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THE IMPACT OF ANTENATAL CORTICOSTEROID ADMINISTRATION ON EARLY OUTCOME PARAMETERS AND LABORATORY FINDINGS IN NEONATES

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This study evaluates the impact of antenatal corticosteroid (ACS) administration on early neonatal outcomes and laboratory parameters in preterm infants born at 28–34 gestational weeks. It assesses the effects of ACS on early morbidity, respiratory support, NICU admission, and metabolic changes reflected in laboratory parameters. A retrospective cohort study analyzed medical records of preterm neonates born between January 2018 and July 2023. Neonatal outcomes were compared between ACS-exposed and non-exposed groups. Statistical analysis was performed using Chi-square and Fisher's exact tests ($p < 0.05$). A total of 150 infants were included; 74 (49.3%) received ACS. No significant differences were found in birth weight, gestational age, Apgar scores, NICU admission, resuscitation needs, respiratory support, or early morbidity. ACS exposure was associated with a lower, though non-significant, rate of critical illness (8.1% vs. 18.4%). Serum magnesium levels were significantly higher in the non-ACS group ($p = 0.003$), likely reflecting maternal magnesium sulfate administration. ACS benefits appear more pronounced at lower gestational ages. In infants born after 32 weeks, ACS appears to have a limited impact on respiratory and early clinical outcomes, while overall prognosis is primarily determined by gestational maturity and baseline neonatal characteristics. These findings highlight the need for further research to refine ACS administration strategies, particularly for late preterm neonates.

Keywords: antenatal corticosteroids, preterm neonates, respiratory distress, magnesium, neonatal outcomes

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INTRODUCTION

Around 15 million babies are born prematurely across the globe each year, with over a million of these infants not surviving (1). Premature birth remains a major health concern, with respiratory distress syndrome (RDS) being a leading cause of neonatal morbidity and mortality. Antenatal corticosteroids (ACS) significantly reduce the risk of RDS, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early-onset sepsis, and neonatal death, with the greatest benefits observed when administered between 26 and 35 weeks of gestation (2). ACS has become a cornerstone in the management of pregnancies at risk of preterm delivery, following evidence from the first randomized controlled trial published in 1972 (3). Their role as a standard intervention was further reinforced in 1994, when the National Institutes of Health in the United States issued a consensus statement endorsing their widespread use for improving neonatal outcomes (4). The World Health Organization and multiple obstetric organizations recommend the use of ACS for pregnancies at risk of premature birth before 34 weeks. Some countries have taken this further, advising that ACS may also be beneficial for women at risk of delivering up to 36 weeks of gestation (5). Antenatal corticosteroids are a crucial therapy for improving neonatal outcomes in pregnancies at risk of preterm birth, with a single course recommended between 24 0/7 and 33 6/7 weeks of gestation, including cases with ruptured membranes and multiple gestations. In certain situations, corticosteroid administration may be considered as early as 23 0/7 weeks or up to 36 6/7 weeks for late preterm births, particularly if no prior course has been given (6). Despite extensive research supporting the benefits of ACS, its impact on early neonatal outcomes in preterm infants remains an area of continuous investigation. The objective of this study was to evaluate the effects of ACS administration on key early neonatal outcomes and laboratory parameters in preterm neonates (28–34 weeks), including the need for resuscitation at birth, aspects of neonatal intensive care unit (NICU) admission, oxygen therapy requirements, need for mechanical ventilation, surfactant administration, and the incidence of pathological conditions such as IVH, NEC, sepsis, and hemodynamic instability, as well as metabolic and physiological effects reflected in laboratory findings. Understanding these associations can help optimize ACS administration strategies and improve neonatal care in preterm populations.

METHODS

This retrospective cohort study analyzed medical records of preterm neonates born between 28+0 and 34+6 weeks of gestation, along with data from their mothers. All neonates within this gestational age range who were admitted to the NICU during the study period were eligible for inclusion. In cases of multiple gestation, each neonate was analyzed individually. Among 27 twin pregnancies (54 neonates), one twin neonate with early neonatal death was excluded from analysis, resulting in a final sample of 150 neonates. This monocentric retrospective cohort study was conducted at a single tertiary Neonatal Intensive Care Unit (NICU), using data collected from the hospital's electronic medical records and neonatal histories between January 1, 2018, and July 1, 2023, while the study period was defined from January 1, 2020, to December 31, 2022. The study compared neonatal outcomes between infants whose mothers received antenatal corticosteroids and those who did not. The standard antenatal corticosteroid regimen followed institutional protocols. It included either two intramuscular doses of 12 mg betamethasone administered 24 hours apart, or four intramuscular doses of 6 mg dexamethasone administered every 12 hours, depending on drug availability and clinical discretion. All women who received corticosteroids completed the regimen within 24 hours prior to delivery. All analyses were conducted at the level of individual neonates, including those from multiple gestations, as the dataset represents the full population of preterm births during the study period, with outcomes assessed per neonate.

Maternal Characteristics

Maternal characteristics were assessed to identify potential confounding factors between the ACS and non-ACS groups. The recorded variables included parity, categorized as primiparous (one previous delivery) or multiparous (two or more deliveries); type of pregnancy, classified as singleton or multiple gestation; and mode of conception, whether natural or via in vitro fertilization (IVF). Additionally, mode of delivery (vaginal birth or cesarean section), medication use during pregnancy (including antihypertensives, antibiotics, and diabetes medications), and maternal comorbidities (such as hypertension, gestational diabetes, anemia, and other pathological conditions) were documented.

Neonatal Characteristics and Early Outcomes

To evaluate the impact of ACS on neonatal health, the study assessed the following early neonatal outcomes: need for

resuscitation at birth, Apgar score at 1 and 5 minutes, and general condition at NICU admission, categorized as stable, mild respiratory distress, or critically ill (defined as requiring immediate mechanical ventilation and/or inotropic support due to respiratory and/or hemodynamic instability). The study also examined the requirement for mechanical ventilation, including the type of ventilation (invasive vs. non-invasive), and the need for surfactant therapy. Additionally, the presence of respiratory disorders, such as RDS, transient tachypnea of the newborn (TTN), and apnea of prematurity, as well as other respiratory complications, was analyzed. Furthermore, the study evaluated pathological conditions, including IVH, NEC, neonatal sepsis, and hemodynamic instability.

Statistical analysis

IBM SPSS Statistics for Windows, version 25 (Armonk, NY: IBM Corp., USA) was used for statistical analysis. Normality of distribution was assessed using the Shapiro–Wilk test, and homogeneity of variance was evaluated using Levene's test. Almost all variables violated the assumption of normality (Shapiro–Wilk $p < 0.05$) in at least one group. In addition, some variables also showed evidence of unequal variances (Levene's test $p < 0.05$). Therefore, the nonparametric Wilcoxon test was deemed the most appropriate method for all comparisons. Results are presented as numbers and percentages, arithmetic mean and standard deviation, and median and interquartile range. The χ^2 test (or Fisher's exact test when expected frequencies were insufficient), independent samples t-test, and Mann-Whitney U test were used to assess the significance of differences. Primary comparisons between exposure groups were initially assessed using univariate statistical tests (Mann–Whitney U test, χ^2 test, Fisher's exact test, as appropriate). In addition, multivariable logistic regression models were performed for six key neonatal outcomes (need for mechanical ventilation, intraventricular hemorrhage, sepsis, mortality, NICU admission, and critical illness at admission). These models were adjusted for specific maternal and pregnancy-related factors. The revised analyses also incorporated essential neonatal variables: gestational age, birth weight, sex, and mode of delivery. The threshold for statistical significance was set at $p = 0.05$. Those p-values that could not be expressed to three decimal places are reported as $p < 0.001$. All variables were complete unless otherwise noted. For medications, pathological conditions, and neonatal blood cultures, a small number of observations were missing due to unavailable documentation or a lack of clinical indication. No imputation was applied; analyses were based on available data. A priori power analysis was conducted to evaluate the adequacy of the sample size. For a two-sample t-test, assuming a medium effect size ($d = 0.5$), significance level of 0.05, and power of 0.80, a minimum of 64 participants per group was required. For chi-square tests with an expected medium effect size ($w = 0.3$), a total sample size of 88 (df = 1), 107 (df = 2), or 121 (df = 3) was needed to achieve 80% power at $\alpha = 0.05$. The final sample of 150 neonates met these criteria, supporting the statistical robustness of the analyses performed. NICU admission status was selected as the primary multivariate outcome because it reflects the neonate's overall clinical condition upon admission, including respiratory, cardiovascular, and hemodynamic parameters. This outcome was considered a more comprehensive indicator of early clinical severity than an isolated RDS diagnosis. A multinomial logistic regression model was used to analyze NICU admission condition (Vital, Moderate (Mild respiratory distress), Critical) as a three-category outcome, with "Vital" as the reference. The model was fitted using the multinom() function from the nnet package in R and included the following predictors: ACS exposure, maternal administration of $MgSO_4$ before birth, corticosteroids within 24 hours of delivery, maternal medications during pregnancy, pathological maternal conditions, and neonatal magnesium levels within the first 24 hours. Since the multinom() function does not support cluster-robust standard errors or generalized estimating equations (GEE), we conducted a sensitivity analysis using a reduced dataset that included only one randomly selected neonate per twin pair. This allowed us to ensure independence of observations. Results from both the full and reduced models are reported in the same comparison table. Categorical thresholds, including gestational age (cut-off at 32 weeks), birth weight bands (<1000 g, 1000–1999 g, ≥2000 g), and NICU length of stay (≤7, 8–14, ≥15 days), were pre-specified based on clinical relevance and were consistently applied in all statistical analyses. Gestational age was categorized using a predefined threshold at 32 weeks, in accordance with guidelines from the American Academy of Pediatrics and the World Health Organization, which define infants born before 32 completed weeks as very preterm (7,8). Birth weight categories (<1000 g, 1000–1999 g, and ≥2000 g) were also defined in advance. Although they differ slightly from the WHO classification, these bands reflect the distribution of our study population (64.7% between 1000 and 1999 g) and correspond to locally relevant clinical groupings used in NICU care (9). Based on clinical relevance and the observed distribution of NICU

length of stay in our cohort, this variable was categorized into three predefined groups: ≤7 days, 8–14 days, and ≥15 days. This approach allowed for more meaningful comparisons, given the skewed distribution of LOS and the need to maintain adequate subgroup sizes (n = 46, n = 72, and n = 32, respectively). In addition to the multinomial regression for NICU admission, we performed separate multivariable logistic regression analyses for other primary neonatal endpoints: need for mechanical ventilation, intraventricular hemorrhage (IVH), sepsis, mortality, and composite "critical illness" at admission. All models were adjusted a priori for gestational age (weeks), birth weight (grams), sex, delivery mode (vaginal vs. cesarean/induced), and maternal pathological conditions and medications during pregnancy. For outcomes with a low number of events, such as mortality, Firth's penalized logistic regression was used to reduce small-sample bias and improve model convergence. The results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p-values. Model fit was evaluated using the likelihood ratio chi-square test and Nagelkerke R^2, and classification accuracy, sensitivity, and specificity were calculated. For continuous outcomes with a statistically significant difference in the main analysis (serum magnesium levels), we repeated the Mann–Whitney U test on a subsample excluding one randomly selected infant from each twin pair to account for within-pair clustering. The results were compared to those from the full dataset to assess robustness.

RESULTS

A total of 124 mothers and 150 neonates were included in the analysis. The difference in sample size reflects the inclusion of 27 twin pregnancies, with each neonate analyzed as a separate observation. Among the 27 pregnant women with multiple pregnancies, antenatal corticosteroids were administered to 15 (25.4%), while 12 (18.5%) did not receive them. Neonatal outcomes were not stratified by type of pregnancy (singleton vs. multiple), but preliminary comparisons did not reveal significant differences between these groups. A total of 59 (47.6%) women received antenatal corticosteroids. The majority received betamethasone (n = 33; 55.9%), dexamethasone (n = 25; 42.4%), and only one received methylprednisolone. Most women received corticosteroids 24 hours before delivery (n = 52; 88.1%). Significantly more mothers who received antenatal corticosteroids during pregnancy also received other medications (Table 1). In other maternal parameters, specifically parity, type of pregnancy, mode of conception, type of delivery, and pathological conditions during pregnancy, no statistically significant differences were found between mothers who received antenatal corticosteroids and those who did not. The sample included 74 newborns whose mothers received ACS and 76 newborns whose mothers did not receive ACS. No statistically significant differences were observed in neonatal characteristics between the ACS and non-ACS groups (Table 2). In the main sample (n = 150; magnesium data available for 146 infants), serum magnesium levels differed significantly between groups despite identical median values (0.84 mmol/L in both groups), reflecting differences in the overall distribution of values. Infants whose mothers had not received ACS had significantly higher mean ranks than those whose mothers had received ACS (84.62 vs. 62.97, respectively; Z = −3.093; p = 0.002). This finding remained unchanged in a reduced dataset excluding one infant per twin pair (N = 124; Mg data available for 121 infants; mean ranks: 71.24 vs. 51.88; Z = −3.031; p = 0.002), confirming that the result was not influenced by twin clustering (Supplementary Table S2).

Table 1. *Maternal parameters based on antenatal corticosteroid administration*

		Received antenatal corticosteroids				
		Yes		No		
		n	%	n	%	p*
Parity	1	24	40.7	25	38.5	0.801
	2+	35	59.3	40	61.5	
Type of pregnancy	Singleton	44	74.6	53	81.5	0.348
	Multiple	15	25.4	12	18.5	
Mode of conception	Natural	56	94.9	63	96.9	0.57
	In vitro fertilization	3	5.1	2	3.1	
Mode of delivery	Vaginal	27	45.8	24	36.9	0.318
	Cesarean	32	55.2	41	63.1	
Medications during pregnancy	No	26	44.1	42	64.6	0.022
	Yes	33	55.9	22	35.4	
Pathological conditions during pregnancy	No	27	45.8	34	52.3	0.467
	Yes	32	54.2	30	47.7	
Magnesium sulfate administration		2	2.7	12	15.8	0.009#

* Chi-square test, #Fisher's exact test

Yes = Received ACS; No = Did not receive ACS
Note: Data on medications and pathological conditions were unavailable for one mother in the non-ACS group (n = 64/65).

Table 2. *Neonatal parameters based on antenatal corticosteroid administration*

		Received antenatal corticosteroids				
		Yes		No		
		n	%	n	%	p*
Sex	Male	39	52.7	44	57.9	0.523
	Female	35	47.3	32	42.1	
Birth weight (grams)	<1000 g	4	5.4	3	3.9	0.616#
	1000-1999 g	45	60.8	52	68.4	
	≥2000 g	25	33.8	21	27.6	
Gestational age (weeks)	-32	28	37.8	32	42.1	0.594
	32-	46	62.2	44	57.9	
APGAR score	-7	16	21.6	19	25	0.625
	8-10	58	78.4	57	75	
Need for resuscitation in the first 24h	Yes	12	16.2	20	26.3	0.131
	No	62	83.8	56	73.7	
General condition on admission to NICU	Vital	34	45.9	39	51.3	0.06
	Mild respiratory distress	34	45.9	23	30.3	
	Critical	6	8.1	14	18.4	
Need for O2	Yes	65	87.8	69	90.8	0.558
	No	9	12.2	7	9.2	
Mechanical ventilation	Yes	41	55.4	35	46.1	0.252
	No	33	44.6	41	53.9	
Surfactant	Yes	19	25.7	18	23.7	0.777
	No	55	74.3	58	76.3	
Type of therapy	Antibiotic	3	4.1	1	1.3	0.109#
	Antibiotic + supportive therapy	29	39.2	42	55.3	
	Antibiotic + supportive therapy + inotropes	42	56.8	33	43.4	
Length of stay in the NICU (days)	-7	23	31.1	23	30.3	0.37
	7-14	32	43.2	40	52.6	
	14+	19	25.7	13	17.1	
Respiratory problems	No	26	35.1	35	46.1	0.174
	Yes	48	64.9	41	53.9	
Pathological conditions	No	3	4.1	9	11.8	0.079
	Yes	71	95.9	67	88.2	
Oral milk intake (days)	1-3	39	52.7	31	40.8	0.144
	3 and more	35	47.3	45	59.2	
Blood culture	Sterile	56	77.8	67	89.3	0.058
	Positive	16	22.2	8	10.7	
Urine culture	Sterile	51	70.8	56	74.7	0.602
	Positive	21	29.2	19	25.3	
Cranial ultrasound within the first 21 days of life	IVH grade 1-2	52	703	57	750	807
	IVH grade 3-4	13	176	11	145	
	No IVH/ultrasound not performed	9	122	8	105	
Cranial ultrasound at discharge	IVH grade 1-2	53	716	57	750	895
	IVH grade 3-4	12	162	11	145	
	No IVH/ultrasound not performed	9	122	8	105	

*Chi-square test; #Fisher's exact test

Yes = Received ACS; No = did not receive ACS
Note: Blood culture data were unavailable for two neonates in the ACS group and one in the non-ACS group, as the test was not performed (n = 72/74 and 75/76, respectively)

A significant difference in magnesium levels in the first 24 hours was therefore observed, with higher levels in the non-ACS group. This difference likely reflects more frequent use of maternal magnesium sulfate in the non-ACS group (12 mothers vs. 2 in the ACS group; p = 0.009, Table 1). No significant differences were found for other laboratory parameters. Diagnostics for normality and homogeneity of variance are provided in Table 3. For each outcome, the type of analysis applied (univariate vs. multivariable) is indicated in the corresponding table and text. Univariate tests were used for descriptive comparisons, while multivariable logistic regression models, adjusted for maternal, pregnancy-related, and neonatal variables, were used to estimate adjusted odds ratios for the six predefined neonatal outcomes. Results from the multinomial logistic regression models are presented in Table 4, comparing both the full dataset (all infants) and the reduced dataset (1 twin per pair). In both models, ACS exposure was not significantly associated with either moderate or critical illness. In contrast, maternal medications during pregnancy were consistently protective against critical illness in both samples, reaching statistical significance in the full (OR = 0.15, p = 0.020) and reduced (OR = 0.11, p = 0.013) models. Pathological maternal conditions showed a borderline significant association with increased risk of critical illness in the full model (p = 0.055), and became statistically significant in the reduced dataset (p = 0.017). No consistent or significant predictors were identified for moderate illness vs. vital status in either model. A side-by-side comparison of results from the full dataset (including all neonates) and the reduced dataset (one neonate per twin pair) showed no major deviations in effect estimates. In both models, maternal medications remained significantly protective against critical illness, and maternal pathological conditions showed consistent directionality with slightly stronger statistical significance in the reduced dataset. These findings confirm the robustness of our main conclusions despite potential bias introduced by the non-independence of twin pairs.

Additional multivariable analyses of primary neonatal outcomes

Need for mechanical ventilation

In the multivariable logistic regression model, gestational age (p = 0.001), sex (p = 0.033), and delivery mode (p = 0.040) were statistically significant predictors of the need for mechanical ventilation. Each additional week of gestation reduced the odds by 42.2% (aOR = 0.578), female sex was protective (aOR = 0.431), and cesarean/induced delivery increased the odds (aOR = 2.440). ACS exposure was not statistically significant (p = 0.106; aOR = 1.846), although it showed a non-significant trend toward higher odds. The model was statistically significant ($\chi^2(6) = 35.448$; $p < 0.001$) and explained 28.6% of the variance (Nagelkerke $R^2 = 0.286$) (Table 5, Table S3).

Intraventricular hemorrhage (IVH)

In the multivariable logistic regression model, gestational age (p = 0.002) and maternal pathological conditions during pregnancy (p = 0.013) were statistically significant predictors of IVH. Each additional week of gestation reduced the odds by 47.5% (aOR = 0.525), while the presence of maternal pathological conditions increased the odds more than fourfold (aOR = 4.270). Female sex showed a non-significant trend towards a protective effect (p = 0.066; aOR = 0.358). ACS exposure was not statistically significant (p = 0.507; aOR = 1.416), and neither was delivery mode or birth weight (both p > 0.20). The model was statistically significant ($\chi^2(6) = 28.261$; $p < 0.001$) and explained 29.7% of the variance (Nagelkerke $R^2 = 0.297$), with an overall classification accuracy of 85.0% (Table 5, Table S3).

Mortality

In the multivariable logistic regression model, none of the examined predictors was significantly associated with neonatal mortality. The model was statistically significant overall ($\chi^2(6) = 16.449$; $p = 0.012$) and explained 36.6% of the variance (Nagelkerke $R^2 = 0.366$), with an overall classification accuracy of 95.9%. Due to the very small

Table S1. *Comparison of birth weight and gestational age between ACS and non-ACS groups when analyzed as continuous variables*

	Received ACS	Did not receive ACS	p-value	Effect Size (r)	95% Confidence Interval	p-value Shapiro-Wilk test	p-value Levene's test
Birth weight (grams)	1781.51 [481.00]	1751.55 [437.87]	0.995	0	[-0.19, 0.18]	< 0.001	0.725
Gestational age (weeks)	31.93 [1.92]	31.92 [1.77]	0.796	0.02	[-0.16, 0.21]	< 0.001	0.835
Note: Values are presented as median [interquartile range]. Mann-Whitney U test was used due to violation of normality (Shapiro-Wilk p < 0.001). Effect size (r) and 95% confidence intervals (CI) are also reported.							

Table S2. *Robustness analysis of neonatal magnesium (Mg) levels by ACS exposure in the full sample and reduced twin-adjusted sample*

Sample	N (total)	N (ACS)	N (no ACS)	Median Mg (ACS)	Median Mg (no ACS)	Z	p-value
Main sample (150 infants)	146	75	71	0.84	0.84	−3.093	0.002
Reduced sample (one twin per pair)	121	64	57	0.84	0.84	−3.031	0.002
Note: p-values are from the Mann–Whitney U test. Groups: 1 = ACS received; 2 = no ACS. Mg levels in mmol/L.							

Table 3. *Laboratory parameters in newborns based on antenatal corticosteroid administration*

	Yes	No	p-value	Effect Size (r/Cohen's d)	95% Confidence Interval	p-value Shapiro-Wilk test	p-value Shapiro Yes	p-value Shapiro No	p-value Levene's test
Blood glucose on admission	3.99 [4.15]	4.48 [4.40]	0.442#	0.07 (r)	[-0.11, 0.25]	< 0.001	< 0.001	< 0.001	0.511
Lactate on admission	2.93 [1.39]	2.64 [1.23]	0.512#	-0.03 (r)	[-0.22, 0.15]	< 0.001	< 0.001	< 0.001	0.539
Red blood cells in the first 24h	4.91 [0.63]	4.98 [0.66]	0.716#	-0.03 (r)	[-0.22, 0.15]	< 0.001	< 0.001	0.113	0.275
Platelets in the first 24h	237.44 [80.60]	240.00 [64.19]	0.304#	-0.10 (r)	[-0.28, 0.09]	0.012	0.001	0.003	0.48
Calcium in the first 24h	2.15 [0.21]	2.14 [0.23]	0.611#	0.05 (r)	[-0.14, 0.23]	0.046	0.794	0.002	0.367
Magnesium in the first 24h	0.86 [0.15]	0.96 [0.27]	0.002#	0.30 (r)	[0.12, 0.46]	< 0.001	< 0.001	< 0.001	0.009
CRP on admission	2.78 [10.69]	2.62 [8.53]	0.627#	0.05 (r)	[-0.14, 0.23]	< 0.001	< 0.001	< 0.001	0.92
Highest CRP during treatment	17.49 [34.50]	38.97 [68.36]	0.287#	0.10 (r)	[-0.08, 0.28]	< 0.001	< 0.001	< 0.001	0.016
Results are presented as the median [interquartile range]; #Wilcoxon rank-sum test (equivalent to the Mann–Whitney U test) Yes = Received ACS; No = Did not receive ACS. "Shapiro Yes" and "Shapiro No" columns represent group-specific p-values from the Shapiro–Wilk test for normality.									

Table 4. *Results from the multinomial logistic regression models*

Comparison	Predictor	Odds Ratio (full sample)	p-value (full sample)	Odds Ratio (1 twin per pair)	p-value (1 twin per pair)
Moderate vs Vital	ACS (Yes)	3.09	0.136	5.1	0.062
Moderate vs Vital	$MgSO_4$ before birth (Yes)	1.56	0.49	2.07	0.323
Moderate vs Vital	Corticosteroids <24h (Yes)	0.51	0.376	0.36	0.244
Moderate vs Vital	Medications during pregnancy (Yes)	0.93	0.904	0.9	0.88
Moderate vs Vital	Pathological maternal conditions (Yes)	1.11	0.864	1.66	0.463
Moderate vs Vital	Magnesium in first 24h	0.35	0.279	0.34	0.287
Critical vs Vital	ACS (Yes)	1.6	0.688	2.42	0.477
Critical vs Vital	$MgSO_4$ before birth (Yes)	0.65	0.725	0.88	0.922
Critical vs Vital	Corticosteroids <24h (Yes)	0.32	0.363	0.27	0.323
Critical vs Vital	Medications during pregnancy (Yes)	0.15	0.02	0.11	0.012
Critical vs Vital	Pathological maternal conditions (Yes)	4.05	0.055	6.71	0.016
Critical vs Vital	Magnesium in first 24h	3.69	0.308	3.28	0.35

Table 5. *Adjusted odds ratios for ACS exposure and primary neonatal outcomes*

Outcome	aOR (ACS)	95% CI*	p-value
Mechanical ventilation	1.846	[0.88, 3.88]	0.106
IVH	1.416	[0.51, 3.96]	0.507
Mortality	1.47×10^8	not estimable	0.997
Sepsis	3.787	[0.94, 15.35]	0.062
NICU admission	0.454	[0.14, 1.48]	0.189
Critical illness	2.173	[0.98, 4.80]	0.055

*95% confidence intervals for ACS are presented here; full regression results for all predictors are shown in Supplementary Table S3.

Note: Models adjusted for gestational age, birth weight, sex, delivery mode, and maternal pathological conditions

number of mortality cases (N = 6), the model did not converge, and the estimated coefficients should be interpreted with caution. Female sex showed a non-significant trend towards a protective effect (p = 0.094; aOR = 0.137). ACS exposure was not significant (p = 0.997; aOR = 1.47×10^8), and neither gestational age, birth weight, maternal pathological conditions, nor delivery mode reached statistical significance (all p > 0.20) (Table 5, Table S3).

Sepsis

In the multivariable logistic regression model, birth weight (p = 0.046) and sex (p = 0.031) were statistically significant predictors of neonatal sepsis. Each additional gram of birth weight was associated with a slight reduction in odds (aOR = 0.997), while female sex was a significant protective factor (aOR = 0.197). ACS exposure was not statistically significant (p = 0.062; aOR = 3.787), but showed a non-significant trend toward higher odds. Gestational age, maternal pathological conditions, and delivery mode were not significant predictors (all p > 0.20). The model was statistically significant ($\chi^2(6) = 18.520$; p = 0.005) and explained 26.3% of the variance (Nagelkerke $R^2 = 0.263$), with an overall classification accuracy of 92.5% but low sensitivity for predicting sepsis cases (23.1%) (Table 5, Table S3).

NICU admission

In the multivariable logistic regression model, gestational age was the only statistically significant predictor of NICU admission (p = 0.014), with each additional week of gestation reducing the odds by 41.2% (aOR = 0.588). ACS exposure (p = 0.189; aOR = 0.454), sex, birth weight, maternal pathological conditions, and delivery mode were not statistically significant predictors (all p > 0.20), although some showed trends toward association. The model was statistically significant ($\chi^2(6) = 18.600$; p = 0.005) and explained 23.2% of the variance (Nagelkerke $R^2 = 0.232$), with an overall classification accuracy of 89.8% but low sensitivity for predicting NICU admissions (17.6%) (Table 5, Table S3).

Critical illness

In the multivariable logistic regression model, sex (p = 0.007), birth weight (p = 0.011), and maternal pathological conditions (p = 0.034) were statistically significant predictors of critical illness. Female sex was associated with a significantly lower risk (aOR = 0.316), higher birth weight was protective (aOR = 0.998 per gram), while maternal pathological conditions increased the risk more than twofold (aOR = 2.427). ACS exposure showed borderline significance (p = 0.055; aOR = 2.173), suggesting a possible trend toward increased risk. Gestational age and delivery mode were not statistically significant predictors (both p > 0.10). The model was statistically significant ($\chi^2(6) = 36.943$; p < 0.001) and explained 30.7% of the variance (Nagelkerke $R^2 = 0.307$), with an overall classification accuracy of 74.1% (sensitivity 86.5%, specificity 51.0%) (Table 5, Table S3).

DISCUSSION

Antenatal corticosteroid (ACS) administration is a well-established intervention to enhance fetal lung maturation and improve neonatal outcomes in preterm infants. This study evaluated the association between ACS exposure and early neonatal outcomes and laboratory parameters in neonates born at 28–34 weeks of gestation. Regarding maternal characteristics, no significant differences were observed in parity, type of pregnancy, mode of conception, or mode of delivery between ACS and non-ACS groups, but other medication use was higher in ACS-exposed mothers (56.7% vs. 34.4%, p = 0.022), likely reflecting a greater prevalence of pregnancy-related complications requiring pharmacologic intervention (10). ACS exposure has been associated with maternal conditions such as preeclampsia, hypertension, and gestational diabetes (11,12). However, our study found no significant differences in baseline maternal characteristics. Mode of delivery was also comparable between groups, consistent with evidence that obstetric factors, rather than ACS exposure, primarily determine delivery method (10). Similarly, no significant difference in maternal mortality has previously been observed following ACS administration, supporting the established maternal

Table S3. *Full multivariable logistic regression results for ACS exposure and neonatal outcomes*

Outcome	Predictor	B	p-value	aOR (Exp(B))
Mechanical ventilation	ACS	0.613	0.106	1.846
	Gestational age (weeks)	-0.548	0.001**	0.578
	Birth weight (g)	0	0.862	1
	Sex (female)	-0.841	0.033*	0.431
	Maternal pathology	0.607	0.13	1.835
	Delivery mode	0.892	0.040*	2.44
IVH	ACS	0.348	0.507	1.416
	Gestational age (weeks)	-0.644	0.002**	0.525
	Birth weight (g)	0	0.628	1
	Sex (female)	-1.028	0.066	0.358
	Maternal pathology	1.452	0.013*	4.27
	Delivery mode	-0.304	0.592	0.738
Mortality	ACS	18.807	0.997	1.47×10^8
	Gestational age (weeks)	0.469	0.313	1.599
	Birth weight (g)	-0.002	0.212	0.998
	Sex (female)	-1.985	0.094	0.137
	Maternal pathology	1.588	0.224	4.895
	Delivery mode	-0.363	0.746	0.696
Sepsis	ACS	1.332	0.062	3.787
	Gestational age (weeks)	0.129	0.617	1.138
	Birth weight (g)	-0.003	0.046*	0.997
	Sex (female)	-1.625	0.031*	0.197
	Maternal pathology	0.931	0.213	2.536
	Delivery mode	-0.952	0.216	0.386
NICU admission	ACS	-0.79	0.189	0.454
	Gestational age (weeks)	-0.531	0.014*	0.588
	Birth weight (g)	0	0.964	1
	Sex (female)	-0.471	0.438	0.624
	Maternal pathology	0.615	0.305	1.851
	Delivery mode	0.813	0.226	2.255
Critical illness	ACS	0.776	0.055	2.173
	Gestational age (weeks)	-0.257	0.13	0.774
	Birth weight (g)	-0.002	0.011*	0.998
	Sex (female)	-1.152	0.007**	0.316
	Maternal pathology	0.887	0.034*	2.427
	Delivery mode	0.33	0.437	1.391

*Models adjusted for gestational age, birth weight, sex, delivery mode, and maternal pathological conditions.

**p < 0.01; *p < 0.05.

safety profile of ACS in the management of preterm birth (10). Neonatal characteristics, including gender distribution, birth weight, and gestational age, were similar between groups. The absence of significant differences in birth weight and gestational age between groups, regardless of whether variables were analyzed continuously or dichotomously, supports baseline comparability (Table S1). Apgar scores, need for resuscitation at birth, and initial NICU stability showed no statistically significant differences between groups. Although the proportion of critically ill neonates upon NICU admission was lower in the ACS group (8.1% vs. 18.4%), this difference did not reach statistical significance ($p = 0.060$), and the study may be underpowered to detect modest effects. The need for resuscitation was comparable (16.2% vs. 26.3%, $p = 0.131$), but ACS may still enhance neonatal adaptation at birth [10]. Some studies suggest that neonates receiving ACS closer to delivery (from one to seven days) may require more

respiratory support due to lower gestational age (13). We found no significant difference in oxygen therapy, mechanical ventilation, or surfactant administration, which is consistent with recent studies suggesting that the universal application of antenatal corticosteroids in this gestational range may not always be justified, as they may have a limited effect in babies with relatively mature lungs (gestational age of 32 weeks and more) (11). The slightly higher ventilation rate in the ACS group may be attributed to factors such as gestational age distribution or illness severity. The effects of ACS are most pronounced at lower gestational ages (24–30 weeks), where they play a crucial role in reducing neonatal mortality, RDS, and severe IVH (10). ACS administration is linked to a significant reduction in RDS and respiratory complications (14), particularly benefiting high-risk neonates, including those with fetal growth restriction or small for gestational age (5). In babies born after 32 weeks of gestation, the effects of ACS are less pronounced, and some studies suggest that ACS may prolong neonatal hypoglycemia and potentially increase the risk of neonatal sepsis (12). However, ACS exposure has also been associated with an increased risk of neonatal pneumonia within the first six months of life (12). It significantly lowers IVH risk without affecting the incidence of NEC (15), though some evidence links ACS to an increased risk of early-life infections, including sepsis, pneumonia, and gastroenteritis [12]. Prolonged hospitalization and additional medical interventions, such as antibiotics and tocolytics, have been reported among ACS-exposed neonates (13). Although ACS has demonstrated a strong protective effect against IVH, no significant difference in IVH incidence was observed in our study. Although the proportion of severe IVH was lower in the ACS group (17.6% vs. 14.5%), this difference was not statistically significant, and the sample size may have been insufficient to detect smaller effects. There were no relevant differences in cranial ultrasound findings, neither in the first three weeks of life nor at discharge. The similar distribution of low-grade and high-grade IVH in both groups suggests ACS had no measurable effect on early neurosonographic outcomes in this gestational range. In the additional multivariable analyses, antenatal corticosteroid exposure did not emerge as an independent predictor of major neonatal outcomes. Instead, gestational age and female sex consistently showed protective effects, while lower birth weight and maternal pathological conditions increased the risk for several adverse endpoints. Cesarean or induced delivery was associated with higher odds of mechanical ventilation. A borderline association was observed between ACS and critical illness at admission ($p = 0.055$), but this did not reach statistical significance. These findings suggest that, after adjustment for key clinical factors, ACS exposure was not independently associated with the evaluated early neonatal outcomes in infants born at 28–34 weeks in our cohort. Rather, gestational maturity and baseline clinical characteristics appear to be the main drivers of neonatal prognosis, which is consistent with previous evidence that the benefit of ACS is most pronounced at lower gestational ages.

Our study identified higher magnesium levels in the non-ACS group, whereas no significant differences were observed in glucose metabolism, blood cell counts, or inflammatory markers. Because maternal magnesium sulfate administration was significantly more frequent in the non-ACS group, this finding is likely attributable to differences in maternal treatment rather than a direct effect of ACS exposure.

Maternal administration of magnesium sulfate has been shown to directly influence neonatal magnesium levels, with studies confirming a strong correlation between maternal and neonatal blood concentrations, indicating that elevated neonatal magnesium primarily reflects transplacental transfer (16). Recent studies have indicated that antenatal corticosteroid exposure may influence not only pulmonary outcomes but also broader systemic processes, including immunological and inflammatory responses. Significant alterations in neonatal immune function, such as changes in cytokine signaling and inflammatory markers, have been observed. This supports the notion that ACS may exert extensive biological effects beyond lung maturation, potentially contributing to the metabolic and immunologic differences (17). Given the complexity of high-risk pregnancies, such as those complicated by severe intrahepatic cholestasis, the administration of antenatal corticosteroids requires careful evaluation and individualized decision-making. In these cases, earlier gestational age at delivery, lower birth weight, and reduced Apgar scores have been observed, highlighting the potential systemic effects on neonates beyond pulmonary maturation and underscoring the need for customized perinatal strategies when considering ACS exposure (18). A slightly higher rate of positive blood cultures in the ACS group was not statistically significant and aligns with studies indicating that ACS does not elevate neonatal infection rates (10). These findings emphasize the need for further research to optimize ACS use in late preterm infants, balancing its potential benefits with associated metabolic effects and neonatal outcomes.

Limitations of this study

This study's retrospective design may introduce selection bias, limiting causal inferences on ACS effects. The sample size, though adequate for general comparisons, may not detect subtle differences in neonatal outcomes. The lack of standardized RDS assessment complicates comparisons with prior studies. Potential confounders, such as maternal health conditions, could have influenced findings, and the timing of ACS administration was not stratified, which may affect neonatal benefits. Future well-designed prospective studies with larger cohorts and long-term follow-up are needed to refine ACS treatment strategies and optimize neonatal outcomes. Additionally, the study did not account for the clustering effect of multiple gestations, as twins were analyzed as independent observations. This may have introduced bias due to correlated outcomes within twin pairs, potentially underestimating variability and affecting the statistical power of comparative analyses. However, the dataset reflects the actual population of preterm neonates admitted during the study period, and outcomes were evaluated per individual neonate, consistent with clinical practice. Clinical and laboratory data were available for the majority of included neonates, with missing values limited to specific parameters as detailed in table footnotes. Furthermore, this study included multiple statistical comparisons across maternal, neonatal, and laboratory variables without formal adjustment for multiple testing. This approach was chosen to preserve sensitivity in an exploratory analysis. It increases the risk of Type I error, and findings should be interpreted with this consideration in mind. While initial group comparisons were based on univariate analyses, multivariable logistic regression models were subsequently performed for six key neonatal outcomes to account for potential confounding. In the revised analysis, these models were expanded to include neonatal variables, such as gestational age, birth weight, sex, and mode of delivery, alongside maternal and pregnancy-related factors, thereby improving the robustness of the findings. Categorizing continuous variables can reduce statistical power and obscure dose–response relationships. For birth weight and gestational age, we observed no differences in results when analyzed as continuous variables (see Supplementary Table 1). NICU length of stay was not available in a continuous format and, therefore, could not be modeled accordingly. Although the proportion of critically ill neonates was lower in the ACS group, this difference was not statistically significant.

Antenatal corticosteroids (ACS) administration remains the standard approach for managing preterm birth, with well-documented benefits in improving neonatal outcomes, particularly in lower gestational ages (24–30 weeks). However, our study found no significant differences in major neonatal outcomes between ACS-exposed and non-exposed neonates born between 28 and 34 weeks of gestation. These findings suggest that the universal application of ACS in this gestational range may not always be justified and that larger prospective studies are needed before conclusions can be drawn regarding the optimal use of ACS in these populations.

Additionally, we observed significantly higher serum magnesium levels in neonates not exposed to ACS, suggesting a potential metabolic effect that might influence neuromuscular function and neonatal adaptation. However, it is important to interpret this difference with caution, as it is likely related to the more frequent administration of maternal magnesium sulfate in the non-ACS group.

While ACS has demonstrated strong protective effects in reducing RDS, IVH, and neonatal mortality at lower gestational ages, its impact at later preterm stages appears less pronounced and may be associated with prolonged neonatal hypoglycemia and an increased risk of infection. These findings highlight the need for further research to refine ACS administration strategies, optimize neonatal care, and better define its role in late preterm infants. In this study, maternal medications during pregnancy emerged as a significant protective factor against critical neonatal illness, even after adjustment for other perinatal factors. Pathological maternal conditions were also associated with an increased risk of severe neonatal outcomes. No statistically significant association was observed between ACS exposure and neonatal outcomes after adjustment, and the limited sample size restricts the ability to detect less pronounced associations. Importantly, the use of a reduced dataset excluding one twin per pair confirmed that our findings were robust to potential bias from twin clustering. These results highlight the critical role of maternal health and antenatal care in shaping early neonatal outcomes. Furthermore, a post hoc sensitivity analysis excluding one twin per pair confirmed that our findings were robust to potential intra-pair clustering.

Practical implications

In preterm infants born after 32 weeks of gestation, our findings did not demonstrate a significant association between antenatal corticosteroid (ACS) exposure and early neonatal outcomes, suggesting limited clinical benefit from routine ACS administration in this gestational age group. Early outcomes in this range appear to be more strongly

influenced by gestational maturity and baseline neonatal condition than by steroid exposure. Given the retrospective design and relatively limited sample size, these findings should be interpreted with caution. Nevertheless, they support further investigation into whether a more individualized approach to ACS administration may be appropriate in selected late-preterm populations.

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Author Contributions

Conceptualization: S.M. and M.J.R.; Methodology: S.M. and M.J.R.; Formal analysis: S.M. and M.J.R.; Investigation: S.M. and M.J.R.; Data curation: S.M. and M.J.R.; Writing – Original Draft Preparation: S.M. and M.J.R.; Writing – Review and Editing: S.M. and M.J.R. All authors have read and approved the published version of the manuscript.

Statement of Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee (approval number 1305/23) on April 11, 2023. As this was a retrospective study using anonymized data, the requirement for informed consent was waived by the Institutional Ethics Committee.

Statement of Competing Interest

The authors declare no relevant conflicts of interest.

Statement of Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Statement of Generative AI Use

No generative AI was used.

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