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RESEARCH ARTICLE

Fetal Medicine

Potential missed opportunities for antenatal corticosteroid exposure and outcomes among periviable births: Observational cohort study

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Abstract

Objective: To test the hypothesis that potential missed opportunities for antenatal corticosteroids increase as gestational age decreases and are associated with adverse outcomes.

Design: Observational cohort study.

Setting: Twenty-four US centers in the Neonatal Research Network.

Population: Actively treated infants at 22–25 weeks of gestation and with birthweight 401–1000 g, without major birth defects, born 2006–18.

Methods: Potential missed opportunity was defined as no antenatal corticosteroids but did have prenatal antibiotics, and/or magnesium sulphate, and/or prolonged rupture of membranes. Poisson regression models adjusted for baseline characteristics.

Main outcome measures: Antenatal corticosteroid exposure, mortality and severe intracranial haemorrhage or periventricular leucomalacia.

Results: A total of 6966 (87.5%) infants were exposed to antenatal corticosteroids, 454 (5.7%) had no exposure but potential missed opportunities for antenatal corticosteroid exposure, and 537 (6.7%) had no exposure and no evidence of potential missed opportunities. Compared with infants born at 25 weeks, potential missed opportunities for antenatal corticosteroid exposure were more likely at 22 weeks (adjusted relative risk [aRR] 11.06, 95% confidence interval [CI] 7.52–16.27) and 23 weeks (aRR 3.24, 95% CI 2.44–4.29) but did not differ at 24 weeks (aRR 1.08, 95% CI 0.82–1.42). Potential missed opportunities for antenatal corticosteroids decreased over time at 22–23 weeks of gestation. Antenatal-corticosteroid-exposed infants had lower risk of death (31.0% versus 54.8%; aRR 0.77, 95% CI 0.70–0.84) and survivors had lower risk of severe brain injury (25.0% versus 44.5%; aRR 0.64, 95% CI 0.55–0.73) compared with infants with potential missed opportunities.

Abbreviations: ANS, antenatal corticosteroids; ICH, intracranial haemorrhage; PVL, periventricular leucomalacia.

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Conclusion: Potential missed opportunities for antenatal corticosteroid exposure increased with decreasing gestational age and were associated with higher rates of death and severe brain injury among actively treated periviable births.

KEYWORDS
antenatal births corticosteroids, extremely preterm infant, infant, intracranial haemorrhage, intraventricular haemorrhage, missed opportunities, mortality, newborn, periviable

Tweetable abstract: Missed opportunities for antenatal steroids among periviable births are associated with death and brain injury.

1 | INTRODUCTION

Antenatal corticosteroid exposure reduces preterm infant mortality and major morbidities including intracranial haemorrhage (ICH).[1] Observational studies suggest that the absolute benefit of antenatal corticosteroids may be highest among periviable infants.[2,3] However, many eligible women[4] do not receive this treatment[5,6] and it is not known whether this is due to policy or a lack of opportunity. Consensus statements from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend administration of antenatal corticosteroids at 24 weeks of gestation and recommend considering steroids at 23 weeks of gestation, but until recently none of these groups have recommended administration at 22 weeks of gestation,[4,7] even when active postnatal treatment is planned.[8]

It has previously been shown that periviable infants are more likely to be exposed to antibiotics before delivery than to antenatal corticosteroids.[9] Treatment with intravenous medications, such as antibiotics or magnesium sulphate, or prolonged rupture of membranes before delivery may indicate that there was potentially sufficient time for intramuscular antenatal corticosteroid administration. We hypothesised that the rate of potential missed opportunities for antenatal corticosteroid exposure would increase as gestational age decreases among actively treated periviable infants. We further hypothesised that missed opportunities for antenatal corticosteroids would be associated with a higher rate of hospital mortality and/or severe brain injury.

2 | METHODS

2.1 | Study population

This retrospective cohort study included infants without major birth defects born at 24 NICHD Neonatal Research Network centres between 1 January 2006 and 31 December 2018 with a gestational age of 22^{+0} to 25^{+6} weeks and a birthweight of 401–1000 g. Best obstetric estimate was used to determine gestational age if available; otherwise, we used best neonatal estimate.[10] These infants were included in a registry of extremely preterm infants maintained by the Neonatal Research Network. The institutional review board at each centre approved participation with either parental consent required or a waiver of consent allowed. Data were collected prospectively including maternal demographic, pregnancy and delivery information, and infant outcomes from birth to discharge, transfer, death or 120 days. Beyond 120 days, limited outcome data were collected until discharge or death up to 1 year after birth. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11] This study was funded by the NICHD (Grant number UG1 HD034216) and the National Heart Lung and Blood Institute (Grant number K23HL157618). The funder was not involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

2.2 | Definitions

Antenatal corticosteroid exposure included infants exposed to partial, complete or repeat courses of antenatal corticosteroids.[1,12] Potential missed opportunities for antenatal corticosteroid exposure were defined as having no exposure to antenatal corticosteroids but having one or more of the following indicators that there was potentially sufficient time for intramuscular antenatal corticosteroid administration: receipt of antibiotics within 72 hours before delivery, administration of antenatal magnesium sulphate (collected beginning April 2011) and rupture of membranes more than 18 hours before delivery. Small for gestational age was defined as birthweight below the 10th centile for sex and gestational age.[13] Severe brain injury was defined as severe ICH or periventricular leucomalacia (PVL) on cranial imaging. Severe ICH was defined as ventricular enlargement with concurrent or previous blood in the ventricles or parenchyma blood or echodensity.[14] Periventricular leucomalacia was defined as cysts or echolucencies in the periventricular white matter. Active postnatal treatment was defined as any of the following: intubation, surfactant, continuous positive airway pressure, bag-and-mask, mechanical ventilation,

chest compressions, epinephrine, volume resuscitation, inotrope support or parenteral nutrition.[8,9,15]

2.3 | Exposure and outcomes

The primary outcome was the overall rate of antenatal corticosteroid exposure and potential missed opportunities for exposure at each gestational age. Secondary outcomes included death, severe ICH/PVL or death, severe ICH/PVL alone and changes in rates of antenatal corticosteroid exposure and potential missed opportunities for exposure by gestational age over time. The composite outcome of severe ICH/PVL or death was defined in two different ways: (1) severe ICH/PVL or death before evaluation by cranial imaging, and (2) severe ICH/PVL or death before discharge.

2.4 | Statistical analysis

Infants who received active postnatal treatment were included in the primary analysis. Infants were excluded from all analyses if missing data were needed to define exposure groups or active treatment. The proportions of infants exposed to antenatal corticosteroids and with potential missed opportunities for exposure were examined overall, by gestational age, and by birth year. Graphs of the proportions by birth year included a local weighted regression (LOESS) curve with a smoothing parameter of 0.4 to fit a smooth curve over the scatter plots to aid in visualisation of trends over time. Statistical significance for unadjusted comparisons between infants in the antenatal corticosteroids and potential missed opportunities for antenatal corticosteroids groups was determined by chi-square test for categorical variables and Kruskal–Wallis test for continuous variables.

Poisson regression models with robust variance estimators were used to assess adjusted comparisons between groups.[16] Adjusted relative risks (aRR), 95% confidence intervals (CI), and p values by the score or Wald chi-square test from these models are reported. All model covariates were selected a priori and comprised known risk factors for adverse outcomes including study centre, maternal characteristics (age, race/ethnicity, education, medical insurance, marital status, any prenatal care, insulin-dependent diabetes, chronic or pregnancy-induced hypertensive disorders, antepartum haemorrhage, clinical chorioamnionitis, multiple birth and delivery mode) and infant characteristics (sex, birthweight in grams and gestational age in weeks). Maternal education was missing for 23% of the cohort and was entered in models with a level indicating missing so as to minimise exclusion of observations with missing values. Each of the other covariates were missing for less than 1% of infants. In total, 2.6% of observations were excluded from models because of missing covariates. The adjusted risk of potential missed opportunities for antenatal corticosteroids at each gestational age was compared with the risk for those born at 25 weeks. Temporal changes in rates of antenatal corticosteroid exposure and in potential missed opportunities were examined with a model that included birth year (continuous) and the interaction between birth year and gestational age in addition to the covariates above.

Secondary outcomes, including death and severe brain injury, were compared between infants in the antenatal corticosteroid and potential missed opportunities for antenatal corticosteroid groups using models that allowed for interaction between exposure group and gestational age, while controlling for the other factors listed above. The interaction was not significant for the outcomes studied, indicating no statistically significant difference in the exposure–outcome relationship by gestational age. Therefore, the overall adjusted relative risks from main effects models and associated p values were reported. As a sensitivity analysis, associations between antenatal corticosteroid exposure and secondary outcomes were also examined after excluding the 46 women included in the potential missed antenatal corticosteroid group because of prolonged rupture alone. Further, to determine if associations between antenatal corticosteroid exposure and outcomes changed over time, we conducted a sensitivity analysis examining 3-year periods with the exception that the first period was 4 years: 2006–09, 2010–12, 2013–15, 2016–18. Models included the interaction between exposure group and birth year period. Sensitivity analyses to examine the proportion of infants with potential missed opportunities for antenatal corticosteroid exposure by gestational age and to assess trends in antenatal corticosteroid exposure were conducted using data from all infants, including those not actively treated. Trends in exposure were also examined among actively treated infants in the subset of 11 centres that participated in the Neonatal Research Network during all study years. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Values of p less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study population

The total cohort included 8967 infants after exclusion of 396 infants with congenital anomalies and 339 infants missing exposure variables (Figure S1). The primary analysis included 7957 (88.7%) infants who were actively treated postnatally. Of these, 6966 were exposed to antenatal corticosteroids (87.5%), 454 (5.7%) had no exposure to antenatal corticosteroids but potential missed opportunities for exposure and 537 (6.7%) had no exposure and no apparent potential missed opportunities for exposure to antenatal corticosteroids. The mean ± standard deviation gestational age of infants actively treated was 24.1 ± 0.9 weeks with a birthweight of 672 ± 127 g. The proportion of actively treated infants varied by gestational age (22 weeks: 32.1%, 23 weeks: 83.1%, 24 weeks: 98.2%, 25 weeks: 99.7%; $p < 0.001$) and by exposure group (Table 1).

Actively treated infants exposed to antenatal corticosteroids were more likely to have mothers with more than a high

TABLE 1 Proportion of infants actively treated at birth by gestational age and antenatal corticosteroid (ANS) group

	Any ANS *n*/*N* (column %)	Potential missed ANS *n*/*N* (column %)	No ANS exposure or potential *n*/*N* (column %)	All *n*/*N* (column %)
By gestational age (weeks)				
22				
Active treatment	170/214 (79.4)	70/352 (19.9)	48/332 (14.5)	288/898 (32.1)
No active treatment	44/214 (20.6)	282/352 (80.1)	284/332 (85.5)	610/898 (67.9)
23				
Active treatment	1333/1432 (93.1)	158/296 (53.4)	162/262 (61.8)	1653/1990 (83.1)
No active treatment	99/1432 (6.9)	138/296 (46.6)	100/262 (38.2)	337/1990 (16.9)
24				
Active treatment	2573/2608 (98.7)	106/116 (91.4)	147/155 (94.8)	2826/2879 (98.2)
No active treatment	35/2608 (1.3)	10/116 (8.6)	8/155 (5.2)	53/2879 (1.8)
25				
Active treatment	2890/2897 (99.8)	120/122 (98.4)	180/181 (99.4)	3190/3200 (99.7)
No active treatment	7/2897 (0.2)	2/122 (1.6)	1/181 (0.6)	10/3200 (0.3)
All gestational ages				
Active treatment	6966/7151 (97.4)	454/886 (51.2)	537/930 (57.7)	7957/8967 (88.7)
No active treatment	185/7151 (2.6)	432/886 (48.8)	393/930 (42.3)	1010/8967 (11.3)

school degree, private medical insurance, and with at least one prenatal visit than actively treated infants with potential missed opportunities for exposure (Table 2). The proportion of white non-Hispanic mothers was higher in the antenatal corticosteroid group but the proportion of Hispanic mothers was lower. Breech vaginal delivery occurred more often in the potential missed opportunities group while caesarean delivery was more frequent in the antenatal-corticosteroid-exposed group.

The proportions of infants in the antenatal corticosteroids and potential missed opportunities groups with mothers who received antibiotics in the 72 hours before birth and had rupture of membranes for more than 18 hours did not differ (Table 2). A larger proportion of infants exposed to antenatal corticosteroids also received magnesium sulphate (84.4% versus 44.3%, $p < 0.001$). Ten percent of infants in the potential missed opportunities group were included in that group solely as the result of rupture of membranes of more than 18 hours and the proportion did not differ by gestational age.

3.2 | Antenatal corticosteroid exposure and potential missed opportunities

The proportions of actively treated infants exposed to antenatal corticosteroids and with potential missed opportunities for exposure varied by gestational age (Figure 1). Receipt of antenatal corticosteroids varied by gestational age (22 weeks: 59.0%, 23 weeks: 80.6%, 24 weeks: 91.0%, 25 weeks: 90.6%). Compared with infants born at 25 weeks, potential missed opportunities for exposure to antenatal corticosteroids were more common for infants born at 22 weeks (aRR 11.06, 95% CI 7.52–16.27, $p < 0.001$) and 23 weeks (aRR 3.24, 95% CI 2.44–4.29, $p < 0.001$) after controlling for potential confounding factors. There was no difference in rates of potential missed opportunities for antenatal corticosteroids between infants born at 24 and 25 weeks.

During the study period, antenatal corticosteroid exposure increased overall from 79.2% (471/595) in 2006 to 91.5% (582/636) in 2018 ($p < 0.001$). Correspondingly, potential missed opportunities for antenatal corticosteroid exposure decreased from 7.9% (47/595) in 2006 to 4.7% (30/636) in 2018 ($p = 0.001$) (Appendix S1). The increase in antenatal corticosteroid exposure varied by gestational age with the largest increase among actively treated infants born at 22 weeks, from 12.5% (2/16) in 2006 to 87.2% (34/39) in 2018, an increase of about 10% per year (aRR per year increase: 1.10, 95% CI 1.07–1.14) (Figure 2, Appendix S1). For infants born at 23 weeks, antenatal corticosteroid exposure increased from 59.8% (64/107) to 89.0% (138/155) during the study period whereas smaller increases were observed among infants born at 24 weeks and those born at 25 weeks. The rate of potential missed opportunities for exposure decreased among infants born at 22 weeks from 68.8% (11/16) in 2006 to 2.6% (1/39) in 2018, a decrease of about 10% per year (aRR 0.90, 95% CI 0.85–0.95, $p < 0.001$). The rate in infants born at 23 weeks also decreased from 16.8% (18/107) in 2006 to 3.9% (6/155) in 2018 ($p < 0.001$). The proportion of infants born at 24 and 25 weeks with potential missed opportunities for exposure to antenatal corticosteroids remained low throughout.

3.3 | Infant outcomes

Overall, 66.4% (5269/7934) of actively treated infants survived to discharge. The proportion of infants who

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TABLE 2 Baseline maternal and infant characteristics among infants actively treated at birth and antenatal corticosteroid (ANS) exposure

n (column %) or as shown[a]	Any ANS, *N* = 6966	Potential missed, ANS *N* = 454	*p* value[b]
Study criteria for groups			
Maternal antibiotics <72 h before birth	5551 (79.7)	365 (80.4)	0.72
Antenatal magnesium sulphate[c]	3637/4310 (84.4)	116/262 (44.3)	<0.001
Rupture of membranes >18 h before delivery	2100 (30.1)	136 (30.0)	0.93
Maternal and delivery characteristics			
Maternal age (years), mean ± SD	27.9 ± 6.3	27.4 ± 6.4	0.18
Married	3138 (45.4)	181 (40.6)	0.05
Highest level of education			
<High school	1036/5382 (19.2)	109/337 (32.3)	<0.001
High school degree	1648/5382 (30.6)	115/337 (34.1)	
>High school	2698/5382 (50.1)	113/337 (33.5)	
Mother's medical insurance			
Public	3705 (53.5)	276 (61.9)	<0.001
Private	2814 (40.7)	114 (25.6)	
Self-pay/uninsured/other	401 (5.8)	56 (12.6)	
Mother's race/ethnicity[d]			
Black non-Hispanic	2830 (40.8)	189 (41.9)	<0.001
White non-Hispanic	2742 (39.5)	132 (29.3)	
Hispanic	1012 (14.6)	109 (24.2)	
Other	349 (5.0)	21 (4.7)	
At least one prenatal visit	6684 (96.1)	416 (91.8)	<0.001
Insulin-dependent diabetes	284 (4.1)	30 (6.7)	0.01
Maternal hypertension	1408 (20.2)	101 (22.2)	0.30
Antepartum haemorrhage	1505 (21.6)	113 (24.9)	0.10
Chorioamnionitis	1436 (20.6)	104 (23.0)	0.24
Multiple birth	1824 (26.2)	114 (25.1)	0.61
Delivery mode			
Vaginal vertex	2319 (33.3)	169 (37.4)	<0.001
Vaginal breech	476 (6.8)	71 (15.7)	
Caesarean section	4167 (59.9)	212 (46.9)	
Infant characteristics			
Gestational age (weeks), mean ± SD	24.2 ± 0.8	23.6 ± 1.0	<0.001
By gestational age (weeks)			
22	170 (2.4)	70 (15.4)	<0.001
23	1333 (19.1)	158 (34.8)	
24	2573 (36.9)	106 (23.3)	
25	2890 (41.5)	120 (26.4)	
Birthweight (grams), mean ± SD	674 ± 126	641 ± 128	<0.001
Small for gestational age	450 (6.5)	14 (3.1)	0.004
Male	3592 (51.6)	222 (48.9)	0.27

[a]Percent denominators are shown for characteristics not collected all years (magnesium sulphate) and for characteristics with information missing for more than 1% of infants (maternal education). Otherwise, information was missing for: marital status, 55 infants; maternal medical insurance, 54 infants; mother's race/ethnicity, 36 infants; prenatal care, 11; insulin-dependent diabetes, 22; maternal hypertension, 3; antepartum haemorrhage, 7; chorioamnionitis, 8; delivery mode, 6; small for gestational age, 4; male sex, 4.

[b]*p*-value by chi-square test (categorical variables) or Kruskal–Wallis test (continuous variables).

[c]Magnesium sulphate was collected beginning 1 April 2011.

[d]Maternal ethnicity was classified as non-Hispanic for 4% of infants whose mothers reported race as black and for less than 1% of infants whose mothers reported race as white but for whom ethnicity was not reported. The 370 infants with other maternal race includes 74% Asian/Pacific Islander, 13% American Indian or Alaska native, and 13% more than one race.

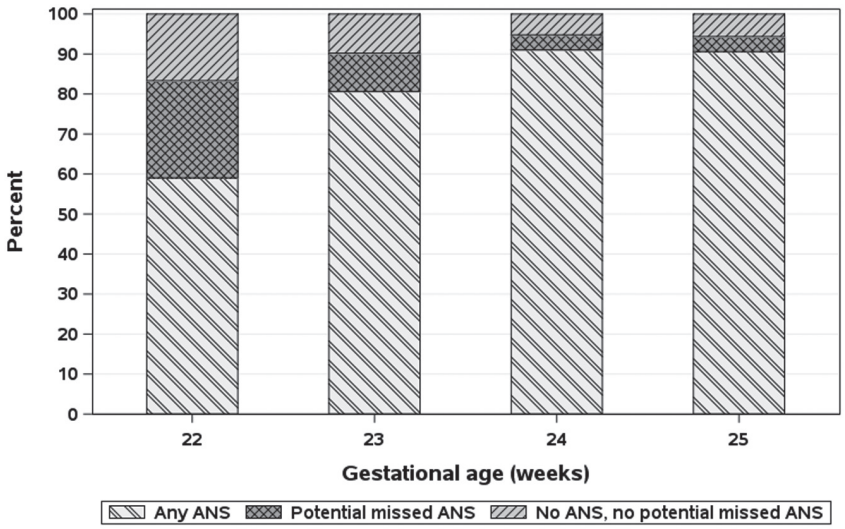

FIGURE 1 Proportion of actively treated infants with antenatal corticosteroid (ANS) exposure, potential missed opportunities for ANS exposure, and no ANS and no evidence of potential missed opportunities for ANS exposure at each gestational age. The proportion of infants exposed to ANS increased with increasing gestational age at 22 and 23 weeks of gestation and did not differ between infants at 24 and 25 weeks of gestation. The proportion of infants with potential missed opportunities for exposure to ANS decreased with increasing gestational age at 22 and 23 weeks of gestation and did not differ between infants at 24 and 25 weeks of gestation.

n/N (column %)	22 weeks	23 weeks	24 weeks	25 weeks
Any ANS exposure	170/288 (59.0)	1333/1653 (80.6)	2573/2826 (91.0)	2890/3190 (90.6)
Potential missed opportunities for ANS	70/288 (24.3)	158/1653 (9.6)	106/2826 (3.8)	120/3190 (3.8)
No ANS and no potential missed opportunities for ANS	48/288 (16.7)	162/1653 (9.8)	147/2826 (5.2)	180/3190 (5.6)

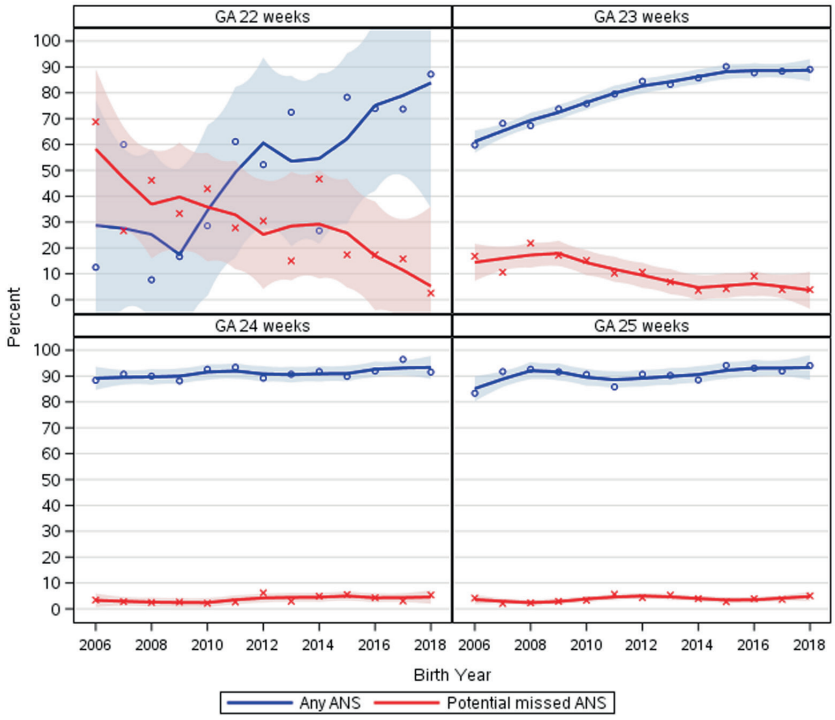

FIGURE 2 Rates of antenatal corticosteroid (ANS) exposure and potential missed opportunities for ANS exposure 2006–18 among infants actively treated at birth. Circles and crosses indicate the percentage of infants born each year in the exposure groups, the smoothed lines show the trends, and the shading shows the 95% confidence intervals (95% CI) for the curves. The year by gestational age (GA) interaction was significant; $p < 0.001$, for both rates.

	Adjusted RR (95% CI) for the change per year			
	22 weeks	23 weeks	24 weeks	25 weeks
Any ANS exposure	1.10 (1.07–1.14)	1.03 (1.02–1.04)	1.004 (1.0002–1.007)	1.004 (1.001–1.007)
Potential missed opportunities for ANS	0.90 (0.85–0.95)	0.87 (0.84–0.91)	1.03 (0.98–1.09)	1.04 (0.99–1.09)

died before discharge was lower among infants exposed to antenatal corticosteroids than among those with potential missed opportunities for antenatal corticosteroids (Table 3). Mortality was 23% lower overall for infants exposed to antenatal corticosteroids than for those in the potential missed opportunities group (31.0% versus 54.8%,

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TABLE 3 Outcomes by exposure to antenatal corticosteroids (ANS) among infants actively treated at birth

Outcome[a]	Any ANS, *N* = 6966	Potential missed ANS, *N* = 454	aRR (95% CI)[b]	*p*-value[c]
Death, *n*/*N* (%)				
All gestational ages	2153/6943 (31.0)	249/454 (54.8)	0.77 (0.70–0.84)	<0.001
22 weeks	108/169 (63.9)	57/70 (81.4)	0.91 (0.77–1.08)	
23 weeks	621/1333 (46.6)	114/158 (72.2)	0.73 (0.65–0.83)	
24 weeks	830/2560 (32.4)	48/106 (45.3)	0.69 (0.56–0.86)	
25 weeks	594/2881 (20.6)	30/120 (25.0)	0.81 (0.59–1.10)	
Death ≤12 hours, *n*/*N* (%)				
All gestational ages	386/6966 (5.5)	103/454 (22.7)	0.47 (0.37–0.59)	<0.001
22 weeks	25/170 (14.7)	30/70 (42.9)	0.47 (0.30–0.73)	
23 weeks	141/1333 (10.6)	53/158 (33.5)	0.47 (0.35–0.64)	
24 weeks	147/2573 (5.7)	12/106 (11.3)	0.57 (0.32–1.01)	
25 weeks	73/2890 (2.5)	8/120 (6.7)	0.35 (0.17–0.72)	
Severe ICH/PVL or death before evaluation, *n*/*N* (%)				
All gestational ages	2179/6947 (31.4)	274/452 (60.6)	0.64 (0.59–0.71)	<0.001
22 weeks	86/170 (50.6)	57/70 (81.4)	0.66 (0.54–0.80)	
23 weeks	580/1328 (43.7)	115/157 (73.2)	0.65 (0.57–0.74)	
24 weeks	839/2568 (32.7)	56/105 (53.3)	0.63 (0.52–0.77)	
25 weeks	674/2881 (23.4)	46/120 (38.3)	0.63 (0.50–0.80)	
Severe ICH/PVL or death before discharge, *n*/*N* (%)				
All gestational ages	3104/6948 (44.7)	316/453 (69.8)	0.78 (0.73–0.84)	<0.001
22 weeks	124/170 (72.9)	62/70 (88.6)	0.89 (0.78–1.02)	
23 weeks	817/1329 (61.5)	139/158 (88.0)	0.75 (0.69–0.82)	
24 weeks	1198/2568 (46.7)	63/105 (60.0)	0.78 (0.66–0.92)	
25 weeks	965/2881 (33.5)	52/120 (43.3)	0.77 (0.62–0.95)	
Survived >12 h and had cranial imaging, *N*	6371	323		
Severe ICH/PVL, *n*/*N* (%)				
All gestational ages	1586/6354 (25.0)	143/321 (44.5)	0.64 (0.55–0.73)	<0.001
22 weeks	46/130 (35.4)	21/34 (61.8)	0.55 (0.38–0.79)	
23 weeks	390/1138 (34.3)	52/94 (55.3)	0.64 (0.51–0.79)	
24 weeks	605/2334 (25.9)	39/88 (44.3)	0.61 (0.48–0.79)	
25 weeks	545/2752 (19.8)	31/105 (29.5)	0.72 (0.53–0.98)	

[a]Information was missing for: final status, 23 infants; severe ICH/PVL or death before evaluation, 21; severe ICH/PVL or death before discharge, 19; severe ICH/PVL, 19. For both composite outcomes, 724 infants who died ≤12 h after birth or died after 12 h but before evaluation by cranial imaging, 1018 infants who had severe ICH/PVL and survived to discharge and 711 infants who had severe ICH/PVL and later died were counted as having the outcome. For the second composite outcome an additional 967 infants without severe ICH/PVL on cranial imaging who died before discharge were counted as having the outcome.

[b]Adjusted relative risks (aRR) and 95% confidence intervals (95% CI) from models that included ANS group (any ANS, potential missed opportunities ANS), study centre, mother's age (continuous), mother's race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), mother's education (<high school degree, high school degree, >high school degree), mother's medical insurance (public, private, self-pay/uninsured/other), marital status, at least one prenatal visit, insulin-dependent diabetes, maternal hypertension, antepartum haemorrhage, chorioamnionitis recorded in the mother's medical record, multiple birth, delivery mode (vaginal vertex, vaginal breech, caesarean section), infant male sex, birthweight (continuous) and gestational age (22, 23, 24, 25 weeks). Initial models included the interaction between ANS group and gestational age. The interaction was not significant for any outcome (death before discharge: $p = 0.16$; death within 12 h: $p = 0.79$; severe ICH/PVL or death before evaluation: $p = 0.99$; severe ICH/PVL or death before discharge: $p = 0.19$; severe ICH/PVL: $p = 0.72$ by the score chi-square test). Hence, for each outcome, the overall aRR and associated p value is shown. Proportions and aRRs are shown by gestational age for descriptive purposes.

[c]Statistical significance was determined by the Wald chi-square test.

aRR 0.77, 95% CI 0.70–0.84, $p < 0.001$, number needed to treat for benefit [NNTb] 5, 95% CI 4–6). Death occurred within 12 hours of birth in 5.5% of infants exposed to antenatal corticosteroids compared with 22.7% of infants in the potential missed opportunities for antenatal corticosteroids group (aRR 0.47, 95% CI 0.37–0.59, $p < 0.001$, NNTb 6, 95% CI 5–8).

Most actively treated infants who survived for longer than 12 hours had cranial imaging (7119/7381, 96%). Of these, 25.0% in the antenatal corticosteroid group and 44.5%

in the potential missed antenatal corticosteroid group were diagnosed with severe ICH and/or PVL (aRR 0.64, 95% CI 0.55–0.73, $p < 0.001$, NNTb 6, 95% CI 4–8) with no significant variation in the relative differences by gestational age. Severe ICH/PVL or death before evaluation by cranial imaging occurred in 31.4% of infants exposed to antenatal corticosteroids compared with 60.6% who had potential missed opportunities for antenatal corticosteroids (aRR 0.64, 95% CI 0.59–0.71, $p < 0.001$, NNTb 4, 95% CI 3–5). Severe ICH/PVL or death before discharge occurred in 44.7% of infants exposed to antenatal corticosteroids compared with 69.8% in the potential missed opportunities for antenatal corticosteroids (aRR 0.78, 95% CI 0.73–0.84, $p < 0.001$, NNTb 4, 95% CI 4–5).

3.4 | Sensitivity analyses

In the complete cohort of 8967 infants, including those not actively treated, the proportions of infants in the antenatal corticosteroid and potential missed opportunities groups varied by gestational age (Appendix S2). Infants born at 22 and 23 weeks were at higher risk for being in the potential opportunities group than infants born at 25 weeks. There was no difference in rates of potential missed opportunities between infants born at 24 and 25 weeks. Antenatal corticosteroid exposure increased overall from 69.6% (495/711) of infants born in 2006 to 86.5% (594/687) of infants born in 2018 ($p < 0.001$) and the largest increase was among infants born at 22 weeks, from 7.3% (6/82) in 2006 to 50.0% (39/78) in 2018 (Appendix S3). Potential missed opportunities for antenatal corticosteroid exposure decreased overall during the period from 12.9% (92/711) in 2006 to 7.4% (51/687) in 2018 ($p = 0.02$) and the largest decrease was among infants born at 22 weeks from 48.8% (40/82) in 2006 to 24.4% (19/78) in 2018 (Appendix S3). The proportion of actively treated infants with potential missed opportunities for antenatal corticosteroids varied across centres at each gestational age (Appendix S4). Changes in rates of exposure and potential missed opportunities for antenatal corticosteroid exposure in the subset of 5327 actively treated infants from centres that participated during all study years were similar in magnitude to those reported for all centres (data not shown).

Among actively treated infants, the relationships between antenatal corticosteroid exposure and the outcomes studied did not vary significantly over the periods (antenatal corticosteroid group × birth year period interaction: death, $p = 0.30$; death ≤12 hours, $p = 0.21$; severe ICH/PVL or death before evaluation, $p = 0.36$; severe ICH/PVL or death before discharge, $p = 0.41$; and severe ICH/PVL in infants who had cranial imaging, $p = 0.69$). In each period, adjusted risks for each outcome were lower for infants exposed to antenatal corticosteroids versus those not exposed. During the most recent years, 2016–18, the adjusted relative risks for infants exposed versus not exposed to antenatal corticosteroids were: death, 0.66 (95% CI 0.53–0.81); death up to 12 hours, 0.32 (95% CI 0.20–0.52); severe ICH/PVL or death before evaluation, 0.59 (95% CI 0.49–0.70); severe ICH/PVL or death before discharge, 0.70 (95% CI 0.60–0.82); severe ICH/PVL in infants with cranial imaging, 0.58 (95% CI 0.44–0.76). A sensitivity analysis excluding the 46 women included in the potential missed antenatal corticosteroid group because of prolonged rupture alone differed minimally from the adjusted relative risks reported in the primary analysis (data not shown).

4 | DISCUSSION

4.1 | Main findings

This study demonstrates that among infants born at 22–25 weeks of gestation who receive active postnatal treatment, potential missed opportunities for antenatal corticosteroids were more common at the lowest gestational ages. Potential missed opportunities for antenatal corticosteroid exposure were observed for nearly one-quarter of infants born at 22 weeks and one tenth of those born at 23 weeks. However, the proportion of infants actively treated who were exposed to antenatal corticosteroids increased during the years studied, especially for infants born at 22 and 23 weeks of gestation. Furthermore, antenatal corticosteroid exposure was associated with lower rates of mortality and severe brain injury. It is possible that increasing the rate of antenatal corticosteroid exposure may further improve outcomes among actively treated periviable infants.

4.2 | Strengths and limitations

We did not have data available on timing of maternal admission. Therefore, we used surrogates, including maternal antibiotics before delivery, magnesium sulphate, and prolonged rupture of membranes, to evaluate potential missed opportunities for antenatal corticosteroids. The use of these surrogate measures is supported by the decreases in potential missed opportunities with corresponding increases in antenatal corticosteroid exposure. Hence, the changes in antenatal corticosteroid exposure and potential missed opportunities among infants at the lowest gestations in the current study probably reflect changes in perinatal decision-making over time. Furthermore, the low rate and lack of difference in potential missed opportunities at 24–25 weeks of gestation supports our hypothesis. Although all infants included in our primary analysis were actively treated, it is possible that some decisions to provide neonatal resuscitation were made postnatally or that postnatal bias related to receipt of antenatal corticosteroids may have affected later treatment decisions.

Our study did not include an inception cohort of mothers who presented with threatened preterm birth but rather analysed data based on gestational age at birth. Therefore, we do

not have data on outcomes of infants whose mothers presented with threatened preterm birth but who then delivered at later gestations. However, meta-analyses of randomised clinical trials of antenatal corticosteroid exposure demonstrated no difference in pregnancy length after corticosteroid exposure and also reported that antenatal corticosteroids improved survival and decreased intraventricular haemorrhage among preterm infants when analysed by gestational age at delivery as well as by gestational age at trial entry. Antenatal corticosteroids are recommended when preterm delivery is thought to be imminent and have no direct effect on age at delivery. Our data, and data from the meta-analysis of randomised clinical trials of antenatal corticosteroid exposure, suggest that gestational age at birth is not a collider or mediator variable but is a confounder for which adjustment is appropriate.[17]

We used data from a subset of academic medical centres but US population-based data sets do not collect such detailed information on perinatal care practices and outcomes.[18] Population-based studies in other high-income countries have found an association between antenatal corticosteroids and improved outcomes.[19,20] Many infants exposed to antenatal corticosteroids at periviable gestations deliver beyond the periviable period,[6] but data on infants exposed but delivered later were not available. This study did not evaluate other major outcomes following preterm birth including neurodevelopmental impairment, bronchopulmonary dysplasia, respiratory distress syndrome, or necrotising enterocolitis that have been associated with antenatal corticosteroid exposure.

4.3 | Interpretation

The mother is recognised as the autonomous decision-maker with regard to treatments that may affect her and her fetus.[21,22] As such, consensus statements recommend that infants who are considered potentially viable based on clinical circumstances and family desires should be treated in a manner consistent with pregnancies at higher gestations.[4] In the current study, rates of antenatal corticosteroid use increased among periviable infants. This may reflect assimilation of newer data on the association between antenatal corticosteroid exposure with higher rates of survival and lower rates of major morbidities among infants at the lowest gestations.[2,3,23,24] Discordance between obstetric and neonatal management at the limits of viability has been noted,[9] but increasing rates of antenatal corticosteroid administration among periviable infants suggest that discordance may be decreasing over time in Neonatal Research Network centres.

Until recently, professional guidelines from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine did not recommend antenatal corticosteroid administration at 22 weeks of gestation.[7] This recommendation was classified as Grade 1A evidence consistent with evidence from well-conducted randomised controlled trials or other overwhelming evidence of benefit or harm.[25] Randomised clinical trials of antenatal corticosteroids were conducted during years when infants at 22–23 weeks of gestation were generally considered below the limit of viability[26] and included relatively few infants at less than 26 weeks of gestation. Further randomised controlled trials among periviable infants are unlikely given the benefits at higher gestations.[1] Findings of our study are consistent with those of observational studies that suggest the absolute benefit of antenatal corticosteroids may be highest among periviable infants.[2,3]

It is not known how the desire to achieve optimal timing of antenatal corticosteroids factored into perinatal decision-making in this study. Our definition of antenatal corticosteroids exposure included partial, complete, or repeat courses. Partial courses of antenatal corticosteroids decreased mortality among preterm infants in the meta-analysis of randomised controlled trials and observational studies that included periviable infants.[1,24] Although antenatal corticosteroid administration 24–47 h before delivery is associated with the lowest risk of death[27] even administration within 3 hours of delivery may lower the risk of death.[28] As the effect on mortality may begin to wane after 1–2 weeks it is possible that some infants in the current study, particularly at higher gestational ages, may have been exposed to repeat courses. However, repeat courses have not been demonstrated to decrease mortality or severe brain injury.[29]

We noted baseline differences between groups in the current study including maternal race/ethnicity, insurance status, education level, and prenatal care. Although our models were adjusted for these factors, it is known that rates of active postnatal treatment vary by race/ethnicity and socioeconomic status.[8,30] The differences we observed in receipt of antenatal corticosteroids by race/ethnicity are consistent with data from observational studies.[31,32] Lack of prenatal care has been associated with lower rates of exposure to antenatal corticosteroids,[2] emphasising the importance of prenatal care.

5 | CONCLUSIONS

Potential missed opportunities for antenatal corticosteroid exposure increased with decreasing gestational age among actively treated periviable infants. During the study period the rate of potential missed opportunities decreased while the rate of antenatal corticosteroid administration increased, especially for infants born at 22 or 23 weeks of gestation. Exposure to antenatal corticosteroids was associated with lower rates of death and severe brain injury in the event of delivery before 26 weeks of gestation.

AUTHOR CONTRIBUTIONS

CPT and WAC conceptualised and designed the study, and drafted, reviewed and revised the manuscript. AD, MAR, EFB, NA, ATT, MP-C and KPVM assisted with study design and critically reviewed the manuscript for important intellectual content. AD and NIH had full access to all the data, completed the data analyses in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Ms Hansen and Dr Das had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTERESTS

WA Carlo is on the board of MEDNAX, Inc; the authors report no other relationships or activities that could appear to have influenced the submitted work. Completed disclosure of interests form available to view online as supporting information.

ETHICS STATEMENT

The UAB Institutional Review Board for Human Use approved this study (IRB-000330023) on 16 November 2020.

DATA AVAILABILITY STATEMENT

Data reported in this paper may be requested through a data use agreement. Further details are available at https://neonatal.rti.org/index.cfm?fuseaction=DataRequest.Home.

The NRN complies with the NIH Data Sharing Policy and the NIH Genomic Data Sharing Policy.

For data sets that have not been previously released in public databases, release of NRN data sets requires the approval of the NRN Steering Committee and a signed Data Use Agreement.

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- The external requestor is asked to acknowledge the use of the NICHD Neonatal Research Network materials in all relevant applications, presentations and publications, along with a disclaimer that: 'The contents of this report represent the views of the authors and do not represent the views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network or the National Institutes of Health.' This statement will be placed in the acknowledgement section unless journals request its placement elsewhere in the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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