 (−0.46 to 0.14)	.30
FEV_1/FVC *z*-score	−1.54 (0.85) 98	−1.35 (0.88) 87	−0.15 (−0.39 to 0.12)	.23
$FEF_{25\% \text{ to } 75\%}$ *z*-score	−1.55 (1.25) 98	−1.29 (1.19) 87	−0.21 (−0.55 to 0.12)	.21
Asthma ever	35.6% (174/489)	35.3% (173/490)	0.99 (0.84 to 1.18)	.94
Breathing medication ever	29.5% (144/488)	27.8% (136/489)	1.05 (0.85 to 1.29)	.66
Blood pressure				
Systolic – *z*-score	−0.26 (0.97) 423	−0.33 (0.96) 425	−0.09 (−0.26 to 0.08)	.32
Diastolic – *z*-score	−1.14 (1.21) 423	−1.05 (1.20) 425	0.07 (−0.07 to 0.20)	.34
Systolic or diastolic >90th percentile	7.1% (30/423)	6.4% (27/425)	1.07 (0.64 to 1.80)	.79
Use of health services				
Any hospital readmission	14% (67/489)	12% (61/291)	1.09 (0.78 to 1.53)	.62
Hospital readmission for respiratory illness	2% (11/489)	3% (14/291)	0.78 (0.36 to 1.72)	.56
Any visits to doctors	78% (377/485)	76% (374/491)	1.00 (0.93 to 1.08)	.91
Functional outcomes				
No limitation with physical activities requiring lots of energy	79% (373/470)	81% (378/465)	0.98 (0.91 to 1.04)	.50
Health Utility Index	0.904 (0.128) 470	0.910 (0.129) 467	−0.006 (−0.023 to 0.011)	.46
Child Health Questionnaire, Physical score	353.5 (59.0) 468	353.7 (60.1) 465	−0.5 (−8.7 to 7.6)	.90
Child Health Questionnaire, Psychosocial score	482.1 (95.7) 465	485.0 (90.5) 463	−2.6 (−15.3 to 10.1)	.68

Data are % (*n*), number with data, or mean (SD), number with data, unless otherwise specified. From test for linear trend over all categories. FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a] Adjusted for gestational age at entry, antepartum hemorrhage, prelabor, preterm rupture of membranes, and for clustering within mother.

of the clinically important neonatal benefits.

Despite widespread use of beneficial, single-course antenatal glucocorticoids,[32] very preterm infants continue to have high neonatal morbidity. In our trial, control infants, all of whom were exposed to a single course of antenatal corticosteroids, frequently developed respiratory distress syndrome (RDS) (41%), severe lung disease (20%), and other serious complications related to preterm birth (26%).[2] Treatment with repeat dose(s) of antenatal corticosteroid substantially reduced these complications (RDS RR [95% CI] 0.82 [0.71 to 0.95]; severe lung disease 0.60 [0.46 to 0.79]; serious neonatal morbidity 0.79 [0.65 to 0.97]). Further, the absolute benefit was similar to that achieved with a single course (number needed to treat [95% CI] to prevent 1 case of RDS: 14 [8 to 50] for repeat dose(s)[2]; 12 [7 to 14] for a single course[32]). This suggests that serial antenatal corticosteroid exposure is required for maximal maturational response in the preterm fetus. By reducing the severity of neonatal morbidities, it is likely that repeat antenatal corticosteroid treatment also reduces health care costs.

Despite evidence of early benefit, repeat antenatal corticosteroids are not commonly prescribed, largely because of concern about possible longer-term adverse effects, particularly on neurologic development.[33,34] In early childhood in our trial, children exposed to repeat corticosteroids were more likely to have scores in the clinical range for attention problems at 2 years' corrected age compared with those exposed to a single course, although no other early childhood outcomes differed between groups.[9] Our results in mid-childhood show that early exposure to repeat corticosteroids does not have any adverse effect on later neurocognitive function, including attention and behavior, with 1 minor exception, suggesting that our earlier finding of an effect on attention scores may have been a type 1 error or reflected a specific developmental delay. Our data are robust, with similar scores and rates of impairment in both groups using an extensive array of assessments, including psychometric tests across multiple domains, including general cognitive ability, executive function, attention, memory and learning, visual-perceptual skills, behavior, and educational achievement. There were also no differences between groups in motor performance and rates of neuromotor impairment. By mid-childhood, cognitive assessments are highly predictive of later function,[35] unlike preschool assessment of cognitive functioning.[36] Therefore, we consider there is now strong evidence that repeat doses of antenatal

TABLE 4 Cognitive, Academic, Attention, Executive Function, and Behavioral Outcomes at Mid-childhood.

Outcome	Repeat Steroids	Placebo	Mean Difference/RR (95% CI)[a,b]	*P*[a,b]
Cognitive				
Full-scale IQ	99.9 (16.2) 444	99.7 (15.8) 445	0.0 (−2.2 to 2.3)	.99
Verbal IQ	100.3 (15.5) 440	101.2 (15.1) 438	−1.3 (−3.5 to 0.9)	.26
Performance IQ	101.5 (14.8) 438	100.4 (13.9) 437	1.0 (−1.0 to 3.1)	.34
Academic skills (WRAT-4)				
Reading	99.1 (16.6) 423	99.2 (17.9) 427	−0.2 (−2.7 to 2.4)	.91
Spelling	99.7 (15.6) 420	100.5 (16.8) 426	−0.9 (−3.4 to 1.6)	.48
Mathematics	96.8 (15.8) 419	96.5 (16.0) 426	0.1 (−2.3 to 2.4)	.97
Attention				
Selective – Sky Search	9.2 (3.1) 426	9.1 (3.3) 428	0.03 (−0.4 to 0.5)	.89
Sustained – Score!	8.7 (3.5) 422	8.8 (3.6) 408	−0.1 (−0.6 to 0.5)	.84
Shifting – Creature Counting	9.7 (3.7) 377	9.5 (3.6) 370	0.2 (−0.4 to 0.7)	.52
Divided – Sky Search Dual Task	58.9 (29) 408	59.8 (29.4) 390	−0.8 (−5.0 to 3.4)	.71
Executive function				
Rey Complex Figure				
Copy score	15.5 (7.7) 426	15.3 (7.9) 422	0.4 (−0.5 to 1.4)	.39
Organization	3.7 (1.2) 424	3.6 (1.2) 421	0.1 (−0.04 to 0.3)	.16
Fruit Stroop – Trial 4, number correct	19.5 (8.3) 413	20.8 (8.4) 416	−0.9 (−2.0 to 0.1)	.08
BRIEF – Parent				
Global Executive Composite	52.5 (13.1) 428	52.1 (12.5) 429	0.3 (−1.6 to 2.1)	.79
Metacognition Index	52.3 (13.0) 428	52.0 (12.7) 430	0.3 (−1.6 to 2.1)	.78
Behavioral Regulation Index	51.9 (12.9) 428	51.5 (12.2) 429	0.3 (−1.6 to 2.1)	.77
BRIEF – Teacher				
Global Executive Composite	53.6 (12.4) 349	55.4 (13.5) 342	−1.9 (−4.1 to 0.3)	.08
Metacognition Index	54.7 (13.4) 349	56.2 (13.9) 341	−1.6 (−3.8 to 0.6)	.14
Behavioral Regulation Index	51.7 (11.5) 351	53.6 (13.5) 343	−2.0 (−4.1 to 0.1)	.05
Memory and Learning - Rey Auditory Verbal Learning Test				
Words correct trial 1	4.5 (1.8) 428	4.8 (1.9) 429	−0.3 (−0.5 to −0.1)	.01
Words correct all trials	37.1 (11.1) 427	37.5 (11.3) 428	−0.3 (−1.8 to 1.2)	.71
Visual-Perceptual Skills				
Visual discrimination	9.0 (3.5) 424	8.6 (3.6) 428	0.3 (−0.2 to 0.8)	.24
Figure ground	10.3 (4.1) 421	10.2 (4.2) 429	0.1 (−0.5 to 0.7)	.72
Visual closure	8.7 (3.9) 421	8.5 (3.8) 428	0.3 (−0.3 to 0.8)	.36
Behavior				
CADS – Parent *t*-scores				
ADHD Index	51.1 (6.7) 432	51.5 (7.0) 435	−0.4 (−1.3 to 0.6)	.43
DSM-IV Inattentive	51.2 (7.6) 432	51.4 (7.1) 435	−0.2 (−1.3 to 0.8)	.65
DSM-IV Hyperactive-impulsive	52.0 (7.2) 432	52.6 (7.0) 435	−0.8 (−1.8 to 0.2)	.13
DSM-IV	51.6 (7.2) 432	52.1 (6.9) 435	−0.5 (−1.5 to 0.5)	.29
CADS – Teacher *t*-scores				
ADHD Index	49.4 (6.6) 351	50.5 (7.4) 345	−1.1 (−2.2 to −0.0)	.06
DSM-IV Inattentive	46.8 (5.7) 351	47.1 (5.7) 345	−0.4 (−1.3 to 0.5)	.35
DSM-IV Hyperactive-impulsive	49.4 (6.8) 351	50.1 (7.0) 345	−0.8 (−1.9 to 0.3)	.15
DSM-IV Total	49.2 (6.3) 351	49.8 (6.3) 345	−0.6 (−1.6 to 0.3)	.24
SDQ Total Difficulties				
– Parent	11.0 (6.9) 431	10.7 (6.4) 434	0.3 (−0.7 to 1.3)	.53
– Teacher	9.2 (6.7) 353	9.8 (7.2) 345	−0.7 (−1.8 to 0.4)	.22

Data are mean (SD), number with data, unless otherwise specified. DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; WRAT, Wide Range Achievement Test.

corticosteroids do not adversely affect long-term neurologic development.

Investigators from the Multiple Courses of Antenatal Corticosteroids Study (MACS) recently reported behavior and developmental outcomes for survivors at 5 years of age by using a parental questionnaire, with formal cognitive assessment completed on <20% of children.[37] They also found no differences in rates of death or severe disability between groups (repeat corticosteroids 25% [217/817]; controls 25% [201/848]; odds ratio 1.02, 95% CI 0.81 to 1.29; $P = .84$), and no differences in body size or blood pressure. They did not report on lung function, and we recognize that the inability to obtain adequate lung function data on most children assessed is a limitation of our study.

Another important concern has been whether exposure to repeat doses of corticosteroids could result in long-term perturbations of metabolic and cardiovascular function, increasing the risk of adult disease, as seen in several animal studies.[6,7] In our trial, repeat corticosteroid treatment was associated with a temporary slowing of fetal growth,[2] a potential marker of fetal programming,[38] although the

effect was small and short-lived,[2] being of similar magnitude to that seen in infants born ≥1 days after a single course of corticosteroids.[32] However, we found no evidence of altered blood pressure, body size, or general health at mid-childhood in those exposed to repeat compared with single courses of antenatal corticosteroids. Further, our in-depth side-study has reported no increase in physiologic risk factors for cardiovascular or metabolic disease at early school age.[39]

Although our trial sample was representative of women at ongoing risk of preterm birth after an initial course of corticosteroids,[40] caution is required in generalizing our results to other treatment protocols or inclusion criteria. The recent Cochrane systematic review included 9 other randomized trials of repeat antenatal corticosteroid treatment, with varying number, frequency, and dose(s) of corticosteroids.[1] Although the meta-analysis confirmed that repeat antenatal corticosteroid treatment is associated with neonatal benefits,[1] broadly similar to those seen in our trial, some heterogeneity of effect was observed, including 2 trials that showed no apparent benefit.[4,5] Until this heterogeneity is adequately explained and later childhood outcomes are reported for different treatment regimens, we recommend that the inclusion criteria and treatment schedule used in our trial be followed. An important feature of our protocol was that the risk of preterm birth was reevaluated on a weekly basis, so that most women received only 1 or 2 repeat doses.

CONCLUSIONS

We have shown that the use of repeat dose(s) of antenatal betamethasone when indicated reduces neonatal morbidity without adverse effects on survival free of neurosensory disability in mid-childhood, and no other apparent harmful or beneficial effects. For women at risk for preterm birth before 32 weeks' gestation, ≥7 days after an initial course of antenatal corticosteroids, clinicians could consider using a single injection of betamethasone, repeated weekly if risk remains.

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Members of the ACTORDS Follow-up Group who collaborated to acquire data for the 6- to 8-year follow-up study are listed as follows.

Central coordinating team University of Adelaide: Caroline Crowther, Pat Ashwood, Vincent Ball, Amy Earl, Carol Holst, Kaye Robinson, Yu Zhang.

Statistical support: Dr Kristyn Willson was the trial biostatistician and conducted the statistical analyses.

The collaborating centers where children were assessed and the participating investigators were as follows (the total number of children assessed at each center is given in parentheses).

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ABBREVIATIONS

ACTORDS: The Australasian Collaborative Trial of Repeat Doses of Corticosteroids
ADHD: attention-deficit hyperactivity disorder
BRIEF: Behavior Rating Inventory of Executive Function
CADS: Connors ADHD/DSM-IV Scales
CI: confidence interval
M: mean
RDS: respiratory distress syndrome
RR: risk ratio
SDQ: Strengths and Difficulties Questionnaire

participated in data interpretation; Dr Doyle conceptualized and designed the study, and participated in data acquisition, analyses, and interpretation; and all authors revised the manuscript and approved the final manuscript as submitted.

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