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ARTICLE

Growth and Neurodevelopmental Outcomes After Early Low-Dose Hydrocortisone Treatment in Extremely Low Birth Weight Infants

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ABSTRACT

BACKGROUND. Low cortisol concentrations in premature infants have been correlated with increased severity of illness, hypotension, mortality, and development of bronchopulmonary dysplasia. A total of 360 mechanically ventilated infants with a birth weight of 500 to 999 g were enrolled in a randomized, multicenter trial of prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia. Mortality and bronchopulmonary dysplasia were decreased in the hydrocortisone-treated patients exposed to chorioamnionitis. We now report outcomes at 18 to 22 months' corrected age.

PATIENTS AND METHODS. Surviving infants were evaluated with standardized neurologic examination and Bayley Scales of Infant Development-II. Neurodevelopmental impairment was defined as a Mental Developmental Index or Psychomotor Developmental Index of <70, cerebral palsy, blindness or deafness.

RESULTS. A total of 252 (87%) of 291 survivors were evaluated. Cerebral palsy was diagnosed in 13% of hydrocortisone-treated versus 14% of placebo-treated infants. Fewer hydrocortisone-treated infants had a Mental Development Index <70, and more of the hydrocortisone-treated infants showed evidence of awareness of object permanence. Incidence of neurodevelopmental impairment was not different (39% [hydrocortisone] vs 44% [placebo]). There were no differences in physical growth measures. Chorioamnionitis-exposed infants treated with hydrocortisone were shorter and weighed less than controls but had no evidence of neurodevelopmental impairment. Among infants not exposed to chorioamnionitis, hydrocortisone-treated patients were less likely to have a Mental Development Index of <70 or to be receiving glucocorticoids at follow-up.

CONCLUSIONS. Early, low-dose hydrocortisone treatment was not associated with increased cerebral palsy. Treated infants had indicators of improved developmental outcome. Together with the short-term benefit previously reported, these data support additional studies of hydrocortisone treatment of adrenal insufficiency in extremely premature infants.

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Key Words
cerebral palsy, hydrocortisone, extremely preterm infant, developmental assessment, postnatal steroid therapy

Abbreviations
BPD— bronchopulmonary dysplasia
NDI—neurodevelopmental impairment
CP— cerebral palsy
ELBW— extremely low birth weight
MDI—Mental Development Index
PDI—Psychomotor Development Index
BRS—Behavior Rating Scale

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EXTREMELY PREMATURE INFANTS are at high risk for numerous adverse outcomes, including death, bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI).[1,2] Early dexamethasone therapy has been shown to prevent or decrease the severity of BPD in preterm infants; however, both short-term and long-term adverse effects have limited its use.[3] Specifically, dexamethasone therapy has been associated with an increase in cerebral palsy (CP) and other NDIs at follow-up.[2–4] Low cortisol values and decreased response to corticotropin stimulation in these infants have been associated with increased severity of illness, increased mortality, and subsequent development of BPD.[5–9] We developed the hypothesis that inadequate adrenal function in the face of critical illness in such infants contributes to adverse outcomes including BPD, and that prophylaxis of early adrenal insufficiency in these infants would improve survival without BPD. A pilot study supported that hypothesis[10] and led to the development of a multicenter, randomized trial of prophylaxis of early adrenal insufficiency to prevent BPD in intubated, extremely low birth weight (ELBW) infants.

This recently completed multicenter, randomized trial showed no overall improvement in survival without BPD for hydrocortisone-treated infants; however, treated infants exposed to chorioamnionitis had significantly increased survival and survival without BPD.[11] Enrollment in the study was stopped at 360 patients, approximately half the planned enrollment, because of an increase in the incidence of spontaneous gastrointestinal perforation in the hydrocortisone-treated infants, likely because of an interaction with early indomethacin therapy.[11] With the exception of the increase in gastrointestinal perforation, the hydrocortisone-treated infants did not experience any of the short-term adverse effects previously reported with early dexamethasone therapy. We are now reporting the outcomes of these infants at 18 to 22 months' adjusted age.

METHODS

Population and Study Protocol

Infants eligible for this follow-up study were surviving infants who had been enrolled in the multicenter study of low-dose hydrocortisone therapy for prophylaxis of early adrenal insufficiency.[11] Details of these methods have been previously reported. Briefly, singletons and twins between 500 and 999 g birth weight were eligible if they were mechanically ventilated via an endotracheal tube at study entry (12–48 hours of life). The study protocol was approved by institutional review boards at all participating institutions, and parental consent was obtained before enrollment. Randomization was stratified by study center and birth weight (500–749 and 750–999 g). Twins were randomized together to the same study arm. Infants received normal saline placebo or hydrocortisone sodium succinate (Solu-Cortef Plain, Amersham Pharmacia & Upjohn, Kalamazoo, MI), 1 mg/kg per day (~8–10 mg/m^2 per day), divided twice daily for 12 days, followed by 0.5 mg/kg per day for 3 days. Because the pilot study demonstrated particular benefit for infants exposed to chorioamnionitis, this group was of specific a priori interest; therefore, all placental histology was reviewed and graded by 2 central readers (Nancy Joste, MD, and Marcia Wills, MD).

Follow-up Study Procedures

At the follow-up visit, demographic and medical histories were obtained. Weight, height, and head circumference were recorded. Growth outcomes were adjusted for corrected age using *z* scores on the basis of the Centers for Disease Control and Prevention 2000 growth charts.[12] Before the follow-up phase of this study, the neurologic examiners met and agreed on a standardized neurologic examination, with specific definitions for each component. CP was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. Functional gross motor level was assessed by using a standardized 5-level classification system.[13]

Development was assessed with the Bayley Scales of Infant Development II.[14] A Mental Development Index (MDI) or Psychomotor Development Index (PDI) >2 SD below the mean (ie, <70) was defined as abnormal. For children who scored <50, a score of 49 was assigned. Behavior was assessed with the Bayley Behavior Rating Scale (BRS). Bayley mental scale items 84, 96, and 102 were predetermined as measures of object permanence to assess prefrontal cortex development. The children were asked to find a toy hidden under 1 of 2 cups, with double visual displacement used to increase the difficulty of the item. All Bayley examiners had been previously certified, and each examiner submitted a scored tape to 1 central examiner (Jean Lowe, PhD) who reviewed the tapes for consistency. Study assignment remained masked throughout the follow-up period, and no examiner was aware of the treatment assignment of any infant.

NDI was defined as at least 1 of the following: CP, MDI < 70, PDI < 70, functional deafness, or functional blindness. Functional deafness was defined as the inability to successfully complete the MDI, PDI, or BRS because of an auditory sensory impairment. Functional blindness was defined as the inability to successfully complete the MDI, PDI, or BRS because of a visual sensory impairment.

Statistical Analysis

Because of the previously reported association of dexamethasone with CP in ELBW infants, the study was powered to detect an increase of 10 percentage points

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(1-sided hypothesis test) in the outcome of CP for hydrocortisone-treated infants compared with placebo-treated infants. A sample size of 712 births (including eligible second twins, the anticipated sample size was 790 infants) was required to achieve a power of .80 to detect the 10% increase with $\alpha = .05$, assuming a survival rate of 85%, follow-up rate of ≥80%, and an incidence of CP ≤20% in the placebo group. Because study enrollment was stopped at 360 infants, statistically insignificant results must be viewed with caution because of the increased probability of a type II error.

All infants evaluated for long-term outcomes were included in an intent-to-treat analysis. Baseline characteristics, 36-week outcomes, and population characteristics at follow-up for the treatment groups were compared by using 2-sample *t* tests for continuous outcomes and χ^2 or Fisher's exact tests for categorical outcomes. Neurodevelopmental outcomes were analyzed by using analysis of covariance for continuous outcomes and logistic regression for binary outcomes. These analyses included adjustment for the stratification variables birth weight (continuous form) and center and the following baseline characteristics: gestational age, prenatal steroid use, outborn, gender, black race, and method of delivery. These maximally adjusted analyses were compared with analyses that included adjustment for only birth weight and gestational age where overfitting was a concern. Similar analyses were conducted for 36-week outcomes and population characteristics at follow-up by using analysis of covariance and logistic regression to examine the impact of stratification variables and risk factors. Unless otherwise noted, all hypotheses tests were 2-sided and used a significance level of .05.

RESULTS

A total of 360 infants were enrolled in this study at 9 study centers between November 2001 and April 2003; 294 of these remained in the study and survived to discharge (Fig 1). Of these, 3 were known to have died before follow-up, leaving 291 available for follow-up. Of these, 252 (87%) were evaluated for long-term outcomes. All baseline characteristics were similar between infants seen in follow-up and those lost to follow-up with the exception of ethnicity. A higher percentage of the children lost to follow-up were Hispanic (10 of 39 lost to follow-up were Hispanic versus 25 of 252 children seen in follow-up).

Table 1 shows the patient characteristics at study entry and outcomes at 36 weeks' postmenstrual age for those infants seen at follow-up. Hydrocortisone-treated and placebo infants were similar, with the exception of gastrointestinal perforation, as previously reported.[11] Tables 2–4 show the characteristics of these infants at the follow-up examination, presented first for the entire study population, then for patients known to have or not have chorioamnionitis on placental histologic examination. Maternal education and household income level were similar between all groups. For the overall study groups, there were no significant differences between the hydrocortisone-treated infants and those who received placebo. In the subset of infants exposed to chorioamnionitis, hydrocortisone-treated infants had significantly lower weight and height than the placebo infants. In the subset of infants not exposed to chorioamnionitis, significantly fewer hydrocortisone-treated infants were being treated with inhaled or systemic corticosteroids.

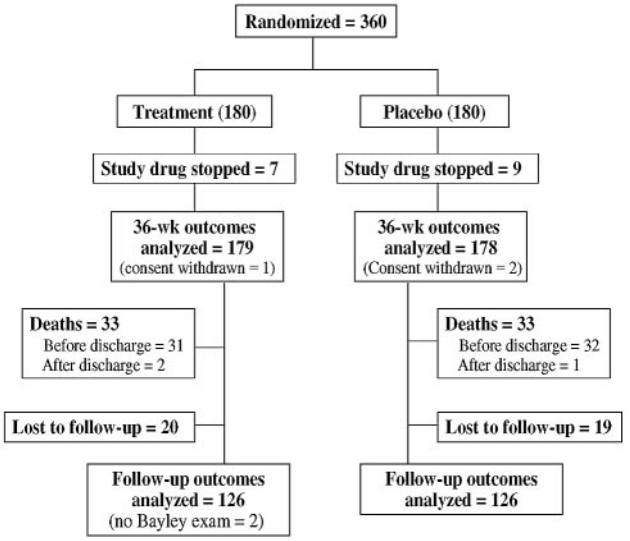

FIGURE 1
Consolidated Standards of Reporting Trials (CONSORT) diagram of patients enrolled in the study. Two infants did not have the Bayley Scales of Infant Development II completed because of parental refusal.

Tables 5–7 present the neurodevelopmental outcomes. The primary outcome variable chosen for the study, CP, was not different between groups. Comparing the overall study groups, significantly fewer hydrocortisone-treated patients had a Bayley MDI of <70 ($P = .017$), and more of the hydrocortisone-treated children showed evidence of awareness of object permanence on the Bayley examination ($P = .035$). Other measures were not significantly different between the groups, although the direction of effect favored the hydrocortisone-treated infants. For chorioamnionitis-exposed infants, there were no differences between groups, with a trend toward more independent feeding in the hydrocortisone-treated infants ($P = .056$). For infants not exposed to chorioamnionitis, fewer hydrocortisone-treated infants had a Bayley MDI of <70 ($P = .025$), and the direction of all differences favored the hydrocortisone-treated infants. There were no differences in the BRS results between groups.

Fourteen of 17 surviving infants who experienced spontaneous gastrointestinal perforation were evaluated. Because of the small size of this group, statistical comparisons would not be meaningful; however, their

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TABLE 1 **Baseline Population Characteristics and Short-term Outcomes of Patients Seen in Follow-up**

Characteristic	Hydrocortisone-Treated Group ($N = 126$)	Placebo Group ($N = 126$)
Birth weight, mean ± SD, g	738 ± 122	738 ± 124
Gestation, mean ± SD, wk	25.3 ± 1.5	25.4 ± 1.6
Head circumference (birth), mean ± SD, cm	22.8 ± 1.6	23.0 ± 1.4
Male gender, *n* (%)	68 (54)	64 (51)
Outborn, *n* (%)	17 (13)	9 (7)
Racial/ethnic group, *n* (%)		
White	68 (54)	50 (40)
Black	41 (33)	51 (40)
Hispanic	12 (10)	13 (10)
Other	5 (4)	12 (10)
Chorioamnionitis, *n*/*N* (%)	57/103 (55)	55/107 (51)
36-wk outcomes		
Weight, mean ± SD, g	2008 ± 299	2047 ± 346
Head circumference, mean ± SD, cm	31.2 ± 1.5	31.0 ± 1.5
BPD (clinical), *n* (%)	74 (59)	76 (60)
BPD (physiologic), *n*/*N* (%)	57/118 (48)	54/111 (49)
Gastrointestinal perforation, *n* (%)	13 (10)	1 (1)[a]
Grade III/IV intracranial hemorrhage, *n*/*N* (%)	17/123 (14)	13/125 (10)
Periventricular leukomalacia, *n*/*N* (%)	7/99 (7)	8/105 (8)
Surgery for retinopathy of prematurity, *n* (%)	17 (13)	17 (13)

BPD (clinical) indicates receiving supplemental oxygen at 36 weeks' postmenstrual age; BPD (physiologic), supplemental oxygen was required to maintain oxygen saturations >89% during a 4-hour observation period.

[a] Significantly different between groups: $P = .01$.

TABLE 2 **Population Characteristics at Follow-up**

Characteristic at Follow-up	Hydrocortisone-Treated Group ($N = 126$)	Placebo Group ($N = 126$)
Adjusted age, mean ± SD, mo	20.0 ± 2.1	20.0 ± 2.1
Maternal education		
High school graduate or less	49	53
Some college/trade school	41	35
At least a college degree	30	34
Unknown	4	4
Household income, median	$30 000–$40 000	$30 000–$40 000
Weight, kg	10.6 ± 2.1	10.9 ± 1.5
z score	−1.08 ± 1.4	−0.80 ± 1.3
Height, cm	80.7 ± 3.5	81.5 ± 4.0
z score	−0.67 ± 1.0	−0.42 ± 1.1
Head circumference, cm	47.1 ± 1.9	47.3 ± 1.8
z score	−0.28 ± 1.3	−0.09 ± 1.3
Current therapies		
Oxygen, *n* (%)	4 (3)	7 (6)
Bronchodilators, *n* (%)	21 (17)	29 (23)
Steroids, systemic/inhaled (total %)	2/21 (19)	3/29 (25)
Rehospitalized after discharge, *n* (%)	65 (52)	67 (53)

outcomes seemed to be similar to the remainder of the patients (eg, NDI: 43% vs 41%; weight: 10.8 vs 10.8 kg).

DISCUSSION

In this multicenter, placebo-controlled, randomized trial of early, low-dose hydrocortisone treatment for prophylaxis of early adrenal insufficiency, we found that infants treated with hydrocortisone did not have an increase in CP or other evidence of NDI at follow-up compared with the placebo group, in contrast to previously reported effects of higher-dose dexamethasone.[3,4] Although patient enrollment was stopped early, decreasing the power to detect a difference, we found no trend toward such outcomes. To the contrary, hydrocortisone-treated infants showed evidence of improved neurologic outcome, with a significantly lower incidence of Bayley MDI of <70 and better awareness of object permanence. Object permanence is considered an early measure of prefrontal cortex maturation, as well as of memory, which is a hippocampal function.[15] Interestingly, although hydrocortisone treatment improved the short-term outcomes of survival and survival without BPD only for infants exposed to chorioamnionitis,[11] the infants not exposed to chorioamnionitis seemed to derive

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TABLE 3 **Population Characteristics at Follow-up: Patients With Chorioamnionitis**

Characteristic at Follow-up	Hydrocortisone-Treated Group ($N = 57$)	Placebo Group ($N = 55$)
Adjusted age, mean ± SD, mo	19.3 ± 1.7	20.0 ± 2.0
Maternal education		
High school graduate or less	20	26
Some college/trade school	18	13
At least a college degree	16	15
Unknown	3	1
Household income, median	$30 000–$40 000	$30 000–$40 000
Weight, kg	10.4 ± 1.4	11.2 ± 1.3
z score	−1.14 ± 1.3	−0.60 ± 1.1[a]
Height, cm	80.1 ± 3.6	82.5 ± 3.9
z score	−0.71 ± 1.1	−0.20 ± 1.1[a]
Head circumference, cm	46.8 ± 1.7	47.5 ± 1.7
z score	−0.45 ± 1.1	−0.04 ± 1.3
Current therapies		
Oxygen, *n* (%)	3 (5)	5 (9)
Bronchodilators, *n* (%)	7 (12)	13 (24)
Steroids, systemic/inhaled (total %)	2/9 (19)	1/10 (20)
Rehospitalized after discharge, *n* (%)	30 (53)	28 (51)

[a] Significantly different between groups: $P < .05$.

TABLE 4 **Population Characteristics at Follow-up: Patients Without Chorioamnionitis**

Characteristic at Follow-up	Hydrocortisone-Treated Group ($N = 46$)	Placebo Group ($N = 52$)
Adjusted age, mean ± SD, mo	20.3 ± 2.3	20.1 ± 2.5
Maternal education		
High school graduate or less	18	13
Some college/trade school	15	18
At least a college degree	11	18
Unknown	0	3
Household income, median	$40 000–$50 000	$40 000–$50 000
Weight, mean ± SD, kg	10.4 ± 1.4	10.6 ± 1.6
z score	−1.25 ± 1.2	−1.04 ± 1.3
Height, cm	80.7 ± 3.3	80.9 ± 4.1
z score	−0.74 ± 1.0	−0.64 ± 1.1
Head circumference, cm	47.4 ± 1.8	47.4 ± 1.8
z score	−0.10 ± 1.3	−0.03 ± 1.3
Current therapies		
Oxygen, *n* (%)	1 (2)	2 (4)
Bronchodilators, *n* (%)	8 (18)	15 (29)
Steroids, systemic/inhaled (total %)	0/4 (9)	2/17 (37)[a]

[a] Significantly different between groups: $P = .002$.

significant benefit in neurodevelopmental and medical outcomes at 18 to 22 months' corrected age. Interpretation of these subgroup findings, although planned a priori, should be made with caution, because the numbers are small.

Few studies have investigated the use of hydrocortisone for treatment or prevention of BPD in premature infants, and even fewer have described long-term outcomes after neonatal hydrocortisone treatment. A small, retrospective cohort study comparing hydrocortisone with dexamethasone suggested that hydrocortisone may be as effective as dexamethasone in reducing BPD, with fewer immediate and long-term adverse effects.[16] Those authors subsequently reported structural and functional brain development at 8 years of age in their patients, finding that hydrocortisone-treated infants had intelligence scores and MRI findings similar to a cohort of preterm infants not treated with hydrocortisone, although the hydrocortisone-treated infants were significantly smaller, more immature, and sicker than infants not treated with postnatal glucocorticoids.[17] In contrast, infants treated with dexamethasone were reported to have adverse developmental outcomes,[4,16] as well as impaired cerebral gray matter growth on MRI.[18]

Both our findings and those of the other studies summarized above are consistent with previously described effects of cortisol and synthetic glucocorticoids in the brain. Using animal models, investigators have delineated an inverted U pattern for cortisol or corticosterone effects on the central nervous system, such that both

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TABLE 5 **Neurodevelopmental Outcomes**

Outcome	Hydrocortisone-Treated Group ($N = 126$)	Placebo Group ($N = 126$)	Odds Ratio (95% Confidence Interval) or *P*
CP, *n* (%)	16 (13)	18 (14)	0.71 (0.33–1.57)
Bayley MDI, mean ± SD	80 ± 19	77 ± 19	.08
Bayley PDI, mean ± SD	83 ± 19	84 ± 20	.82
Bayley BRS, mean ± SD	36 ± 27	36 ± 27	.76
Awareness of object permanence, %	89	79	2.19 (1.06–4.52)[a]
Bayley MDI < 70, %	27	37	0.47 (0.25–0.87)[b]
Bayley PDI < 70, %	26	23	1.03 (0.55–1.91)
NDI	39	44	0.66 (0.37–1.14)
NDI or death, *n*/*N* (%)	81/156 (52)	88/158 (56)	0.68 (0.41–1.10)
Normal functional gross motor, *n* (%)	97 (77)	93 (74)	1.36 (0.74–2.51)
Normal gait, *n* (%)	90 (71)	84 (67)	1.36 (0.75–2.44)
Independent feeding, *n* (%)	90 (73)	82 (65)	1.72 (0.96–3.08)

Odds ratios and *P*-value analyses were adjusted for stratification variables as described in the text.
Significantly different between groups:
[a] $P = .03$.
[b] $P = .017$.

TABLE 6 **Neurodevelopmental Outcomes: Patients With Chorioamnionitis**

Outcome	Hydrocortisone-Treated Group ($N = 57$)	Placebo Group ($N = 55$)	Odds Ratio (95% Confidence Interval) or *P*
CP, *n* (%)	7 (12)	7 (13)	0.94 (0.24–3.71)
Bayley MDI, mean ± SD	81 ± 19	78 ± 18	.97
Bayley PDI, mean ± SD	82 ± 19	86 ± 20	.35
Bayley BRS, mean ± SD	34 ± 25	35 ± 25	.68
Awareness of object permanence, %	90	77	2.77 (0.87–8.84)
Bayley MDI <70, %	30	31	1.09 (0.40–2.96)
Bayley PDI <70, %	30	22	1.73 (0.64–4.65)
NDI, %	40	40	1.22 (0.48–3.11)
NDI or death, *n*/*N* (%)	33/67 (49)	40/73 (55)	0.64 (0.29–1.42)
Normal functional gross motor, %	81	75	1.56 (0.53–4.61)
Normal gait, %	68	71	0.68 (0.26–1.80)
Independent feeding, %	77	60	2.57 (0.98–6.74)

Odds ratios and *P*-value analyses were adjusted for stratification variables as described in the text.

TABLE 7 **Neurodevelopmental Outcomes: Patients Without Chorioamnionitis**

Outcome	Hydrocortisone-Treated ($N = 46$)	Placebo ($N = 52$)	Odds Ratio (95% Confidence Interval) or *P*
CP, *n* (%)	6 (13)	8 (15)	0.75 (0.16–3.43)
Bayley MDI, mean ± SD	81 ± 20	77 ± 20	.33
Bayley PDI, mean ± SD	84 ± 21	82 ± 20	.49
Bayley BRS, mean ± SD	39 ± 32	36 ± 29	.93
Awareness of object permanence, %	88	81	1.75 (0.55–5.62)
Bayley MDI <70, %	24	42	0.24 (0.07–0.84)[a]
Bayley PDI <70, %	22	25	0.49 (0.12–1.99)
NDI, %	37	48	0.41 (0.14–1.24)
NDI or death, *n*/*N* (%)	28/55 (51)	32/59 (54)	0.52 (0.20–1.32)
Normal functional gross motor, %	76	71	1.76 (0.60–5.18)
Normal gait, %	76	60	1.99 (0.71–5.55)
Independent feeding, %	77	65	1.94 (0.67–5.56)

Odds ratios and *P* values analyses adjusted for stratification variables as described in text.
[a] Significant difference between groups, $P = .025$.

very low and very high concentrations are associated with adverse central nervous system effects.[19–21] Thus, although sustained excessive cortisol concentrations produce detrimental effects, particularly in the hippocampus, adrenalectomy also adversely affects structure and function.[20] Cortisol occupies both mineralocorticoid receptors and glucocorticoid receptors in the brain, binding preferentially to mineralocorticoid receptors at normal physiologic concentrations.[19] Dexamethasone, however, binds only to glucocorticoid receptors. For that reason, and also because of its limited transmission into the brain, it was postulated that dexamethasone exerts

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its adverse effects on the hippocampus by causing a "chemical adrenalectomy."[21] Consistent with that hypothesis, administration of corticosterone to adrenalectomized adult rats was protective against the apoptotic effects of dexamethasone.[22]

Although our findings that hydrocortisone did not increase the incidence of CP and instead conferred possible neurodevelopmental benefit must be confirmed in future trials, there are plausible mechanisms to explain these findings. First, the absence of neurodevelopmental harm likely resulted from the much lower dose of glucocorticoid administered; high doses of all glucocorticoids produce global growth impairment.[23,24] In addition, the hydrocortisone preparation did not contain a sulfite preservative, which has been associated with adverse neurologic effects in animal models.[25] The neurodevelopmental benefit may have resulted from improved cardiovascular function and better perfusion of the brain, and/or from direct interaction of hydrocortisone with the brain. One important such interaction is modulation of the immune response. In the rat model, corticosterone was shown to play a major role in controlling cerebral innate immunity, specifically suppressing microglial uptake of glutamate and production of tumor necrosis factor α.[26,27] Administration of a glucocorticoid receptor inhibitor in that model leads to an amplified immune response to inflammatory stimulus and results in neurotoxicity,[26] again suggesting that adrenal insufficiency is deleterious to the brain.

Similar to previous reports, the infants in this study who were exposed to chorioamnionitis had higher cortisol concentrations at study entry.[11] Other studies have also shown that premature infants exposed to chorioamnionitis have both higher cortisol concentrations and increased inflammation early in life.[10,28,29] Therefore, our finding of early benefit in regard to death and BPD in infants exposed to chorioamnionitis may have derived from the antiinflammatory effects of hydrocortisone in the lung. On the other hand, because infants not exposed to chorioamnionitis have lower cortisol concentrations in the first weeks of life, the long-term neurodevelopmental benefits seen in those infants may have derived from the effects of hydrocortisone therapy on adrenal insufficiency. Accumulating evidence supports the occurrence of relative adrenal insufficiency in very preterm infants. Lower cortisol values have been documented in infants with higher illness scores, those receiving vasopressor support, and those who die, as well as those who subsequently develop BPD.[5–9,30] In addition, infants with vasopressor-resistant hypotension typically respond to administration of hydrocortisone, and hydrocortisone is being increasingly used for this purpose in extremely preterm infants.[31,32]

In our study, we found that physical growth measures were not different in the overall study groups, but weight and length were lower in the group of hydrocortisone-treated patients exposed to chorioamnionitis compared with those in the placebo group. The reason for this is not clear, particularly because the hydrocortisone-treated children had no evidence of increased NDI, which would have been consistent with decreased physical growth, as reported for infants exposed to dexamethasone.[4] These findings may represent a survivor effect, because significantly more hydrocortisone-treated infants survived than did the placebo infants in this group.[11] Alternatively, among chorioamnionitis-exposed infants, the hydrocortisone-treated group had a mean birth weight 4% lower and head circumference 3% smaller than the placebo-treated infants at study entry, and those differences may have persisted at outcome. The finding could also be an artifact of a smaller than planned sample size.

The adverse event that caused early closure of the study, gastrointestinal perforation, seems likely to be because of an interaction with early indomethacin therapy in infants with high cortisol concentrations.[11,33–35] To help balance risk and benefit, future studies may monitor cortisol concentrations to guide therapeutic decision making for individual patients.

CONCLUSIONS

We found that low-dose hydrocortisone therapy for prophylaxis of early adrenal insufficiency did not increase the incidence of CP and seemed to confer some neurodevelopmental benefit at 18 to 22 months' corrected age in extremely preterm infants. This contrasts with dexamethasone, which has been shown to have adverse neurodevelopmental effects, prompting the American Academy of Pediatrics and the Canadian Paediatric Society to strongly caution against its use.[36] Our findings, together with the growing evidence that low cortisol concentrations in this population correlate with adverse clinical manifestations, support additional randomized, controlled studies of low-dose hydrocortisone treatment in extremely preterm infants.

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STUDY FINDS INCREASE IN BABY TEETH CAVITIES

"Tooth decay in young children's baby teeth is on the rise, according to the largest government study of the nation's dental health in more than 25 years. . . . 'Overall, we can say that most Americans are noticing an improvement in their oral health,' said the lead author, Dr Bruce Dye of the National Center for Health Statistics. The prevalence of cavities in baby teeth of children ages 2 to 5 increased to 28 percent in 1999–2004, from 24 percent in 1988–1994. Tooth decay in young children had been decreasing for 40 years. The new report contains the first statistically significant proof the trend has reversed, experts said. A reason is that parents are giving their children more processed snack foods than in the past, and more bottled water or other drinks instead of fluoridated tap water, Dr Dye said. Inadequate dental care may also play a role. Cavities in children can form quickly, and parents should begin bringing their children to the dentist at age 1, said Dr Joel Bergof of the University of Washington."

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Growth and Neurodevelopmental Outcomes After Early Low-Dose Hydrocortisone Treatment in Extremely Low Birth Weight Infants

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