

ANTENATAL GLUCOCORTICOID TREATMENT AND CYSTIC PERIVENTRICULAR LEUKOMALACIA IN VERY PREMATURE INFANTS

OLIVIER BAUD, M.D., LAURENCE FOIX-L'HELIAS, M.D., MONIQUE KAMINSKI, M.S.C., FRANÇOIS AUDIBERT, M.D.,
PIERRE-HENRI JARREAU, M.D., PH.D., EMILE PAPIERNIK, M.D., CATHERINE HUON, M.D., JACQUES LEPERCO, M.D.,
MICHEL DEHAN, M.D., AND THIERRY LACAZE-MASMONTEIL, M.D., PH.D.

ABSTRACT

Background Antenatal glucocorticoid therapy decreases the incidence of several complications among very premature infants. However, its effect on the occurrence of cystic periventricular leukomalacia, a major cause of cerebral palsy, remains unknown.

Methods We retrospectively analyzed a cohort of 883 live-born infants, with gestational ages ranging from 24 to 31 weeks, who were born between January 1993 and December 1996 at three perinatal centers in the Paris area. The mothers of 361 infants had received betamethasone before delivery, the mothers of 165 infants had received dexamethasone before delivery, and the mothers of 357 infants did not receive glucocorticoids. We compared the rates of cystic periventricular leukomalacia among the three groups of infants in bivariate and multivariate analyses after adjustment for confounding factors.

Results The rate of cystic periventricular leukomalacia was 4.4 percent among the infants whose mothers had received betamethasone, 11.0 percent among the infants whose mothers had received dexamethasone, and 8.4 percent among the infants whose mothers had not received a glucocorticoid. After adjustment for gestational age, the mode of delivery, and the presence or absence of chorioamnionitis, prolonged interval between the rupture of membranes and delivery (>24 hours), preeclampsia, and the use of tocolytic drugs, antenatal exposure to betamethasone was associated with a lower risk of cystic periventricular leukomalacia than was either the absence of glucocorticoid therapy (adjusted odds ratio, 0.5; 95 percent confidence interval, 0.2 to 0.9) or exposure to dexamethasone (adjusted odds ratio, 0.3; 95 percent confidence interval, 0.1 to 0.7). The adjusted odds ratio for the group of infants whose mothers had received dexamethasone as compared with the group of infants whose mothers had not received a glucocorticoid was 1.5 (95 percent confidence interval, 0.8 to 2.9).

Conclusions Antenatal exposure to betamethasone but not dexamethasone is associated with a decreased risk of cystic periventricular leukomalacia among very premature infants. (N Engl J Med 1999;341:1190-6.)

©1999, Massachusetts Medical Society.

ANTENATAL glucocorticoid therapy can prevent several life-threatening complications of preterm delivery such as the respiratory distress syndrome and intraventricular hemorrhage.¹ The recommended glucocorticoid regimens consist of the administration to the mother of either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone given intramuscularly 12 hours apart.² As compared with placebo, both regimens are associated with a similar decrease in the incidence of the respiratory distress syndrome.³ Several controlled studies have compared the in utero effects of maternal betamethasone and dexamethasone administration.⁴⁻⁶ In two of them, betamethasone administration was associated with a significant reduction in fetal movements and heart-rate variability.^{4,5} Because a decrease in the variability of the fetal heart rate can be misinterpreted as a sign of fetal distress in fetuses with growth retardation, treatment with dexamethasone may be preferable.⁵ In all other circumstances, the choice of the regimen depends on such factors as a center's usual approach to treatment, availability, cost, or the number of injections needed.

A National Institutes of Health consensus conference on the effect of glucocorticoids on fetal maturation identified several areas that need to be studied, including the effects of antenatal glucocorticoid administration on perinatal hypoxic-ischemic brain injury.² Indeed, in contrast to the case of intraventricular hemorrhage, little is known about the relation between antenatal glucocorticoid administration and the incidence of cystic periventricular leukomalacia, the most frequent cause of cerebral palsy in children who are born prematurely. Therefore, we assessed the effect of various obstetrical variables, including antenatal exposure to betamethasone and dexamethasone, on the incidence of cystic periventricular leukomalacia in very premature infants.

From the Services de Réanimation Néonatale et Gynécologie-Obstétrique, University Hospital Antoine Béchère, Clamart (O.B., L.F.-L., F.A., M.D., T.L.-M.); the Unité de Recherches Epidémiologiques sur la Santé des Femmes et des Enfants, INSERM, Unité 149, Villejuif (L.F.-L., M.K.); the Services de Réanimation Néonatale et Gynécologie-Obstétrique, University Hospital Cochin Port Royal, Paris (P.-H.J., E.P.); and the Services de Réanimation Néonatale et Gynécologie-Obstétrique, University Hospital Saint Vincent de Paul, Paris (C.H., J.L.) — all in France. Address reprint requests to Dr. Lacaze-Masmonteil at Réanimation et Pédiatrie Néonatales, Hôpital Antoine Béchère, Assistance Publique-Hôpitaux de Paris, 157, rue de la Porte-de-Trivaux, 92141 Clamart, France.

METHODS

This retrospective study was carried out in three perinatal centers of the Assistance Publique-Hôpitaux de Paris organization. We studied all 883 infants with gestational ages ranging from 24 to 31 weeks who were born in these centers and who were subsequently admitted to the neonatal intensive care unit between January 1993 and December 1996. We reviewed the records of all the mothers to determine the causes of preterm delivery, the dates of administration and number of courses of glucocorticoid, the glucocorticoid regimen used, any use of tocolytic and antibiotic therapy, and the mode of delivery. We also reviewed the records of the infants.

Glucocorticoid Therapy

At the time of the study, the recommended antenatal glucocorticoid regimen consisted of the administration to the women of either two 12-mg doses of betamethasone (Célestène or Célestène chronodose, Roche, Paris) given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone (Soludecadron, Merck, Paris) given intramuscularly 12 hours apart. Both glucocorticoids were used in the three centers during the study period. If the women had not delivered and were still at risk for preterm delivery, additional courses of the same regimen were administered every 7 to 10 days.

Antenatal Events

Gestational age was based on the date of the last menstrual period and on ultrasonographic findings during the first trimester of pregnancy. The main causes of preterm delivery were chorioamnionitis, rupture of amniotic membranes more than 24 hours before delivery, vaginal bleeding (placenta previa or placental abruption), intrauterine growth retardation, and preeclampsia. Chorioamnionitis was defined by the presence of preterm labor in association with at least two of the following prepartum or post-

partum criteria: maternal temperature of more than 38°C on at least two occasions, maternal serum C-reactive protein concentration of more than 20 mg per liter (normal, <10), positive bacterial culture of amniotic fluid obtained by amniocentesis, and documented neonatal sepsis. Intrauterine growth retardation was diagnosed by ultrasonography; all cases were confirmed after delivery (on the basis of a birth weight below the 10th percentile).⁷ Preeclampsia was defined on the basis of the finding of urinary protein excretion of more than 300 mg per 24 hours and a blood pressure of more than 140/90 mm Hg on two occasions.

In addition to antenatal glucocorticoid therapy, maternal treatments considered in the study were the use of intravenous tocolysis with albuterol (Glaxo, Boulogne, France), intravenous antibiotics, and antihypertensive drugs. Magnesium sulfate was not used as a tocolytic agent or for the treatment of preeclampsia during the study period.

Short-Term Neonatal Outcomes

All outcomes, including death, were recorded until the infants were discharged from the hospital. Respiratory distress syndrome was diagnosed when at least two of the following were present during the first 48 hours of life: respiratory failure requiring either mechanical ventilation with supplemental oxygen for at least 48 hours or the administration of exogenous surfactant, typical findings on chest x-ray film (reticulogranular pattern in the lungs with air bronchograms), or biologic evidence of lung immaturity on assay of tracheal aspirates (TDx Fetal-Lung-Maturity Assay II, Abbott Laboratories, North Chicago, Ill.). Bronchopulmonary dysplasia was defined by the need for supplemental oxygen at 28 days of life; its incidence was calculated in survivors at the same age. Necrotizing enterocolitis was diagnosed with the use of a standard combination of clinical signs and radiographic findings.⁸

Cranial ultrasonography was usually performed twice within the first week of life and weekly thereafter until 36 weeks of gestational age, and all three centers used similar techniques. Electro-

TABLE 1. MATERNAL CHARACTERISTICS ACCORDING TO THE ANTENATAL USE OF GLUCOCORTICOIDS.*

CHARACTERISTIC	NO GLUCOCORTICOIDS (N=357)	BETAMETHASONE (N=361)	DEXAMETHASONE (N=165)	P VALUE†	P VALUE‡	P VALUE§
Chorioamnionitis — %	34.5	33.5	29.7	0.80	0.30	0.40
Interval between rupture of membranes and delivery >24 hr — %	20.7	35.5	25.4	0.001	0.23	0.02
Vaginal bleeding — %	7.8	4.1	4.2	0.05	0.13	0.90
Intrauterine growth retardation — %	16.5	16.9	27.9	0.90	0.003	0.004
Preeclampsia — %	24.9	18.0	22.4	0.02	0.53	0.23
Tocolytic drugs — no./total no. (%)	184/356 (51.7)	219/360 (60.8)	71/165 (43.0)	0.01	0.07	0.001
Adrenergic-antagonist drugs — %	12.9	11.4	7.3	0.53	0.06	0.15
Antibiotic treatment — no./total no. (%)	156/353 (44.2)	190/361 (52.6)	69/160 (43.1)	0.02	0.80	0.05
Courses of glucocorticoid — %						0.60
1	—	62.0	66.7			
2	—	20.3	17.0			
≥3	—	17.7	16.3			
Interval between the last course of glucocorticoids and delivery — no./total no.(%)						0.42
0-47 hr	—	108/357 (30.3)	40/162 (24.7)			
48 hr-7 days	—	180/357 (50.4)	90/162 (55.6)			
>7 days	—	69/357 (19.3)	32/162 (19.8)			

*The study cohort consisted of 883 infants who were born to 718 women.

†P values are for the comparison of the betamethasone group with the untreated group.

‡P values are for the comparison of the dexamethasone group with the untreated group.

§P values are for the comparison of the betamethasone group with the dexamethasone group.

encephalography was performed at least once a week up to an average of 34 weeks of gestational age.⁹ The infants were assessed for severe intraventricular hemorrhage (grades 3 and 4 according to the classification of Papile et al.¹⁰) and cystic periventricular leukomalacia. The presence of the latter was suggested by a finding of rolandic sharp waves on electroencephalography⁹ and confirmed by a finding of bilateral hyperechoic lesions on cranial ultrasonography soon after birth, which evolved into localized or extensive echolucent areas within the brain parenchyma.¹¹

Ophthalmoscopy was performed 4 weeks after birth and every 2 weeks thereafter until 36 to 40 weeks of gestational age. Only the most severe stages of retinopathy of prematurity (stages 3 to 5) were recorded.¹²

Statistical Analysis

Antenatal events and neonatal outcome were compared by bivariate analysis according to whether or not the mother had received either betamethasone or dexamethasone. The rates of cystic periventricular leukomalacia in each of the three groups (untreated, exposed to betamethasone, and exposed to dexamethasone) were then analyzed after stratification according to maternal and neonatal variables. Finally, the relations between antenatal glucocorticoid treatment and the occurrence of cystic periventricular leukomalacia were estimated by two separate multiple logistic-

regression models.¹³ In the first model, each of the two treated groups was compared with the untreated group; in the second model, the betamethasone group was compared with the dexamethasone group. Pearson's chi-square test was used to analyze categorical data. All P values were based on two-sided tests. Bivariate and multivariate analyses were performed with SAS statistical software (SAS Institute, Cary, N.C.) and BMDP software (BMDP Statistical Software, Los Angeles), respectively.

RESULTS

Characteristics of the Infants and Their Mothers

The study cohort consisted of 883 infants who were born between 24 and 31 weeks of gestation to 718 women; 361 infants (41 percent) were exposed to betamethasone, 165 (19 percent) to dexamethasone, and 357 (40 percent) to neither glucocorticoid. The maternal characteristics are shown in Table 1, and neonatal characteristics in Table 2. There were significant differences in the distribution of gestational age among the three groups, with fewer of the most immature infants in the treated groups. As

TABLE 2. CHARACTERISTICS OF THE NEONATES ACCORDING TO THE ANTENATAL USE OF GLUCOCORTICOIDS.

CHARACTERISTIC	No GLUCOCORTICOIDS (N=357)	BETAMETHASONE (N=361)	DEXAMETHASONE (N=165)	P VALUE*	P VALUE†	P VALUE‡
Intrauterine growth retardation — %	16.5	16.9	27.9	0.90	0.003	0.004
Delivered by cesarean section — %	56.9	62.9	67.3	0.10	0.02	0.30
Male sex — %	54.6	55.1	52.7	0.90	0.70	0.60
Singleton — %	68.1	53.7	63.0	0.001	0.30	0.05
Gestational age — %				0.001	0.02	0.60
24–26 wk	15.1	7.8	7.3			
27–29 wk	40.6	34.3	38.8			
30–31 wk	44.3	57.9	53.9			
Birth weight <1500 g — %	80.7	76.7	81.8	0.20	0.70	0.20
Apgar score <5 at 5 min — %	3.1	4.7	1.8	0.30	0.40	0.11
Respiratory distress syndrome — no./total no. (%)	209/356 (58.7)	164/360 (45.6)	64/165 (38.8)	0.001	0.001	0.15
Need for exogenous surfactant — no./total no. (%)	194/356 (54.5)	153/360 (42.5)	57/165 (34.5)	0.003	0.001	0.08
Need for supplemental oxygen — no./total no. (%)						
At 28 days§	93/299 (31.1)	66/330 (20.0)	33/148 (22.3)	0.001	0.005	0.60
At 36 wk	35/293 (11.9)	26/326 (8.0)	11/145 (7.6)	0.10	0.16	0.90
Neonatal sepsis — no./total no. (%)	71/357 (19.9)	74/361 (20.5)	18/164 (11.0)	0.80	0.01	0.008
Necrotizing enterocolitis — no./total no. (%)	16/356 (4.5)	6/360 (1.7)	3/164 (1.8)	0.03	0.13	0.90
Grade 3 or 4 intraventricular hemor- rhage — no./total no. (%)	39/357 (10.9)	17/361 (4.7)	7/164 (4.3)	0.002	0.01	0.80
Cystic periventricular leukomalacia — no./total no. (%)	30/357 (8.4)	16/361 (4.4)	18/164 (11.0)	0.03	0.30	0.005
Stage 3, 4, or 5 retinopathy of prema- turity — no./total no. (%)	2/356 (0.6)	4/360 (1.1)	2/164 (1.2)	0.40	0.40	0.90
Death — %				0.003	0.08	0.10
Within 7 days after birth	11.8	6.4	5.4			
More than 7 days after birth	9.0	5.0	9.7			

*P values are for the comparison of the betamethasone group with the untreated group.

†P values are for the comparison of the dexamethasone group with the untreated group.

‡P values are for the comparison of the betamethasone group with the dexamethasone group.

§The need for supplemental oxygen at 28 days of life was considered to indicate the presence of bronchopulmonary dysplasia.

TABLE 3. GESTATIONAL AGE, USE OF ANTENATAL GLUCOCORTICOID TREATMENT, AND INCIDENCE OF CYSTIC PERIVENTRICULAR LEUKOMALACIA, ACCORDING TO CENTER.*

CHARACTERISTIC	CENTER 1 (N=431)	CENTER 2 (N=140)	CENTER 3 (N=312)
Maternal			
Antenatal glucocorticoid administration — %			
None	33.9	44.2	47.8
Betamethasone	38.0	32.9	48.4
Dexamethasone	28.1	22.9	3.8
Infant			
Gestational age — %			
24–26 wk	13.9	4.3	9.0
27–29 wk	37.4	37.1	38.4
30–31 wk	48.7	58.6	52.6
Cystic periventricular leukomalacia — no./total no. (%)	35/430 (8.1)	14/140 (10.0)	15/312 (4.8)
Cystic periventricular leukomalacia according to antenatal glucocorticoid treatment — no./total no. (%)			
None	14/146 (9.6)	7/62 (11.3)	9/149 (6.0)
Betamethasone	9/164 (5.5)	4/46 (8.7)	3/151 (2.0)
Dexamethasone	12/120 (10.0)	3/32 (9.4)	3/12 (25.0)

*The study cohort consisted of 883 infants who were born to 718 women.

compared with the infants whose mothers had not received glucocorticoids, the infants whose mothers had received either betamethasone or dexamethasone were less likely to require exogenous surfactant and had lower rates of respiratory distress syndrome, bronchopulmonary dysplasia (indicated by the need for supplemental oxygen at 28 days of life), and grade 3 or 4 intraventricular hemorrhage (Table 2).

Infants with intrauterine growth retardation were more likely to have been exposed to dexamethasone than to betamethasone, whereas infants born after a prolonged interval between the rupture of amniotic membranes and delivery were more likely to have been exposed to betamethasone (Tables 1 and 2). There was no significant difference between the two treated groups in the number of full courses of glucocorticoid given antenatally. The interval between the first intramuscular injection of the last course of glucocorticoid and delivery was not significantly different in the two treated groups. The frequency of respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, and stage 3, 4, or 5 retinopathy of prematurity was similar in the two treated groups (Table 2). However, as compared with either the infants with no exposure to glucocorticoids or the infants whose mothers received dexamethasone, the infants whose mothers received betamethasone were less likely to have cystic periventricular leukomalacia. As compared with the infants with no exposure to glucocorticoids, the infants whose mothers had re-

ceived betamethasone had a significantly lower overall rate of death (Table 2).

The rates of use of dexamethasone or betamethasone differed in the three centers (Table 3). The rate of cystic periventricular leukomalacia was the lowest in the center in which betamethasone was given more often. Moreover, at each center, the rate of cystic periventricular leukomalacia was lowest in the group of infants whose mothers had received betamethasone (Table 3).

Risk Factors for Cystic Periventricular Leukomalacia

The overall incidence of cystic periventricular leukomalacia ranged from 12.9 percent among infants whose gestational age was 24 to 26 weeks to 4.2 percent among infants whose gestational age was 30 to 31 weeks (Table 4). Chorioamnionitis, a prolonged interval between the rupture of membranes and delivery, the use of tocolytic drugs, and vaginal delivery were the peripartum events associated with a higher rate of cystic periventricular leukomalacia. In contrast, cystic periventricular leukomalacia was rare among infants whose mothers had preeclampsia.

Effect of Antenatal Glucocorticoid Treatment on the Risk of Cystic Periventricular Leukomalacia

For any degree of immaturity and in almost all subgroups, there was a trend toward a lower frequency of cystic periventricular leukomalacia in the betamethasone group than in either the untreated group or the dexamethasone-exposed group (Table 5). The relation between the type of glucocorticoid

TABLE 4. INCIDENCE OF CYSTIC PERIVENTRICULAR LEUKOMALACIA ACCORDING TO SELECTED MATERNAL AND NEONATAL CHARACTERISTICS.*

CHARACTERISTIC	CYSTIC PERIVENTRICULAR LEUKOMALACIA	NO. OF INFANTS	P VALUE
	percent		
Maternal			
Chorioamnionitis			
No	5.1	590	0.001
Yes	11.6	292	
Interval between rupture of membranes and delivery >24 hr			
No	5.9	639	0.01
Yes	10.7	243	
Vaginal bleeding			
No	6.3	832	0.30
Yes	10.0	50	
Preeclampsia			
No	8.4	691	0.01
Yes	3.1	191	
Tocolytic drugs			
No	5.4	407	0.05
Yes	8.9	473	
Antibiotics			
No	6.3	459	0.20
Yes	8.4	414	
Mode of delivery			
Cesarean section	5.6	540	0.01
Vaginal	9.9	342	
Infant			
Intrauterine growth retardation			
No	7.7	716	0.30
Yes	5.4	166	
Singleton			
No	5.9	341	0.20
Yes	8.1	541	
Gestational age			
24–26 wk	12.9	93	0.001
27–29 wk	9.9	333	
30–31 wk	4.2	456	
Respiratory distress syndrome			
No	7.0	444	0.80
Yes	7.3	436	
Neonatal sepsis			
No	6.1	719	0.006
Yes	12.3	163	

*The study cohort consisted of 883 infants who were born to 718 women. Data on outcome were missing for one infant in the dexamethasone group.

given and the risk of cystic periventricular leukomalacia was estimated in two multiple logistic-regression models, after adjustment for the covariates that were significantly associated with that outcome: gestational age, the mode of delivery, and the presence or absence of chorioamnionitis, prolonged interval between rupture of membranes and delivery, preeclampsia, and use of tocolytic drugs. As compared with no treatment (Table 6), antenatal administration of betamethasone was associated with a lower risk of cystic periventricular leukomalacia (adjusted odds ratio, 0.5; 95 percent confidence interval, 0.2 to 0.9; $P=0.03$), whereas dexamethasone was asso-

ciated with a higher risk, but not a significantly higher risk (adjusted odds ratio, 1.5; 95 percent confidence interval, 0.8 to 2.9; $P=0.20$).

In a separate multiple logistic-regression model, the administration of betamethasone was associated with a lower risk of cystic periventricular leukomalacia than was the administration of dexamethasone (unadjusted odds ratio, 0.4; 95 percent confidence interval, 0.2 to 0.8; adjusted odds ratio, 0.3; 95 percent confidence interval, 0.1 to 0.7; $P=0.003$). Although the proportion of infants who were exposed to either betamethasone or dexamethasone varied according to the center and during the study period, the associations were not affected by the addition of these two variables to the models. The results were similar after the exclusion of infants who had died within the first seven days after birth.

Among infants from multiple pregnancies, there was no evidence of concordance for disease outcome with respect to the risk of cystic periventricular leukomalacia. A separate analysis was nevertheless performed for singleton infants. Among singleton infants, the adjusted odds ratio in the betamethasone-exposed group as compared with the unexposed group was 0.6 (95 percent confidence interval, 0.3 to 1.4) and the adjusted odds ratio for the comparison of the betamethasone-exposed group with the dexamethasone-exposed group was 0.3 (95 percent confidence interval, 0.1 to 0.8).

DISCUSSION

Several observational studies have identified a relation between chorioamnionitis, cystic periventricular leukomalacia, and cerebral palsy.¹⁴⁻¹⁷ In contrast, the infants of mothers who had preeclampsia have a low risk of either cystic periventricular leukomalacia or cerebral palsy.^{15,16} Antenatal glucocorticoid therapy with betamethasone or dexamethasone reduces the risk of intracranial hemorrhage in neonates.¹ Our results suggest that exposure to betamethasone but not dexamethasone is associated with a decreased risk of cystic periventricular leukomalacia.

Several limitations of our study must be underlined. First of all, it was observational. Despite the repeated use of cranial ultrasonography and electroencephalography at the three centers, a few cases of cystic periventricular leukomalacia may not have been detected. It is likely, however, that any undetected cases were evenly distributed among the three groups. It is also impossible to control completely for indication bias in such an observational study; Table 1 shows that the prevalence of antenatal risk factors for cystic periventricular leukomalacia varied according to the antenatal glucocorticoid treatment given. However, chorioamnionitis and a prolonged interval between the rupture of membranes and delivery — two high-risk factors for cystic periventricular leukomalacia — were more frequent among in-

TABLE 5. INCIDENCE OF CYSTIC PERIVENTRICULAR LEUKOMALACIA ACCORDING TO THE ANTENATAL USE OF GLUCOCORTICOIDS.*

CHARACTERISTIC	NO GLUCOCORTICOIDS		BETAMETHASONE		DEXAMETHASONE	
	INCIDENCE OF PVL	TOTAL NO. OF INFANTS	INCIDENCE OF PVL	TOTAL NO. OF INFANTS	INCIDENCE OF PVL	TOTAL NO. OF INFANTS
	%		%		%	
Maternal						
Chorioamnionitis						
No	5.1	234	3.3	240	8.6	116
Yes	14.6	123	6.6	121	16.7	48
Interval between rupture of membranes and delivery >24 hr						
No	7.1	283	3.9	233	7.3	123
Yes	13.5	74	5.5	128	21.9	41
Preeclampsia						
No	10.4	268	5.1	296	11.8	127
Yes	2.2	89	1.5	65	8.1	37
Tocolytic drugs						
No	5.2	172	4.3	141	7.4	94
Yes	11.4	184	4.6	219	15.7	70
Courses of glucocorticoids						
1	—	—	3.6	224	13.8	109
2	—	—	8.2	73	7.1	28
≥3	—	—	3.1	64	3.7	27
Interval between the last course of glucocorticoids and delivery						
<48 hr	—	—	4.6	108	22.5	40
48 hr–7 days	—	—	4.4	180	6.7	89
>7 days	—	—	2.9	69	9.4	32
Mode of delivery						
Vaginal	11.0	154	5.2	134	18.5	54
Cesarean section	6.4	203	4.0	227	7.3	110
Infant						
Intrauterine growth retardation						
No	9.4	298	4.3	300	11.9	118
Yes	3.4	59	4.9	61	8.7	46
Singleton						
No	8.8	114	3.6	167	6.7	60
Yes	8.1	243	5.2	194	13.5	104
Gestational age						
24–26 wk	11.1	54	3.6	28	45.4	11
27–29 wk	10.3	145	7.3	124	14.1	64
30–31 wk	5.7	158	2.9	209	4.5	89
Respiratory distress syndrome						
No	8.8	147	4.1	196	9.9	101
Yes	7.7	209	4.9	164	12.7	63
Neonatal sepsis						
No	6.3	286	4.2	287	9.6	146
Yes	16.9	71	5.4	74	22.2	18

*The study cohort consisted of 883 infants who were born to 718 women. PVL denotes cystic periventricular leukomalacia. Data on outcome were missing for one infant in the dexamethasone group.

fants whose mothers had received betamethasone than among infants whose mothers had received dexamethasone. Moreover, at each center, the infants whose mothers had received betamethasone had the lowest rate of cystic periventricular leukomalacia. Finally, the consistent decrease in the risk of cystic periventricular leukomalacia that was associated with antenatal exposure to betamethasone, which was apparent in both the stratified analysis and the multiple logistic-regression analyses, suggests that this beneficial effect is due to the treatment and not only to the characteristics of the women who received it.

Whether the subtle structural difference in the configuration of the methyl group on position 16 — the only difference between betamethasone and dexamethasone — accounts for the neuroprotective effects of betamethasone remains speculative. Alternatively, the presence of sulfiting agents in the dexamethasone preparation (the preparation available in France contains 0.155 mg of sulfite per milligram of dexamethasone) may account for its lower efficacy. Sulfite acts in vitro as a neurotoxic agent, especially in combination with peroxynitrite.^{18,19}

Betamethasone has a more pronounced effect than

TABLE 6. RESULTS OF MULTIPLE LOGISTIC-REGRESSION ANALYSIS OF THE RISK OF CYSTIC PERIVENTRICULAR LEUKOMALACIA.*

CHARACTERISTIC	UNADJUSTED ODDS RATIO (95% CI)	ADJUSTED ODDS RATIO (95% CI)†	P VALUE‡
Maternal			
Chorioamnionitis			
No§	1.0	1.0	
Yes	2.5 (1.5–4.1)	1.5 (0.8–2.7)	0.20
Interval between rupture of membranes and delivery >24 hr			
No§	1.0	1.0	
Yes	1.9 (1.1–3.2)	1.6 (0.9–2.9)	0.09
Preeclampsia			
No§	1.0	1.0	
Yes	0.3 (0.1–0.8)	0.5 (0.2–1.4)	0.17
Tocolytic drugs			
No§	1.0	1.0	
Yes	1.7 (1.0–2.9)	1.2 (0.7–2.3)	0.50
Mode of delivery			
Cesarean section§	1.0	1.0	
Vaginal	1.9 (1.1–3.1)	1.2 (0.6–2.1)	0.60
Antenatal glucocorticoid administration			
None§	1.0	1.0	
Betamethasone	0.5 (0.3–0.9)	0.5 (0.2–0.9)	0.03
Dexamethasone	1.3 (0.7–2.5)	1.5 (0.8–2.9)	0.20
Infant			
Gestational age			
30–31 wk§	1.0	1.0	
27–29 wk	2.5 (1.4–4.5)	2.4 (1.3–4.4)	0.01
24–26 wk	3.4 (1.6–7.3)	2.4 (1.0–5.5)	0.05

*A total of 880 infants were included in the analysis; data on the use of tocolytic drugs were missing for 2 infants (1 in the betamethasone group and 1 in the group given no glucocorticoids), and data on outcome were missing for 1 infant in the dexamethasone group. CI denotes confidence interval.

†Each odds ratio was adjusted for all the other listed covariates.

‡The P values are for the adjusted odds ratio.

§Infants in this category served as the reference group.

dexamethasone on the variation in fetal heart rate, which may confound the assessment of the well-being of fetuses with growth retardation.^{4,5} Nonetheless, in addition to the unexpected protective effect of betamethasone in this study, there is other evidence to suggest that betamethasone may be preferable to dexamethasone. First, the offspring of pregnant mice given betamethasone performed neurobehavioral-development tasks better than the offspring of pregnant mice given dexamethasone.²⁰ Second, meta-analyses of randomized trials have shown that although both glucocorticoids reduce the frequency of the respiratory distress syndrome, only betamethasone reduces neonatal mortality.³ Finally, both drugs have similar beneficial effects on all the other major adverse outcomes of severe prematurity, and treat-

ment with betamethasone requires fewer intramuscular injections. For all these reasons, betamethasone may prove to be the better choice for pregnant women at risk for preterm delivery.

We are indebted to the staff members of the departments of obstetrics and pediatrics of the participating hospitals; to Drs. R. Lenclen and Y. Ville at the Hospital of Poissy; and to Drs. P. Blanchard (Sherbrooke University, Sherbrooke, Que., Canada), M.V. Sénat (Antoine Béchère Hospital, Clamart, France), P. Truffert (Jeanne de Flandre Hospital, Lille, France), and V. Zupan (Antoine Béchère Hospital, Clamart, France) for their advice during the preparation of this article.

REFERENCES

- Crowley P. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. *Am J Obstet Gynecol* 1995;173:322-35.
- NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995;273:413-8.
- Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. *Am J Obstet Gynecol* 1995;173:254-62.
- Mulder EJH, Derks JB, Visser GHA. Antenatal corticosteroid therapy and fetal behaviour: a randomised study of the effects of betamethasone and dexamethasone. *Br J Obstet Gynaecol* 1997;104:1239-47.
- Senat MV, Minoui S, Multon O, Fernandez H, Frydman R, Ville Y. Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labour: a randomised study. *Br J Obstet Gynaecol* 1998;105:749-55.
- Magee LA, Dawes GS, Moulden M, Redman CW. A randomised controlled comparison of betamethasone and dexamethasone: effects on the antenatal fetal heart rate. *Br J Obstet Gynaecol* 1997;104:1233-8.
- Leroy B, Lefort F. A propos du poids et de la taille des nouveau-nés à la naissance. *Rev Fr Gynecol Obstet* 1971;66:391-6.
- Kliegman RM, Fanaroff AA. Necrotizing enterocolitis. *N Engl J Med* 1984;310:1093-103.
- Baud O, d'Allest AM, Lacaze-Masmonteil T, et al. The early diagnosis of periventricular leukomalacia in premature infants with positive rolandic sharp waves on serial electroencephalography. *J Pediatr* 1998;132:813-7.
- Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529-34.
- de Vries LS. Neurological assessment of the preterm infant. *Acta Paediatr* 1996;85:765-71.
- The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130-4.
- Hosmer DW Jr, Lemeshow S. *Applied logistic regression*. New York: Wiley, 1989:307.
- Nelson KB, Ellenberg JH. Predictors of low and very low birth weight and the relation of these to cerebral palsy. *JAMA* 1985;254:1473-9.
- Zupan V, Gonzalez P, Lacaze-Masmonteil T, et al. Periventricular leukomalacia: risk factors revisited. *Dev Med Child Neurol* 1996;38:1061-7.
- Murphy DJ, Sellers S, MacKenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. *Lancet* 1995;346:1449-54.
- Spinillo A, Capuzzo E, Stronati M, Ometto A, De Santolo A, Acciano S. Obstetric risk factors for periventricular leukomalacia among preterm infants. *Br J Obstet Gynaecol* 1998;105:865-71.
- Reist M, Marshall KA, Jenner P, Halliwell B. Toxic effects of sulfite in combination with peroxynitrite on neuronal cells. *J Neurochem* 1998;71:2431-8.
- Leist M, Fava E, Montecucco C, Nicotera P. Peroxynitrite and nitric oxide donors induce neuronal apoptosis by eliciting autocrine excitotoxicity. *Eur J Neurosci* 1997;9:1488-98.
- Rayburn WE, Christensen HD, Gonzalez CL. A placebo-controlled comparison between betamethasone and dexamethasone for fetal maturation: differences in neurobehavioral development of mice offspring. *Am J Obstet Gynecol* 1997;176:842-51.