

Antenatal Corticosteroids and Outcome at 14 Years of Age in Children With Birth Weight Less Than 1501 Grams

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ABSTRACT. *Objective.* To determine whether exposure to antenatal corticosteroid therapy was associated with adverse effects on growth, sensorineural outcome, or lung function of children of birth weight <1501 g at 14 years of age.

Design. Cohort study.

Setting. The Royal Women's Hospital, Melbourne, Australia.

Subjects. One hundred fifty-four consecutive survivors born from October 1, 1980 to March 31, 1982.

Interventions. The mothers of 78 survivors (51%) had been given corticosteroids antenatally to accelerate fetal lung maturation. Treatment with antenatal corticosteroids was nonrandom. No mother received >1 course of corticosteroids.

Outcome Measures. The children were assessed at 14 years of age, corrected for prematurity. All assessors were unaware of the exposure of the child to antenatal corticosteroids. The assessments included measurements of growth and neurological, cognitive, and lung function. Growth measurements were converted into z scores (standard deviation) for the appropriate age and gender.

Results. Of the 154 survivors, 130 (84%) were assessed at 14 years of age. Overall, the children exposed to antenatal corticosteroids were significantly taller (height z score; mean difference: .39; 95% confidence interval: .001–.79) and had better cognitive functioning (Wechsler Intelligence Scale for Children-Third Edition Full Scale; IQ mean difference: 6.2; 95% confidence interval: .8–11.6) than those not exposed to corticosteroids. There were no other differences in sensorineural outcomes between the groups. Lung function was not significantly different between the groups. No conclusions were altered by adjustment for confounding variables.

Conclusions. Exposure to 1 course of antenatal corticosteroid therapy was associated with some clinically and statistically improved outcomes at 14 years of age in children of birth weight <1501 g, with no obvious adverse effects on growth or on sensorineural, cognitive, or lung function. *Pediatrics* 2000;106(1). URL: <http://www.pediatrics.org/cgi/content/full/106/1/e2>; *corticosteroids, growth, cognitive, IQ, lung function, adolescence.*

ABBREVIATIONS. BPD, bronchopulmonary dysplasia; CVH, cerebroventricular hemorrhage; SD, standard deviation; WISC-III, Wechsler Intelligence Scale for Children-Third Edition; WRAT, Wide Range Achievement Test; CI, confidence interval.

Corticosteroids given to mothers who are threatening to deliver preterm are 1 of the few perinatal interventions known from the results of randomized, controlled trials to improve the short-term outcome for the preterm infant.¹ Corticosteroids have been known for many years to have powerful biological effects, some of which could be harmful.² In humans, outcomes in early childhood of survivors from the randomized trials have been encouraging, and no major deleterious effects have been reported.^{3–7} However, it is possible that detrimental effects may still occur in later life, even into adulthood.

The aim of this study was to determine whether exposure to antenatal corticosteroid therapy was associated with adverse effects on the growth, sensorineural outcome, or lung function of children of birth weight <1501 g at 14 years of age.

METHODS

The subjects of this study comprised 154 consecutive survivors of birth weight <1501 g, born in the Royal Women's Hospital, Melbourne, Australia from October 1, 1980 to March 31, 1982. The mothers of 78 (51%) survivors had been given corticosteroids (betamethasone) antenatally to accelerate fetal lung maturation. The mother's doctor determined treatment with antenatal corticosteroid therapy, and hence, the allocation was nonrandom. No mother received >1 course of corticosteroids. Other details of perinatal care of these children have been reported.^{8,9} These children were born before exogenous surfactant was available. Bronchopulmonary dysplasia (BPD) was diagnosed in children who had required assisted ventilation in the newborn period and beyond 28 days, had respiratory distress, required oxygen therapy, and an abnormal chest radiograph consistent with Northway stage 3 or 4 BPD.^{10,11} Children had been scanned extensively for the presence of cerebrotentorial hemorrhage (CVH), as described elsewhere.¹²

Of the 154 survivors, 130 (84%) were assessed at 14 years of age, corrected for prematurity. Assessors were unaware of the child's exposure to antenatal corticosteroids. Children had a standard neurological examination, and the pediatrician administered a standardized motor test (Test of Motor Impairment¹³). Height, weight, and head circumference were measured according to standard guidelines. Growth measurements were converted into z scores (standard deviation [SD]) for the appropriate age and gender, relative to the British Growth Reference of 1990.¹⁴ Parental heights were measured, where possible, and midparental height z scores were calculated. Cognition was assessed by the Wechsler Intelligence Scale for Children-Third Edition (WISC-III),¹⁵ with the

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main scales of Full, Verbal, and Performance. In addition, other cognitive tests included the subscales of the WISC-III, the Bead Memory Test from the Stanford-Binet Intelligence Scale¹⁶ to estimate visual memory, the Complex Figure Test of Rey¹⁷ to assess visual motor, memory, and organizational skills, and the Wide Range Achievement Test (WRAT3)¹⁸ to assess academic achievement. Lung volumes and flow rates were measured according to standard guidelines, as described elsewhere,¹⁹ and results were expressed as percent predicted for the child's age, height, and gender relative to contemporary Australian children free of lung disease,²⁰ unless otherwise indicated.

Social class was determined by the occupation of the major income earner in the family and was dichotomized into higher (professional, skilled, and semiskilled) and lower (unskilled and unemployed) classes. Years of maternal schooling were dichotomized into <10 years and ≥10 years. Asthma was defined as recurrent wheezing treated with bronchodilators in the previous 12 months, and smoke exposure was assessed by asking the children about active smoking (in the absence of their parents) or by inquiring about smoking by any members of the household in which the child resided.

Data were analyzed using SPSS for Windows programs (SPSS, Chicago, IL).²¹ Continuous variables were contrasted by Student's *t* test and mean differences and 95% confidence intervals (CIs) were calculated. Skewed continuous variables were compared by Mann-Whitney *U* test. Dichotomous variables were contrasted by χ^2 analysis. Potential confounding variables were adjusted for by multiple linear regression, and adjusted mean differences and 95% CIs were calculated. For all outcomes gestational age, birth weight, birth weight *z* score, gender, and BPD were considered to be potential confounders. The other major confounding variables included in the regression analyses differed with the outcome: for growth, it was midparental height; for IQ, they were CVH, social class, and maternal education, and for lung function, they were asthma at 14 years of age and smoke exposure. For comparisons of all primary outcomes, *P* values <.05 were considered statistically significant. To allow for multiple comparisons of WISC-III subscales, *P* values <.01 were considered statistically significant. The study had 80% power to detect differences in continuous variables as small as .5 SD in continuous variables, or absolute differences of 24% if the expected rate of a dichotomous outcome was 50% or 19% if the expected rate of outcome was 10%.

RESULTS

The demographic characteristics of the 2 groups were similar, except for a shorter duration of oxygen therapy after birth in children exposed to antenatal corticosteroids (Table 1). The follow-up rates at 14 years of age were similar between the 2 groups. Of the 24 children not fully assessed by the research team at 14 years of age, 6 (1 corticosteroid group) were lost, 16 (6 corticosteroid group) refused, and 3 (2 corticosteroid group) were inaccessible. Most children assessed had entered puberty and there were no substantial differences between the 2 groups in the testicular volumes of boys or in the rates of menarche or of breast development in girls.

At 14 years of age, children exposed to antenatal corticosteroids were significantly taller, but there were no significant differences in weight or head circumference (Table 2). The major confounding variables for growth were birth weight *z* score for weight, height, and head circumference; midparental height *z* score for height; and BPD for head circumference. Adjusting for these confounding variables altered no statistical conclusions concerning antenatal corticosteroid therapy (Table 2).

No children in either group were blind or deaf. Fewer children in the corticosteroid group had cerebral palsy (5.8%; 4/69) than in the control group (9.8%; 6/61), but the difference was not statistically

TABLE 1. Demographic Characteristics

	Antenatal CS <i>n</i> = 78	No antenatal CS <i>n</i> = 76
Gestational age, wk*	29.4 (1.9)	29.3 (2.0)
Birth weight, g*	1174 (216)	1201 (211)
Birth weight <i>z</i> score*	-.72 (1.03)	-.57 (.99)
Days of assisted ventilation†	0 (0-5)	1.5 (0-5)
Days of assisted oxygen therapy†	3.5 (0-9.5)	7 (1-26)‡
Male, % (<i>n</i>)	50.0% (34)	55.3% (42)
CVH, % (<i>n</i>)	24.7% (19/77)	28.0% (21/75)
BPD, % (<i>n</i>)	10.3% (8)	15.8% (12)
Assessed at 14 y of age, % (<i>n</i>)	88.5% (69)	80.3% (61)
Higher social class, % (<i>n</i> assessed)	56.5% (39)	54.1% (33)
Mother's schooling <10 y, % (<i>n</i> assessed)	34.8% (24)	19.5% (18)
Midparental height, <i>z</i> score*	-.34 (.77)	-.40 (.91)
Smoke exposure, % (<i>n</i> assessed)	56.5% (39)	41.0% (25)
Asthma at 14 y of age, % (<i>n</i> assessed)	20.6% (14/68)	18.3% (11/60)
Males, <i>n</i> assessed	34	34
Testicular volume, right (mL)*	19.5 (6.4)	18.9 (5.8)
Testicular volume, left (mL)*	19.4 (6.7)	18.9 (5.6)
Females, <i>n</i> assessed	35	27
Menarche, % (<i>n</i> females assessed)	88.6% (31)	96.3% (26)
Breast stage 3+, % (<i>n</i> females assessed)	91.4% (32)	100.0% (27)

CS indicates corticosteroids.

* Mean (SD).

† Median (interquartile range).

‡ Statistically significant difference between groups.

significant. Fewer children in the corticosteroid group failed the Test of Motor Impairment (9.0%; 6/67) than in the control group (17.2%; 10/58), but the difference was not statistically significant.

Children exposed to antenatal corticosteroids had significantly better cognitive functioning as assessed by the WISC-III Full Scale and Performance Scale than did those not exposed to corticosteroids (Table 3). The major confounding variables for cognitive function were social class and maternal education for all 3 scales, and BPD, CVH, and birth weight *z* score for the Performance Scale only. Adjusting for these confounding variables altered no statistical conclusions concerning antenatal corticosteroid therapy (Table 3). Of the WISC-III subscales, the only significant difference was in the Coding subscale (Table 4). The children in the corticosteroid group scored higher on the Bead Memory Test, the Complex Figure of Rey, and all scales of the WRAT3, but no differences were statistically significant (Table 4).

There were no significant differences in lung function between the 2 groups (Table 5). The major confounding variables for lung function were BPD and asthma for most variables, and smoke exposure for the flow rate at 75% of vital capacity ($V'_{EMAX75\%}$). Adjusting for these confounding variables altered no statistical conclusions concerning antenatal corticosteroid therapy (data not shown).

DISCUSSION

Antenatal corticosteroids have been proved in many randomized, controlled trials to have definite

TABLE 2. Growth z Scores and Exposure to Antenatal Corticosteroid Therapy

Growth Variable	Antenatal CS <i>n</i> = 69 Mean (SD)	No Antenatal CS <i>n</i> = 61 Mean (SD)	Mean Difference (95% CI)	Adjusted Mean Difference* (95% CI)
Weight	.04 (1.13)	-.08 (1.04)	.12 (-.26, .50)	.13 (-.24, .51)
Height	-.03 (1.14)	-.42 (1.08)	.39 (.001, .79)	.36 (.01, .72)
Head circumference	-.59 (1.16)	-.62 (1.34)	.03 (-.41, .47)	.02 (-.41, .45)

CS indicates corticosteroids.

* Adjusted for statistically significant confounders.

TABLE 3. Main WISC-III Scales and Exposure to Antenatal Corticosteroid Therapy

	Antenatal CS <i>n</i> = 69 Mean (SD)	No Antenatal CS <i>n</i> = 69 Mean (SD)	Mean Difference (95% CI)	Adjusted Mean Difference* (95% CI)
WISC-III scales				
Full	98.2 (15.5)	92.0 (15.1)	6.2 (.8, 11.6)	6.3 (1.6, 11.0)
Verbal	96.4 (16.4)	91.4 (16.6)	5.0 (-.8, 10.8)	5.0 (-.1, 10.0)
Performance	100.7 (15.0)	94.4 (16.6)	6.3 (.7, 11.9)	5.5 (.6, 10.4)

CS indicates corticosteroids.

* Adjusted for confounding variables.

TABLE 4. Other Cognitive Outcomes and Exposure to Antenatal Corticosteroid Therapy

	Antenatal CS <i>n</i> = 69	No Antenatal CS <i>n</i> = 61	
WISC-III subscales			
Information	8.9 (3.1)	8.3 (2.9)	.6 (-.8, 2.0)*
Similarities	9.6 (3.5)	9.0 (3.4)	.6 (-1.0, 2.2)*
Arithmetic	9.0 (3.3)	8.4 (3.4)	.5 (-1.0, 2.1)*
Vocabulary	9.4 (3.4)	8.5 (3.2)	.9 (-.6, 2.4)*
Comprehension	9.6 (3.3)	8.6 (3.4)	.9 (-.6, 2.5)*
Digit span	10.4 (3.7)	9.2 (3.4)	1.1 (-.5, 2.8)*
Picture completion	10.4 (2.8)	9.8 (3.2)	.5 (-.9, 1.9)*
Coding	10.0 (3.6)	8.0 (3.5)	2.0 (.4, 3.7)*
Picture arrangement	9.5 (3.4)	8.5 (3.4)	1.0 (-.5, 2.6)*
Block design	10.5 (4.2)	9.6 (4.4)	1.0 (-1.0, 3.0)*
Object design	9.6 (3.1)	9.1 (3.6)	.6 (-1.0, 2.1)*
Symbol search	12.2 (4.0)	10.6 (4.0)	1.6 (-.6, 3.7)*
Bead Memory Test	95.8 (17.6)	93.2 (18.9)	2.6 (-4.4, 9.7)†
Complex Figure of Rey	34.0 (30.0,35.0)‡	33.0 (31.8,35.2)‡	
WRAT			
Reading standard score	98.4 (14.6)	94.4 (14.3)	4.0 (-1.3, 9.4)†
Spelling standard score	95.4 (16.5)	92.2 (16.2)	3.3 (-2.7, 9.3)†
Arithmetic standard score	90.4 (13.6)	87.1 (14.0)	3.3 (-1.8, 8.3)†

CS indicates corticosteroids.

Data are mean (SD), unless otherwise indicated.

* Mean difference and 99% CI.

† Mean difference and 95% CI.

‡ Median and interquartile range.

short-term advantages, with mortality reduced by nearly 40%, and lower rates of other morbidities, such as respiratory distress and CVH.¹ Despite the benefits, however, there has been concern that corticosteroids could also have harmful effects. More than 2 decades ago, Tausch² summarized the animal studies of corticosteroids, which documented diminished somatic, brain, and lung growth and poorer brain function. Despite the results from the animal studies, reports of outcome early in childhood from some of the randomized trials in humans have found little evidence for harmful effects of antenatal corticosteroids.³⁻⁷

There have been many randomized, controlled trials of antenatal corticosteroid therapy; however, there are long-term follow-up studies from only 3.³⁻⁷ MacArthur et al^{3,4} reported on the outcome at 4 and

6 years of age of a subgroup of 258 of 305 (85%) survivors in the original Auckland trial from which there were nearly 1000 survivors. Follow-up to 3 years of age was reported for only 406 of the 646 (63%) survivors from the Collaborative Study of Antenatal Steroid Therapy⁵ and to 10 to 12 years of age for 90 of the 102 (88%) survivors from a study from The Netherlands.^{6,7} Compared with the children in our study, children in the follow-up studies from these randomized, controlled trials were larger and more mature at birth, with mean birth weights well over 1500 g and mean gestational ages 31 weeks or greater. There are some similarities and some differences between our results and the follow-up studies from the randomized, controlled trials.

In our study, we found that antenatal corticosteroid therapy was associated with significantly higher

TABLE 5. Lung Function and Exposure to Antenatal Corticosteroid Therapy

Lung Function Variable	Antenatal CS <i>n</i> = 69 Mean (SD)	No Antenatal CS <i>n</i> = 61 Mean (SD)	Mean Difference (95% CI)
FEV ₁ , % pr	96.1 (14.0)	94.9 (15.0)	1.2 (-4.1, 6.5)
FVC, % pr	100.0 (12.7)	99.7 (12.3)	.4 (-4.2, 4.9)
FEV ₁ /FVC, %	84.4 (8.8)	83.5 (9.4)	.9 (-2.4, 4.2)
FEF _{25%-75%} , % pr	84.8 (26.3)	82.3 (25.5)	2.6 (-6.9, 12.0)
V' _{EMAX75%} , % pr	95.7 (20.8)	93.3 (22.9)	2.3 (-5.6, 10.3)
V' _{EMAX50%} , % pr	96.5 (28.6)	94.9 (27.9)	1.6 (-9.7, 11.9)
V' _{EMAX25%} , % pr	96.6 (38.8)	90.9 (35.1)	5.8 (-7.7, 19.3)
RV, % pr	110.7 (28.0)	123.4 (52.8)	-12.7 (-27.7, 2.3)
TLC, % pr	97.9 (11.8)	101.2 (15.4)	-3.4 (-8.3, 1.6)
RV/TLC, %	27.5 (7.3)	28.8 (8.8)	-1.2 (-4.2, 1.7)

CS indicates corticosteroids; % pr, % predicted for height, age and gender; FEV₁, forced expired volume in 1 second; FVC, forced vital capacity; FEF_{25%-75%}, forced mid-expiratory flow; V'_{EMAX75%}, flow rate at 75% of vital capacity; V'_{EMAX50%}, flow rate at 50% of vital capacity; V'_{EMAX25%}, flow rate at 25% of vital capacity; RV, residual volume; TLC, total lung capacity. No differences statistically significant.

height z scores at 14 years of age. This is consistent with some of the growth data from the randomized, controlled trials. MacArthur et al⁴ reported that girls were heavier and taller in the corticosteroid group, and the Collaborative Study of Antenatal Steroid Therapy⁵ also reported significantly higher weight and length at 3 years of age in the corticosteroid group. There were no significant differences in growth at 10 to 11 years of age in the Dutch study.⁶

The rate of cerebral palsy was lower in the corticosteroid group in our study, but the difference was not statistically significant. The trend to lower rates of cerebral palsy with corticosteroids was also observed in both the Collaborative and the Dutch studies. In the Collaborative study, 4.6% of children in the corticosteroid group had cerebral palsy at 3 years of age compared with 7.4% of controls.⁵ In the Dutch study, 4.0% of children in the corticosteroid group had cerebral palsy at 11 years of age, compared with 5.9% of controls.⁶ As in the Dutch study,⁶ we found no significant difference in motor function between our cohorts.

IQ at 14 years of age was significantly higher with antenatal corticosteroid therapy in our study. In contrast, in none of the follow-up studies from the randomized, controlled trials were there significant differences in IQ.^{3-5,7} In the Auckland study, there were several small differences on other cognitive tests that favored the control group at 6 years of age,⁴ but these were not found in the Dutch study⁷ or in our study. The size of 6 points in the WISC-III Full Scale represents a difference of .4 SD. This can be a large enough difference to ensure that more children not exposed to antenatal corticosteroid therapy have IQs < -1SD below the mean. Children in this range will have considerable difficulty coping with the more complex tasks of high school. Of the subscales of the WISC-III, only the Coding subscale was significantly different between the groups, with the corticosteroid group scoring higher. The Coding subscale assesses a child's speed of visual processing, visual motor skills, and visual memory.

We found no significant differences in lung function at 14 years of age between the corticosteroid and control groups. Lung function after 6 years of age

from a subgroup of children enrolled in the Collaborative Study of Antenatal Steroid Therapy was not significantly different between children exposed to dexamethasone and children in the placebo group.²² However, the number of children studied, 9 dexamethasone and 11 control children, was small, particularly considering there were 135 survivors from that center. Moreover, the children were more mature (mean gestational age: >34 weeks) than in our study. Smolders-de Haas et al⁶ measured respiratory function between 10 and 11 years of age of 74% (75/102) of surviving children from the Dutch study. They found no significant differences in forced vital capacity, forced expired volume in 1 second, forced vital capacity/forced expired volume in 1 second, or mid-expiratory flow between the corticosteroid or placebo groups. The results of our observational study of over 120 children with lung function in adolescence combined with the data on lung function from the randomized trials would suggest that 1 course of antenatal corticosteroid therapy may not adversely affect lung function in later life. However, possible interactions between antenatal corticosteroid therapy and environmental exposures, particularly to tobacco smoke, remain to be determined, because few children in our study acknowledged they were actively smoking.

Crowley,¹ in her meta-analysis, concluded that further follow-up studies of growth or psychomotor development were probably not warranted. This does not preclude studies of other outcomes. Moreover, because the period of follow-up from the randomized, controlled trials was relatively short and events in the uterus may affect health well into adulthood,²³ even growth and psychomotor development should be further evaluated. It seems that none of the investigators from the original randomized, controlled trials are attempting to follow their cohorts later than has already been reported. Furthermore, new placebo-controlled, randomized trials of single courses of antenatal corticosteroids are unlikely given the known benefits, especially on survival, with little evidence of harm. Our cohort study may be the next best design to a randomized, controlled trial in attempting to address issues of causation and

the impact of antenatal corticosteroid therapy on outcomes into adulthood.

We cannot conclude with certainty from our study that antenatal corticosteroids contributed to the higher IQ and height SD scores in the group so exposed because of the nonrandomization of therapy between the groups. However, because corticosteroids enhance the survival of smaller or more immature children and because outcomes such as IQ and growth vary negatively with weight or gestational age at birth, complete cohorts of survivors from the randomized, controlled trials may differ in their perinatal characteristics between those exposed and those unexposed to antenatal corticosteroids. The corticosteroid groups could be lighter or more immature at birth, as was the case in the follow-up study from Auckland,^{3,4} and hence, IQ and growth might be affected by an imbalance in these important confounding variables. This may partly explain why the randomized trials that reported IQ did not find any benefit of antenatal corticosteroid therapy.

The reason why the children in our study exposed to antenatal corticosteroids were taller and more intelligent could be the influence of better health in the first days after birth, with a lower rate or severity of respiratory distress. Alternatively, they could be examples of helpful programming in utero, ie, beneficial, rather than harmful, examples of the Barker hypothesis.²³

CONCLUSION

In summary, in our study, exposure to 1 course of antenatal corticosteroid therapy was associated with some clinically and statistically improved outcomes at 14 years of age in children of birth weight <1501 g, with no obvious adverse effects on growth, sensorineural function, cognition, or lung function. Further studies are required to determine the health outcomes into adulthood of antenatal corticosteroid therapy and also to determine possible interactions with newer therapies, such as exogenous surfactant.

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