Early Human Development 130 (2019) 44–50

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Neonatal outcomes of antenatal corticosteroids in preterm multiple pregnancies compared to singletons

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ARTICLE INFO

Keywords:
Antenatal steroids
Preterm multiple pregnancies
Neonatal outcomes

ABSTRACT

Background: Antenatal corticosteroids (ACS) during preterm labour reduce neonatal mortality and morbidity. Evidence on preterm multiple pregnancies is limited and contradictory.
Objective: Compare the effect of ACS on very low birth weight infant's (VLBW) mortality and morbidity among singleton and multiple pregnancies.
Study design: Retrospective cohort study, employing prospectively collected data, of infants 23 to 34 weeks' gestation and 500 to 1500 g born at the Neocosur Neonatal Network centers during 2007–2016. Neonatal outcomes were compared among singleton and multiple pregnancies exposed to at least one dose of ACS to those not exposed using logistic regression analyses controlled for birthweight, gestational age, sex, small for gestational age (SGA) and mode of delivery.
Results: A total of 13,864 infants were studied; 2948 multiple (21.3%) and 10,904 singleton pregnancies (78.7%). Overall, 11,218 (81.4%) received at least one dose of ACS with a significant reduction in the risk of death, RDS and grade III or IV IVH compared to those not exposed. Both singleton and multiple pregnancies exposed to ACS showed similar reduced risk of death (aRR 0.41 [95% CI, 0.36–0.47] vs. aRR 0.46 [95% CI, 0.34–0.64]). However, ACS were not associated with reduced odds of RDS (aRR 0.89 [95% CI, 0.66–1.23]) or grade III or IV IVH (aRR 0.99 [95% CI, 0.67–1.48]) in multiple pregnancies.
Conclusion: The benefit of administration of at least one dose of ACS in VLBW multiple and singleton pregnancies is comparable in terms of death. However, ACS showed no relevant impact in short-term morbidity in multiple pregnancies.

1. Introduction

Corticosteroid administration in pregnant women at risk of preterm delivery is currently one of the most effective perinatal strategy known to improve neonatal outcomes [1]. Administration of a single course of antenatal corticosteroids (ACS) to the mother prior to anticipated preterm birth between 24 and 34 weeks' gestation reduces the risk of perinatal and neonatal death, respiratory distress syndrome (RDS) and the need for respiratory support, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and early-onset systemic infections [2]. Although less certain, corticosteroid therapy has been extended to periviable infants born at 23 weeks' gestation [3] and near-term infants born by elective caesarean section to reduce associated respiratory morbidity [4]. However, little is known about the efficacy and safety of ACS in special neonatal subgroups, such as preterm infants of multiple-gestation pregnancies. With the advent of fertility treatments and older maternal age at childbearing, multiple-gestation pregnancies have increased substantially over the last decades [5,6]. Multiple birth contributes significantly to neonatal short and long-term morbidity and mortality [7–10], accounting for nearly 20% of admissions to the Neonatal Intensive Care Unit (NICU) [11,12]. A number of studies have reported positive effects of ACS in the reduction of respiratory

Abbreviations: ACS, antenatal corticosteroids; VLBW, very low birth weight infant; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity

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https://doi.org/10.1016/j.earlhumdev.2019.01.008
Received 11 October 2018; Received in revised form 8 January 2019; Accepted 9 January 2019

morbidity [13–15] and severe neurological injury [16] similar in magnitude to that observed among singletons, while some others show contradictory findings [17–20]. The attenuated beneficial effect of ACS in multiple pregnancies proposed by several authors has been attributed to differences in pharmacokinetics profile, such as shorter half-life and faster clearance of steroids, that may result in sub-therapeutic drug levels for fetal lung maturation [17,21]. However, there are contradictory findings regarding this hypothesis as well [22,23].

The purpose of this study was to compare the effect of ACS on the incidence of main short-term morbidity and mortality in a large cohort of preterm singleton and multiple very low birth weight (VLBW) infants.

2. Materials and methods

2.1. Study design

This is a retrospective cohort study, employing prospectively collected data, of infants between 23 and 34 weeks' gestation and birthweight 500 to 1500 g born at any of the 26 South American NICUs participating in the Neocosur Neonatal Network during the period 2007–2016. Infants born with major congenital anomalies or any chromosomal abnormality were excluded from the analyses.

The Neocosur Neonatal Network is a voluntary non-profit association of NICUs across six South American countries (Argentina, Brazil, Chile, Paraguay, Peru, and Uruguay), whose main objective is to improve neonatal outcomes in the region. All network centers are tertiary care and university affiliated. Data on VLBW infants born at the participating centers is prospectively collected at each site by trained nurses and physicians using predefined diagnostic criteria and an online registry system that is periodically validated by local statisticians. Information includes maternal sociodemographic details, pregnancy history, delivery, infant's status at delivery, diagnoses, complications, procedures and treatments during hospitalization, and outcome at discharge.

Variables for this study included gestational age, birthweight (BW), small for gestational age (SGA, BW < 10th percentile according to the World Health Organization growth charts, WHO), plurality of pregnancy (singleton/multiple), antenatal corticosteroids exposure (complete/incomplete course), mode of delivery (caesarean with labour, caesarean without labour, and vaginal delivery), Apgar scores at 1 and 5 min after birth, neonatal morbidities and mortality during hospital stay (including death in the delivery room).

Neonatal outcomes were compared among singleton and multiple pregnancies exposed to ACS to those not exposed to ACS. Multiple pregnancy was defined as twin, triplet or any higher-order gestation. The gestational age (GA) in completed weeks was defined as the best estimate of GA based on the last menstrual period and early prenatal ultrasound examination. Exposure to ACS was defined as administration of at least one dose of any corticosteroid with proven efficacy to the mother prior to anticipated preterm delivery. Complete courses were defined as administration of either 2 doses of 12 mg of betamethasone intramuscularly every 24 h or 4 doses of 6 mg of dexamethasone every 12 h. Information on the timing of ACS doses together with exposure to either betamethasone or dexamethasone was not available in the Network database and therefore, was not taken into consideration in the study design.

Mortality was defined as the primary outcome and included death before hospital discharge or transfer. Secondary outcomes included: 1) clinical respiratory distress syndrome (RDS) defined as increased work of breathing and requirement for oxygen within the first 24 h of life; 2) grade III-IV intraventricular hemorrhage (IVH), diagnosed by cranial ultrasound or autopsy and classified in grades I to IV according to Papile's criteria [24]; 3) necrotizing enterocolitis (NEC), defined clinically and radiologically by Bell's criteria [25] and; 4) retinopathy of prematurity (ROP), diagnosed by examination performed by an ophthalmologist and classified in grades 1 to 5 according to the international classification [26].

This study was approved by the Ethics Committee and Institutional Review Board of Pontificia Universidad Católica de Chile, School of Medicine.

2.2. Statistical analysis

Standard descriptive statistics were used for continuous variables expressed as mean and standard deviation, minimum and maximal values. Categorical variables are shown as number of cases and percentages.

Multivariate matching methods were used to compare outcomes between infants exposed to ACS and those not exposed to ACS. Crude and adjusted relative risks (cRR, aRR) and 95% confidence intervals (CI) were calculated by logistic regression analyses and controlled for birthweight, gestational age, sex, SGA and mode of delivery. Statistical analyses were performed using the SPSS 17.0 software (Chicago, IL, USA).

3. Results

3.1. Characteristics of the general study population

A total of 13,864 infants born with a mean gestational age of 29 weeks (range, 23–34 weeks) and birthweight of 1087 g (500–1500 g) were identified during the study period. Fifteen percent of infants were born at or before 25 weeks' gestation and 15.8% were SGA. Of this cohort, 2948 were multiple (21.3%) and 10,904 were singleton pregnancies (78.7%). Eight infants were excluded from the study due to major congenital malformations. None of the infants were diagnosed with chromosomal abnormalities.

Eighty-one percent of the infants received at least one dose of ACS. Reasons for omissions in the 18.6% of infants who did not receive ACS were not documented in the database. However, we believe that the gap in ACS exposure corresponds mostly to precipitous or emergent preterm delivery with insufficient time to administer corticosteroids to the mother on admission to the hospital.

Of the total study population, about 51% of infants were born via C-section without labour, 22.7% via C-section with labour, and 26.2% presented with spontaneous vaginal delivery. The rate of clinical RDS in our study population was 77.6% and the rate of mechanical ventilation following birth was 62.9%. About 11.2% of infants were diagnosed with NEC, 9.4% with grade III or IV IVH, and 21.8% with ROP. Overall mortality rate was 22.4%. Baseline characteristics and outcomes of singletons vs multiples are shown in Table 1.

3.2. Efficacy of ACS in the general study population

All infants who received at least one dose of ACS showed a statistically significant reduction in the risk of death, RDS and grade III or IV IVH when compared to those not exposed to ACS. Mortality rate was 38.2% in the group of infants not exposed to ACS compared to 18.7% in the group exposed to ACS (RR 0.37 [95% CI, 0.34–0.41]). When considering morbidities, RDS presented in 80.6% of infants who did not receive ACS compared to 77% in infants exposed to at least one dose of ACS (RR 0.81 [95% CI, 0.72–0.90]). Infants who did not receive ACS had a 13.1% rate of grade III or IV IVH compared to 8.5% in infants who received ACS (RR 0.62 [95% CI, 0.54–0.71]). There was no statistically significant reduction in the risk of NEC or ROP for any of the groups: 11.5% of infants not exposed to ACS developed NEC compared to 11.1% of infants exposed to ACS (RR 0.96 [95% CI, 0.83–1.09]). ROP presented in 22.1% of infants not exposed to ACS compared to 21.7% of infants exposed to ACS (RR 0.98 [95% CI, 0.85–1.12]).

Table 1
Baseline characteristics and outcomes of singletons vs multiples.

	Singletons	Multiples	*P* value
Gestational age (weeks), mean (SD)	28.6 (2.7)	29.0 (2.7)	< 0.001
Birthweight (g), mean (SD)	1080.7 (275.8)	1112.2 (281.4)	< 0.001
Small for gestational age (g), n (%)	1730 (15.9%)	464 (15.7%)	0.851
Antenatal corticosteroids, n (%)	8687 (80.2%)	2521 (85.9%)	< 0.001
Complete course	6354 (73.8%)	2057 (82.3%)	< 0.001
Incomplete course	2254 (26.2%)	443 (17.7%)	< 0.001
Mode of delivery, n (%)			
Spontaneous labour	3248 (29.9%)	378 (12.9%)	< 0.001
C-section without labour	5633 (51.8%)	1417 (48.2%)	< 0.001
C-section with labour	1999 (18.4%)	1146 (39.0%)	< 0.001
Apgar scores at 1 min ≤ 3, n (%)	2536 (23.3%)	446 (15.1%)	< 0.001
Apgar scores at 5 min ≤ 3, n (%)	716 (6.6%)	128 (4.3%)	< 0.001
Mortality, n (%)	2498 (22.9%)	595 (20.2%)	0.002
Respiratory distress syndrome, n (%)	8332 (77.8%)	2237 (76.7%)	0.219
Mechanical ventilation, n (%)	6797 (63.5%)	1768 (60.7%)	0.005
Necrotizing enterocolitis, n (%)	1220 (11.4%)	303 (10.4%)	0.128
Intraventricular hemorrhage grade III or IV, n (%)	1038 (9.7%)	241 (8.3%)	0.022
Retinopathy of prematurity, n (%)	1656 (22.4%)	412 (19.7%)	0.008

3.3. Efficacy of ACS in multiple pregnancies compared to singletons

Crude and adjusted relative risks were calculated for all variables included in the study, however, we decided to use the adjusted relative risk given that the difference between the calculated cRR and aRR was > 20% for most of the variables (Table 2).

Our analysis showed that there was a statistically significant reduction in mortality for both singleton (aRR 0.41 [95% CI, 0.36–0.47]) and multiple pregnancies (aRR 0.46 [95% CI, 0.34–0.64]) exposed to at least one dose of ACS. In addition, there was a statistically significant reduction in the odds of RDS in singleton pregnancies exposed to ACS (aRR 0.83 [95% CI, 0.72–0.95]). However, reduction in the risk of RDS in multiple pregnancies was not statistically significant (aRR 0.89 [95% CI, 0.66–1.23]). We found a statistically significant reduction in the risk of severe IVH for singleton pregnancies exposed to ACS (aRR 0.83 [95% CI, 0.70–0.97]), which was not observed in multiple pregnancies (aRR 0.99 [95% CI, 0.67–1.48]). Neither of the groups exposed to ACS showed a statistically significant reduction in the risk of NEC (singleton aRR 1.09 [95% CI, 0.94–1.28]) and multiple aRR 1.08 [95% CI, 0.75–1.54]), nor did they show a statistically significant reduction in the odds of ROP (singleton aRR 0.94 [95% CI, 0.79–1.11]) and multiple aRR 0.89 [95% CI, 0.59–1.35]).

We performed a secondary analysis to evaluate the efficacy of ACS in twins compared to higher order gestations using the same logistic regression model. Of the 12,919 infants included in this analysis, 1682 (13%) were twins and 334 (2.6%) were higher order gestations. ACS were not associated in higher-order gestations with a significant reduction in the risk of death (aRR 0.33 [95% CI, 0.09–1.14]), severe IVH (aRR 1.8 [95% CI, 0.39–8.37]), RDS (aRR 0.87 [95% CI, 0.22–3.5]), NEC (aRR 1.89 [95% CI, 0.43–8.40]) or ROP (aRR 1.8 [95% CI, 0.34–9.80]) when compared to twins.

Moreover, we assessed whether administration of a complete course compared to an incomplete course of ACS had impact on the main neonatal outcomes for both singleton and multiple pregnancies. From a total of 13,864 infants, 13,676 had available data on the number of corticosteroids doses, 2562 (18.5%) did not receive any dose, 2697 (19.7%) received one or more doses, and 8419 (60.7%) received a complete course of ACS. For singletons, there was a statistically significant reduction in the risk of death following administration of either an incomplete or complete course of ACS (aRR 0.56 [95% CI, 0.48–0.65] and 0.35 [95% CI, 0.31–0.41], respectively). We also observed a statistically significant reduction in the risk of grade III or IV IVH (aRR 0.71 [95% CI, 0.60–0.84]) as well as in the risk of RDS (aRR 0.75 [95% CI, 0.66–0.87] after exposure to a complete course of ACS in this group. However, there was no reduction in the risk of severe IVH or RDS following an incomplete course of ACS (aRR 1.07 [95% CI, 0.89–1.30] and aRR 1.09 [95% CI, 0.92–1.29], respectively). For multiple pregnancies, there was a statistically significant reduction in the risk of death following administration of a complete course of ACS (aRR 0.39 [95% CI, 0.28–0.55]), however, no statistical significance was observed for incomplete courses (aRR 0.80 [95% CI, 0.54–1.18]). There was no reduction in the risk of severe IVH or RDS after an incomplete (aRR 1.07 [95% CI, 0.66–1.72] and aRR 1.28 [95% CI, 0.85–1.92], respectively) or complete course of ACS (aRR 0.96 [95% CI, 0.64–1.46] and aRR 0.84 [95% CI, 0.61–1.15], respectively) in this group. Administration of a complete course of ACS showed no further

Table 2
Association between administration of ACS and neonatal outcomes in multiple and singleton pregnancies (logistic regression model).*

Neonatal outcomes	Singleton pregnancies			Multiple pregnancies		
	ACS		No ACS	ACS		No ACS
	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)	n (%)
Mortality	1641 (18.9%)	0.41 (0.36–0.47)	838 (39%)	448 (17.8%)	0.46 (0.34–0.64)	141 (34.1%)
RDS	6642 (77.2%)	0.83 (0.72–0.95)	1648 (80.9%)	1913 (76.3%)	0.89 (0.66–1.23)	311 (78.7%)
IVH grade III or IV	754 (8.7%)	0.83 (0.70–0.97)	278 (13.5%)	195 (7.8%)	0.99 (0.67–1.48)	44 (11%)
NEC	976 (11.3%)	1.09 (0.94–1.28)	237 (11.6%)	258 (10.3%)	1.08 (0.75–1.54)	44 (11.1%)
ROP	1395 (22.3%)	0.94 (0.79–1.11)	251 (22.5%)	365 (19.6%)	0.89 (0.59–1.35)	45 (20%)

Abbreviations: RDS: respiratory distress syndrome; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; ACS: antenatal corticosteroids; aRR: adjusted relative risk; CI: confidence interval.

* Adjusted RR (aRR) and 95% confidence intervals estimated with the group not exposed to ACS were used as reference. Logistic regressions adjusted for birthweight, gestational age, sex, SGA and mode of delivery.

Table 3
Efficacy of complete and incomplete courses of ACS in singleton and multiples born at 23–27 6/7 weeks' vs 28–34 weeks' gestation.*

Singleton pregnancies								
	23–27 6/7 weeks				28–34 weeks			
	n: 3750 (74.6% with ACS)				n: 6966 (82.9% with ACS)			
	Incomplete ACS		Complete ACS		Incomplete ACS		Complete ACS	
	n: 877 (23.4%)		n: 1920 (51.2%)		n: 1369 (19.6%)		n: 4409 (63.3%)	
	aRR	95% CI	aRR	95% CI	aRR	95% CI	aRR	95% CI
Mortality	0.52	(0.42–0.65)	0.32	(0.27–0.39)	0.64	(0.50–0.81)	0.43	(0.35–0.52)
IVH grade III or IV	1.14	(0.91–1.44)	0.77	(0.62–0.95)	0.85	(0.61–1.17)	0.53	(0.39–0.69)
RDS	1.82	(1.28–2.57)	1.31	(0.98–1.74)	0.83	(0.68–1.01)	0.55	(0.46–0.64)
NEC	1.39	(1.07–1.79)	1.15	(0.91–1.46)	1.14	(0.87–1.48)	0.84	(0.67–1.06)
ROP	1.04	(0.76–1.43)	0.95	(0.72–1.25)	1.05	(0.80–1.37)	0.92	(0.74–1.61)
Multiple pregnancies								
	23–27 6/7 weeks				28–34 weeks			
	n: 832 (80.8% with ACS)				n: 2068 (87.7% with ACS)			
	Incomplete ACS		Complete ACS		Incomplete ACS		Complete ACS	
	n: 173 (20.8%)		n: 500 (60.0%)		n: 268 (12.9%)		n: 1548 (74.8%)	
	aRR	95% CI	aRR	95% CI	aRR	95% CI	aRR	95% CI
Mortality	0.76	(0.45–1.31)	0.41	(0.26–0.64)	0.79	(0.44–1.44)	0.37	(0.23–0.61)
IVH grade III or IV	1.58	(0.92–2.73)	1.26	(0.77–2.06)	0.29	(0.10–0.85)	0.43	(0.22–0.84)
RDS	6.36	(1.78–22.66)	2.70	(1.22–5.98)	0.93	(0.59–1.45)	0.61	(0.43–0.87)
NEC	1.53	(0.77–3.06)	2.02	(1.10–3.69)	0.67	(0.36–1.26)	0.72	(0.45–1.15)
ROP	2.00	(0.85–4.72)	1.16	(0.55–2.41)	0.83	(0.44–1.56)	0.69	(0.42–1.15)

Abbreviations: RDS: respiratory distress syndrome; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; ACS: antenatal corticosteroids; aRR: adjusted relative risk; CI: confidence interval.

* Logistic regressions adjusted for birthweight, gestational age, sex, SGA and mode of delivery.

benefit in the risk of NEC or ROP compared to administration of an incomplete course for both singleton and multiple pregnancies.

Finally, in an effort to investigate the impact of exposure to ACS in subsets of gestational age, we analysed the effect of complete and incomplete courses of ACS on mortality and short-term morbidity for singletons and multiples born at 23 0/7 to 27 6/7 weeks' gestation and at 28 0/7 to 34 0/7 weeks' gestation. By logistic regression, we observed that a complete course of ACS was associated with a reduction in death, RDS and severe IVH in both singleton and multiple infants born at 28 to 34 weeks' gestation. However, less benefit was observed for infants younger than 28 weeks' gestation as complete courses of ACS were associated with a reduction in the risk of death for both groups and, in addition, a reduction in the risk of severe IVH for singletons. No benefit was observed for multiples born at < 28 weeks' gestation with exposure to an incomplete course of ACS. Adjusted relative risks and CI are presented in Table 3.

4. Discussion

4.1. Primary findings

ACS have proven long ago to be safe and effective in reducing neonatal complications of prematurity. The beneficial effects of corticosteroid administration before preterm delivery were first reported in animal models [27], and were subsequently supported by human studies [28–30]. A 2017 Cochrane review of all RCT comparing treatment with ACS versus placebo in patients at risk for preterm birth before 34 weeks' gestation demonstrated a significant reduction in the risk of neonatal death, RDS and the need for respiratory support, IVH, NEC, and early-onset systemic infections [2]. Corticosteroids accelerate maturation of both structure and function of developing fetal and neonatal tissues such as the lung epithelium and the intestinal mucosal barrier as well as immature vasculature, and promote circulatory stability in the germinal matrix, contributing to the improved clinical outcome after ACS administration [31]. However, efficacy of ACS in multiples, including extremely preterm multiple pregnancies is still a matter of debate.

We present a large retrospective cohort study of prospectively collected data during the period 2007–2016 with the aim of shedding light on the efficacy and clinical application of ACS in multiple pregnancies. Our main finding, after adjusting for potential confounders, was a statistically significant reduction in the risk of death for multiple pregnancies exposed to at least one dose of ACS, comparable to the effect observed in singletons. However, we could not demonstrate a relevant impact on short-term morbidities such as RDS, IVH, NEC or ROP following administration of ACS in multiple pregnancies.

Previous findings have been limited and contradictory. While some studies suggested that ACS are beneficial on short-term morbidity in multiple pregnancies [13–16], others have failed to show comparable benefits to singleton pregnancies [17–20]. More recently, a retrospective cohort study conducted by the Canadian Neonatal Network including 9466 infants (2516 twins) born between 24 and 34 weeks' gestation showed a significant reduction in terms of death, RDS and severe neurological injury in multiple pregnancies [16]. Data presented by Boghossian et al. in a study carried out by the National Institute of Child Health and Human Development (NICHD) with a total study population of 6925 multiples < 28 weeks' gestation showed similar findings; infants with exposure to ACS showed lower rates of in-hospital

mortality and severe IVH compared with no exposure, with no significant differences for the composite of neurodevelopmental impairment or death [32].

4.2. Impact of our study

As the number of multiple pregnancies rises in times of increasing assisted fertilization techniques and older maternal age at childbearing, therapies in this subgroup population need to be proven effective. Potential pharmacokinetic changes in multiple pregnancies such as increased volume of distribution, shorter half-life and a faster clearance of glucocorticoids have been proposed as one of the mechanisms underlying the decreased effect of ACS in these infants, suggesting that current dosing may be suboptimal for this population [18,21,33]. However, these concerns have not been sustained in recent studies [22,23,34]. Gyamfi et al. did not find a significant association between betamethasone levels and plurality [22]. Administration of two doses of 12 mg of betamethasone given 24 h apart in preterm pregnancies has shown observable physiologic and behavioral changes in twin pairs irrespective of their composition, indicating that the levels of glucocorticoids are sufficient for both twin members [34]. Therefore, current recommended dosing is not likely to explain the apparent inefficacy of ACS in multiple pregnancies. Further research must be done to enlighten us in the mechanism underlying this question.

To our knowledge, this is the largest cohort study to date evaluating efficacy of ACS in multiple pregnancies. The power of our study can be estimated by the large sample size and by the width of the calculated confidence intervals. Our findings suggest that the benefit of administration of at least one dose of ACS in VLBW multiple and singleton pregnancies is comparable in terms of death. However, ACS did not prove to be effective in reducing the rates of RDS, HIV, NEC or ROP in multiple pregnancies.

Mortality is 5 to 7-fold and 10 to 12-fold higher for twins and higher-order gestations, respectively, compared to singletons, probably due to the increasing rate of prematurity together with the subsequent fetal growth restriction with increasing number of fetuses [35,36]. The relative reduction of ACS in the risk of RDS has been described as plurality-dependent with the lowest effect observed in triplets, suggesting that larger or repeated doses may be needed in higher-order gestations [35]. We did not observe a reduction in the risk of death or short-term morbidity following administration of ACS in higher-order gestations compared to twins. However, the secondary analysis resulted in a reduction of the sample size that could be insufficient to draw statistical conclusions.

Because of the retrospective design of this study, potential methodological limitations should be considered. As an example, we were not able to evaluate the role of each specific type of corticosteroid, neither did we assess the timing of administration in relation to delivery or chorionicity, as this information was not available in our database. Accumulating evidence shows a reduced effect of ACS when interval between administration and delivery exceeds 7 days [14,16,37,38]. RDS is seven times more likely in infants exposed to ACS beyond 7 days compared to those exposed to ACS within the window of efficacy [39]. Preterm infants < 34 weeks' gestation exposed to ACS within 8–14, 15–21, and 22–28 days from delivery are at increased risk for intubation compared to infants exposed within 0–7 days from delivery [37]. Therefore, should the timing have been taken in consideration, the results might have shown statistical significance in the secondary outcomes.

Future studies should also consider zygosity status and chorionicity, as monochorionicity has been associated with higher mortality and morbidity including increased risk for neurological impairment compared to dichorionic twins [35,40]. The influence of birth order cannot be dismissed as second twins have shown to be at increased risk for RDS, ROP and death compared to first-born twins even in the era of ACS and postnatal surfactant [36,41]. It might have been interesting to evaluate the existence of a differential efficacy of ACS among the first and second fetus, however, only 2/3 of multiples were identified in our database as first or second twin. Further research using multivariate logistic regression analyses accounting for all confounding variables are needed.

We acknowledge another weakness of our study is that the diagnosis of RDS was based solely on clinical criteria. This could explain, together with the high rate of C-sections without labour, the high incidence of clinical RDS (77.6%) reported in our cohort of infants.

While multicenter studies are challenging because of inherent intercenter variations in the practice of clinical care, all centers participating in the Neocosur Neonatal Network fulfill standardized entry criteria in relation to the level of care and technology in an attempt to ameliorate such intercenter variability. We did not find any differences in the main outcomes when the variable “center” was included in the logistic regression model. Because of considerable differences in sample sizes between centers, we decided to leave this variable out of the analysis. Considering the 10-year study period, we acknowledge that standard NICU care might have change throughout the years biasing the results of the study.

Between 2009 and 2016, the Vermont Oxford Network (VON) reported an increase in ACS exposure from 80.2% to 87.1% in mothers delivering inborn at 24 to 29 weeks' gestation at 782 North American Hospitals. However, outborn infants experienced a quality of care gap of approximately 40% [42]. Across centers from our network, ACS coverage of mothers delivering preterm infants at 23 to 34 weeks' gestation has increased from 80% to 84.8% between 2011 and 2016. Currently, reasons for omissions of ACS therapy are not available in the database. Because identification of women at risk for preterm delivery is often imprecise and preterm delivery may present precipitously and represent a significant percentage of emergent deliveries, increasing the evidenced-based practice of ACS administration is a crucial target for quality improvement in our network.

4.3. Current recommendations

The American College of Obstetricians and Gynecologists recommends a single course of corticosteroids for pregnant women at risk for preterm delivery between 24 0/7 weeks' and 33 6/7 weeks' gestation, including multiple gestations and ruptured membranes. This recommendation can be extended to late preterm pregnancies between 34 0/7 and 36 5/7 weeks' gestation at risk for delivery within 7 days and who have not received ACS previously and may also be considered in periviable pregnancies as early as 23 0/7 weeks' gestation at risk for preterm delivery within 7 days based on family's decision to resuscitate and regardless of plurality and ruptured membranes. When indicated, rescue corticosteroids could be administered as early as 7 days from previous dose [1]. The optimal therapeutic window following a complete course of ACS is when delivery occurs 24 h to 7 days, however, corticosteroids administered 3 h prior to delivery have shown to decrease neonatal mortality approximately in 25% compared to those who did not receive ACS [31]. Regarding the best option for corticoid therapy, evidence on the benefit of betamethasone over dexamethasone is contradictory and insufficient to support the recommendation of one regimen over the other [31].

Despite limited evidence on multiple pregnancies, current guidelines advocate for corticosteroid therapy in these pregnancies at risk for preterm delivery [1,43]. While it seems reasonable to administer ACS in most cases of threatened preterm delivery, evidence should not be extrapolated to all neonatal subgroups without clear evidence of benefit as long-term adverse effects may exist [44]. More studies are needed to fully understand the effects of ACS in twins and higher-order gestations, particularly in the current epidemic of multiple pregnancies. The 2017 Cochrane review on ACS has also called for further research to examine its effects in multiple pregnancies [2].

5. Conclusions

The benefit of administration of at least one dose of ACS in VLBW multiple and singleton pregnancies is comparable in terms of death. However, ACS showed no relevant impact in short-term morbidity in multiple pregnancies. The present study supports ACS administration in immature (< 34 weeks' gestation) multiple pregnancies until further investigation is carried out.

Conflict of interest statement

None declared.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Acknowledgments

The following members from the Neocosur Network collaborated in this study:

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Perú: Veronica Webb, Margarita Llontop, Lili Chancafe, Sicilia Bellomo (Hospital Cayetano Heredia, Lima); Cesar García, Oscar Chumbes, Anne Castañeda, Jorge Mucha, Alcides Carrion (Hospital Guillermo Almenara, Lima).

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