Title

Antenatal Betamethasone: A Prolonged Time Interval from Administration to Delivery Is Associated with an Increased Incidence of Severe Intraventricular Hemorrhage in Infants Born before 28 Weeks Gestation

Authors

Liebowitz, Melissa
Clyman, Ronald I

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Antenatal betamethasone: a prolonged time interval from administration to delivery is associated with an increased incidence of severe intraventricular hemorrhage in infants born before 28 weeks gestation

Melissa Liebowitz, MD[1] and **Ronald I. Clyman, MD**[2]

[1]Department of Pediatrics, University of California San Francisco, CA 94143

[2]Cardiovascular Research Institute and Department of Pediatrics, University of California San Francisco, CA 94143

Abstract

Objective—To examine the effects of antenatal steroids on severe intraventricular hemorrhage (IVH) in infants born during the IVH vulnerable period (<28 weeks gestational age) and to evaluate rates of IVH correlated with the time interval between treatment or retreatment and birth.

Study design—429 infants (< 28 weeks gestation), who delivered ≥24 hours after the first BMZ course (two doses), were divided into groups based on the interval between the first course of BMZ and delivery: <10 days or ≥10 days. The primary outcome was severe IVH. Multiple regression analyses were performed to adjust for potential confounders.

Results—392 infants delivered after a single BMZ course (312 delivered <10 days; 80 ≥10 days). The incidence of severe IVH was 17% for infants delivered ≥10 days and 7% for those delivered <10 days after a single BMZ course (aOR 4.16; 95% CI 1.59–10.87, p=0.004). 37 infants (born ≥10 days from the first BMZ course) received a second/rescue BMZ course. The incidence of severe IVH among infants receiving a second/rescue course was 8%, which was similar to the incidence among infants born <10 days (aOR 1.7; 95% CI 0.41–6.6, p=0.48).

Conclusion—In infants born before 28 weeks gestation, delivery ≥10 days from the first BMZ course is associated with a higher incidence of severe IVH; a second/rescue course may reverse this effect.

Keywords

intracranial hemorrhage; newborn; corticosteroids; premature birth

Address for correspondence: Ronald Clyman, MD, University of California San Francisco, 513 Parnassus Ave., Room 1408 HSW, UCSF Box 1346, San Francisco, CA 94143-0544, 415-476-4462; FAX 415-502-2993, clymanr@peds.ucsf.edu.

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Although randomized controlled trials (RCTs) demonstrate that infants exposed to antenatal corticosteroids have a decreased incidence of death, respiratory distress syndrome (RDS) and severe grades (grades 3 and 4) (1) of intraventricular hemorrhage (IVH) (2), there are unanswered questions about the duration of the beneficial effects and whether retreatment is required. In vitro (3) and in vivo (4) studies suggest that BMZ's beneficial effects on the preterm lung are reversible and begin to wane after the first week. In addition, a meta-analysis of the RCTs that examined the use of repeat doses of corticosteroids in women still at risk of preterm birth 1–2 weeks after an initial course found that retreatment decreases the incidence of RDS (5).

Whether the beneficial effects of antenatal corticosteroids on other morbidities (e.g., severe IVH) also wane with time is much less clear. None of the corticosteroid retreatment RCTs (5) found a difference in the incidence of severe IVH between infants who received a single course and those who received repeat dosing (5–11). Although these findings suggest that retreatment may not affect the incidence of severe IVH, and that the beneficial effects of corticosteroids on severe IVH may not wane with time, there are important considerations that need to be examined before one can accept this conclusion. Severe IVH occurs almost exclusively in infants born before 28 weeks gestation; the incidence is 27% among infants born below 26 weeks, but less than 2% among those born at 28 weeks or older (12). Unfortunately, the infants that delivered before 28 weeks gestation in the "retreatment" RCTs made up only 7% (range 0–16%) of the study population and the overall incidence of severe IVH was only 2.6% (range 0–5%) (6–11). Therefore, we designed an observational study to examine the effects of antenatal steroids on severe IVH in infants born during the IVH vulnerable period (<28 weeks gestation). We hypothesized that the beneficial effects of antenatal steroids on severe IVH are time-limited and wane with time, in neonates born before 28 weeks gestation, and that retreatment with a second course of antenatal BMZ can restore its beneficial effects.

METHODS

This project was approved by the University of California San Francisco's Institutional Review Board. A single neonatologist prospectively evaluated and recorded the perinatal and neonatal risk factors and outcome measures from all infants born at ≤27–6/7 weeks' gestation and admitted, within the first 24 hours of birth, to the William H. Tooley Intensive Care Nursery at the University of California San Francisco between January 1998 and December 2015. Infants with major congenital malformations were excluded. Six hundred sixty-seven patients were eligible for the study. Perinatal characteristics of the study population are listed in Table I (available at www.jpeds.com).

Criteria used to evaluate specific neonatal and perinatal risk factors that may affect the incidence of severe IVH have been previously described (13, 14). Gestational age was determined by the date of last menstrual period and early ultrasounds (before 24 weeks gestation). If there were discrepancies, the early ultrasound dating was used. Intrauterine growth restriction was defined as birthweight less than the tenth-percentile for gestational age using the growth curves from Olsen et al (15).

Detailed descriptions of our approach to respiratory and hemodynamic support have been published elsewhere (13, 16, 17). Oxygen Saturation target limits for this population were 88–94% throughout the study period.

All infants were examined with serial bedside cranial ultrasounds that included a study on postnatal day 3 or 4, followed by weekly or biweekly studies for the first 4 weeks. A single neonatologist (RIC) prospectively reviewed all of the cranial ultrasound examinations with an ultrasonographer. IVH was classified using the four-level grading system (2). Grades 3 and 4 IVH were considered “severe IVH” (2).

Bronchopulmonary dysplasia (BPD) was defined by a modified physiologic room-air challenge test performed between 36 and 37 weeks postmenstrual age (18).

Necrotizing enterocolitis (NEC) was defined as Bell’s classification II or greater (this included NEC that was treated medically or surgically, and “spontaneous perforations” that occur before 7 days) (19).

The criteria for diagnosis, follow up and treatment of ROP have been previously described (14).

Infants were divided into groups depending on the interval between the first dose of the first course of antenatal BMZ and delivery. A complete course of antenatal BMZ consisted of two 12-mg doses that were administered 24 hours apart. Group A consisted of infants who were either never treated or delivered within 6 hours of the initiation of antenatal BMZ. Group B consisted of infants who delivered between 7 and 23 hours of the initiation of antenatal BMZ. Group C consisted of infants who delivered between 24 hours and 9 days (group C-1, between 24 and 47 hours; group C-2, between 48 hours and 7 days; and group C-3 between 8 and 9 days) after the initiation of antenatal BMZ. Group D consisted of infants who delivered 10 days or more after the initiation of antenatal BMZ.

Statistical analyses

Statistical analyses were performed using STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). A Chi Square test was used to compare categorical baseline characteristics between infants who delivered at different times after the initiation of antenatal BMZ treatment. The Student t-test was used to compare continuous parametric variables (gestational age, birth weight).

Because our study period spanned 17 years, we were concerned that unmeasured changes in practice or risk factors may have occurred that could have affected the rates of our primary study outcome (severe IVH). Therefore, we created a categorical variable (“birth year epoch”) that divided the study period into the 3 epochs (1998–2003, 2004–2009, 2010–2015). We included the “birth year epoch” variable in all of our multivariate regression analyses to adjust for any unmeasured practice changes that may have occurred over time (see below).

We first examined the relationship between the time interval from the first dose of BMZ to delivery and neonatal morbidity by conducting a multivariate regression analysis. Logistic

regression was used for categorical outcomes and linear regression was used for continuous outcome variables. Regression covariates were selected a priori. For these analyses the following covariates were included in the model: gestational age, birth year epoch, pregnancy complications (small for gestational age, multiple gestation, gestational diabetes, chorioamnionitis, preeclampsia), delivery mode, out born status and race. For all regression models, sensitivity analyses were conducted for other baseline characteristics (including male sex, prophylactic indomethacin and 5 minute Apgar score) that were not included in the primary models. Addition of these variables to the model did not change the point estimates.

We next investigated the waning effects of a complete (two-dose) course of BMZ on neonatal morbidity by examining a subset of our population who either delivered between 24 hours and 9 days (Group C), or delivered 10 days or more (Group D) after the initiation of antenatal BMZ. Multivariate regression model covariates were selected a prior and included gestational age, birth year epoch, small for gestation, preeclampsia, multiple gestation and gestational diabetes. Variation inflation factors were used to check for collinearity between variables in our models. If the distribution of an outcome variable was skewed, bootstrapping (with 100 repetitions) was employed to overcome the normality assumption of the linear regression model and bias corrected confidence intervals were calculated and reported.

For all statistical tests, a p-value of 0.05 was considered significant.

RESULTS

Among the 667 infants in the study, 28% delivered prior to or within 6 hours of the first dose of BMZ, 8% delivered between 7 and 23 hours of the first dose, and 64% delivered after completing the full two-dose course of BMZ (≥24 hours after the first dose). We first examined the relationship between neonatal morbidity and the interval from the first dose of BMZ to delivery to see how our population compared with previous study populations that were used to examine the effects of BMZ on neonatal morbidity. Infants who delivered after completing the full two-dose course of BMZ differed from those who delivered prior to or within 6 hours of receiving the first dose of BMZ in several of the perinatal baseline characteristics (Table I). These differences are similar to what have been observed in prior observational studies that have examined this issue (20–23). We used multivariate regression analyses to adjust for these confounders and found that delivery after completing the full two-dose BMZ course was associated with a significant decrease in the incidence of severe IVH, a decrease in the need for higher levels of respiratory support at 24 hours of life (both intubated-mechanical ventilation and Respiratory Severity Score), and a decrease in the incidence of death compared with infants who were inadequately treated with BMZ (Table II). There was no association between completing a two-dose course of BMZ and the incidence of BPD, NEC, or severe ROP (Table II). These findings are similar to those of previous studies that have examined the effects of BMZ in infants born before 28 weeks gestation (20–23).

Our primary goal was to determine if the IVH lowering effects of BMZ might be time-limited, because this would increase the risk that a severe IVH might occur if an infant delivered more than a week (≥10 days) after BMZ treatment and still within the IVH vulnerable period (<28 weeks gestation). Four hundred twenty-nine infants were exposed to antenatal BMZ for ≥24 hours. The Figure shows the incidence of severe IVH stratified by the time to delivery after the first dose of BMZ.

Three hundred ninety-two infants received only a single (two-dose) course of BMZ: 312 delivered less than 10 days and 80 delivered ≥10 days after the first dose of a single course of BMZ (Figure and Table III). Several perinatal variables (birth year epoch, preeclampsia, gestational diabetes, multiple gestation, gestational age and small for gestational age) differed significantly between infants born <10 days and those born ≥10 days after a single BMZ course (Table III). After adjusting for these potential confounders we found that infants who delivered ≥10days after the first dose of BMZ had an increased risk of developing a severe IVH (Table IV). The incidence of severe IVH was 17% in infants born ≥10 days and 7% in those born <10 days after a single completed course of BMZ.

Thirty-seven infants received a second, or “rescue”, course of antenatal BMZ when their mothers remained pregnant for more than 9 days after their first BMZ course. All 37 infants delivered within 8 days of the second/rescue course of BMZ (gestational age = 26.5±0.9 weeks; time to delivery after the 1st course of BMZ = 17.9±5.3 days; time to delivery after the 2nd course of BMZ = 3.05±2.3 days). Despite the prolonged interval between the first course of BMZ and delivery, the incidence of severe IVH in infants, whose mothers received a second/rescue course of BMZ, was only 8% (Figure). This is similar to the rate of severe IVH (7%) among infants born <10 days after the first completed BMZ course. After adjusting for the potential confounders listed in Table IV, we found no difference in the incidence of severe IVH when infants who received a second/rescue course of BMZ were compared with infants who delivered within 9 days of the first completed BMZ course (adjusted OR 1.7; 95% CI 0.41–6.6, p=0.48).

We also examined whether the risks of other morbidities, that are modified by antenatal BMZ treatment (eg, levels of respiratory support at 24 hours after birth and death)(2) (Table II), waned with time in our population (Table IV). We found that the association between BMZ and the need for initial respiratory support (both mechanical ventilation and Respiratory Severity Score) appeared to wane with time (Table IV), and that a repeat or rescue course of BMZ was associated with persistence of BMZ’s beneficial effects. There was no difference in the need for mechanical ventilation (adjusted OR 0.98; 95% CI 0.38–2.54, p=0.97) or in the Respiratory Severity Score (adjusted Coefficient = 0.20; 95% CI −0.28 to 0.6.8, p=0.42)) when infants who received a second/rescue course of BMZ were compared with infants who delivered within 9 days of the first BMZ course. On the other hand, the effects of BMZ on neonatal mortality did not appear to be time-limited (Table IV). Our findings about the need for respiratory support and death after BMZ treatment are similar to those of previous studies (20–23).

DISCUSSION

Although the benefits of antenatal corticosteroids in infants born before 28 weeks gestation have not been proven in RCTs, evidence from observational studies suggests their benefits. As in prior observational studies (21–26), we also found that in infants delivering before 28 weeks gestation exposure to a two-dose course of antenatal BMZ was associated with a decreased incidence of severe IVH, need for increased levels of respiratory support at 24 hours after birth, and death (but not BPD, NEC, or severe ROP) (Table II).

Among infants delivered before 28 weeks gestation, the most consistent and largest change associated with BMZ administration was a decreased incidence of severe IVH (21–23) (Table II). Therefore, we felt that it was important to determine whether the IVH sparing effects associated with antenatal BMZ were persistent or waned with time. We found that the risk of severe IVH increased in infants who delivered ≥10 days after the first dose of antenatal BMZ (Table IV). We also found that a repeat or rescue course of BMZ was associated with persistence of BMZ's IVH sparing effects in infants who delivered remote from their first course of BMZ but still within the period of IVH vulnerability (before 28 weeks). Our findings differ from most of the prior studies that have examined the waning effects of antenatal BMZ on severe IVH. We suggest that this difference may be due to the fact that most of the prior studies examined populations with an insufficient number of infants that actually delivered during the IVH vulnerable period. Even in these studies a relationship can be seen between the incidence of severe IVH and the BMZ-to-delivery time interval, if infants delivering at the youngest gestational ages are examined separately (4, 24, 27–29).

The causes of IVH are multifactorial. They depend on the fragility of the immature germinal matrix microvasculature, fluctuations in cerebral blood flow, and coagulation disorders (30–34). In addition to altering the severity of an infant's lung disease, antenatal corticosteroid administration stabilizes the germinal matrix vasculature by downregulating vascular endothelial growth factor, suppressing angiogenesis, increasing coverage of nascent endothelial cells with pericytes and astrocyte foot processes, increasing basal lamina fibronectin levels, inhibiting neurovascular proteases, and increasing vascular tone and blood pressure stability (35–37). In the future, knowing which of these effects are reversible with time may identify crucial pathways for future manipulation.

There are several limitations to our study. Our study uses a prospectively collected, single center, observational data set that spans 17 years. Thus, our findings may not be generalizable to other centers. Our study was performed over a prolonged time interval. Even though we adjusted our analyses for the epoch in which the infants were born, there may have been unmeasured changes in practice that may have occurred during the study period that could have affected the rates of severe IVH. As an observational study, the reason for the non-administration of antenatal BMZ or for the timing of delivery after the BMZ course could not be controlled. Although we controlled for important confounders that differed between study groups, there is still the possibility of unmeasured residual confounding. The confidence intervals for our adjusted OR estimate of 4.16 are wide, (1.59–10.87) (Table IV). Therefore, the OR of severe IVH in these infants could be as low as 1.59

or as high as 10.87. However, most of the 95% confidence interval is above our point estimate suggesting the "true" effect may be larger than what we have observed. Certain obstetrical practices were introduced during the later third of the study period (magnesium for brain protection and delayed cord clamping). We were unable to reliably collect data about them during the early phases of their implementation and therefore have not included them in our data set. However, as of this time, neither antenatal Magnesium (38, 39) nor delayed cord clamping (40) has been shown to alter the incidence of severe IVH in preterm infants. It is possible that our study was underpowered to detect small differences in neonatal outcomes; the number of infants that delivered ≥10 days after the first dose of BMZ was small and the cohort that received a second course of steroids was even smaller.

On the other hand, there are also strengths to our study. The single center aspect of the study meant that the same consensus-driven, standardized approaches to respiratory, hemodynamic, fluid, nutrition and PDA management were consistent among the infants in each of the study eras. The same neonatologist reviewed all of the infants' cranial ultrasounds in addition to prospectively following the clinical course of all of the study infants and recording all of the study data.

Currently the American Congress of Obstetricians and Gynecologists recommends that a "*single rescue course of antenatal corticosteroids may be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 6/7 weeks, and the women are judged by the clinician to be likely to give birth within the next week*" (41). As corticosteroid treatment is initiated earlier in gestation, in an attempt to resuscitate periviable infants, the optimal timing of a repeat course has become a clinical dilemma. Unfortunately, obstetricians are limited in their ability to predict when preterm delivery will occur and are likely to both overestimate the risks of delivery, and administer the corticosteroids too early (42, 43), when the beneficial effects might dissipate, as well as to underestimate the risks (9), and administer them too late, when imminent delivery might preclude completion of the planned treatment. Recent studies suggest that long-term neurodevelopmental morbidity after preterm birth is most highly correlated with IVH, BPD and ROP (44) but *not* RDS. Depending on the goals for treatment, knowing that rescue BMZ does not decrease the risks of BPD or ROP, and might only be beneficial in decreasing the incidence of IVH (if infants deliver before 28 weeks) and RDS (if infants deliver before 34 weeks), makes the question of when to use a rescue dose even more of a conundrum. Replication of this study in other observational data sets is warranted and if our results are confirmed could help guide recommendations on the timing of rescue courses of betamethasone.

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Abbreviations

RCT randomized controlled trial

PDA	patent ductus arteriosus
NEC	necrotizing enterocolitis
ROP	retinopathy of prematurity
IVH	intraventricular/intracranial hemorrhage
RDS	respiratory distress syndrome
BPD	bronchopulmonary dysplasia
BMZ	betamethasone
OR	odds ratio

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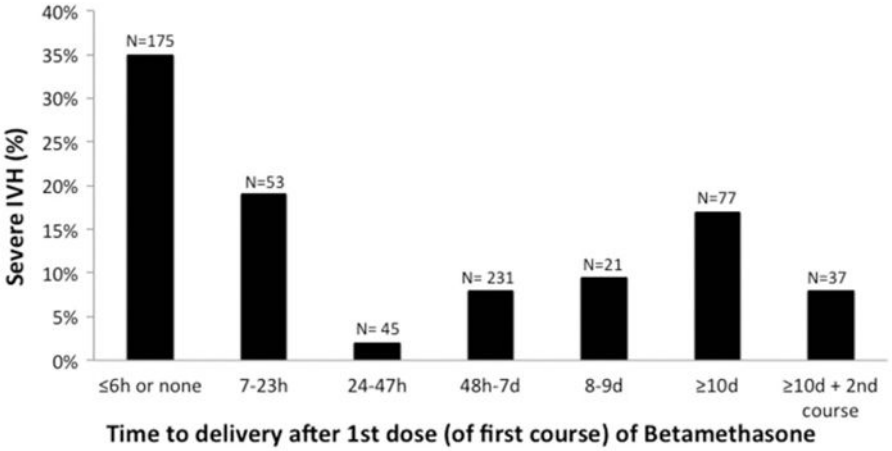

Figure.

Relationship between the time to delivery after the first course of betamethasone and the incidence of severe (grades 3 and 4) intraventricular hemorrhage. Among the 667 infants in the study population, 28 died before 4 days and before the highest grade of intraventricular hemorrhage could be determined: n=8, in the group that delivered ≤6 hours from the initiation of BMZ; n=2, in the group that delivered between 7 and 23 hours; n=3, in the group that delivered between 24 and 47 hours; n=12, in the group that delivered between 48 hours and 7 days; n=0, in the group that delivered between 8 and 9 days; n=3, in the group that delivered 10 days or more after a single course of BMZ; and, n=0, in the group that delivered after a second/rescue course of BMZ.

Table 1; online

Characteristics of infants who received no betamethasone or betamethasone ≤6 hours prior to delivery and those who received a two-dose course of betamethasone ≥24 hours prior to delivery

Characteristic	Time to delivery after 1st dose of betamethasone		
	None or ≤ 6 hours N= 183	≥24 hours N= 429	P value
Birth year epoch (%)			0.03
1998 – 2003	46	37	
2004 – 2009	36	35	
2010 – 2015	19	28	
Preeclampsia (%)	4	23	<0.0001
Gestational Diabetes (%)	3	8	0.03
Clinical Chorioamnionitis (%)	14	26	0.02
Cesarean Delivery (%)	59	69	0.02
Presentation at delivery (%)			0.94
Vertex	59	60	
Breech	35	34	
Transverse	6	6	
Multiple Birth (%)	28	35	0.11
Caucasian (%)	35	48	0.02
Outborn (%)	80	9	<0.0001
Gestational age <26 weeks (%)	58	39	<0.0001
Gestational age (mean ± SD)	25.6 ± 1.2	26.1 ± 1.1	<0.0001
Small for gestational age (%)	6	20	<0.0001
Birth weight (mean ± SD)	830 ± 188	803 ± 197	0.12
Male	59	49	0.04
5 minute Apgar score ≥6 (%)	55	71	<0.0001
Prophylactic indomethacin (%)	72	70	0.77
Early Onset Sepsis (%)	4	5	0.64

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Table 2

Relationship between the time to delivery after the first dose of betamethasone and Neonatal Morbidities

Neonatal Morbidity	Time to delivery after 1st dose of betamethasone			Unadjusted Odds ratio (or Coefficient) for Time to delivery ≥ 24 hours (95% CI)	Adjusted* Odds ratio (or Coefficient) for Time to delivery ≥24 hours (95% CI)	P value†
	≤6 hrs N= 183	7–23 hrs N = 55	≥24 hrs N = 429			
Severe IVH‡ (%)	35	19	9	0.18 (0.12, 0.29)	0.13 (0.07, 0.27)	<0.0001
Intubated-Mechanical Ventilation at 24h (%)	88	67	76	0.45 (0.27, 0.73)	0.47 (0.23, 0.98)	0.043
Respiratory Severity Score at 24h (mean ± SD)§	2.7±2.3	1.6 ± 0.6	2.1 ± 1.4	−0.57 (−0.98, −0.26)	−0.42 (−0.72, − 0.01)	0.014
Death (%)	35	25	17	0.39 (0.32, 1.25)	0.25 (0.13, 0.47)	<0.0001
BPD ** (%)	33	29	32	0.96 (0.62, 1.48)	0.82 (0.43, 1.56)	0.541
BPD or death (%)	55	47	42	0.58 (0.41, 0.82)	0.46 (0.26, 0.79)	0.005
NEC †† (%)	21	21	14	0.63 (0.38, 1.03)	0.62 (0.30, 1.28)	0.200
NEC or death (%)	43	31	26	0.45 (0.32, 0.65)	0.34 (0.25, 0.65)	0.001
ROP‡‡ requiring treatment (%)	16	19	12	0.76 (0.42, 1.36)	1.30 (0.51, 3.12)	0.615

*Betamethasone ≤6 hours referent. Adjusted for gestational age, small for gestation, gestational diabetes, race, preeclampsia, multiple birth, outborn, chorioamnionitis, delivery mode and birth year epoch.

†P value for adjusted odds ratio or coefficient.

‡Severe IVH, grade 3 or 4 among infants who survived at least 4 days. N= 639 (some infants died prior to the time the morbidity was able to be determined)

§*Respiratory Severity Score (RSS)* = mean airway pressure x fraction of inspired oxygen. By convention, mean airway pressure = liter flow rate when infants received nasal cannula flows of ≤3 liter/min; measurements made at 24 hours after birth. N= 654 (some infants died prior to the 24-hour time point). Linear regression with bootstrapping coefficient and bias corrected confidence interval reported.

**_Bronchopulmonary Dysplasia (BPD)_*, physiologic definition by room air challenge at 36 weeks post-menstrual age. N= 528 (some infants died prior to 36 weeks post- menstrual age)

††_Necrotizing enterocolitis (NEC)_, Bell's classification ≥II (treated medically or surgically) or "spontaneous perforations". N= 564 (some infants died prior to the time the morbidity was able to be determined, i.e., prior to 21 days postnatal age or prior to receiving enteral feedings greater than 80 ml/kg/day)

‡‡*Retinopathy of Prematurity (ROP)*, requiring treatment. N= 524 (some infants died prior to the time the morbidity was able to be determined at 38 weeks post-menstrual age)

Table 3

Characteristics of infants who received a single course (two doses) of betamethasone: comparison of those who delivered less than 10 days after the first betamethasone dose with those who delivered greater than or equal to 10 days after the first betamethasone dose

Characteristic	Time to delivery after 1st dose of betamethasone		P value
	<10 days (N = 312)	≥10 days (N = 80)	
Birth year epoch (%)			0.012
1998 – 2003	39	21	
2004 – 2009	33	43	
2010 – 2015	28	36	
Preeclampsia (%)	26	13	0.013
Gestational Diabetes (%)	6	14	0.030
Clinical Chorioamnionitis (%)	25	29	0.494
Cesarean Delivery (%)	69	71	0.726
Presentation at delivery (%)			0.483
Vertex	60	66	
Breech	34	28	
Transverse	6	6	
Multiple Gestation (%)	29	48	0.001
Caucasian (%)	46	55	0.158
Outborn (%)	10	10	0.917
Gestational age <26 weeks (%)	48	11	<0.0001
Gestational age (mean ± SD)	25.8 ± 1.1	26.7 ± 0.7	<0.0001
Small for gestational age (%)	26	5	<0.0001
Birth weight-gm (mean ± SD)	766 ±193	919 ± 183	<0.0001
Male (%)	50	43	0.231
5 minute Apgar score ≥6 (%)	69	73	0.561
Prophylactic indomethacin (%)	69	71	0.726
Early Onset Sepsis (%)	4	8	0.216
Time to delivery * - days (mean ± SD)	3.9 ± 2.1	14.9 ± 4.0	<0.0001

* Time to delivery after 1st dose of betamethasone; all infants delivered at least 24 hours after the 1st dose of betamethasone

Table 4

Waning effects of a single course of antenatal betamethasone on neonatal morbidly

Neonatal Morbidity	Unadjusted Odds ratio (or Coefficient) for Time to delivery ≥ 10 days (95% CI)	Adjusted* Odds ratio (or Coefficient) for Time to delivery ≥ 10 days (95% CI)	P value†
Severe IVH‡ (%)	2.67 (1.26–5.61)	4.16 (1.59–10.87)	0.004
Intubated-Mechanical Ventilation at 24h (%)	1.05 (0.58–1.89)	3.23(1.59–6.57)	0.001
Respiratory Severity Score at 24h (mean ± SD)§	0.19 (CI −0.22, 0.59)	0.39 (CI 0.10–0.84)	0.029
Death (%)	0.40 (0.09–1.80)	1.37 (0.58–3.20)	0.468
BPD ** or death (%)	1.50 (0.64–3.60)	1.26(0.68–2.4)	0.460
NEC †† or death (%)	1.00 (0.39–2.60)	1.30 (0.65–2.6)	0.468

Note: all infants completed a two dose course of antenatal betamethasone

*Adjusted for gestational age at birth, small for gestational age, preeclampsia, multiple birth, gestational diabetes and birth year epoch.

†P value for adjusted odds ratio or coefficient

‡Grade 3 or 4

§*Respiratory Severity Score (RSS) =* mean airway pressure x fraction of inspired oxygen. By convention, mean airway pressure = liter flow rate when infants received nasal cannula flows of ≤3 liter/min; measurements made at 24 hours after birth; linear regression with bootstrapping coefficient and bias corrected confidence interval reported

**_Bronchopulmonary Dysplasia (BPD),_ physiologic definition by room air challenge at 36 weeks post menstrual age

††_Necrotizing enterocolitis_, Bell's classification ≥II (treated medically or surgically) and "spontaneous perforations"