

ADVERSE EFFECTS OF EARLY DEXAMETHASONE TREATMENT
IN EXTREMELY-LOW-BIRTH-WEIGHT INFANTS

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ABSTRACT

Background Early administration of high doses of dexamethasone may reduce the risk of chronic lung disease in premature infants but can cause complications. Whether moderate doses would be as effective but safer is not known.

Methods We randomly assigned 220 infants with a birth weight of 501 to 1000 g who were treated with mechanical ventilation within 12 hours after birth to receive dexamethasone or placebo with either routine ventilatory support or permissive hypercapnia. The dexamethasone was administered within 24 hours after birth at a dose of 0.15 mg per kilogram of body weight per day for three days, followed by a tapering of the dose over a period of seven days. The primary outcome was death or chronic lung disease at 36 weeks' postmenstrual age.

Results The relative risk of death or chronic lung disease in the dexamethasone-treated infants, as compared with those who received placebo, was 0.9 (95 percent confidence interval, 0.8 to 1.1). Since the effect of dexamethasone treatment did not vary according to the ventilatory approach, the two dexamethasone groups and the two placebo groups were combined. The infants in the dexamethasone group were less likely than those in the placebo group to be receiving oxygen supplementation 28 days after birth ($P=0.004$) or open-label dexamethasone ($P=0.01$), were more likely to have hypertension ($P<0.001$), and were more likely to be receiving insulin treatment for hyperglycemia ($P=0.02$). During the first 14 days, spontaneous gastrointestinal perforation occurred in a larger proportion of infants in the dexamethasone group (13 percent, vs. 4 percent in the placebo group; $P=0.02$). The dexamethasone-treated infants had a lower weight ($P=0.02$) and a smaller head circumference ($P=0.04$) at 36 weeks' postmenstrual age.

Conclusions In preterm infants, early administration of dexamethasone at a moderate dose has no effect on death or chronic lung disease and is associated with gastrointestinal perforation and decreased growth. (N Engl J Med 2001;344:95-101.)

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CHRONIC lung disease develops in approximately 30 percent of infants with a birth weight of less than 1 kg who survive the initial hospitalization.¹ Lung inflammation resulting from mechanical injury, a high oxygen concentration, or infection contributes to the development of this condition.^{2,3} Low base-line serum cortisol concentrations and poor responses to physiologic doses of corticotropin have been associated with an increased risk of chronic lung disease among infants with very low weight at birth,^{4,5} suggesting that the inflammatory response to lung injury may be exaggerated.

Data from some, though not all, clinical trials suggest that the early administration of dexamethasone (with the first dose given within 24 to 48 hours after delivery) may reduce the risk of chronic lung disease.⁶⁻¹¹ In these studies, the initial dose of dexamethasone was high (≥ 0.5 mg per kilogram of body weight per day), and many infants had adverse effects, such as hypertension or hyperglycemia. We performed a study to determine whether treatment with a moderate dose of dexamethasone would reduce the risk of chronic lung disease and have minimal adverse effects.

METHODS**Infants**

Inclusion criteria were a birth weight of 501 to 1000 g, treatment with mechanical ventilation within 12 hours after birth, and the presence of an indwelling vascular catheter. For infants whose birth weight was 751 to 1000 g, additional inclusion criteria were ventilation at a fraction of inspired oxygen of 0.3 or more and the administration of at least one dose of surfactant. We excluded infants with major congenital anomalies, congenital nonbacterial infection, findings indicating a very low likelihood of recovery (pH < 6.8 or hypoxemia with bradycardia for more than two hours), or prior

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postnatal treatment with a glucocorticoid. The study was conducted at 13 participating centers between February 1998 and February 1999. The protocol was approved by the institutional review board at each center, and written informed consent was obtained from a parent of each infant.

Randomization

In a two-by-two factorial design, we tested both dexamethasone treatment and a strategy of minimal ventilatory support (permissive hypercapnia). Infants were randomly assigned to one of four groups according to the study medication (dexamethasone or placebo) and ventilatory treatment (routine treatment with the goal of maintaining the partial pressure of carbon dioxide at a level below 48 mm Hg or minimal ventilatory support with the goal of maintaining the partial pressure of carbon dioxide at a level above 52 mm Hg)¹² with the use of a random, permuted-block algorithm. The treatment assignments were stratified according to the center and the infant's birth weight (501 to 750 g or 751 to 1000 g). All staff members except the pharmacist were unaware of the drug-group assignments, but the ventilatory-group assignments were not masked.

Study Protocol

Treatment with the study medication was initiated within 24 hours after birth. The dexamethasone-treated infants received a 10-day tapered course (0.15 mg of dexamethasone per kilogram per day for three days, followed by 0.10 mg per kilogram for three days, 0.05 mg per kilogram for two days, and 0.02 mg per kilogram for two days), with the daily dose divided in half and given at 12-hour intervals intravenously or orally, if an intravenous catheter was no longer in place. The initial dose was approximately equivalent to five times the estimated cortisol-replacement dose.¹³ The infants in the placebo groups received equal volumes of saline. During the 10-day treatment period, we discouraged the prescription of open-label glucocorticoids by the attending neonatologist, and we recorded any use of glucocorticoid therapy during hospitalization.

Outcomes

The primary outcome was the combination of death by 36 weeks' postmenstrual age or chronic lung disease (defined by a need for supplemental oxygen at least 12 hours per day) at 36 weeks' postmenstrual age. Secondary outcomes included chronic lung disease, death by 36 weeks' postmenstrual age, a need for supplemental oxygen 28 days after birth, open-label glucocorticoid treatment, the level of respiratory support (mechanical ventilation, continuous positive airway pressure, or supplemental oxygen alone) at 28 days after birth and at 36 weeks' postmenstrual age, and the duration of oxygen therapy, ventilatory support, and the hospital stay.

During the 10-day intervention period, we recorded hypertension (systolic pressure, >80 mm Hg), drug treatment for hypertension, hyperglycemia (blood glucose concentration, >180 mg per deciliter [10 mmol per liter]), insulin treatment for hyperglycemia, and evidence of upper gastrointestinal bleeding (a heme-positive gastric aspirate or emesis). We also recorded nosocomial infection, necrotizing enterocolitis, spontaneous gastrointestinal perforation, pulmonary interstitial emphysema, pneumothorax, pulmonary hemorrhage, patent ductus arteriosus, intracranial hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and growth at the time of discharge or death or at 120 days of age, if the infant remained hospitalized. Research nurses collected all study data according to defined criteria and transmitted the data to a central coordinating center.

Statistical Analysis

Using the Neonatal Research Network data base, we calculated that to determine whether treatment with dexamethasone would reduce the primary outcome from 55 percent to 44 percent (i.e., reduce the relative risk of the outcome by 20 percent), we would need a sample of 532 infants in each group. To ensure an ade-

quate number of infants to evaluate the neurodevelopmental outcome, which we expected to do at 18 months' corrected age, we planned to enroll 600 infants in each group.

We performed an intention-to-treat analysis. Base-line data for infants enrolled in the study and for eligible infants who were not enrolled were compared by t-tests for continuous variables and by chi-square tests for categorical data. Logistic regression was used to analyze differences in outcomes and complications between the treatment groups. Multiple logistic-regression analysis was used for categorical variables with more than two values (e.g., respiratory support). Initially, the analyses included dexamethasone treatment, ventilatory treatment, and an interaction term for dexamethasone and ventilatory treatment as factors. Because none of the interactions were significant, the analyses were repeated without the interaction term, and we report the resulting P values for the main effects.

RESULTS

The trial was monitored by an independent data and safety monitoring committee. The committee's initial evaluation, performed because of a high rate of unanticipated adverse events, identified frequent gastrointestinal perforations among the infants treated with dexamethasone. Because of the uncertainty involved in weighing the relative importance of potential benefits and adverse outcomes, the committee recommended continuation of the trial with a modification of the consent form to include this complication. However, the steering committee voted to terminate the trial.

Infants

During the study period, 340 infants were eligible for enrollment, and 220 were enrolled. The other 120 eligible infants were not enrolled because of a parent's refusal (55 percent), the unavailability of a parent to provide consent or failure to seek consent (41 percent), the physician's refusal (2 percent), or other, unknown reasons (2 percent). The infants who were not enrolled were similar to the enrolled infants with regard to birth weight (mean, 743 g in the group of unenrolled infants and 735 g in the enrolled group), gestational age (mean, 25.7 and 25.6 weeks, respectively), male sex (51 percent and 52 percent, respectively), vaginal delivery (42 percent in both groups), and antenatal glucocorticoid therapy (77 percent and 75 percent, respectively), but they differed in racial distribution (26 percent white vs. 41 percent, 52 percent black vs. 47 percent, and 20 percent Hispanic vs. 10 percent, respectively).

Because the effect of dexamethasone treatment did not vary according to the type of ventilatory treatment, the ventilatory-treatment groups were combined for the purpose of analysis. The base-line characteristics of the infants in the dexamethasone and placebo groups were similar (Table 1).

Outcomes

The relative risk of death or chronic lung disease at 36 weeks' postmenstrual age in the dexamethasone group was 0.9 (95 percent confidence interval, 0.8 to

TABLE 1. BASE-LINE CHARACTERISTICS OF THE INFANTS ACCORDING TO THE TREATMENT ASSIGNMENT.*

CHARACTERISTIC	DEXAMETHASONE (N=111)	PLACEBO (N=109)
Birth weight — g	734±131	736±135
Gestational age — wk	25.3±1.7	25.4±1.6
Small size for gestational age — no. (%)	25 (23)	23 (21)
Male sex — no. (%)	59 (53)	55 (50)
Race — no. (%)		
White	45 (41)	46 (42)
Black	55 (50)	48 (44)
Hispanic	10 (9)	13 (12)
Other	1 (1)	2 (2)
Vaginal delivery — no. (%)	47 (42)	46 (42)
Apgar score ≤3 — no. (%)		
At 1 min	48 (43)	42 (39)
At 5 min	7 (6)	8 (7)
Antenatal glucocorticoid therapy — no. (%)	82 (74)	82 (75)
Surfactant — no. (%)	106 (95)	105 (96)
Respiratory status before randomization		
Fraction of inspired oxygen	0.49±0.24	0.48±0.24
Mean airway pressure — cm of water	8.1±2.0	7.8±2.0
Age — hr		
At randomization	6.9±3.0	6.7±2.9
When initial dose of study drug was administered	14.2±5.8	14.3±5.9

*Plus-minus values are means ±SD. Because of rounding, percentages may not total 100.

1.1) (Table 2). The relative risk did not differ significantly between the two birth-weight groups. Mortality at 36 weeks' postmenstrual age and the rate of chronic lung disease among the infants who survived also did not differ significantly between the dexamethasone and placebo groups.

Twenty-eight days after birth, the infants in the dexamethasone group were less likely to be receiving supplemental oxygen or to have died than those in the placebo group (relative risk, 0.8) (Table 2). Although mortality at 28 days was similar in the two groups, a smaller proportion of infants in the dexamethasone group were receiving oxygen supplementation at 28 days.

The mean (±SD) proportion of doses of the study drug that were actually given was lower in the dexamethasone group (93±16 percent) than in the placebo group (98±12 percent, P=0.01), reflecting in part doses withheld because of complications potentially attributable to the study drug. Infants in the dexamethasone group were less likely than those in the placebo group to receive open-label glucocorticoid treatment during hospitalization (34 percent vs. 51 percent, P=0.01). Only one infant in the dexamethasone group received open-label glucocorticoid treatment during the 10-day intervention period, as compared with eight infants in the placebo group. Among the infants who received supplemental treatment with open-label dexamethasone, the mean duration of treatment was 25±33 days in the dexamethasone group and 27±35 days in the placebo group (P=0.82). The proportion of infants who required

TABLE 2. RELATIVE RISKS OF CHRONIC LUNG DISEASE OR DEATH AT 36 WEEKS' POSTMENSTRUAL AGE AND OF OXYGEN SUPPLEMENTATION OR DEATH 28 DAYS AFTER BIRTH.

OUTCOME	DEXAMETHASONE	PLACEBO	RELATIVE RISK (95% CI)*	P VALUE
	no./total no. (%)			
36 Weeks' postmenstrual age				
Chronic lung disease or death†				
All infants	70/111 (63)	75/109 (69)	0.9 (0.8–1.1)	0.38
Birth weight, 501–750 g	45/62 (73)	54/66 (82)	0.9 (0.7–1.1)	0.35
Birth weight, 751–1000 g	25/49 (51)	21/43 (49)	1.1 (0.7–1.6)	0.68
Chronic lung disease	47/88 (53)	49/83 (59)	0.9 (0.7–1.8)	0.47
Death	23/111 (21)	26/109 (24)	0.9 (0.5–1.4)	0.57
28 Days after birth				
Oxygen supplementation or death				
All infants	91/111 (82)	104/109 (95)	0.8 (0.8–0.9)	0.003
Birth weight, 500–750 g	59/62 (95)	65/66 (98)	1.0 (0.9–1.0)	0.36
Birth weight, 751–1000 g	32/49 (65)	39/43 (91)	0.7 (0.5–0.9)	0.007
Oxygen supplementation	71/91 (78)	82/87 (94)	0.8 (0.7–0.9)	0.004
Death	20/111 (18)	22/109 (20)	0.9 (0.5–1.5)	0.68

*The relative risk is the risk of the outcome in the dexamethasone group as compared with the placebo group. CI denotes confidence interval.

†This was the primary outcome.

mechanical ventilation, continuous positive airway pressure, or supplemental oxygen alone 28 days after birth or at 36 weeks' postmenstrual age did not differ significantly between the two study groups. Similarly, there were no significant differences between the groups in the duration of oxygen therapy or mechanical ventilation or in the median hospital stay among either infants who survived or those who did not.

Pulmonary interstitial emphysema was diagnosed less frequently in the dexamethasone group than in the placebo group (relative risk, 0.4), although the frequencies of pneumothorax, pulmonary hemorrhage, and patent ductus arteriosus did not differ significantly between the two groups (Table 3). The rates of other outcomes ascertained at death or discharge or at 120 days among hospitalized infants did not differ significantly between the dexamethasone and placebo groups (Table 3).

Complications

A higher proportion of infants in the dexamethasone group than in the placebo group had hypertension or received antihypertensive drugs (Table 4). Although the frequency of hyperglycemia was similar in the two groups, a larger proportion of infants in the dexamethasone group were treated with insulin. Upper gastrointestinal bleeding was uncommon, and the proportion of infants with this complication did not differ significantly between the two groups.

When an early increase in spontaneous intestinal perforations was noted in the dexamethasone group, additional data were obtained by reviewing medical records. During the first 14 days after birth, 14 infants in the dexamethasone group (13 percent) and 4 in the placebo group (4 percent) had spontaneous intestinal perforations without evidence of necrotizing enterocolitis (P=0.02). Three additional infants in each group had necrotizing enterocolitis with perforation. All but one of the infants with spontaneous perforation underwent laparotomy or peritoneal drain placement. The site of perforation was the small bowel in 13 infants and the stomach in 1; the site was unknown in 4 infants. During the remainder of the study period, four additional infants in the placebo group and one in the dexamethasone group had spontaneous perforations (Table 3).

Perforation appeared to be associated with indomethacin treatment within the first 24 hours (P=0.02), and the effect of dexamethasone on the perforation rate also appeared to be greater in the presence of indomethacin than in its absence (Table 5). Perforation occurred in 19 percent of infants treated with both dexamethasone and indomethacin, in 2 percent of those treated with dexamethasone alone, in 5 percent of those who received placebo and indomethacin, and in none of the infants who received only placebo (Table 5). Although indomethacin treatment was not randomly assigned, the difference in the

TABLE 3. OTHER CLINICAL OUTCOMES.*

OUTCOME	DEXAMETHASONE	PLACEBO	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Respiratory disorder				
Pulmonary interstitial emphysema	10/111 (9)	25/109 (23)	0.4 (0.2–0.8)	0.01
Pneumothorax	5/111 (5)	9/109 (8)	0.5 (0.2–1.6)	0.25
Pulmonary hemorrhage	18/111 (16)	18/109 (17)	1.0 (0.5–1.8)	0.96
Patent ductus arteriosus	38/111 (34)	49/109 (45)	0.8 (0.5–1.1)	0.10
Neurologic disorder				
Intracranial hemorrhage				
Any grade	44/111 (40)	40/109 (37)	1.1 (0.8–1.5)	0.61
Severe (grade 3 or 4)	24/111 (22)	26/109 (24)	0.9 (0.6–1.5)	0.73
Periventricular leukomalacia	8/82 (10)	8/79 (10)	1.0 (0.4–2.4)	0.94
Retinopathy of prematurity				
Any stage	73/88 (83)	66/80 (82)	1.0 (0.9–1.2)	0.94
Severe (stage 3 or higher)	18/88 (20)	24/80 (30)	0.7 (0.4–1.2)	0.68
Infection				
Nosocomial infection	51/111 (46)	48/109 (44)	1.0 (0.8–1.4)	0.77
Bacterial	47/111 (42)	46/109 (42)	1.0 (0.7–1.4)	0.97
Fungal	10/111 (9)	13/109 (12)	0.8 (0.3–1.7)	0.49
Early infection (≤3 days after birth)	3/111 (3)	0/109	—	—
Gastrointestinal disorder				
Necrotizing enterocolitis	14/111 (13)	10/109 (9)	1.4 (0.6–3.0)	0.41
Spontaneous perforation	15/111 (14)	8/109 (7)	1.8 (0.8–4.2)	0.13

*Data are for outcomes at the time of discharge or death, or at 120 days among infants who remained hospitalized.

†The relative risk is the risk of the outcome in the dexamethasone group as compared with the placebo group. CI denotes confidence interval.

TABLE 4. COMPLICATIONS ATTRIBUTABLE TO THE STUDY DRUG.

COMPLICATION	DEXAMETHASONE	PLACEBO	RELATIVE RISK	P VALUE
	(N=111)	(N=109)	(95% CI)*	
	no. (%)			
Systolic pressure				
>80 mm Hg	30 (27)	4 (4)	7.4 (2.7–20.2)	<0.001
>90 mm Hg	7 (13)	0	—	0.01
Treatment for hypertension	14 (13)	5 (5)	2.7 (1.0–7.4)	0.04
Blood glucose >180 mg/dl (10 mmol/liter)	52 (47)	44 (40)	1.2 (0.9–1.6)	0.30
Insulin treatment	26 (23)	13 (12)	2.0 (1.1–3.6)	0.02
Upper gastrointestinal bleeding	6 (5)	2 (2)	2.9 (0.6–14.3)	0.18

*Relative risks indicate the occurrence of the complication in the dexamethasone group as compared with the placebo group. CI denotes confidence interval.

TABLE 5. GASTROINTESTINAL PERFORATION WITHIN 14 DAYS AFTER BIRTH, ACCORDING TO WHETHER INDOMETHACIN WAS ADMINISTERED WITH OR WITHOUT DEXAMETHASONE.

TREATMENT	ALL INFANTS	INFANTS WITH PERFORATION
	no.	no. (%)
Dexamethasone and indomethacin	70	13 (19)
Dexamethasone alone	41	1 (2)
Placebo and indomethacin	82	4 (5)
Placebo alone	27	0
Total	220	18 (8)

rates of perforation between the infants who received indomethacin and those who did not was significant in both the dexamethasone group and the placebo group ($P=0.05$).

Weight, length, and head circumference were similar in the two study groups at birth (Table 6). The infants in the dexamethasone group weighed less than those in the placebo group 10 days after birth ($P=0.001$) and at 36 weeks' postmenstrual age ($P=0.02$) and had a smaller head circumference ($P=0.04$) and tended to be shorter at 36 weeks' postmenstrual age.

DISCUSSION

Unlike some previous investigators,⁶⁻⁹ we found no significant difference in the relative risks of chronic lung disease at 36 weeks' postmenstrual age, death, or the combined outcome in extremely-low-birth-weight infants treated with dexamethasone or placebo. However, since a criterion for enrollment in our study was a birth weight of 501 to 1000 g, our infants were relatively immature and at high risk for a poor respiratory outcome.

TABLE 6. MEAN (\pm SD) GROWTH MEASUREMENTS.

VARIABLE	DEXAMETHASONE		PLACEBO		P VALUE
	MEAN VALUE	NO. OF INFANTS	MEAN VALUE	NO. OF INFANTS	
At birth					
Weight (g)	734 \pm 131	111	736 \pm 135	109	0.94
Length (cm)	32.6 \pm 2.4	107	32.7 \pm 2.4	106	0.80
Head circumference (cm)	23.0 \pm 1.5	108	23.1 \pm 1.9	106	0.87
10 Days after birth					
Weight (g)	644 \pm 121	101	705 \pm 144	98	0.001
Head circumference (cm)	22.8 \pm 2.2	96	23.1 \pm 2.1	94	0.34
28 Days after birth					
Weight (g)	862 \pm 175	88	893 \pm 192	86	0.25
Length (cm)	34.3 \pm 2.6	69	34.8 \pm 2.4	74	0.21
Head circumference (cm)	24.8 \pm 1.8	82	24.8 \pm 1.9	83	0.99
At 36 weeks' postmenstrual age					
Weight (g)	1701 \pm 316	82	1825 \pm 368	78	0.02
Length (cm)	40.0 \pm 2.6	70	40.9 \pm 3.6	68	0.07
Head circumference (cm)	30.2 \pm 1.7	80	30.9 \pm 2.8	76	0.04

Infants in the dexamethasone group were less likely than those in the placebo group to require oxygen 28 days after birth, a finding that may be related to an antiinflammatory effect of dexamethasone treatment.^{14,15} Furthermore, infants in the placebo group were more likely than those in the dexamethasone group to be treated with open-label dexamethasone. Since the decision to administer open-label dexamethasone was made by the attending neonatologist, these infants may have had a poorer clinical status than those who received early treatment with dexamethasone. An increased use of subsequent glucocorticoid treatment in the placebo group has been noted in

other trials of early systemic^{9,10} or inhaled¹⁶ glucocorticoid treatment, and such use may minimize differences in the respiratory outcome between the glucocorticoid and placebo groups.

Although the risk of necrotizing enterocolitis did not differ between the two study groups, the rate of spontaneous gastrointestinal perforation within the first two weeks in the dexamethasone group was more than three times that in the placebo group, and this complication appeared to be associated with the administration of indomethacin. Because indomethacin treatment was not assigned randomly, the infants who received indomethacin may have been more susceptible to perforation. Nevertheless, the high perforation rate in the dexamethasone group was unanticipated and resulted in termination of the trial.

Spontaneous perforation has been reported in very-low-birth-weight infants^{17,18} and has also been associated with dexamethasone treatment for chronic lung disease¹⁹ and indomethacin treatment for patent ductus arteriosus.²⁰⁻²² The small numbers of extremely-low-birth-weight infants enrolled in previous trials of dexamethasone may have limited the ability to detect this adverse event. In a recent large trial of a short course of dexamethasone given soon after birth, perforation during the first week occurred in 8 percent of the dexamethasone-treated infants and in 1 percent of the infants who received placebo, although there was no significant difference between the groups in the overall rate of perforation.⁹ Similarly, in a large trial of a 12-day course of dexamethasone or placebo, perforation occurred more often in the dexamethasone group, although the difference was not statistically significant.¹⁰

The mechanism of perforation may be related to the role of prostaglandins in maintaining gastrointestinal mucosal integrity.²³ Glucocorticoids and indomethacin inhibit prostaglandin production at two points in the synthetic pathway,^{24,25} perhaps explaining the association with perforation.

Hypertension and hyperglycemia are recognized complications of dexamethasone therapy.^{7,9,10,26,27} In our study, hypertension and insulin treatment were more frequent in the dexamethasone group than in the placebo group, although the rates of hypertension and insulin treatment were lower in our dexamethasone-treated infants than in similar infants given a higher dose of dexamethasone and a longer course of treatment.¹⁰ Use of other glucocorticoids or physiologic replacement²⁸ rather than therapeutic doses may further reduce complications.

Dexamethasone treatment has been reported to have both transient and sustained negative effects on growth.^{7,10,29} In our study, the dexamethasone-treated infants weighed less than the placebo-treated infants at the end of the intervention period. In addition, the infants who received dexamethasone weighed less and had a smaller head circumference at 36 weeks' post-

menstrual age, even though a larger proportion of infants in the placebo group were subsequently treated with open-label dexamethasone. Extremely-low-birth-weight infants may be especially susceptible to the catabolic effects of glucocorticoid treatment³⁰ during the early postnatal period, when they are likely to receive too few calories, and this susceptibility may affect their subsequent growth.³¹

In summary, we found that a 10-day tapered course of dexamethasone given at a moderate dose had no discernible effect on chronic lung disease or mortality in extremely-low-birth-weight infants. The dose we used, although substantially lower than the initial doses used in other trials or in clinical practice, was associated with an increased risk of spontaneous gastrointestinal perforation, as well as with known complications of glucocorticoid therapy. The risk of perforation appears to be associated with concomitant indomethacin treatment. Given these serious complications and the lack of a discernible benefit, we believe that early treatment with dexamethasone to prevent chronic lung disease in extremely-low-birth-weight infants is not indicated.

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APPENDIX

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