Original Investigation | COMPARATIVE EFFECTIVENESS RESEARCH

Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study
Outcomes in Children at 5 Years of Age (MACS-5)

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IMPORTANCE A single course of antenatal corticosteroid therapy is recommended for pregnant women at risk of preterm birth between 24 and 33 weeks' gestational age. However, 50% of women remain pregnant 7 to 14 days later, leading to the question of whether additional courses should be given to women remaining at risk for preterm birth. The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) was an international randomized clinical trial that compared multiple courses of antenatal corticosteroids with a single course in women at risk of preterm birth.

OBJECTIVE To determine the effects of single vs multiple courses of antenatal corticosteroid therapy on death or neurodevelopmental disability (neuromotor, neurosensory, or neurocognitive/neurobehavioral function) at 5 years of age in children whose mothers participated in MACS. Our secondary aims were to determine the effect on height, weight, head circumference, blood pressure, intelligence, and specific cognitive (visual, spatial, and language) skills.

DESIGN, SETTING, AND PARTICIPANTS Cohort follow-up study of children seen between June 2006 and May 2012 at 55 centers. In total, 1724 women (2141 children) were eligible for the study, of whom 1728 children (80.7% of the 2141 eligible children) participated and 1719 children contributed to the primary outcome.

INTERVENTION Single and multiple courses of antenatal corticosteroid therapy.

MAIN OUTCOMES AND MEASURES The primary outcome was death or survival with a neurodevelopmental disability in 1 of the following domains: neuromotor (nonambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual/hearing aids), or neurocognitive/neurobehavioral function (abnormal attention, memory, or behavior).

RESULTS There was no significant difference between the groups in the risk of death or neurodevelopmental disability: 217 of 871 children (24.9%) in the multiple-courses group vs 210 of 848 children (24.8%) in the single-course group (odds ratio, 1.02 [95% CI, 0.81 to 1.29]; P = .84).

CONCLUSIONS AND RELEVANCE Multiple courses, compared with a single course, of antenatal corticosteroid therapy did not increase or decrease the risk of death or disability at 5 years of age. Because of a lack of strong conclusive evidence of short-term or long-term benefits, it remains our opinion that multiple courses not be recommended in women with ongoing risk of preterm birth.

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Preterm birth remains a significant health problem worldwide.[1,2] A single course of antenatal corticosteroid therapy is an example of a treatment that yields improved health outcomes and cost savings and is recommended for pregnant women at risk of preterm birth between 24 and 33 weeks' gestational age.[3,4] However, 50% of women remain pregnant 7 to 14 days later, leading to the question of whether additional courses should be given to women remaining at risk for preterm birth.[5] The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study (MACS) was an international, multicenter, double-masked randomized clinical trial comparing multiple courses of antenatal corticosteroids vs a single course in women at risk for preterm birth.[6] The initial results showed that infants born to women in the multiple-courses group had a similar rate of the composite outcome as infants in the single-course group.[6] However, multiple courses were associated with reduced fetal growth.[6,7] The follow-up studies of the clinical trials on multiple/repeated courses of antenatal corticosteroids reported no significant differences in the rates of death or neurodevelopmental difficulties.[8-11] One study did note a nonsignificant increase in cerebral palsy in the multiple-courses group.[10] Animal studies evaluating the effects of corticosteroids on the developing brain have shown decreased hippocampal weight and neuron number; impairment in myelination, neurologic development, retinal maturation, and axonal myelination of optic and auditory nerves; abnormal auditory function; and altered behaviors.[12-14] Long-term follow-up for these children remains critical because short-term benefits can be offset by long-term problems as was seen by long-term studies of postnatal corticosteroid treatment in preterm infants.[15] In view of this, our primary aim was to determine the effects of single vs multiple courses of antenatal corticosteroid therapy on death or neurodevelopmental disability (neuromotor, neurosensory, or neurocognitive/neurobehavioral function) at 5 years of age. Our secondary aims were to determine the effect on height, weight, head circumference, blood pressure, intelligence, and specific cognitive (visual, spatial, and language) skills.

Methods

Population

Ethics approval was obtained at all participating centers; written informed consent was obtained from a parent or guardian for each child. Women were enrolled in MACS if they were between 25 and 32 weeks' gestation, remained pregnant 14 to 21 days following an initial course of antenatal corticosteroid therapy, and continued to remain at risk of preterm birth. A total of 1858 women were enrolled. Central randomization, with stratification according to center and gestational age at enrollment, took place from April 9, 2001, to August 31, 2006. All centers were encouraged to participate and all children were considered eligible for the 5-year follow-up. The children's families, clinicians, and researchers associated with the trial remained unaware of the random assignments to the 5-year follow-up.

Intervention

Women assigned to the multiple-courses arm received 2 doses of 12 mg of betamethasone intramuscularly 24 hours apart; those assigned to the single-course arm received a similar-appearing placebo injection. The study medication was given every 2 weeks until 33 weeks of gestation or birth, whichever happened first. All children alive at 5 years of age underwent the 5-year assessment, which included a neurologic assessment to determine the presence of cerebral palsy and any hearing/visual difficulties and the completion of 2 parent questionnaires. The institutions were encouraged to contact the families of all surviving children even if no contact had been made at 18 to 24 months of age. The target date for the visit was the child's fifth chronological birthday; completing the assessments within 4 months of the target date was encouraged, but efforts to locate and assess the children continued beyond this age when necessary. The 5-year follow-up began in June 2006 and was complete by May 2012.

Primary Outcome for the 5-Year Follow-up

The primary outcome was a composite of death or survival with a neurodevelopmental disability in at least 1 of the following domains: neuromotor (nonambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual or hearing aids), or neurocognitive/neurobehavioral function (abnormal attention, memory, or behavior). These abnormalities represented a spectrum of difficulties that could be manifested as a result of interference in the developing brain or nerve involvement from potential exposure to antenatal corticosteroids. Nonambulatory cerebral palsy was present if the child had a nonprogressive motor impairment characterized by abnormal muscle tone and decreased range of movements, with a gross motor function score of 3 to 5 as defined in the Gross Motor Function Classification System.[16] Neurosensory disability was defined as blindness, deafness, or need for visual or hearing aids based on local criteria. Neurocognitive/neurobehavioral disability was defined as an abnormally elevated score (>1.5 SDs greater than the normative control sample) on either 1 of 2 parent-administered questionnaires: the Behavior Rating Inventory of Executive Function–Preschool Version and the Child Behavior Checklist-1½-5.[17,18] A child with a score more than 1.5 SDs presented with a higher chance of abnormality of attention, memory, and behavior in the domain of neurobehavioral/neurocognitive difficulties.[17,18] Personnel for the completion of the assessments and examination of the children were trained in neurodevelopmental assessments and worked in follow-up programs, developmental assessment centers, and/or treatment centers for disabilities. Permission agreements were obtained for translations and validation of the questionnaires into the 13 languages required for the study.

Secondary Outcomes for the 5-Year Follow-up

All children were assessed for growth (height, weight, and head circumference) and blood pressure. For logistical reasons, only the children in 11 Canadian centers participated in the assessments for intelligence and specific cognitive skills. The Wechsler Preschool and Primary Scale of Intelligence–Third Edition[19]

was administered to assess intelligence; the Developmental Test of Visual-Motor Integration–Fifth Edition,[20] for visual and motor abilities and integration; and the Peabody Picture Vocabulary Test-Third Edition,[21] for vocabulary knowledge development and receptive language abilities. All assessments were administered by qualified psychologists.

Statistical Analysis

We assumed the probability of death or neurodevelopmental disability in the single-course arm to be 0.14 based on previous trials of single courses of antenatal corticosteroid therapy.[22] We estimated a total sample size of 1200; with this total, we had a power of 80% to achieve statistical significance at the .05 level, 2-sided, if multiple courses reduced the probability of the outcome to 0.08.

The analysis was based on an "intention-to-treat" approach. Descriptive statistics were used to check for dissimilarity in the 2 groups.

The primary outcome was compared between treatment arms using a general linear model for a binary response with repeated measures for children from the same pregnancy. The model included the stratification variable gestational age at randomization (<28 vs ≥28 weeks). Generalized estimating equations were used to fit the model. A 2-sided level of .05 was considered significant. Odds ratios (OR) and their corresponding 95% confidence intervals were calculated. A similar model was used to compare treatment arms while controlling for preterm prelabor rupture of membranes, multiple birth, and gestational age at randomization. A supportive analysis to compare the treatment arms with respect to the 4 domains composing the primary outcome (death and neuromotor, neurosensory, and neurocognitive/neurobehavioral disability) was performed using the same approach as the composite primary outcome.

As in the other trials, one-third of the infants in MACS were born at term. Because of concerns regarding exposure to steroids in infants who had gone on to be born at term[6] and to examine the treatment effect in the absence of the risk of neonatal morbidities often noted in the preterm population,[2] we undertook a post hoc exploratory analysis comparing the treatment effect in term infants (≥37 weeks) and preterm infants (<37 weeks). The interaction between treatment group and gestational age was examined for the primary outcome and its 4 components, and the treatment effect in the 2 groups was determined, using the same models as described earlier.

The secondary outcomes of growth (height, weight, and head circumference) and blood pressure in the main sample and the measures of intelligence and cognitive skills in the Canadian subset were compared between treatment arms using a general linear model for normal response, with repeated measures for children from the same pregnancy. The model included the stratification variable gestational age at randomization. Generalized estimating equations were used to fit the model. A 2-sided nominal of 0.0125 was used to maintain an overall level of .05.

The pregnancies of those children included in the analysis of intelligence and cognitive skill were compared with those

not included with respect to the baseline variables, preterm prelabor rupture of membranes, multiple birth, and gestational age at randomization because the pregnancies used for these outcomes were from a smaller subsample of the original MACS pregnancies. The Fisher exact test was used for preterm prelabor rupture of membranes and multiple birth and t tests for gestational age. A 2-sided level of .05 was considered significant.

Results

Study Participants

Of the original 1858 women enrolled, 1724 women and their 2141 children were eligible for the present study (Figure). For the 5-year follow-up, 413 children were unable to be followed up because they could not be located or parents declined participation and 1 child lost after maternal enrollment was found, leaving 1728 children (80.7% of the 2141 eligible children and 528 greater than the estimated sample size) to contribute to the outcomes of the 5-year follow-up. The baseline maternal characteristics of the original and the 5-year cohorts were similar (Table 1). The neonatal outcomes were consistent with the results of the primary report (eTable in the Supplement). The characteristics and outcomes of those not followed up are outlined in eTable 2 and eTable 3 in the Supplement.

Of the 1728 children, 93 deaths were reported, leaving 1635 surviving children. Of the surviving children, all but 19 had adequate information to contribute to the primary outcome. Additional information was obtained and reviewed by an adjudication committee, with 10 having adequate information to contribute to the primary outcome and the remaining 9 not. In total, 1719 children contributed to the primary outcome (Figure). The median age for the 5-year assessments was 5.2 years for both groups.
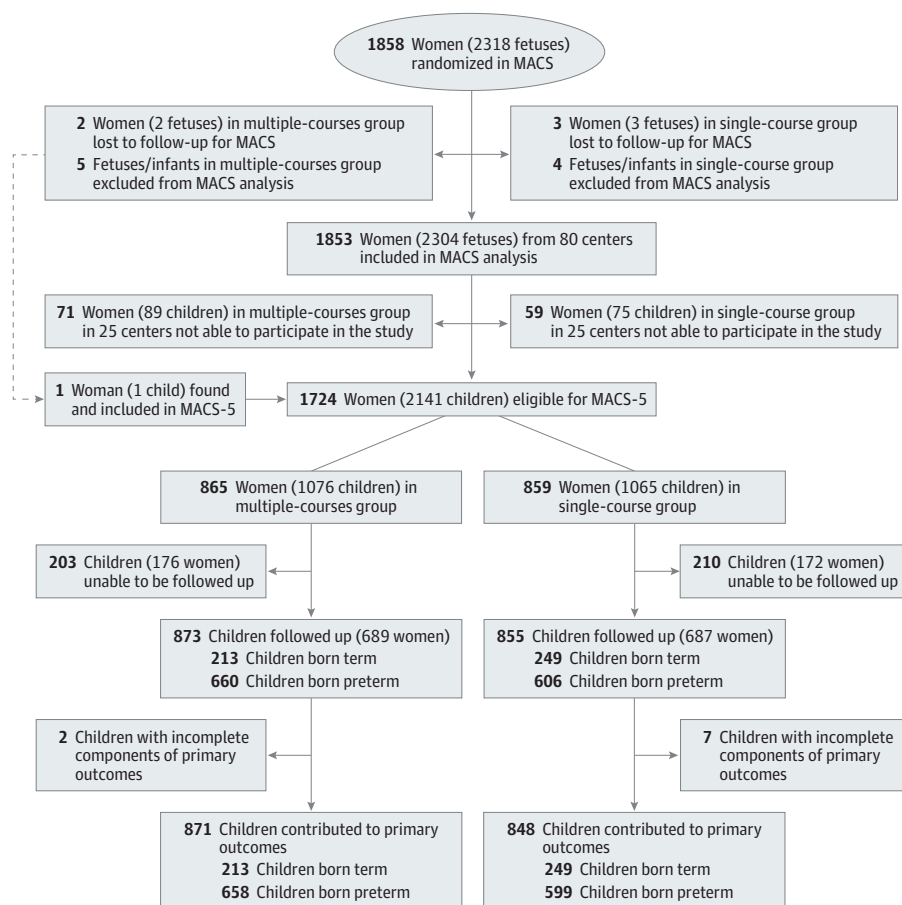
Primary Outcome

The results of the composite primary outcome and its components are shown in Table 2. There was no statistically significant difference between the treatment groups in the risk of death or neurodevelopmental disability: 217 of 871 children (24.9%) in the multiple-courses group vs 210 of the 848 children (24.8%) in the single-course group (OR, 1.02 [95% CI, 0.81 to 1.29]; P = .84).

There was no association between type of pregnancy (single vs multiple) and the primary outcome. Preterm prelabor rupture of membranes at randomization was associated with an increased risk of the primary outcome (OR, 2.31 [95% CI, 1.74 to 3.07]; P < .001). Randomization prior to 28 weeks' gestation was associated with an increase in the risk of the primary outcome (OR, 1.52 [95% CI, 1.18 to 1.95]; P = .002).

Among infants who were born at term (≥37 weeks' gestation), those randomized to the multiple courses were at increased risk of the primary outcome (OR, 1.69 [95% CI, 1.04 to 2.77]; P = .04) and increased risk of neurosensory disability (OR, 3.70 [95% CI, 1.57 to 8.75]; P = .004) (Table 3 and Table 4). There was a statistically significant interaction between treatment group and gestational age at birth for the primary outcome (P = .02) and for

Figure. Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study 5-Year Follow-up (MACS-5) Trial Profile

neurosensory disability (*P* = .005). We did not identify a dose response for the effect on neurosensory disability.

Secondary Outcomes: Growth and Other Health Outcomes

The mean weight, height, head circumference, and blood pressure for children at age 5 years in the multiple-courses group were not significantly different from those in the single-course group (**Table 5**). Similar to the primary outcome, there was a significant effect of preterm prelabor rupture of membranes at randomization on weight (mean difference, −0.51 kg [95% CI, −1.00 to −0.014]; *P* = .046) and head circumference (mean difference, −0.54 cm [95% CI, −0.85 to −0.23]; *P* = .001).

Secondary Outcomes: Intelligence and Specific Neurocognitive Abilities

In total, 460 children in 11 Canadian centers (342 women) were eligible to participate in the assessments of intelligence and specific cognitive skills. Of these, 175 (83 in the multiple-courses group and 92 in the single-course group) were unable to be followed up or declined participation and 2 children (1 in each group) could not be assessed secondary to severe disabilities, leaving 283 children (140 in the multiple-courses group and 143 in the single-course group). The findings were similar between the 2 groups (Table 5). There were only marginal effects on visual-motor abilities and integration measures (Developmental Test of Visual-Motor Integration–Fifth Edition score mean difference, −4.13 [95% CI, −8.09 to −0.17]; *P* = .05).

Discussion

The enhancement of lung maturity with antenatal corticosteroid therapy prior to preterm birth reduces neonatal mortality and morbidity and is the primary reason for the conclusion put forward by the current Cochrane systematic review that the short-term benefits of less respiratory distress support the use of multiple doses of antenatal corticosteroids for women at risk of preterm birth.[24,25] However, as with most interventions, there needs to be a balance between benefits and potential risks. To our knowledge, this is the first randomized trial to report on the 5-year follow-up of children exposed to single vs multiple courses of antenatal corticosteroids. Overall, this study found no difference in survival rates or the presence of a disability at 5 years of age. In spite of a previous report of behavioral challenges in children exposed to multiple courses of antenatal

Table 1. Characteristics at Baseline and Exposure to Study Drug for Women of the Children Participating in MACS-5

	No. (%)			
	MACS Women Followed up in Initial Trial (n = 1853)		MACS-5 Women Actually Followed up (n = 1376)	
Characteristic	Multiple-Courses Group (n = 935)	Single-Course Group (n = 918)	Multiple-Courses Group (n = 689)[a]	Single-Course Group (n = 687)
Maternal age, y, mean (SD)	29 (6.2)[b]	29 (6.2)	29 (6.2)	29 (6.2)
Multiple pregnancy	198 (21.2)	192 (20.9)	161 (23.4)	146 (21.3)
No. of fetuses				
Singleton	737 (78.8)	726 (79.1)	528 (76.6)	541 (78.8)
Twin	162 (17.3)	158 (17.2)	133 (19.3)	118 (17.2)
Triplet	36 (3.9)	34 (3.7)	28 (4.1)	28 (4.1)
Gestational age at randomization, wk, mean (SD)	29.3 (2.0)	29.4 (2.0)	29.3 (1.9)	29.4 (2.0)
Gestational age at randomization, wk				
<25	1 (0.1)	0	0	0
25-27	256 (27.4)	255 (27.8)	183 (26.6)	185 (26.9)
28-32	678 (72.5)	661 (72.0)	506 (73.4)	500 (72.8)
>32	0	2 (0.2)	0	2 (0.3)
PPROM at randomization	149 (15.9)	142 (15.5)	106 (15.4)	117 (17.0)
National perinatal mortality rate of country[c]				
≤10 per 1000	623 (66.6)	612 (66.7)	458 (66.5)	446 (64.9)
>10-20 per 1000	239 (25.6)	238 (25.9)	190 (27.6)	194 (28.2)
>20 per 1000	73 (7.8)	68 (7.4)	41 (6.0)	47 (6.8)
No. of courses of study drug				
0	5 (0.5)	5 (0.5)	3 (0.4)	3 (0.4)
1	385 (41.2)	365 (39.8)	275 (39.9)	274 (39.9)
2	305 (32.6)	273 (29.7)	230 (33.4)	207 (30.1)
3	150 (16.0)	169 (18.4)	112 (16.3)	125 (18.2)
4	90 (9.6)	104 (11.3)	69 (10.0)	77 (11.2)
Missing		2 (0.2)	1 (0.2)	
Gestational age at delivery, wk				
<28	39 (4.2)	27 (2.9)	31 (4.5)	25 (3.6)
28-32	280 (29.9)	254 (27.7)	207 (30.0)	187 (27.2)
33-36	338 (36.2)	319 (34.8)	250 (36.3)	239 (34.8)
≥37	278 (29.7)	318 (34.6)	201 (29.2)	236 (34.4)
Method of delivery				
Vaginal delivery	396 (42.4)	415 (45.2)	291 (42.2)	312 (45.4)
Cesarean section	537 (57.4)	501 (54.6)	396 (57.5)	373 (54.3)
Missing	2 (0.2)	2 (0.2)	2 (0.3)	2 (0.3)

Abbreviations: MACS-5, Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study 5-year follow-up; PPROM, preterm prelabor rupture of membranes.

[a] One case lost to follow-up was found and included at 5 years.

[b] New information available after primary results published.

[c] Countries with a national perinatal mortality rate of 10 per 1000 or less included Canada, Chile, Denmark, Germany, Hungary, Israel, the Netherlands, Poland, Spain, Switzerland, the United Kingdom, and the United States; countries with a national perinatal mortality rate of more than 10 to 20 per 1000 included Argentina, Brazil, and Peru; and countries with a national perinatal mortality rate of more than 20 per 1000 included Bolivia, China, Colombia, Jordan, and Russia.[23]

corticosteroids,[26] we did not identify differences in global behavioral or executive functioning parameters between the groups as determined by the parent-administered questionnaires. Our probability of 25% for the primary outcome in the single-course arm was higher than expected, but with 1728 children in our sample, we had an 85% power of achieving significance if the probability of the primary outcome was 6 percentage points lower in the multiple-courses arm.

In MACS, 32% of the women gave birth at term.[6] These children had an almost 1.7-fold increased odds of death or disability at 5 years of age. More specifically, these children experienced an almost 4-fold increased odds of neurosensory disability. The absence of a dose response suggested that those children exposed to 1 additional course and then born at term were just as

likely to experience the increased risk of neurosensory disability as those exposed to 4 courses of antenatal corticosteroid therapy. A possible explanation is that the term infant, unlike the preterm infant, is exposed to not only the exogenous corticosteroid treatment but also the natural endogenous surge of cortisol in late pregnancy critical for normal fetal growth and development.[27,28] The combined effects of exogenous and endogenous corticosteroid may account for the observed effect. To our knowledge, this is the first long-term follow-up study to identify a population of infants who did not benefit from this approach in care and who were shown to have an increased risk of a difficulty later in childhood. Longer follow-up of the cohort will be valuable to assess for evidence of further ongoing neurosensory and neurobehavioral function.

Table 2. Outcomes of Children at 5 Years of Age

Outcomes	No./ Total No. (%)		OR (95% CI)	P Value
	Multiple-Courses Group	Single-Course Group		
Total children followed up (N = 1728)	n = 873	n = 855		
Death or severe disability (neuromotor, neurosensory, or neurocognitive)[a]	217/871 (24.9)	210/848 (24.8)	1.02 (0.81-1.29)	.84
Death up to 5 y (n = 93)	46/873 (5.3)	47/855 (5.5)	0.94 (0.61-1.46)	.79
Stillbirth	8	10		
Death ≤28 d	32	30		
Death ≤24 mo	5	7		
Death >24 mo	1	0		
Surviving children (n = 1635)	n = 827	n = 808		
Neuromotor disability (nonambulatory cerebral palsy)[b]	4/827 (0.5)	11/808 (1.4)	0.35 (0.11-1.10)	.06
Neurosensory disability[c]	70/827 (8.5)	61/808 (7.6)	1.12 (0.77-1.63)	.55
Blindness	1 (0.1)	2 (0.3)		
Preexisting (diagnosed at ≤2 y)	1	2		
New (diagnosed >2 y)	0	0		
Needing visual aids	61 (7.4)	52 (6.4)		
Deafness	11 (1.3)	6 (0.7)		
Preexisting (diagnosed at ≤2 y)	4	4		
New (diagnosed >2 y)	7	2		
Needing amplification/hearing aids	4 (0.5)	5 (0.6)		
Neurocognitive/neurobehavioral disability	108/822 (13.1)	109/793 (13.8)	0.98 (0.73-1.33)	.91
BRIEF-P GEC score	76 (9)	75 (9)		
Mean (SE)	47.4 (0.53)	47.1 (0.49)		
CBCL/1½-5 total score	76 (9)	84 (11)		
Mean (SE)	48.3 (0.51)	48.7 (0.51)		

Abbreviations: ACS, antenatal corticosteroid; BRIEF-P, Behavior Rating Inventory of Executive Function–Preschool Version; CBCL/1½-5, Child Behavior Checklist–1½-5; GEC, global executive composite; OR, odds ratio.

[a] Clinical information of 19 cases missing/inadequate BRIEF-P and CBCL/1½-5 scores were reviewed by an adjudication committee (10 cases were adjudicated to contribute to analysis and primary outcome; 9 had insufficient information).

[b] Nonambulatory cerebral palsy was defined as Gross Motor Function Classification System score of 3, 4, or 5.

[c] A child could have more than 1 component of the neurosensory component.

Table 3. Treatment Comparisons (Multiple Courses vs Single Course of ACS) of Primary Outcome and Components by Gestational Age at Birth (Preterm vs Term)

Outcome (N = 1719)	OR (95% CI); P Value		P Value for Interaction[a]
	Preterm Infants (<37 wk) (n = 1257)	Term Infants (≥37 wk) (n = 462)	
Primary composite	0.87 (0.67-1.14); .32	1.69 (1.04-2.77); .04	.02
Death[b]	0.91 (0.58-1.41); .66	0.58 (0.52, 6.47); .65	.72
Neuromotor disability	No convergence	No convergence	No convergence
Neurosensory disability	0.84 (0.55-1.29); .43	3.70 (1.57-8.75); .004	.005
Neurocognitive disability	0.89 (0.62-1.28); .53	1.31 (0.75-2.29); .35	.31

Abbreviations: ACS, antenatal corticosteroid; OR, odds ratio.

[a] P value for testing hypothesis that OR for preterm infants equals OR for term infants.

[b] Covariates not included because of lack of convergence.

Table 4. Neurosensory Disability by Study Dose Received and Gestational Age at Birth 1635 Infants

	Preterm Infants (n = 1176)		Term Infants (n = 459)	
	Sample Size	No. (%) With Neurosensory Disability	Sample Size	No. (%) With Neurosensory Disability
No. of multiple courses of ACS received				
0	564[a]	55[b] (9.62)	247	7 (2.83)
1	263	31 (11.79)	49	5 (10.20)
2	194	14 (7.22)	88	5 (5.68)
3	103	5 (4.85)	39	5 (12.82)
4	52	0	35	4 (11.43)
Missing	0	0	1[c]	0

Abbreviation: ACS, antenatal corticosteroid.

[a] Three women randomized to the multiple-courses preterm group gave birth prior to receiving an additional course of ACS.

[b] One of the children from the 3 women identified in footnote a (who were randomized to the multiple-courses ACS group who went on to give birth before receiving additional courses) was identified as having a neurosensory disability.

[c] One woman was lost to follow-up during the initial trial after randomization but was found at the 5-year point and the child was assessed at 5 years of age; no maternal and neonatal study data available.

Table 5. Growth and Health Outcomes and Intelligence and Specific Neurocognitive Skills
of Children at 5 Years of Age

	Mean (SE)		Mean Difference (95% CI)	P Value
	Multiple-Courses Group	Single-Course Group		
Growth and health outcomes (n = 1635)	n = 827	n = 808		
Weight, kg	19.3 (0.15)	19.5 (0.15)	−0.21 (−0.60 to 0.17)	.28
Height, cm	110.7 (0.26)	111.1 (0.25)	−0.40 (−1.04 to 0.25)	.23
Head circumference, cm	51.1 (0.09)	51.2 (0.10)	−0.06 (−0.30 to 0.18)	.65
Blood pressure, mm Hg				
Systolic	98.5 (0.49)	98.2 (0.49)	0.30 (−0.95 to −1.55)	.64
Diastolic	61.0 (0.40)	60.3 (0.44)	0.70 (−0.36 to −1.77)	.20
Intelligence and specific neurocognitive skills (n = 283)	n = 140	n = 143		
WPPSI-III FSIQ	101.8 (1.40)	100.7 (1.39)	1.03 (−2.64 to 4.69)	.58
Beery VMI	99.6 (1.31)	100.4 (1.06)	−0.78 (−3.86 to 2.29)	.62
PPVT-III	108.8 (1.24)	107.0 (1.49)	1.88 (−1.35 to 5.11)	.26

Abbreviations: Beery VMI, Beery
Developmental Test of Visual-Motor
Integration–Fifth Edition;
FSIQ, full-scale IQ; PPVT-III, Peabody
Picture Vocabulary Test–Third
Edition; WPPSI-III, Wechsler
Preschool and Primary Scale of
Intelligence–Third Edition.

There have been infant studies evaluating hearing and exposure to multiple courses of antenatal corticosteroids on preterm infants.[29,30] These studies showed no deleterious effects on hearing in small numbers of preterm infants at the time of discharge from the neonatal intensive care unit but did not include long-term follow-up to determine the status of hearing later in life. To our knowledge, there have not been any other human studies to date evaluating childhood neurosensory function (vision and/or hearing) in infants exposed to multiple courses of antenatal corticosteroids.

There are limitations to these findings. This was a post hoc analysis, and as such, its findings should be viewed with caution since the analysis was not prespecified. However, the strength of the findings is that the data came from a large randomized clinical trial and that greater than 80% of the cohort was followed up.

The adverse effects on in utero growth remain worrisome and unclear because they may represent the potential for multiple courses to be associated with harm. The developmental origins of the adult-onset disease hypothesis suggest that an association exists with reduced size in utero and later obesity and indicators of cardiovascular risk.[31,32] Exposure to certain stimuli during critical periods of prenatal and postnatal life can influence developmental pathways resulting in permanent changes in cardiovascular, metabolic, and neurologic/neurodevelopmental function, leading to increased susceptibility to chronic disease or dysfunction,[31,32] and may not manifest until later childhood, adolescence, or adulthood.[32-36] With respect to the present cohort, longer-term follow-up is needed to determine the potential associations, if any, between antenatal corticosteroid therapy and the development of chronic diseases.

Finally, children in both groups born to mothers who experienced preterm prelabor rupture of membranes had an increased risk of disability that will require further study. This highlights the importance of further research in the management of preterm prelabor rupture of membranes.

This study has a number of major strengths: (1) the rigor of the randomized trial design facilitating the comparison of the 2 groups and (2) a high follow-up rate yielding a large cohort group enabling generalizability of the findings. Weaknesses include (1) our post hoc analysis, although major confounders were controlled for, and (2) that analyses of neurobehavioral function were limited to global indices and specific neurocognitive skills in the Canadian children; effects might still exist when subscales are analyzed.

Conclusions

Multiple courses, compared with a single course, of antenatal corticosteroid therapy did not increase or decrease the risk of death or disability at 5 years of age. Because of a lack of strong conclusive evidence of short-term or long-term benefits, it remains our opinion that multiple courses should not be recommended in women with ongoing risk of preterm birth. Efforts should be made to ensure that a single course is given at the most beneficial time for the fetus rather than exposing women and their fetuses to multiple courses. The possibility of ongoing long-term harm needs further evaluation. Research in this area is needed to answer questions on late-presenting neurobehavioral function, neurosensory disabilities, and susceptibility to metabolic and cardiovascular disease. These outcomes may be equally, if not more, important to consider to justify a therapy such as multiple courses of antenatal corticosteroids.

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