

## ORIGINAL ARTICLE

# Long-Term Outcomes after Repeat Doses of Antenatal Corticosteroids

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## ABSTRACT

**BACKGROUND**

Previous trials have shown that repeat courses of antenatal corticosteroids improve some neonatal outcomes in preterm infants but reduce birth weight and increase the risk of intrauterine growth restriction. We report long-term follow-up results of children enrolled in a randomized trial comparing single and repeat courses of antenatal corticosteroids.

**METHODS**

Women at 23 through 31 weeks of gestation who remained pregnant 7 days after an initial course of corticosteroids were randomly assigned to weekly courses of betamethasone, consisting of 12 mg given intramuscularly and repeated once at 24 hours, or an identical-appearing placebo. We studied the children who were born after these treatments when they were between 2 and 3 years of corrected age. Prespecified outcomes included scores on the Bayley Scales of Infant Development, anthropometric measurements, and the presence of cerebral palsy.

**RESULTS**

A total of 556 infants were available for follow-up; 486 children (87.4%) underwent physical examination and 465 (83.6%) underwent Bayley testing at a mean ( $\pm$ SD) corrected age of 29.3 $\pm$ 4.6 months. There were no significant differences in Bayley results or anthropometric measurements. Six children (2.9% of pregnancies) in the repeat-corticosteroid group had cerebral palsy as compared with one child (0.5% of pregnancies) in the placebo group (relative risk, 5.7; 95% confidence interval, 0.7 to 46.7;  $P=0.12$ ).

**CONCLUSIONS**

Children who had been exposed to repeat as compared with single courses of antenatal corticosteroids did not differ significantly in physical or neurocognitive measures. Although the difference was not statistically significant, the higher rate of cerebral palsy among children who had been exposed to repeat doses of corticosteroids is of concern and warrants further study. (ClinicalTrials.gov number, NCT00015002.)

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ADMINISTRATION OF CORTICOSTEROIDS to mothers before preterm delivery significantly reduces perinatal morbidity and mortality. In 1994, the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes consensus conference sponsored by the National Institutes of Health (NIH) concluded that giving a single course of corticosteroids to pregnant women at risk for preterm delivery reduces the risk of death, respiratory distress syndrome, and intraventricular hemorrhage in their preterm infants.<sup>1</sup>

In vitro and clinical studies suggest that the effects of antenatal corticosteroids in accelerating fetal maturation may diminish as the interval after administration increases.<sup>2-4</sup> The 1994 panel noted that the optimal benefit of antenatal corticosteroid therapy lasted for 7 days, that the potential benefits and risks of repeating antenatal corticosteroid administration if 7 days had passed since the previous course were unknown, and that additional research in this area was required. Despite these caveats, the use of repeat courses of antenatal corticosteroids became widespread in the United States, the United Kingdom, and Australia.<sup>5,6</sup> In response to this practice, the NIH reconvened a consensus panel in 2000 to review critically the research on repeat courses of antenatal corticosteroid therapy.<sup>7</sup> This group concluded that there was insufficient information from studies in either humans or animals to argue for or against the use of repeat courses and recommended that repeat courses of antenatal corticosteroids should be reserved for patients enrolled in well-designed, randomized, controlled trials of sufficient power to evaluate both short-term and long-term efficacy and safety.<sup>7</sup>

The Maternal-Fetal Medicine Units (MFMU) Network of the National Institute of Child Health and Human Development (NICHD) therefore designed a randomized clinical trial to compare the outcomes of infants whose mothers were treated with weekly corticosteroids with those of infants whose mothers were treated with a single course.<sup>8</sup> We previously reported no significant benefit of repeat courses of corticosteroids, as compared with a single dose, on the primary outcome of this trial, a composite of severe respiratory distress syndrome, grade III or IV intraventricular hemorrhage, chronic lung disease, or periventricular leukomalacia. However, repeat doses did result in better neonatal lung function than did a single course, particularly among infants delivered

before 32 weeks of gestation.<sup>8</sup> This outcome included significantly less need for mechanical ventilation, continuous positive airway pressure, and surfactant use. There was also a reduction in the frequency of pneumothorax. A trial performed in Australia and New Zealand likewise demonstrated this beneficial effect, with babies exposed to repeat courses of corticosteroids having lower rates of respiratory distress syndrome or severe lung disease than babies exposed to a single dose.<sup>9</sup>

Both trials found a reduction in birth weight in infants exposed to repeat courses after adjustment for gestational age. In our earlier report,<sup>8</sup> neonates exposed to four or more corticosteroid courses were more likely to have birth weights below both the 5th and the 10th percentiles. We report here the effects of repeat courses of antenatal corticosteroids on patterns of early childhood growth and development in the children enrolled in the MFMU Network trial.

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## METHODS

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### POPULATION

The children evaluated in this study were those whose mothers were enrolled in the MFMU Network trial of single versus repeat courses of antenatal corticosteroids at the clinical centers that were still active in 2002. The details of the trial have been previously reported.<sup>8</sup> The study was approved by the institutional review boards of all participating centers. The women gave written informed consent at the time of initial enrollment in the study. Eligible women were carrying a single fetus or twins between 23 weeks 0 days and 31 weeks 6 days of gestation with intact membranes and met the study criteria for high risk of spontaneous preterm delivery. All subjects had received one course of either betamethasone (12 mg given intramuscularly and repeated once at 24 hours) or dexamethasone (6 mg given intramuscularly every 12 hours for four doses) 6 to 10 days previously. Consenting women were randomly assigned to either weekly courses of 12 mg of betamethasone given intramuscularly and repeated once at 24 hours or an identical-appearing placebo. All infants underwent a detailed evaluation at birth and ultrasound examination of the head within the first 14 days of life. If the baby was born before 33 weeks of gestation, the evaluation and ultrasound examination were repeated at discharge. For infants delivered at or beyond 33 weeks

of gestation, an ultrasound examination was performed by 14 days of age.

After 67 patients had been enrolled, repeat dosing was restricted to four study courses (for a total of five) in response to theoretical safety concerns about excessive dosing. After 495 patients had been enrolled, the data and safety monitoring committee recommended stopping the trial early. This recommendation was based on the results of the second interim analysis, which showed a tendency toward decreased birth weight in the repeat-corticosteroid group without any evident reduction in the primary composite neonatal outcome; it also took into account difficulties in recruitment and the emerging literature from cohort studies and studies in animals raising questions about the safety of repeat courses of antenatal corticosteroids. All women in the trial at the time of the decision to stop in April 2003 were allowed to complete their assigned courses. Details of this decision have been reported elsewhere.<sup>10</sup>

#### EVALUATION OF CHILDREN

The cohort of enrolled patients was contacted by study personnel at least every 3 months. The children were to return for evaluation when they were between 24 and 35 months of age, corrected for gestational age at birth, for a detailed medical history, evaluation of developmental milestones, physical and neurologic examination, and measurement of Psychomotor and Mental Developmental Index scores from the Bayley Scales of Infant Development, second edition. Centrally trained and certified study personnel, who were unaware of treatment assignment, performed the follow-up examinations using a standardized protocol. Blood pressure was measured in the arm with an aneroid sphygmomanometer with the child in a relaxed position. Health outcomes of the child were assessed by querying the mother or health care provider about specific diagnoses or events with the use of standardized criteria. The diagnosis of asthma was based on the answer to a question about the presence of chronic diseases.

Neurologic examinations were performed by pediatricians or pediatric neurologists. Bayley Psychomotor and Mental Developmental Index scores were determined by trained study psychologists or psychometrists and calculated on the basis of corrected age. The diagnosis of cerebral palsy required at least two of the following three cri-

teria: severe delay in gross motor milestones, defined as failure to walk by 17 months of corrected age; abnormality of tone or reflexes; and aberration of primitive reflexes or postural reactions. In the absence of two of these criteria, a diagnosis of spastic diplegia was made if any of the following were present bilaterally: toe walking, increased lower-extremity tone, scissoring (turning in and crossing of both legs on vertical suspension of the child), definite increase in lower-extremity reflexes, and persistent or sustained ankle clonus. Severity of impairment was classified according to criteria derived from Palisano et al.<sup>11</sup>

Children who returned for evaluation when they were between 36 and 42 months of corrected age were included and underwent both physical and Bayley assessments. Children evaluated after 42 months of corrected age had only a physical assessment. Examinations were performed between July 2002 and May 2006.

#### STATISTICAL ANALYSIS

The prespecified developmental outcome for the study was the Bayley Mental Developmental Index score. On the assumption of a mean ( $\pm$ SD) Bayley score of  $100\pm 15$ , a type I error of 5% for a two-sided test, and a power of 90%, a sample of 200 children per group would be required to detect a five-point difference in Bayley scores. Other prespecified outcomes included the Bayley Psychomotor Developmental Index score; measurements of weight, height, and head circumference; and the occurrence of cerebral palsy.

The outcomes were evaluated on an intention-to-treat basis. The chi-square test or Fisher's exact test was used for categorical variables, with the more severe outcome used for twin pairs. The Wei-Lachin procedure was used for continuous variables in consideration of the potential correlation of the results for twin pairs.<sup>12</sup> The Breslow-Day test was used to evaluate the homogeneity of odds ratios. A nominal two-sided P value of less than 0.05 was considered to indicate statistical significance; no adjustment was made for multiple comparisons.

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#### RESULTS

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The study group is illustrated in Figure 1. Of the 583 infants discharged alive, 4 died between discharge and follow-up, and 23 were not available

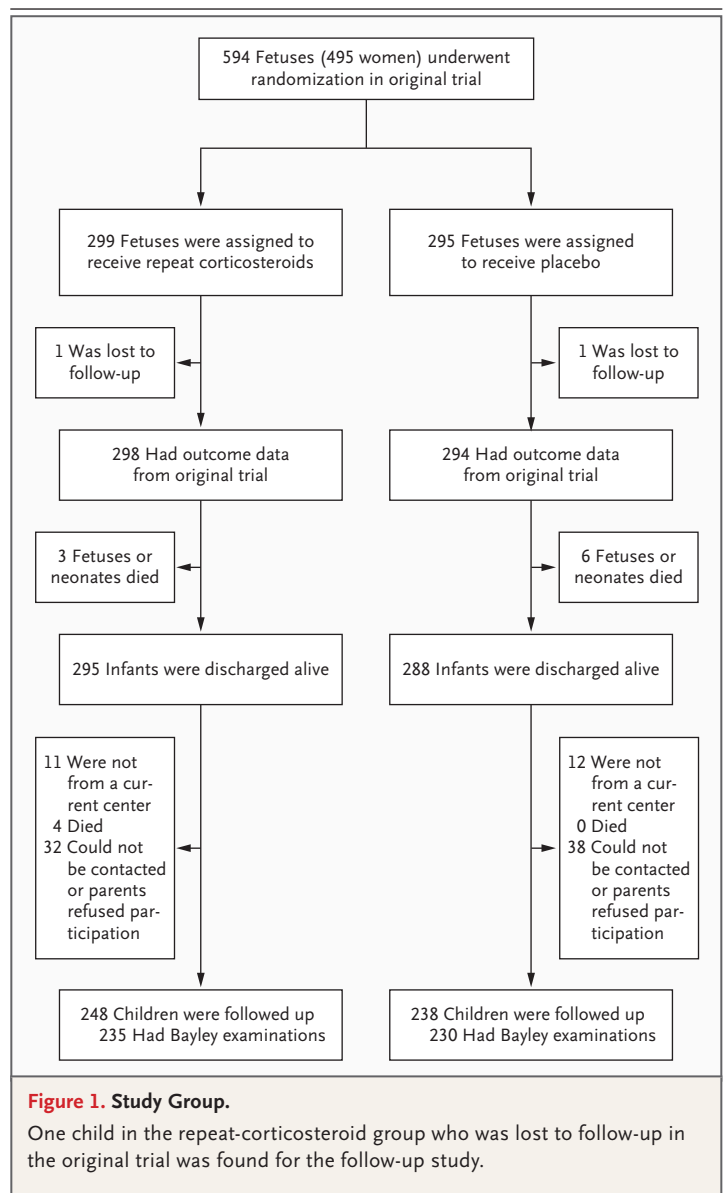
because they were born at a center that discontinued participation in the MFMU Network in 2001. Of the remaining 556 children, 486 (87.4%) underwent physical and neurologic examinations and 465 (83.6%) underwent Bayley testing. There was no significant difference in the frequency of patients lost to follow-up between the placebo group (13.8%) and the repeat-treatment group (11.4%).

Table 1 shows the demographic characteristics and birth outcomes of the follow-up cohort. There was a higher proportion of children with birth weights below the 10th percentile in the group exposed to repeat courses of antenatal corticosteroids than in the group exposed to a single course ( $P=0.048$ ). There were no other measured significant differences between the two groups.

As compared with the follow-up cohort, the group not assessed had a significantly higher proportion of black patients and significantly lower proportions of whites and Hispanics. There were no other significant differences between these groups (data not shown).

The mean ( $\pm$ SD) corrected age was  $30.0\pm 5.9$  months at the follow-up physical examination and  $29.3\pm 4.6$  months at the Bayley examination. At follow-up, there were no significant differences in mean weight, height, or head circumference between the groups (Table 2). The percentages of children with height, weight, or head circumference below the age-specific 10th percentile of published standard populations<sup>13,14</sup> were slightly higher in the repeat-treatment group than in the placebo group, but these differences were not significant. Being small for gestational age at birth (below the 10th percentile) was associated with a weight at follow-up that was below the 10th percentile; this effect was consistent between the groups.

At follow-up examination, the median Bayley scores were similar in the two groups, as were the frequencies of scores that were less than 85 and those that were less than 70 for both the mental and the psychomotor scales (Table 2). There was no significant difference in Bayley scores between children who had been exposed to more than four repeat antenatal treatments and those who had been exposed to fewer antenatal treatments (data not shown). There were no significant differences between the groups in specific health outcomes, including seizures, pneumonia, and hospitalizations. Asthma was reported somewhat less frequently in the repeat-treatment group



( $P=0.05$ ); systolic and diastolic blood pressures were similar in the two groups. Cerebral palsy was diagnosed in six infants in the repeat-treatment group (2.9%) and one infant in the placebo group (0.5%) (relative risk, 5.7; 95% confidence interval [CI], 0.7 to 46.7). Details regarding these children are presented in Table 3. Five of the six children with cerebral palsy in the repeat-treatment group had been exposed to four or more courses of study treatment (for a total of five or more courses). Of the six children with cerebral palsy in the repeat-treatment group, five were born at 34 weeks or more of gestation. The one child with

**Table 1. Demographic and Birth Characteristics of Mothers and Infants.\***

Characteristic	Repeat Corticosteroids (N=206 Pregnancies and 248 Infants)	Placebo (N=195 Pregnancies and 238 Infants)	P Value
No. of treatment courses — median (range)	4 (1–11)	4 (1–9)	0.35
Gestational age at birth — wk	34.9±3.9	35.1±3.7	0.74
Birth weight — g	2204±778	2321±768	0.08
Birth weight <10th percentile — %†	24.4	16.4	0.048
Twin pregnancy — %‡	21.4	22.6	0.77
Race or ethnic group — %§			0.99
Black	38.8	39.5	
White	34.0	33.9	
Hispanic or other	27.2	26.7	
Maternal education — yr	11.9±2.5	12.1±2.6	0.23
Intraventricular hemorrhage — %†	5.7	6.9	0.64
Respiratory distress syndrome — %†	9.8	13.3	0.26
Severe respiratory distress syndrome — %†	2.9	3.1	0.93
Chorioamnionitis — %	3.4	2.1	0.41

\* Plus–minus values are means ±SD.

† The percentage of pregnancies in which one or both infants had the characteristic is given.

‡ The numbers of infants do not include one in the placebo group and two in the repeat-corticosteroid group who died before the follow-up evaluation.

§ Race or ethnic group was self-reported. The percentages may not sum to 100 because of rounding.

cerebral palsy in the placebo group was born at 33 weeks of gestation.

## DISCUSSION

Although long-term follow-up studies have suggested that exposure in utero to a single course of antenatal corticosteroids may result in less neurodevelopmental delay and possibly fewer cases of cerebral palsy, information on the long-term effects of exposure to multiple courses has previously been limited to cohort studies.<sup>15–20</sup> We found that at approximately 30 months of corrected age, children whose mothers were assigned to repeat courses of antenatal corticosteroids and those whose mothers received a single course had similar anthropometric measurements and similar Bayley scores evaluating neurocognitive and motor development. These findings are reassuring in light of the similar results reported in this issue of the *Journal* from the trial by Crowther et al.<sup>20</sup> Despite the results of these two studies, caution is still required, since the two-year Bayley scores are only moderately correlated with developmental outcomes in school-age children.<sup>21</sup>

Our finding of an increased frequency of cere-

bral palsy in children who had been exposed to repeat courses, although not statistically significant, raises concern about potential risks of this treatment strategy. The observations that five of the six affected infants in the repeat-treatment group were born at or after 34 weeks of gestation, when cerebral palsy is less likely, and that four had normal ultrasound examinations of the head make this increased frequency even more troubling. All affected children had been exposed to a total of four or five courses, an observation that raises the possibility of a threshold or dose-response effect. However, there were no appreciable dose-related effects of antenatal corticosteroids on Bayley scores, health outcomes, or anthropometric measurements. The number of cases of cerebral palsy in the present trial was small, and data are needed from other studies to confirm an increased risk of cerebral palsy with repeat doses of antenatal corticosteroids.

Studies in both animals and neonates have suggested that repeat exposure to antenatal corticosteroids could have neurologic consequences. Randomized trials evaluating the postnatal treatment of preterm infants with dexamethasone to prevent chronic lung disease have reported an

**Table 2. Outcomes of the Children at Follow-up.\***

Outcome	Repeat Corticosteroids (N=206 Pregnancies and 248 Children)	Placebo (N=195 Pregnancies and 238 Children)	Relative Risk (95% CI)	Difference (95% CI)	P Value
Age at neurologic examination — mo	29.9±6.1	30.1±5.7		-0.2 (-1.3 to 0.9)	0.47
Hospital readmission after discharge — %†	31.6	36.4	0.9 (0.7 to 1.1)		0.30
Asthma — %†	8.3	14.4	0.6 (0.3 to 1.0)		0.05
Seizures — %†	3.4	4.6	0.7 (0.3 to 1.9)		0.53
Pneumonia after discharge — %†	12.1	13.9	0.9 (0.5 to 1.5)		0.61
Blood pressure — mm Hg					
Systolic	91.7±13.2	94.6±14.8		-2.9 (-5.5 to -0.2)	0.16
Diastolic	57.5±9.9	58.5±11.0		-1.0 (-3.0 to 0.9)	0.32
Anthropometric measurements					
Weight — kg	13.5±2.7	13.7±2.6		-0.2 (-0.7 to 0.2)	0.19
Height — cm	90.5±6.4	91.1±5.7		-0.6 (-1.7 to 0.5)	0.26
Head circumference — cm	49.0±1.9	49.1±1.8		-0.1 (-0.4 to 0.2)	0.84
Weight percentile‡	49.5±31.8	54.1±33.1		-4.6 (-10.4 to 1.2)	0.16
Height percentile‡	48.6±30.5	52.3±29.2		-3.8 (-9.1 to 1.6)	0.24
Head circumference percentile‡	51.2±32.6	51.7±31.6		-0.5 (-6.2 to 5.3)	0.79
Weight <10th percentile — %‡	13.7	12.0	1.1 (0.7 to 1.9)		0.62
Height <10th percentile — %‡	11.7	7.3	1.6 (0.9 to 3.0)		0.14
Head circumference <10th percentile — %‡	19.5	14.0	1.4 (0.9 to 2.2)		0.14
Bayley PDI score — median (range)	99.0 (<50 to 138)	96.0 (<50 to 133)		2 (-1 to 5)	0.32
Bayley PDI score <85 — %†	24.9	28.5	0.9 (0.6 to 1.2)		0.43
Bayley PDI score <70 — %†	12.4	11.8	1.1 (0.6 to 1.8)		0.86
Bayley MDI score — median (range)	88.0 (<50 to 125)	87.0 (<50 to 126)		0 (-3 to 4)	0.87
Bayley MDI score <85 — %†	43.0	44.9	1.0 (0.8 to 1.2)		0.71
Bayley MDI score <70 — %†	18.7	16.0	1.2 (0.7 to 1.8)		0.50
Cerebral palsy — no./total no. (%) †	6/206 (2.9)	1/195 (0.5)	5.7 (0.7 to 46.7)		0.12
Cerebral palsy in pregnancies with ≥4 treatment courses — no./total no. (%) †	5/139 (3.6)	1/124 (0.8)	4.5 (0.5 to 37.7)		0.22
Cerebral palsy or death in pregnancies with ≥4 treatment courses — no./total no. (%) †	9/161 (5.6)	2/143 (1.4)	4.0 (0.9 to 18.2)		0.05

\* Plus-minus values are means ±SD. All medical conditions were assessed by parental report to the examining physician or by the physician's observation. Except for asthma, specific definitions for the conditions were used to verify the parental responses. MDI denotes Mental Developmental Index, and PDI Psychomotor Developmental Index.

† The percentage of pregnancies in which one or both children had the outcome is given.

‡ Percentiles are derived from published standard populations.<sup>13,14</sup>

increased risk of cerebral palsy in exposed infants; one study, for example, reported an odds ratio for cerebral palsy of 4.6 (95% CI, 2.4 to 9.0) associated with postnatal corticosteroid treatment.<sup>22</sup> As in our study, most of those children who had cerebral palsy had normal head-imaging results. Other studies have shown a similar effect of postnatal corticosteroids,<sup>23-25</sup> demonstrat-

ing the potential vulnerability of the preterm brain to high doses of corticosteroids. However, caution is warranted in extrapolating from studies of postnatal corticosteroid exposure. The corticosteroid levels in these studies were higher and the period of exposure was longer than in studies of antenatal exposure; moreover, these studies used dexamethasone, which may have different

**Table 3.** Details of the Seven Children with a Diagnosis of Cerebral Palsy.\*

Treatment Group and Child	Gestational Age at Birth wk	Birth Weight g	Medical Complications	Severity of Cerebral Palsy	Type of Cerebral Palsy	No. of Courses of Study Treatment	Small for Gestational Age†	Twin	Neonatal Ultrasound Examination of the Head
<b>Repeat corticosteroids</b>									
1	38.7	3200	None	Mild	Diplegic	4	No	No	Normal
2	36.4	1600	None	Mild	Diplegic	4	Yes	Yes	Normal
3	35.9	2200	None	Mild	Unclassified	4	No	Yes	Normal
4	34.6	2400	Respiratory distress	Mild	Diplegic	3	No	No	Normal
5	34.1	1610	Perinatal stroke	Mild	Hemiplegic	4	Yes	No	Slit ventricles
6	30.9	1149	Respiratory distress and IVH	Mild	Hemiplegic	4	No	Yes	Grade I IVH
<b>Placebo</b>									
1	33.3	1985	Respiratory distress	Severe	Quadriplegic	4	No	No	Normal

\* IVH denotes intraventricular hemorrhage.

† An infant with a birth weight below the 10th percentile was considered small for gestational age.

effects from those of the betamethasone used in studies of antenatal exposure.

Studies in animals have also demonstrated detrimental effects of repeat courses of antenatal corticosteroids on neural development. Studies in sheep have shown decreased brain size,<sup>26-28</sup> altered nerve growth, a delayed rate of myelination,<sup>29,30</sup> and altered retinal development.<sup>31</sup> Similarly, studies in monkeys have found that multiple courses are associated with both a decrease in the number of neurons and a dose-dependent degeneration of neurons in the hippocampus.<sup>32</sup> Studies in small animals may be less representative of the effect of steroids in humans but have also raised concerns.<sup>33</sup>

The anthropometric measurements of children who had been exposed to weekly courses of antenatal corticosteroids were similar to those of children who had been exposed to only a single course. Despite growth differences seen in the neonatal period,<sup>8</sup> there were no significant differences between the groups in average weight, head circumference, or height on follow-up examination. More children in the repeat-treatment group than in the single-treatment (placebo) group had anthropometric measurements below the 10th percentile, but the differences between the groups were not statistically significant; further evaluation is warranted in future studies.

Although studies in animals have suggested that in utero exposure to corticosteroids may result in a tendency to hypertension,<sup>34</sup> we did not find significant differences between the groups in blood pressure at 2 to 3 years of corrected age. We did observe a lower frequency of asthma in the children who had been exposed to repeat courses, although the difference was not statistically significant; such an effect would be plausible, since infants who had been exposed to repeat courses had less severe lung disease in the neonatal period. However, we did not validate reported diagnoses of asthma by review of medical records or other testing, and misclassification is possible.

Although repeat dosing of antenatal corticosteroids may improve the neonatal condition after preterm birth, the present findings indicate no evident long-term benefit and possible harm. These data argue against the weekly administration of antenatal corticosteroids after a single course in women who are at risk for preterm delivery.

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#### APPENDIX

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