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ORIGINAL RESEARCH

MRI BRAIN lesions and growth after antenatal steroids in preterm infants: Does timing matter?

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Abstract

Introduction: Antenatal corticosteroids (ACS) are widely used to improve outcomes in preterm infants, with known benefits on respiratory morbidity and intraventricular hemorrhage (IVH). However, the effect of ACS timing on brain injury and development remains unclear. We aimed to evaluate the impact of a complete course of ACS (ccACS), with particular attention to timing, on brain lesions, growth, and neurodevelopment in very low birth weight (VLBW) infants using magnetic resonance imaging (MRI).

Material and Methods: In this historical cohort study, all VLBW infants admitted to a tertiary neonatal intensive care unit between January 2019 and December 2021 were included. Clinical data, including timing of ACS administration, were collected. The primary outcome was the occurrence of brain injury on MRI at term-equivalent age, including IVH, white matter lesions (WML), and cerebellar hemorrhage (CBH). Secondary outcomes were brain growth and maturation on MRI and neurodevelopment at 2 years assessed using the Griffiths Mental Development Scales. Outcomes were compared between infants with and without ccACS and according to different administration-to-birth intervals.

Results: A total of 189 infants were included, of whom 139 (73.5%) received ccACS. Infants exposed to ccACS had a lower incidence of WML ($p = 0.02$) and moderate/severe IVH ($p = 0.04$). In extremely preterm infants (<28 weeks), IVH was significantly less frequent when ccACS was administered within 7 days before birth ($p = 0.006$). No significant differences were observed in brain growth, maturation, or neurodevelopmental outcomes at 2 years.

Conclusions: A complete course of ACS was associated with unadjusted lower rates of brain injury in VLBW infants, particularly when administered within 7 days before

Abbreviations: ACS, antenatal corticosteroids; BPW, biparietal width; CBH, cerebellar hemorrhage; ccACS, complete course of antenatal corticosteroids; DQ, developmental quotient; GMDS, Griffiths Mental Development Scales; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging; TCD, transcerebellar diameter; TMS, total maturation score; VLBW, very low birth weight; WML, white matter lesions.

Andrea Rossi and Luca A. Ramenghi contributed equally to this work and share last authorship.

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birth in extremely preterm infants, without adverse effects on brain growth, maturation, or neurodevelopment at 2 years.

KEYWORDS
betamethasone, infant, premature, infant, very low birth weight, intraventricular hemorrhage, magnetic resonance imaging, neurodevelopmental disorders, white matter lesions

1 | INTRODUCTION

The administration of antenatal corticosteroids (ACS) to women at risk of preterm birth has proven over the years to be one of the most effective life-saving treatments in perinatal medicine. The review by Crowley in 1990 demonstrated the ACS effectiveness in accelerating lung maturation, thus preventing RDS and neonatal mortality, as well as its association with a significant reduction in the risk of intraventricular hemorrhage (IVH).[1] This led to the recommendation of ACS treatment for all women at risk of preterm birth before 34 weeks of gestation, starting from the 24th week,[2] administering betamethasone as the first-choice steroid, when available, in a two-dose regimen of 12 mg each intramuscularly, 24 h apart.

Nevertheless, there are still open questions in the use of ACS, one of them being the timing of its administration. Some women give birth before completing the prophylaxis, while for others, a long interval elapses between prophylaxis administration and the actual date of delivery. Studies on these time intervals have allowed a better understanding of the short- and long-term effects of ACS and its timing in extremely preterm infants. In a Canadian cohort study, higher probabilities of severe neonatal morbidity or mortality were recognized in preterm neonates born at 24–33 weeks of gestation with an interval between ACS administration and birth of less than 1 day or longer than 7 days, with more pronounced results in infants born before the 29th week.[3] A Swedish study suggests an optimal interval for ACS administration in extremely preterm neonates of 1–7 days.[4] Additionally, this study highlights the importance of completing the prophylaxis cycle in severe preterm births.[4]

A better understanding of the effect of ACS on the brain could be of help in creating new protocols for their administration. Neonatal brain MRI is known to be more sensitive to diagnose milder forms of intraventricular hemorrhage (IVH) than cranial ultrasound used in previous studies[5,6] Therefore, our study aimed to assess the association between prenatal steroid administration and its timing on cerebral outcomes in very low birth weight (VLBW) neonates with the use of neonatal MRI.

Key message

A complete course of antenatal corticosteroids reduces white matter lesions and severe intraventricular hemorrhage in very low birth weight infants. In extremely preterm neonates, the protective effect declines when birth occurs more than seven days after administration.

2 | MATERIAL AND METHODS

2.1 | Study population and data recording

This was a single-center historical observational cohort study. The study population included all neonates with a birth weight less than 1500 grams ("Very Low Birth Weight," VLBW) admitted within the first day after birth to the NICU of Istituto Giannina Gaslini (Genoa, Italy) from January 2019 to December 2021. Included infants underwent brain MRI at the term-equivalent age (TEA, between 37 and 42 weeks of corrected age), as part of the routine neuroradiological screening program for all VLBW neonates in our hospital. Demographic and clinical data were collected through chart review. For each patient, the following data were extracted: prenatal (multiple pregnancy, gestational diabetes, gestational hypertension, clinical or histological chorioamnionitis, premature rupture of membranes, fetal growth restriction, ACS course: number of doses, interval between treatment and birth); perinatal (gender, birth weight, gestational age at birth, mode of delivery and Apgar scores at 1, 5, and 10 min); postnatal (need for intubation/reintubation, surfactant use, duration of mechanical ventilation, pneumothorax, use of inotropes in the first 72 h of life, early-onset sepsis (EOS) defined as bacteremia or bacterial meningitis within the first 72 h of life, late-onset sepsis (LOS) characterized by clinical deterioration after the first 72 h of life requiring antibiotic therapy, spontaneous intestinal perforation (SIP), necrotizing enterocolitis (NEC), the presence of patent ductus arteriosus (PDA) requiring treatment, bronchopulmonary dysplasia (BPD) defined as the need for oxygen at 36 weeks of corrected age, presence and treatment of retinopathy of prematurity (ROP), plasma, platelet, and red blood cell transfusions).

Clinical and imaging data were retrospectively extracted from electronic medical records and anonymized before analysis. Data completeness was checked before statistical analysis. Eight cases with missing key outcome data were excluded from the corresponding analyses.

2.2 | MRI acquisition and image analysis

MRI scans were performed at term-equivalent age during spontaneous sleep using the "feed and wrap" technique.[7] The need for sedation (oral midazolam, 0.1 mg/kg) to prevent head motion was

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determined in agreement with the neuroradiologist, based on initial image quality and the infant's level of arousal. Hearing protection was used in all patients, and heart rate and oxygen saturation were monitored noninvasively throughout the examination.

MRI was performed on a 3 T scanner (Ingenia CX, Philips, Best, The Netherlands) using a 32-channel head coil. The standard imaging protocol included axial and coronal T2-weighted fast spin-echo sequences, axial susceptibility-weighted imaging (SWI), isotropic 3D T1-weighted imaging, and diffusion-weighted imaging (DWI). Informed consent, including information on the significance and limitations of MRI at term-equivalent age, was obtained in all cases.

Neuroradiological data were retrospectively collected from clinical MRI reports generated by experienced neuroradiologists (each performing more than 200 neonatal brain MRI examinations per year) and used to identify white matter lesions (WML), germinal matrix–intraventricular hemorrhage (GMH-IVH), and cerebellar hemorrhage (CBH). Prematurity-related brain lesions were classified as mild, moderate, or severe according to previously described criteria.[8] Given the retrospective nature of the study, blinding to clinical variables was not feasible. As MRI scans were interpreted in the clinical setting, neuroradiologists had access to routine clinical information, although they were not involved in clinical management. Linear parameters of brain growth, including biparietal width (BPW) and transcerebellar diameter (TCD), were measured by a trained operator (FP), as previously described.[9]

Finally, MRI scans were reviewed by a trained operator (FP) to qualitatively assess brain maturation using a previously validated scoring system.[10] Briefly, four parameters were evaluated: myelination, cortical folding, germinal matrix involution, and involution of periventricular bands of migrating cells. Each parameter was assigned a score (ranges: 1–7 for myelination, 1–6 for cortical folding, 1–4 for germinal matrix, and 1–4 for migrating cell bands), and the total maturation score was calculated as the sum of these values.

At two years of corrected age, the neurodevelopmental evaluation of the patients was performed using the Griffiths Mental Developmental Scales (GMDS)[11] administered by a single operator with 10 years of experience. In our routine follow-up program, the examiner is independent from neonatal care and does not routinely access neonatal medical records, MRI reports, or prenatal exposure information during the neurodevelopmental assessment.

Raw numbers were converted to standardized developmental quotients (DQ), and total DQ, reflecting global development, was registered. Values below 70 were defined as pathologic, from 70 to 79 as at limit, from 80 to 89 as below the mean, and from 90 on as normal. Patients too severely impaired to perform GMDS were assigned DQ values of 50.

2.3 | Statistical analysis

First, clinical parameters, presence of brain lesions (white matter lesions—WML, intraventricular hemorrhages—IVH, and cerebellar hemorrhages—CBH), brain size and maturation were compared between two groups of the population: those who had received a complete course of antenatal corticosteroids (ccACS) versus those who had received no or only one dose of ACS (absent or incomplete course). ACS course was considered complete when two doses of betamethasone, 12 mg each, were administered intramuscularly with a 24 h interval between each other. The analysis was initially performed in the overall study population. Subsequently, infants were stratified according to antenatal corticosteroid exposure (complete course vs. absent/incomplete course), and separate subgroup analyses were conducted according to gestational age at birth (< 28 weeks vs. ≥28 weeks of gestation) to reduce the potential confounding effect of gestational age on brain outcomes.

Then, to analyze potential impact of the timing of ACS on brain outcomes, subgroups of infants that have received ccACS were further divided based on the interval between ccACS administration and delivery being less vs. more than 7, 14, and 21 days, and presence of brain lesions was compared between those groups. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, Illinois USA). No formal sample size calculation was performed due to the retrospective exploratory nature. Descriptive statistics were generated for the whole cohort and data were expressed as mean and standard deviation (SD) or median (range) as appropriate. Differences between groups were evaluated with Student *t*-test or Mann Whitney *U* test for continuous variables and with chi-squared or Fisher's exact test for categorical variables. A p-value <0.05 was considered statistically significant, and all p-values were based upon two-tailed tests. No adjustment for multiple comparisons was performed given the exploratory nature of the analyses.

3 | RESULTS

Between January 2019 and December 2021, 189 very low birth weight (VLBW) neonates were admitted to our NICU (Figure 1). A complete course of antenatal corticosteroids was administered to 139/189 infants (74%). The median interval between corticosteroid administration and delivery was 8 days (range 1–68 days). Among these, 100 were male (53%), and 89 were female (47%). The mean birth weight was 1094 ± 302 grams, with gestational ages ranging from 22 to 37 weeks, with a mean of 29 ± 3 weeks. Fifty-one neonates (27%) were born from multiple pregnancies, and 62 (32.8%) were diagnosed antenatally with fetal growth restriction (FGR). Additional clinical characteristics of the total cohort are summarized in Table 1.

3.1 | General and respiratory outcome

The univariate analysis comparing infants with and without a complete course of ACS showed higher 1- and 5-min Apgar scores, although Apgar scores at 5 min were within the normal range in both groups. Complete ACS exposure was also associated with less need for reintubation (defined as any endotracheal reintubation not related to surgical or procedural requirements) and surfactant administration,

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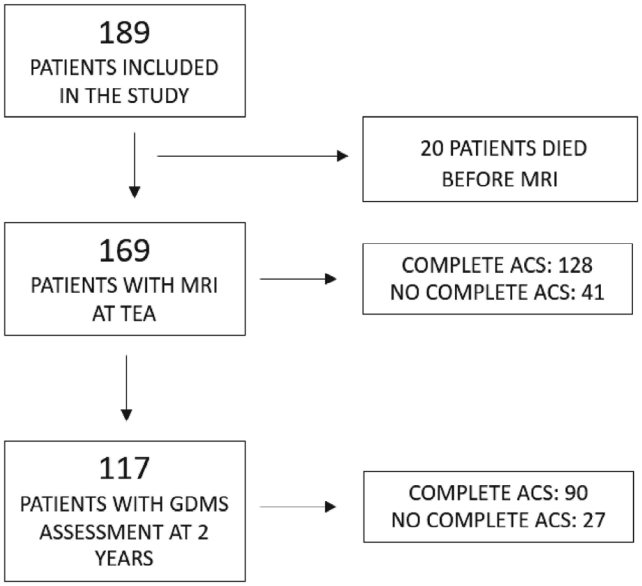

FIGURE 1 Flow diagram of the study. ACS, antenatal corticosteroid; GMDS, Griffiths Developmental Mental Score; MRI, magnetic resonance imaging.

and numerically lower mortality and shorter duration of invasive ventilation, although these differences were not statistically significant (see Table 1). It is necessary to note, though, that those differences could in part be explained by higher gestational age at birth of infants in this group. Taking into consideration the subgroup of extremely preterm infants (gestational age at birth <28 weeks, $N=55$), those with a complete ACS course confirmed having higher 1- and 5-min Apgar scores, while respiratory characteristics were almost the same in the two groups. On the other hand, in the subgroup of infants ≥28 weeks of gestational age at birth ($N=134$), the need for reintubation and use of surfactant was lower in those with a complete ACS course (Table 2).

3.2 | Brain lesions

Among the 189 patients included in the study, 169 survived until term-equivalent age and underwent brain MRI. Among these, 128 had received ccACS (75%). IVH was observed in 37 neonates (21.9%), WML were present in 13.6% of infants, and cerebellar hemorrhages were observed in 8.9%. In the univariate analysis, a higher incidence of cerebral lesions was noted in neonates without ccACS, with statistically significant differences observed in both moderate/severe IVH ($p=0.04$) and white matter lesions (WML) ($p=0.02$) (Table 3). In the subgroup of extremely preterm infants, we have also observed a trend for a lower incidence of white matter lesions in infants with ccACS, but such a difference did not reach statistical significance. In the subgroup of infants with gestational age at birth ≥28 weeks, there were no statistically significant differences in outcomes between groups (Table 4). When analyzing the timing of ACS administration in extremely preterm neonates, a significant difference ($p=0.006$) in the incidence of IVH emerged between those who had received ccACS within 7 days of birth and those with an administration-to-birth interval exceeding 7 days. A similar trend was observed in relation to other cerebral lesions, although without statistical significance. Similar patterns were seen when comparing intervals of administration-to-birth greater or less than 14 and 21 days (Table 5). In neonates with gestational age ≥28 weeks at birth, there were no significant differences based on the timing of ACS administration in relation to the presence of cerebral lesions.

3.3 | Brain growth and maturation

When analyzing brain maturation using Total Maturation Score (TMS) and brain dimensions measured by Biparietal Width (BPW) and Transcerebellar Diameter (TCD), no significant differences were observed between neonates with and without ccACS (see Table 3). The same was also true for the subgroups of infants divided by gestational age at birth (Table 4).

3.4 | Neurodevelopmental outcomes

At two years of corrected age, 117 patients (90 with a complete ACS, 76%) underwent neurodevelopmental evaluation using GMDS. No significant difference in the mean total DQ (developmental quotient) was observed between the two groups (85.6 ± 12.2 vs. 84.2 ± 11.9; $p=0.59$) (Table 3). This finding was consistent even after stratification by gestational age at birth, with no significant differences in DQ in either the <28 weeks or ≥28 weeks subgroups (Table 4).

When considering the administration-to-birth interval, no significant associations with DQ were observed in infants born at <28 weeks (Table 5). Among neonates with gestational age ≥28 weeks, infants with an interval >21 days had a lower mean DQ than those exposed within ≤21 days (83.2 vs. 89.6; $p=0.037$) (Table 6). Given the exploratory nature of these analyses, the number of comparisons performed, and the lack of adjustment for potential confounders, this finding should be interpreted with caution.

4 | DISCUSSION

In the current study, a complete course of ACS was associated with lower unadjusted rates of brain injury, such as WML and severe IVH, in VLBW infants without adverse effects on brain growth or maturation. In extremely preterm infants, the unadjusted rates of brain injury were lower if birth occurred within 7 days of ACS administration.

Use of MRI allowed us to identify with precision the presence of hemorrhagic lesions, such as IVH or CBH. Across the entire population, these findings are in line with the existing literature's viewpoint that ACS treatment is associated with a significant reduction in the risk of moderate/severe IVH.[12,13] Indeed, corticosteroids

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TABLE 1 Clinical characteristics of included patients.

Characteristic	Total cohort (*N* = 189)	ACS complete course (*N* = 139)	ACS incomplete or absent (*N* = 50)	*p* value
Multiple pregnancy, *n* (%)	51 (27)	35 (25)	16 (32)	0.36
Fetal growth restriction, *n* (%)	62 (33)	52 (37)	10 (20)	0.06
Gestational diabetes	23 (12)	15 (11)	8 (16)	0.33
Gestational hypertension, *n* (%)	53 (29)	44 (32)	9 (18)	0.06
Chorioamnionitis	4 (2)	4 (3)	0 (0)	0.22
Premature rupture of membranes	61 (32)	46 (33)	15 (30)	0.69
Caesarean section, *n* (%)	149 (79)	114 (82)	35 (70)	0.07
Gestational age at birth (weeks), mean ± SD	29.0 ± 3.0	29.5 ± 2.8	27.9 ± 3.1	**0.002**
Birth weight (g), mean ± SD	1093 ± 302	1121 ± 302	1017 ± 292	0.36
Male gender, *n* (%)	100 (53)	69 (50)	31 (62)	0.14
Apgar score at 1 min, median (min–max)	6 (0–9)	6 (1–9)	5 (0–8)	**0.0001**
Apgar score at 5 min, median (min–max)	8 (0–10)	8 (3–10)	7 (0–9)	**0.0001**
Intubation in delivery room, *n* (%)	96 (51)	68 (49)	28 (56)	0.39
Intubation during first 72 h, *n* (%)	122 (65)	84 (60)	38 (76)	0.06
Reintubation, *n* (%)		16 (12)	12 (24)	**0.04**
Surfactant, *n* (%)	107 (57)	70 (50)	37 (74)	**0.005**
Invasive ventilation days, mean ± SD	4.1 ± 6.7	3.4 ± 5.6	5.9 ± 8.9	0.06
Non-invasive ventilation days, mean ± SD	23.8 ± 24.8	23.8 ± 25.6	23.7 ± 22.3	0.82
Pneumothorax, *n* (%)	5 (3)	4 (3)	1 (2)	1
Inotropic support, *n* (%)	16 (9)	10 (7)	6 (12)	0.37
Bronchopulmonary dysplasia, *n* (%)	26 (14)	21 (15)	5 (10)	0.48
Retinopathy of prematurity, *n* (%)	49 (26)	31 (22)	18 (36)	0.06
Patent ductus arteriosus, *n* (%)	88 (47)	60 (43)	28 (56)	0.13
Late onset sepsis, *n* (%)	23 (12)	16 (12)	7 (14)	0.64
Necrotizing enterocolitis, *n* (%)	8 (4)	5 (4)	3 (6)	0.44
Death, *n* (%)	22 (12)	13 (9)	9 (18)	0.12

Note: Bold identifies statistically significant *p* value.

seem to exert important vasoconstrictive effects on fetal cerebral blood flow,[13] protecting the fetus from potential IVH development at rest and in conditions causing vasodilation, such as hypercapnia.[13] Intriguingly, we have also observed fewer white matter lesions in infants after a complete ACS course, possibly via interacting with inflammation processes.

When analyzing the role of time, we have observed a significant drop in the preventive capacity of ACS towards IVH when more than 7 days pass between their administration and birth in a group of less mature infants (<28 weeks of gestational age at birth). This observation suggests a diminishing protective effect against IVH as the interval between administration and birth lengthens. In older infants, there were no significant differences observed regarding the timing of administration. It is interesting to note how studies by Melamed and Norberg indicate major effect of ACS on lung maturation with an interval of less than 7 days between ACS administration and birth, particularly in infants born before the 29th week of gestation.[3,4] We can therefore hypothesize similar pathogenetic mechanisms between two observations, even if future studies are needed to elucidate it properly.

We have observed no significant differences in neurodevelopmental outcome, measured as total DQ at Griffiths Scales at 2 years of age, between groups of infants that have or have not received a complete ACS course. Nevertheless, among patients born ≥28 weeks of gestation, those with an administration-to-birth interval longer than 21 days had a mean total DQ significantly lower than their peers. Even if statistically significant, this observation could be due to pure coincidence or some confounding factor that we have not considered; on the other hand it could be another sign of gradually diminishing protective effect on brain of ACS course does diminish with time.

Lastly, we conducted analyses regarding the effects of ccACS in VLBW infants on brain size, assessing biparietal (BPW) and transcerebellar (TCD) diameters, as well as brain maturation based on the TMS. These analyses did not reveal any significant differences associated with ACS administration, both within the entire study population and among subgroups categorized by gestational age at birth. Therefore, we found no significant evidence suggesting negative effects of a complete prenatal corticosteroid course on brain growth or cerebral maturation in VLBW infants.

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TABLE 2 General and respiratory outcome in infants with and without complete antenatal corticosteroid course according to gestational age at birth.

	<28 weeks			≥28 weeks		
	ACS complete course (*N* = 35)	ACS incomplete or absent (*N* = 20)	*p* value	ACS complete course (*N* = 104)	ACS incomplete or absent (*N* = 30)	*p* value
Death, *n* (%)	8 (23)	7 (35)	0.36	5 (5)	2 (7)	0.65
Apgar score at 1′, median (min–max)	4 (1–8)	3 (0–6)	**0.004**	7 (1–9)	6 (1–8)	**0.03**
Apgar score at 5′, median (min–max)	7 (3–9)	5 (0–9)	**0.005**	9 (5–10)	8 (2–9)	**0.01**
Intubation, *n* (%)	33 (94)	19 (95)	1	51 (49)	19 (63)	0.21
Reintubation, *n* (%)	14 (40)	8 (40)	1	2 (2)	4 (13)	**0.02**
Surfactant, *n* (%)	28 (82)	18 (90)	0.69	42 (40)	19 (63)	**0.04**

Note: Bold identifies statistically significant *p* value.

TABLE 3 Brain lesions, growth and maturation in patients with and without complete ACS course: whole cohort.

	ACS complete course (*N* = 128)	ACS incomplete or absent (*N* = 41)	*p* value
IVH any grade. *n* (%)	26 (20)	11 (27)	0.38
Moderate/severe IVH, *n* (%)	4 (3)	5 (12)	**0.04**
WML any grade, *n* (%)	13 (10)	10 (24)	**0.02**
Moderate/severe WML, *n* (%)	4 (3)	3 (7)	0.36
CBH any grade, *n* (%)	10 (8)	5 (12)	0.36
Moderate/severe CBH, *n* (%)	1 (1)	1 (2)	0.42
BPW, mean ± SD	78.1 ± 5.7	77.8 ± 5.7	0.78
TCD, mean ± SD	51.6 ± 4.6	49.6 ± 8.6	0.25
TMS, median (min–max)	14 (9–17)	14.5 (9–17)	0.15
Total DQ at 2 years, mean ± SD	85.6 ± 12.2	84.2 ± 11.9	0.59

Note: Bold identifies statistically significant *p* value.

Abbreviations: BPW, biparietal width; CBH, cerebellar hemorrhage; DQ, developmental quotient; IVH, intraventricular hemorrhage; TCD, transcerebellar diameter; TMS, Total maturation score; WML: white matter lesions.

Potential risks of antenatal steroid exposure are well described in the literature, with animal studies suggesting a list of possible negative long-term effects.[14–16] It is also hypothesized that excess prenatal exposure to corticosteroids may be a relevant mechanism underlying the fetal origin of adult disease, correlating altered fetal growth with subsequent cardiovascular diseases, type 2 diabetes, dyslipidemia, and hypertension.[17] Rakers et al. have shown that in 8- to 9-year-old children, antenatal exposure to betamethasone for suspected preterm birth could be associated with alterations in autonomic nervous system activity and neurofunctional outcome,[18] even if these discrepancies did not continue into adolescence.[19]

Therefore, the use of repeated doses of prenatal corticosteroids for women who undergo prophylaxis but do not deliver in the following days or weeks is a question widely discussed in the literature and clinical practice. In one study, repetition of prenatal corticosteroids administered to women who remain at risk of preterm birth 7 or more days after an initial cycle reduced intrinsic respiratory complications of prematurity and improved the health outcomes of preterm infants. However, adverse outcomes regarding cognitive development have also been reported.[20,21] In our hospital, repetition of corticosteroid cycles is not a habitual practice, and we could not analyze directly its effect on neonatal outcomes. Nevertheless, evidence of possible attenuation of protective effects of corticosteroids on IVH prevention and neurodevelopmental outcomes with the lengthening of administration-to-birth interval suggests the need for future studies to investigate the usefulness of this practice.

Regarding short-term respiratory outcomes, complete ACS exposure was associated with lower reintubation rates only among infants born at ≥28 weeks of gestation, whereas no difference was observed in the extremely preterm subgroup. A possible explanation is that, in infants born before 28 weeks, the severity of pulmonary immaturity and the frequent need for prolonged respiratory support may have outweighed the beneficial pulmonary effects of ACS. Conversely, in more mature preterm infants, the respiratory benefits of antenatal corticosteroids may have become more clinically evident.

The retrospective observational design of the study does not allow conclusions regarding causality between antenatal

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TABLE 4 Brain lesions, size and maturation in patients with and without complete ACS course according to gestational age at birth.

	<28 weeks			≥28 weeks		
	ACS complete course (*N* = 27)	ACS incomplete or absent (N = 13)	*p* value	ACS complete course (*N* = 101)	ACS incomplete or absent (*N* = 28)	*p* value
IVH any grade, *n* (%)	13 (48)	6 (46)	0.91	13 (13)	5 (18)	0.54
Moderate/severe IVH, *n* (%)	3 (11)	3 (23)	0.37	1 (1)	2 (7)	0.12
WML any grade, *n* (%)	3 (11)	5 (39)	0.08	10 (10)	5 (18)	0.31
Moderate/severe WML, *n* (%)	1 (4)	1 (8)	0.29	3 (3)	2 (7)	0.30
CBH any grade, *n* (%)	4 (15)	1 (8)	0.52	6 (6)	4 (14)	0.22
Moderate/severe CBH, *n* (%)	1 (4)	1 (8)	0.29	0 (0)	0 (0)	n/a
BPW (mean ± SD)	76.8 ± 6.3	77.3 ± 6.8	0.80	78.5 ± 5.5	78.0 ± 5.2	0.70
TCD (mean ± SD)	49.3 ± 5.3	48.7 ± 5.4	0.63	52.2 ± 4.2	50.0 ± 9.8	0.54
TMS median (min–max)	13 (9–16)	14 (9–16)	0.36	14 (9–17)	15 (11–17)	0.19
Total DQ at 2 years, mean ± SD	79.4 ± 11	79.3 ± 17	0.56	87.3 ± 12	86.7 ± 8	0.36

Abbreviations: BPW, biparietal width; CBH, cerebellar hemorrhage; DQ, developmental quotient; IVH, intraventricular hemorrhage; TCD, transcerebellar diameter; TMS, total maturation score; WML, white matter lesions.

TABLE 5 Brain lesions in infants with different administration-to-birth intervals: Subgroup <28 weeks of gestational age at birth.

	≤7 days (*N* = 15)	>7 days (*N* = 11)	*p* value	≤14 days (*N* = 22)	>14 days (N = 4)	*p* value	≤21 days (*N* = 24)	>21 days (*N* = 2)	*p* value
IVH any grade, *n* (%)	4 (27)	9 (82)	**0.006**	10 (45)	3 (75)	0.59	12 (50)	1 (50)	0.95
Moderate/severe IVH, *n* (%)	1 (7)	2 (18)	0.55	2 (9)	1 (25)	0.41	3 (13)	0 (0)	0.86
WML any grade, *n* (%)	1 (7)	2 (18)	0.18	2 (9)	1 (25)	0.41	3 (13)	0 (0)	0.86
Moderate/severe WML, *n* (%)	0 (0)	1 (9)	0.42	0 (0)	1 (25)	0.15	1 (4)	0 (0)	0.93
CBH any grade, *n* (%)	1 (7)	3 (27)	0.27	3 (14)	1 (25)	0.51	4 (17)	0 (0)	0.86
Moderate/severe CBH, *n* (%)	0 (0)	1 (9)	0.42	0 (0)	1 (25)	0.15	1 (4)	0 (0)	0.86
Total DQ at 2 years, mean ± SD	80.25	76.83	0.56	79	79.67	0.93	78.76	85	0.2

Note: Bold identifies statistically significant *p* value.

Abbreviations: CBH, cerebellar hemorrhage; DQ, developmental quotient; IVH, intraventricular hemorrhage; WML, white matter lesions.

TABLE 6 Brain lesions in infants with different administration-to-birth intervals: Subgroup ≥28 weeks of gestational age at birth.

	≤7 days (*N* = 40)	>7 days (*N* = 60)	*p* value	≤14 days (*N* = 53)	>14 days (*N* = 47)	*p* value	≤21 days (*N* = 66)	>21 days (*N* = 34)	*p* value
IVH any grade, *n* (%)	6 (15)	8 (11.7)	0.81	8 (15)	5 (11)	0.51	8 (12)	5 (15)	0.76
Moderate/severe IVH, *n* (%)	1 (3)	0 (0)	0.40	1 (2)	0 (0)	1	1 (2)	0 (0)	1
WML any grade, *n* (%)	4 (10)	6 (10)	1	5 (9)	5 (11)	1	6 (9)	4 (12)	0.73
Moderate/severe WML, *n* (%)	0 (0)	3 (5)	0.27	1 (2)	2 (4)	0.60	1 (2)	2 (6)	0.27
CBH any grade, *n* (%)	3 (8)	3 (5)	0.68	3 (6)	3 (6)	1	4 (6)	2 (6)	1
Moderate/severe CBH, *n* (%)	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Total DQ at 2 years, mean ± SD	89.4	85.7	0.21	89.3	85.5	0.19	89.6	83.2	**0.037**

Note: Bold identifies statistically significant *p* value.

Abbreviations: CBH, cerebellar hemorrhage; DQ, developmental quotient; IVH, intraventricular hemorrhage; WML, white matter lesions.

corticosteroid exposure and brain outcomes. Therefore, our findings should be interpreted as associative. Nevertheless, a potential protective cerebrovascular effect of antenatal corticosteroids has been hypothesized; therefore, future studies integrating fetal hemodynamic assessment with advanced in utero imaging modalities could provide further insight into the effects of antenatal corticosteroids on fetal cerebral perfusion and brain development.

We acknowledge several limitations of our study. First, our study is a retrospective study of VLBW infants from a single center. Second, the lower gestational age of the infants in the group that has not

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completed the ACS course is a major confounding factor, even if we have tried to mitigate its effect by dividing infants into two subgroups by gestational age at birth. We must acknowledge that the association of ACS with outcomes studies is significantly attenuated when examined in the cohort of <28 weeks GA in our study. Third, the use of MRI conducted at the corrected term age has the limitation of potentially missing early disappearing lesions, such as some punctate white matter lesions. On the other hand, the use of the SWI sequence, which is highly sensitive to hemosiderin deposits, has allowed us to potentially identify smaller brain hemorrhages. Indeed, brain MRI is more sensitive to various brain lesions than traditionally used brain ultrasound, and its use has allowed as to evaluate brain growth and maturation as well,[5,6,10,22] correlating analyzed parameters to neurodevelopmental outcome. Forth, all the analyses are unadjusted analyses, and we have not addressed confounding that occurs due to variables associated with exposure and outcomes. Fifth, the numbers in some of the analyses are extremely small, and results should be interpreted with caution. Sixth, we have not adjusted for multiple comparisons.

5 | CONCLUSION

In conclusion, among VLBW preterm infants, the analysis of brain MRI performed at the term equivalent age revealed that antenatal corticosteroids may be associated with a lower rate of intraventricular hemorrhages and white matter lesions. The timing of ccACS administration may be important in extremely preterm infants, as the association with cerebral lesions diminished population after 7 days from administration. There was no association between brain size and cerebral maturation and a complete course of antenatal corticosteroids; however, all analyses were unadjusted for confounders.

AUTHOR CONTRIBUTIONS

Mariya Malova: Conceptualization, methodology, data collection, manuscript drafting. **Samuele Caruggi:** Data curation, writing – review and editing. **Flavia Pozzi:** data collection, manuscript drafting, data verification. **Paolo Massirio:** Clinical data acquisition, neonatal clinical supervision. **Francesco Vinci:** Data collection. **Irene Bonato:** Support in data extraction and clinical dataset organization. **Andrea Calandrino:** Assistance in clinical data management and manuscript editing. **Diego Minghetti:** NICU clinical supervision, project coordination. **Maria Grazia Calevo:** Statistical supervision, methodological oversight. **Federico Prefumo:** Obstetric interpretation and manuscript supervision. **Martina Resaz:** Interpretation and reporting of MRI data. **Mariasavina Severino:** Interpretation and reporting of MRI data. **Domenico Tortora:** Interpretation and reporting of MRI data. **Andrea Rossi:** Neuroradiological support and methodological validation. **Luca A. Ramenghi:** Senior supervision, critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This historical cohort study was approved by the Regional Institutional Ethics Committee of Liguria, Italy (Protocol No. 278/2024, approved on 25 October 2024). Written informed consent for MRI examinations and follow-up assessments was obtained according to institutional policy.

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