Original Article

Neonatal Med 2018 November;25(4):161-169
https://doi.org/10.5385/nm.2018.25.4.161
pISSN 2287-9412 . eISSN 2287-9803

neonatal medicine

Antenatal Corticosteroids and Clinical Outcomes of Preterm Singleton Neonates with Intrauterine Growth Restriction

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ABSTRACT

Purpose: We assessed the influence of antenatal corticosteroid (ACS) on the in-hospital outcomes of intrauterine growth restriction (IUGR) infants.

Methods: A retrospective study was conducted with singletons born at 23^{+0} to 33^{+6} weeks of gestation at Seoul National University Hospital from 2007 to 2014. We compared clinical outcomes between infants who received ACS 2 to 7 days before birth (complete ACS), at <2 or >7 days (incomplete ACS), and those who did not receive ACS in IUGR and AGA infants. Multivariate logistic regression using Firth's penalized likelihood was performed.

Results: 304 neonates with 91 IUGR neonates were eligible. Among AGA neonates, mortality (adjusted odds ratio [aOR], 0.13; 95% confidence interval [CI], 0.02 to 0.78), hypotension within 7 postnatal days (aOR, 0.20; 95% CI, 0.06 to 0.64), and severe bronchopulmonary dysplasia (BPD) or death (aOR, 0.24; 95% CI, 0.07 to 0.77) were lower in complete ACS group after adjusting for pregnancy induced hypertension and uncontrolled preterm labor. Mortality (aOR, 0.18; 95% CI, 0.04 to 0.78), hypotension (aOR, 0.26; 95% CI, 0.09 to 0.70), and severe BPD or death (aOR, 0.33; 95% CI, 0.12 to 0.92) were also lower in the incomplete ACS group. Among IUGR infants, after adjusting for birth weight and 5-minute Apgar score, inhaled nitric oxide use within 14 postnatal days was lower in both complete ACS (aOR, 0.07; 95% CI, 0.01 to 0.67) and incomplete ACS (aOR, 0.04; 95% CI, 0.01 to 0.37) groups.

Conclusion: ACS was not effective in reducing morbidities in IUGR preterm infants.

Key Words: Prenatal care, Steroids, Fetal growth retardation, Premature infant, Outcome assessment (health care)

Received: 17 July 2018
Revised: 24 August 2018
Accepted: 19 September 2018

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INTRODUCTION

New international guidelines suggest to administer a single course of antenatal corticosteroids (ACS) to pregnant women between 24^{+0} weeks and 33^{+6} weeks of gestation who are at risk of preterm delivery within 7 days[1]. In neonates whose mothers received ACS, a low incidence of respiratory distress syndrome (RDS) has been reported with a reduction of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), duration of mechanical ventilation, systemic infections in the first 48 hours after birth, and overall neonatal death[2,3]. Although ACS treatment less than 24 hours from birth is still associated with reduced neonatal mortality and morbidities in preterm infants, ACS treatment is known to be most beneficial at 2 to 7 days after the initial dose[1,4].

Although beneficial effects of ACS have been established in singleton preterm infants, there are controversies on the beneficial effects of ACS use on neonatal outcomes in specific neonatal or maternal conditions such as multiple gestation, premature rupture of membranes, and intrauterine growth restriction (IUGR). Recently, many reports have supported the use of ACS between 24^{+0} weeks and 33^{+6} weeks age of gestation in multifetal gestations and in mothers with ruptured membranes[1,5]. However, in infants with IUGR, there are still controversies about the effectiveness of ACS on neonatal outcomes.

Regarding the efficacy of ACS on the neonatal outcomes of IUGR infants, there have been many studies on small for gestational age (SGA) neonates[6-8]; however, there is still no clear consensus on intrauterine growth restricted infants. Some large population studies demonstrated decreased risks of neonatal death and RDS[9,10]; however, other studies showed no difference[11-13]. SGA overlaps IUGR, but they do not coincide with each other[14]. It is one of the reasons why we are unable to obtain clear results about the effect of ACS on neonatal outcomes in IUGR preterm infants.

The aim of this study was to investigate whether IUGR preterm infants can benefit from ACS administration as normally grown neonates.

MATERIALS AND METHODS

1. Study design

We retrospectively analyzed the medical records and perinatal databases of 1,011 preterm neonates who were born at 23^{+0} to 33^{+6} weeks of gestation between January 2007 and December 2014 at Seoul National University Hospital. We excluded infants with multiple gestations (n=595), any major congenital anomalies (n=19), fetal hydrops (n=4), incomplete information on both neonatal and perinatal history (n=5), large-for-gestational age (n=10), multiple ACS administration (n=3), infants who were transferred to other hospitals (n=2), and SGA without fetal umbilical artery Doppler abnormalities (n=33). Finally, a total of 340 preterm infants were included in the analysis (Figure 1).

We categorized our study population into two groups: the IUGR group and the appropriate for gestational age (AGA) without documented IUGR group. After that, we divided each group according to the status of maternal ACS administration: complete ACS group, incomplete ACS group, and no ACS group. We compared the baseline demographic characteristics and neonatal outcomes between the complete, incomplete and no ACS groups among the IUGR neonates and the AGA without IUGR neonates. Demographic characteristics included gestational age at birth, birth weight, gender, cesarean section, cord pH, Apgar score at 1 minute and 5 minutes, maternal histologic chorioamnionitis, pregnancy induced hypertension (PIH), short cervix, gestational diabetes mellitus, oligohydramnios, and uncontrolled preterm labor. Neonatal outcomes included mortality, RDS, surfactant use (total, prophylactic, and rescue), patent ductus arteriosus with treatment, sepsis, NEC ≥stage 2b of modified Bell's criteria[15], IVH ≥grade 3 of Papile's classification[16], hypotension within 7 days from birth, inhaled nitric oxide (iNO) use within 14 postnatal days, relative adrenal insufficiency requiring hydrocortisone treatment, moderate to severe bronchopulmonary dysplasia (BPD), retinopathy of prematurity requiring treatment, discharge with respiratory support, and hospital stay.

2. Definitions

IUGR was defined as any fetal growth restriction (estimated fetal weight <10th percentile) documented from serial maternal medical records or a birth weight of less than the 10th percentile based on the growth curve of Olsen et al.[17] with absent or reverse umbilical artery end-diastolic flow in the fetal Doppler studies.

Complete course of ACS (complete ACS) was defined as the administration of 4 doses of dexamethasone or 2 doses of betamethasone, and the initial dose was given more than 24 hours and less than 7 days before birth. If the initial dose of ACS was administered less than 24 hours or more than 7 days before

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https://doi.org/10.5385/nm.2018.25.4.161

delivery or the course was not completed such as 4 doses of dexamethasone within a 12-hour interval and 2 doses of betamethasone within a 24-hour interval, it was defined as incomplete ACS.

RDS was defined as chest radiographic findings consistent with RDS such as diffuse ground glass appearance together with an oxygen requirement of more than 0.4 fractions of inspired oxygen (FiO_2)[18]. Surfactant use was defined as the administration of any prophylactic or rescue surfactant. Prophylactic surfactant was defined as the administration of a surfactant in the delivery room. PIH was defined as any maternal diagnoses of preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Sepsis was defined as the presence of clinical symptoms and signs with proven causative organisms documented from blood cultures. If the organisms were identified within 3 postnatal days, it was defined as early onset sepsis. If the organisms were identified after 3 or more postnatal days, it was defined as late onset sepsis.

3. Statistical analysis

All the continuous variables are expressed as the median (range), and the categorical variables are expressed as numbers and proportions. We used chi-square test or Fischer's exact test for the categorical variables and Kruskal-Wallis test for the continuous variables to compare the demographic, perinatal, and neonatal characteristics of the complete ACS, incomplete ACS, and no ACS groups in the IUGR infants and in the AGA without IUGR infants.

Multivariate logistic regression analysis using Firth's penalized likelihood was performed to investigate the effect of ACS on neonatal outcomes after adjusting for the significant variables (P<0.1) in the univariate analysis of the demographic characteristics between the complete ACS, incomplete ACS, and no ACS groups in the IUGR infants and in the AGA without IUGR infants. In the AGA without IUGR infants, multivariate logistic analysis was done after adjusting for PIH and uncontrolled preterm labor. In the IUGR infants, multivariate logistic regression was done after adjusting for birth weight and 5-minute Apgar score. All analyses were performed with R version 3.1.2 (http://www.r-project.org) with the statistical significance set at a P-value of <0.05.

RESULTS

A total of 340 neonates were included. Among them, 91 (26.8%) of them were intrauterine growth restricted infants (Figure 1). Two hundred and ninety-eight infants (87.6%) received ACS, including 215 infants (86.3%) in the AGA without IUGR group and 83 infants (91.2%) in the IUGR group. In the AGA without IUGR infants, the complete ACS group consisted of 89 infants (35.7%), the incomplete ACS group with 126 infants (50.6%), and the no ACS group

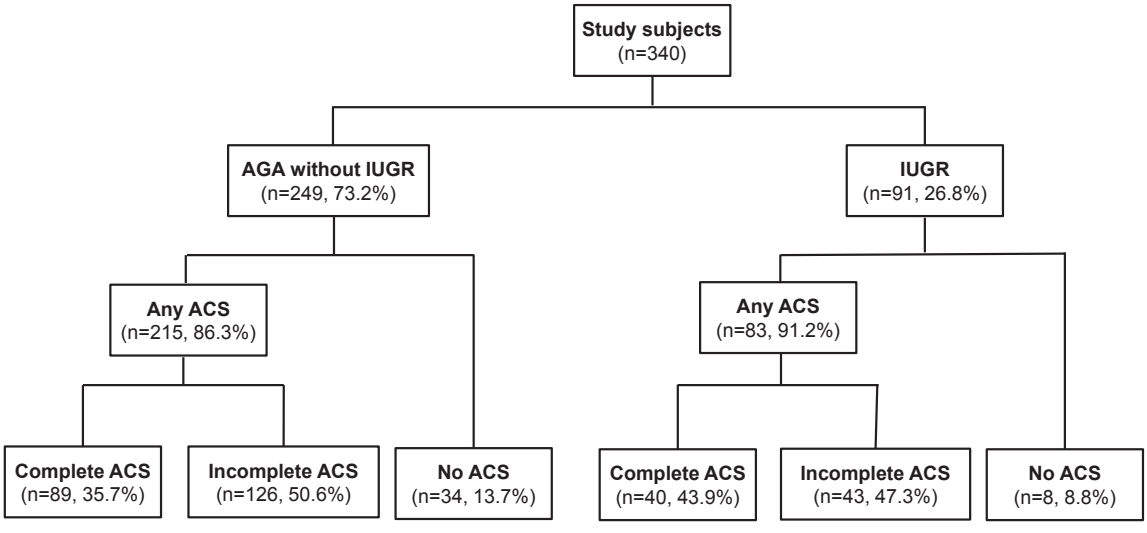

Figure 1. Flow chart of the study population. A total of 340 singleton infants born at 23^{+0} to 33^{+6} weeks age of gestation between January 2007 and December 2014, satisfying the inclusion criteria of eligibility for this study. There was no significant difference in the proportion of each group divided according to antenatal corticosteroid (ACS) use (P=0.271). Abbreviations: AGA, appropriate for gestational age; IUGR, intrauterine growth restriction.

with 34 infants (13.7%). In the IUGR infants, the complete ACS group consisted of 40 infants (43.9%), the incomplete ACS group with 43 infants (47.3%), and the no ACS group with eight infants (8.8%). There was no significant difference in the proportion of complete, incomplete, and no ACS groups in both the AGA without IUGR and IUGR infants (*P*= 0.271).

1. Demographic and baseline characteristics

When comparing the demographic characteristics between the complete ACS, incomplete ACS, and no ACS groups, there were no significant differences in the AGA without IUGR infants. The frequency of maternal PIH and uncontrolled preterm labor were different between the complete ACS, incomplete ACS, and no ACS groups with marginal significance (*P*=0.088 and *P*=0.065). However, in the IUGR group, the birth weight and 5-minute Apgar score of the incomplete ACS group were significantly lower than those of the complete ACS group (Table 1).

2. Mortality and in-hospital outcome

In the AGA without IUGR infants, the mortality was lower in the complete ACS group (2.2%) and in the incomplete ACS group (4.0%) when compared with the no ACS group (11.8%); however, they only showed a statistically marginal significance in the univariate analysis. Among the neonatal morbidities, hypotension within 7 postnatal days was significantly lower in the complete ACS group when compared with the no ACS group (6.7 % vs. 26.5%, *P*=0.012) (Table 2).

In the IUGR infants, there were no significant differences in mortality and neonatal morbidities between the complete ACS, incomplete ACS, and no ACS groups in the univariate analysis (Table 2).

In the AGA without IUGR infants, multivariate logistic regression analysis, after adjusting for the maternal PIH and uncontrolled preterm labor, showed that the mortality was significantly lower in both the complete ACS group (adjusted odds ratio [aOR], 0.13; 95% confidence interval [CI], 0.02 to 0.78) and the incomplete ACS group (aOR, 0.18; 95% CI, 0.04 to 0.78)

Table 1. Demographic Characteristics of the Complete, Incomplete, and No ACS Group among AGA and IUGR Infants

Characteristic	AGA without IUGR					IUGR				
	Total (n=249)	Complete ACS (n=89, 35.7%)	Incomplete ACS (n=126, 50.6%)	No ACS (n=34, 13.7%)	*P*-value	Total (n=91)	Complete ACS (n=40,43.9%)	Incomplete ACS (n=43,47.3%)	No ACS (n=8, 8.8%)	*P*-value
GA (wk)	30^{+4} (27^{+5}–32^{+6})	31^{+1} (27^{+3}–32^{+5})	30^{+2} (28^{+1}–32^{+6})	31^{+0} (25^{+5}–33^{+1})	0.958	30^{+1} (28^{+2}–31^{+4})	30^{+2} (29^{+1}–32^{+2})	29^{+2} (27^{+5}–31^{+0})	30^{+2} (27^{+4}–32^{+5})	0.092
Birthweight (g)	1,480 (990–1,890)	1,510 (945–1,860)	1,440 (1,098–1,843)	1,560 (729–2,055)	0.954	840 (640–1,040)	890 (720–1,135)	750 (590–940)	920 (708–1,205)	0.034*
Male sex	136 (54.6)	45 (50.6)	69 (54.8)	22 (64.7)	0.370	42 (46.2)	17 (42.5)	21 (48.8)	4 (50.0)	0.818
CS	125 (50.2)	41 (46.1)	69 (54.8)	15 (44.1)	0.340	84 (92.3)	37 (92.5)	39 (90.7)	8 (100.0)	1.000
Short cervix	45 (18.1)	11 (12.4)	25 (19.8)	9 (26.5)	0.146	7 (7.7)	1 (2.5)	5 (11.6)	1 (12.5)	0.247
GDM	15 (6.0)	3 (3.4)	9 (7.1)	3 (8.8)	0.398	5 (5.5)	2 (5.0)	2 (4.7)	1 (12.5)	0.601
PIH	39 (15.7)	20 (22.5)	15 (11.9)	4 (11.8)	0.088	56 (61.5)	24 (60.0)	27 (62.8)	5 (62.5)	0.948
HCA	107 (43.3)	34 (39.1)	61 (48.4)	12 (35.3)	0.239	21 (23.1)	8 (20.0)	11 (25.6)	2 (25.0)	0.757
Oligohydramnios	31 (12.4)	10 (11.2)	17 (13.5)	4 (11.8)	0.929	23 (25.3)	7 (17.5)	13 (30.2)	3 (37.5)	0.300
Fetal distress	26 (10.4)	6 (6.7)	14 (11.1)	6 (17.6)	0.190	61 (67.0)	29 (72.5)	27 (62.8)	5 (62.5)	0.635
Uncontrolled preterm labor	158 (63.5)	53 (59.6)	88 (69.8)	17 (50.0)	0.065	16 (17.6)	8 (20.0)	6 (14.0)	2 (25.0)	0.599
Cord pH	7.30 (7.26–7.35)	7.31 (7.27–7.35)	7.30 (7.25–7.34)	7.29 (7.25–7.32)	0.130	7.24 (7.18–7.29)	7.26 (7.21–7.29)	7.22 (7.16–7.28)	7.24 (7.18–7.31)	0.512
1-min AS	5 (3–7)	6 (4–7)	5 (3–7)	5 (2–7)	0.135	4 (3–6)	4 (3–6)	4 (2–5)	4 (3–6)	0.423
5-min AS	7 (6–8)	7 (6–8)	7 (6–8)	7 (5–8)	0.178	7 (6–7)	7 (6–8)	7 (5–7)	7 (6–8)	0.024*

Values are expressed as median (range) or number (%). Chi-square test, Fisher's exact test, or Kruskal-Wallis test.
*P<0.05 when complete ACS versus incomplete ACS.
Abbreviations: ACS, antenatal corticosteroid; AGA, appropriate for gestational age; IUGR, intrauterine growth restriction; GA, gestational age; CS, cesarean section; GDM, gestational diabetes mellitus; PIH, pregnancy induced hypertension; HCA, histologic chorioamnionitis; AS, Apgar score.

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https://doi.org/10.5385/nm.2018.25.4.161

Table 2. Clinical Outcomes of the Complete, Incomplete, and No ACS Group among AGA and IUGR Infants

Characteristic	AGA without IUGR					IUGR				
	Total (n=249)	Complete ACS (n=89, 35.7%)	Incomplete ACS (n=126, 50.6%)	No ACS (n=34, 13.7%)	*P*-value	Total (n=91)	Complete ACS (n=40, 43.9%)	Incomplete ACS (n=43, 47.3%)	No ACS (n=8, 8.8%)	*P*-value
Death	11 (4.4)	2 (2.2)	5 (4.0)	4 (11.8)	0.072	11 (12.1)	2 (5.0)	7 (16.3)	2 (25.0)	0.119
RDS	63 (25.3)	18 (20.2)	32 (25.4)	13 (38.2)	0.121	25 (27.5)	11 (27.5)	11 (25.6)	3 (37.5)	0.828
Surfactant use	76 (30.5)	22 (24.7)	40 (31.7)	14 (41.2)	0.190	36 (39.6)	12 (30.0)	20 (46.5)	4 (50.0)	0.242
Prophy S	21 (8.4)	5 (5.6)	14 (11.1)	2 (5.9)	0.353	14 (15.4)	3 (7.5)	10 (23.3)	1 (12.5)	0.109
Rescue S	60 (24.1)	18 (20.2)	30 (23.8)	12 (35.3)	0.216	24 (26.4)	10 (25.0)	11 (25.6)	3 (37.5)	0.732
Surfactant multiple	11 (4.4)	3 (3.4)	6 (4.8)	2 (5.9)	0.690	5 (5.5)	3 (7.5)	2 (4.7)	0 (0.0)	0.793
PDA with treatment	88 (35.3)	30 (33.7)	43 (34.1)	15 (44.1)	0.514	46 (50.5)	21 (52.5)	21 (48.8)	4 (50.0)	0.951
Pharmacological	80 (32.1)	28 (31.5)	39 (31.0)	13 (38.2)	0.712	43 (47.3)	19 (47.5)	21 (48.8)	3 (37.5)	0.905
Surgical	27 (10.8)	10 (11.2)	11 (8.7)	6 (17.6)	0.337	9 (9.9)	3 (7.5)	5 (11.6)	1 (12.5)	0.669
Sepsis	40 (16.1)	17 (19.1)	18 (14.3)	5 (14.7)	0.622	21 (23.1)	7 (17.5)	11 (25.6)	3 (37.5)	0.396
Early	12 (4.8)	5 (5.6)	6 (5.6)	0 (0.0)	0.503	3 (3.3)	0 (0.0)	3 (7.0)	0 (0.0)	0.313
Late	33 (13.3)	13 (14.6)	15 (11.9)	5 (14.7)	0.839	19 (20.9)	7 (17.5)	9 (20.9)	3 (37.5)	0.439
NEC ≥stage 2b	7 (2.8)	4 (4.5)	2 (1.6)	1 (2.9)	0.359	6 (6.6)	1 (2.5)	4 (9.3)	1 (12.5)	0.326
IVH ≥grade 3	12 (4.8)	5 (5.6)	5 (4.0)	2 (5.9)	0.772	5 (5.5)	1 (2.5)	4 (9.3)	0 (0.0)	0.480
Hypotension	27 (10.8)	6 (6.7)	12 (9.5)	9 (26.5)	0.012*	15 (16.5)	3 (7.5)	10 (23.3)	2 (25.0)	0.089
iNO use within 14 d	17 (6.8)	3 (3.4)	11 (8.7)	3 (8.8)	0.262	9 (9.9)	3 (7.5)	3 (7.0)	3 (37.5)	0.069
AI-HCS	11 (4.4)	2 (2.2)	7 (5.6)	2 (5.9)	0.434	4 (4.4)	1 (2.5)	3 (7.0)	0 (0.0)	0.737
Moderate to severe BPD	38 (15.9)	14 (16.1)	18 (14.8)	6 (20.0)	0.750	26 (31.3)	10 (26.3)	13 (34.2)	3 (42.9)	0.564
Severe BPD	16 (6.7)	4 (4.6)	8 (6.6)	4 (13.3)	0.255	13 (15.7)	5 (13.2)	6 (15.8)	2 (28.6)	0.600
ROP requiring treatment	15 (6.3)	4 (4.6)	7 (5.7)	4 (13.3)	0.211	5 (5.8)	1 (2.6)	4 (10.0)	0 (0.0)	0.486
Discharge with respiratory support	38 (15.3)	14 (15.7)	18 (14.3)	6 (17.6)	0.879	19 (20.9)	7 (17.5)	11 (25.6)	1 (12.5)	0.630
Hospital day	36 (18–69)	33 (18–70)	39 (19–68)	31 (14–63)	0.608	59 (35–81)	54 (32–76)	66 (39–88)	50 (33–69)	0.325
Hospital day in survivors	38 (20–69)	33 (20–71)	39 (20–70)	36 (16–73)	0.838	62 (43–88)	55 (37–80)	70 (53–93)	55 (34–79)	0.081

Values are expressed as number (%) or median (range). Chi-square test, Fisher's exact test, or Kruskal-Wallis test.
*P<0.05 when complete ACS versus no ACS.
Abbreviations: ACS, antenatal corticosteroid use; AGA, appropriate for gestational age; IUGR, intrauterine growth restriction; RDS, respiratory distress syndrome; Prophy S, prophylactic surfactant use; Rescue S, rescue surfactant use; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; iNO, inhaled nitric oxide; AI-HCS, transient adrenal insufficiency with hydrocortisone use; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.

when compared with the no ACS group. Hypotension within 7 postnatal days was also less frequent in both the complete ACS group (aOR, 0.20; 95% CI, 0.06 to 0.64) and the incomplete ACS group (aOR, 0.26; 95% CI, 0.09 to 0.70) when compared with the no ACS group. The risk of severe BPD or death was also lower in both the complete ACS (aOR, 0.24; 95% CI, 0.07 to 0.77) and the incomplete ACS group (aOR, 0.33; 95% CI, 0.12 to 0.92) (Table 3).

In the IUGR group, multivariate analysis, after adjusting for birth weight and Apgar score at 5 minutes, showed that only the frequency of iNO within 14 days after birth was statistically significantly lower in both the complete ACS group (aOR, 0.07; 95% CI, 0.01 to 0.67) and the incomplete ACS group (aOR, 0.04; 95% CI, 0.01 to 0.37) when compared with the no ACS group (Table 3).

DISCUSSION

This retrospective cohort study suggests that administering ACS to IUGR infants does not improve the overall neonatal mortality and major morbidities, except for iNO use within 14 postnatal days. However, in AGA infants, ACS appears to reduce death

Table 3. Multivariate Logistic Regression Analysis of Neonatal Outcomes in the ACS Group Compared with the No ACS Group (Baseline: No Steroid Use Group)

Variable	AGA without IUGR*				IUGR†			
	Complete courses of ACS use		Incomplete courses of ACS use		Complete courses of ACS use		Incomplete courses of ACS use	
	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
Primary outcomes								
Death	0.13 (0.02–0.78)	0.026‡	0.18 (0.04–0.78)	0.021‡	0.06 (0.00–1.07)	0.055	0.11 (0.01–1.61)	0.107
RDS	0.44 (0.18–1.05)	0.063	0.58 (0.26–1.31)	0.189	0.39 (0.06–2.40)	0.309	0.16 (0.02–1.08)	0.060
Surfactant use	0.49 (0.21–1.13)	0.094	0.68 (0.31–1.49)	0.331	0.19 (0.02–1.94)	0.162	0.14 (0.01–1.47)	0.102
Prophylactic surfactant use	0.84 (0.15–4.63)	0.837	1.64 (0.35–7.75)	0.533	0.41 (0.03–5.38)	0.497	1.02 (0.10–10.92)	0.987
Rescue surfactant use	0.50 (0.21–1.21)	0.126	0.62 (0.27–1.41)	0.255	0.39 (0.06–2.40)	0.309	0.16 (0.02–1.08)	0.060
Secondary outcomes								
PDA treatment	0.60 (0.27–1.37)	0.226	0.63 (0.29–1.38)	0.249	1.17 (0.24–5.73)	0.845	0.78 (0.16–3.92)	0.762
IVH ≥grade 3	0.80 (0.14–4.46)	0.799	0.54 (0.10–2.99)	0.482	0.54 (0.02–82.19)	0.726	1.12 (0.09–159.48)	0.941
NEC ≥stage 2b	1.90 (0.20–18.30)	0.580	0.67 (0.06–7.94)	0.752	0.11 (0.01–2.59)	0.172	0.28 (0.02–3.87)	0.344
Sepsis	1.32 (0.44–3.97)	0.619	0.88 (0.30–2.60)	0.814	0.22 (0.03–1.63)	0.138	0.19 (0.03–1.43)	0.106
iNO within 14 d	0.41 (0.08–2.15)	0.289	1.05 (0.27–4.12)	0.944	0.07 (0.01–0.67)	0.020‡	0.04 (0.01–0.37)	0.005‡
Hypotension within 7 d	0.20 (0.06–0.64)	0.006‡	0.26 (0.09–0.70)	0.008‡	0.08 (0.00–1.57)	0.096	0.16 (0.01–2.70)	0.205
Moderate to severe BPD or death	0.51 (0.20–1.30)	0.159	0.45 (0.18–1.11)	0.083	0.18 (0.02–1.75)	0.140	0.12 (0.01–1.21)	0.071
Severe BPD or death	0.24 (0.07–0.77)	0.016‡	0.33 (0.12–0.92)	0.035‡	0.16 (0.02–1.55)	0.113	0.12 (0.01–1.19)	0.069

*Adjusted for pregnancy induced hypertension, uncontrolled preterm labor; †Adjusted for birthweight, Apgar score at 5 minutes; ‡$P<0.05$ when compared with no ACS.

Abbreviations: ACS, antenatal corticosteroid; AGA, appropriate for gestational age; IUGR, intrauterine growth restriction; aOR, adjusted odds ratio; CI, confidence intervals; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; iNO, inhaled nitric oxide; BPD, bronchopulmonary dysplasia.

before discharge, severe BPD and/or death, and hypotension that occurred within 7 days after birth, requiring management with inotropes.

Unlike previous reports about the effect of ACS on neonatal outcomes[3,7], RDS or surfactant use was not lower in the ACS use group, even in the AGA without IUGR infants. However, upon closer review, complete ACS use in the AGA without IUGR group and incomplete ACS use in the IUGR group reduced the risk of RDS when compared with the no ACS group with marginal statistical significance ($P<0.1$). The small number of patients could be a reason why the results on RDS are inconclusive. No statistically significant difference was observed in postnatal surfactant use, and this may be due to the policy of routine prophylactic surfactant use in extremely preterm infants. Such prophylactic surfactant use masks the clinical symptoms of RDS.

Elevated endogenous corticosteroid levels in IUGR is one of the reasons why many studies, including our study, revealed that ACS has no beneficial effect on IUGR[19,20]. Intrauterine growth restricted fetuses are under stress of malnutrition and hypoxemia due to placental insufficiency[14], and cortisol production is stimulated by fetal adrenal gland. In addition to this, the expression and activity of 11-beta-hydroxysteroid dehydrogenase type II (11-βHSD II) is reduced in IUGR, and this leads to less conversion of cortisol to cortisone, which induces excessive fetal exposure to maternal endogenous corticosteroids[21,22]. For IUGR fetuses, exogenous administration of ACS can introduce exaggerated exposure to corticosteroid, and this may cause adverse effects on fetal hypothalamo-pituitary-adrenal (HPA) axis programming and lung maturation. In animal model study, repetitive doses of corticosteroids lowered lung and liver weight[23] and induced hypertension[24]. Others showed that chronic intrauterine stress may also accelerate pulmonary maturation, resulting in a lower risk of RDS in IUGR infants rather than in AGA neonates[25]. There are still controversies about the effect of exogenous corticosteroids on lung growth and surfactant protein expression in the IUGR animal model[23].

There are conflicting results about the efficacy of ACS in improving preterm neonatal outcomes for SGA infants. Riskin-

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Mashiah et al.[26], using the Israel neonatal network database, reported that ACS decreased mortality and composite adverse outcomes. In a study using the Canadian neonatal network, a complete course of ACS use in SGA neonates decreased death, any mechanical ventilation, severe brain injury, and composite outcomes[7]. However, many other studies showed no significant differences in the neonatal outcomes of IUGR infants[27]. A population-based study, using a large cohort, classified their study population according to the presence of SGA, less than 10th percentile birth weight, and non-usage of maternal data or fetal ultrasonography. According to McGillick et al.[28] review, many of the studies on ACS use in infants with fetal growth restriction defined fetal growth restriction as a birth weight of <10th percentile. The main strength of our study is that we defined IUGR more accurately using maternal medical records and umbilical artery Doppler studies, and not just birth weight of <10th percentile alone.

We also categorized ACS use as complete and incomplete according to the previous reports from the American Committee of Obstetrics and Gynecology. In our study, any ACS use reduced the mortality and hypotension within 7 postnatal days in AGA without IUGR infants and any ACS use reduced the frequency of iNO use within 14 days after birth in IUGR infants (data not shown). In addition to this, there was no significant difference between complete ACS and incomplete ACS on neonatal outcomes. Elimian et al.[29] also assessed the effectiveness of an incomplete course in reducing the need for vasopressors, IVH, and neonatal death rates; however, a complete course was excluded from the study.

Unlike previous studies, we included iNO use within 14 postnatal days as one of the secondary outcomes. iNO use can be associated with persistent pulmonary hypertension (PPHN), lung hypoplasia, or initial respiratory distress, which are postnatal complications of IUGR. Reduction of iNO use can be explained by the mechanism of vasodilation caused by corticosteroids. ACSs in IUGR was shown to induce vasodilation, which increases blood flow to the major organs such as the heart and the brain, through several animal experiements[30]. Early pulmonary hypertension is often related to RDS and BPD. Though the RDS rate showed no significant difference in ACS treated infants, ACS treatment and use of a surfactant may lower the severity of PPHN[31]. Moreover, this may have an effect on the long-term outcome such as the duration of mechanical ventilator use, which was not included in our study.

There are several limitations in our study. First, this is a retrospective study with a small number of study subjects. If the analyses had been done with a larger number of subjects, the outcomes in the IUGR neonates that showed a marginal significance such as the neonatal death rate in the complete ACS group and the RDS and moderate to severe BPD or death rate in the incomplete ACS group could have been lower than those in the no ACS group. Second, we did not analyze the long-term outcomes such as neurological developments in each group. There are also conflicting results on ACS and brain development. Some cumulative evidence suggests that brain injury is associated with ACS use in IUGR, which is caused by oxidative stress and cerebral reperfusion[10,21]. Others have observed that there are no long-term neurological benefits from ACS use[6,32]. To clarify the neurological effect of ACS, neurological follow-up data assessed by various tools should be analyzed.

In our study, both complete and incomplete ACS treatments did not reduce mortality or major morbidities in IUGR infants, except for early iNO use. Although there was no adverse effect from the ACS treatment on the neonatal outcomes in the IUGR infants, we should take careful consideration in giving ACS to IUGR fetus. In addition to this, a randomized controlled trial with a multicenter, large cohort study is needed to clarify the benefits and adverse effects of ACSs in IUGR.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Committee on Obstetric Practice. Committee opinion no. 713: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol 2017;130:e102-9.
2. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50:515-25.
3. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017;3:CD004454.
4. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consens Statement 1994;12:1-24.

5. Magann EF, Haram K, Ounpraseuth S, Mortensen JH, Spencer HJ, Morrison JC. Use of antenatal corticosteroids in special circumstances: a comprehensive review. Acta Obstet Gynecol Scand 2017;96:395-409.
6. Ishikawa H, Miyazaki K, Ikeda T, Murabayashi N, Hayashi K, Kai A, et al. The effects of antenatal corticosteroids on short- and long-term outcomes in small-for-gestational-age infants. Int J Med Sci 2015;12:295-300.
7. Melamed N, Pittini A, Barrett J, Shah J, Yoon EW, Lemyre B, et al. Antenatal corticosteroids and outcomes of small-for-gestational-age neonates. Obstet Gynecol 2016;128:1001-8.
8. Kim WJ, Han YS, Ko HS, Park IY, Shin JC, Wie JH. Antenatal corticosteroids and outcomes of preterm small-for-gestational-age neonates in a single medical center. Obstet Gynecol Sci 2018;61:7-13.
9. Torrance HL, Mulder EJ, Brouwers HA, van Bel F, Visser GH. Respiratory outcome in preterm small for gestational age fetuses with or without abnormal umbilical artery Doppler and/or maternal hypertension. J Matern Fetal Neonatal Med 2007;20:613-21.
10. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol 2000;182(1 Pt 1):198-206.
11. van Stralen G, van der Bos J, Lopriore E, Te Pas AB, Bloemenkamp KW, Walther FJ, et al. No short-term benefits of antenatal corticosteroid treatment in severely preterm growth restricted fetuses: a case-control study. Early Hum Dev 2009;85:253-7.
12. Schaap AH, Wolf H, Bruinse HW, Smolders-De Haas H, Van Ertbruggen I, Treffers PE. Effects of antenatal corticosteroid administration on mortality and long-term morbidity in early preterm, growth-restricted infants. Obstet Gynecol 2001;97:954-60.
13. Simchen MJ, Alkazaleh F, Adamson SL, Windrim R, Telford J, Beyene J, et al. The fetal cardiovascular response to antenatal steroids in severe early-onset intrauterine growth restriction. Am J Obstet Gynecol 2004;190:296-304.
14. Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clin Med Insights Pediatr 2016;10:67-83.
15. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
16. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
17. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010;125:e214-24.
18. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants: 2013 update. Neonatology 2013;103:353-68.
19. Economides DL, Nicolaides KH, Linton EA, Perry LA, Chard T. Plasma cortisol and adrenocorticotropin in appropriate and small for gestational age fetuses. Fetal Ther 1988;3:158-64.
20. Torrance HL, Derks JB, Scherjon SA, Wijnberger LD, Visser GH. Is antenatal steroid treatment effective in preterm IUGR fetuses? Acta Obstet Gynecol Scand 2009;88:1068-73.
21. Miller SL, Chai M, Loose J, Castillo-Melendez M, Walker DW, Jenkin G, et al. The effects of maternal betamethasone administration on the intrauterine growth-restricted fetus. Endocrinology 2007;148:1288-95.
22. McTernan CL, Draper N, Nicholson H, Chalder SM, Driver P, Hewison M, et al. Reduced placental 11beta-hydroxysteroid dehydrogenase type 2 mRNA levels in human pregnancies complicated by intrauterine growth restriction: an analysis of possible mechanisms. J Clin Endocrinol Metab 2001;86:4979-83.
23. Ozdemir H, Guvenal T, Cetin M, Kaya T, Cetin A. A placebo-controlled comparison of effects of repetitive doses of betamethasone and dexamethasone on lung maturation and lung, liver, and body weights of mouse pups. Pediatr Res 2003;53:98-103.
24. Bertram C, Trowern AR, Copin N, Jackson AA, Whorwood CB. The maternal diet during pregnancy programs altered expression of the glucocorticoid receptor and type 2 11beta-hydroxysteroid dehydrogenase: potential molecular mechanisms underlying the programming of hypertension in utero. Endocrinology 2001;142:2841-53.
25. Morrison JL, Orgeig S. Antenatal glucocorticoid treatment of the growth-restricted fetus: benefit or cost? Reprod Sci 2009;16:527-38.
26. Riskin-Mashiah S, Riskin A, Bader D, Kugelman A, Boyko V, Lerner-Geva L, et al. Antenatal corticosteroid treatment in singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a population-based study. BJOG 2016;123:1779-86.
27. Ting JY, Kingdom JC, Shah PS. Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age. Am J Obstet Gynecol 2018;218(2S):S818-28.
28. McGillick EV, Orgeig S, Williams MT, Morrison JL. Risk of respiratory distress syndrome and efficacy of glucocorticoids: are they the same in the normally grown and growth-restricted infant? Reprod Sci 2016;23:1459-72.
29. Elimian A, Figueroa R, Spitzer AR, Ogburn PL, Wiencek V, Quirk JG. Antenatal corticosteroids: are incomplete courses beneficial? Obstet Gynecol 2003;102:352-5.

Neonatal Med 2018 November;25(4):161-169
https://doi.org/10.5385/nm.2018.25.4.161

30. Miller SL, Supramaniam VG, Jenkin G, Walker DW, Wallace EM. Cardiovascular responses to maternal betamethasone administration in the intrauterine growth-restricted ovine fetus. Am J Obstet Gynecol 2009;201:613.e1-8.
31. Lai MY, Chu SM, Lakshminrusimha S, Lin HC. Beyond the inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Pediatr Neonatol 2018;59:15-23.
32. Mitsiakos G, Kovacs L, Papageorgiou A. Are antenatal steroids beneficial to severely growth restricted fetuses? J Matern Fetal Neonatal Med 2013;26:1496-9.