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Effects of antenatal corticosteroids on neonatal outcomes in twin and singleton pregnancies: a Korean national cohort study

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ABSTRACT

Objective To investigate whether effects of antenatal corticosteroids on neonatal outcomes in preterm infants with very low birth weight were different by plurality.

Design Nationwide prospective cohort study.

Patients Twins and singletons with very low birth weight (<1500 g) who were born between 23^{+0} and 33^{+6} weeks of gestation and registered in the Korean Neonatal Network from January 2014 to December 2019.

Main outcome measures Morbidity and mortality before discharge from neonatal intensive care unit.

Results Among a total of 9531 preterm infants with very low birth weight, there were 2364 (24.8%) twins and 7167 (75.2%) singletons. While 83.9% of singletons were exposed to at least one dose of antenatal corticosteroids, so were 87.9% of twins.

Interaction analysis demonstrated that there was no significant difference in the effect of antenatal corticosteroids on morbidities or mortality between twins and singletons in either gestational age group (23–28 weeks or 29–33 weeks).

Antenatal corticosteroids significantly decreased the risk of surfactant use (adjusted relative risk (aRR): 0.972 (95% CI: 0.961 to 0.984)), high-grade intraventricular haemorrhage (aRR: 0.621 (95% CI: 0.487 to 0.794)), periventricular leucomalacia (aRR: 0.728 (95% CI: 0.556 to 0.954)) and mortality (aRR: 0.758 (95% CI: 0.679 to 0.846)) in the gestational age group of 23–28 weeks. In the gestational age group of 29–33 weeks, antenatal corticosteroids significantly decreased the risk of surfactant use (aRR: 0.914 (95% CI: 0.862 to 0.970)) and mortality (aRR: 0.409 (95% CI: 0.269 to 0.624)) but increased the risk of sepsis (aRR: 1.416 (95% CI: 1.018 to 1.969)).

Conclusion This study demonstrates that effect of antenatal corticosteroids on neonatal outcomes of preterm infants with very low birth weight does not differ significantly by plurality (twin or singleton pregnancy).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antenatal corticosteroids (ACS) administered before preterm delivery can decrease neonatal morbidity and mortality in singleton pregnancies. However, data about such effects of ACS in multiple pregnancies are still limited.

WHAT THIS STUDY ADDS

⇒ The effect of ACS administered before preterm delivery on neonatal morbidity and mortality does not differ by plurality (twin or singleton pregnancy).

⇒ Infants exposed to ACS were more likely to survive and require less surfactant therapy in both 23–28 weeks and 29–33 weeks gestational age groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the need for further investigation to fully understand effects of ACS on multiple pregnancies, given the increasing prevalence of multiple pregnancies worldwide.

INTRODUCTION

Antenatal corticosteroid (ACS) has been established as the standard therapy for pregnant women at risk of preterm delivery within 7 days between 24^{+0} and 33^{+6} weeks of gestation.[1] Currently, ACS is equally recommended for twin and singleton pregnancies with the same regimen based on previous studies.[2–4] A recent study has shown that a complete course of ACS administered before preterm twin delivery is associated with a significant decrease in neonatal mortality, short-term respiratory morbidity and severe neurological injury in a magnitude similar to those observed for a singleton pregnancy.[3] However, data that demonstrate comparable effects of ACS therapy in twin pregnancies are limited.

As a result of increasing childbirth age and use of assisted reproductive technology, twin pregnancies are increasing in many countries, including Korea.[5 6] However, twin pregnancies are more likely to have preterm birth, low birth weight and longer hospital stays than singleton pregnancies.[7 8] In addition, mono-chorionicity, birth weight discordance and obstetric complications associated

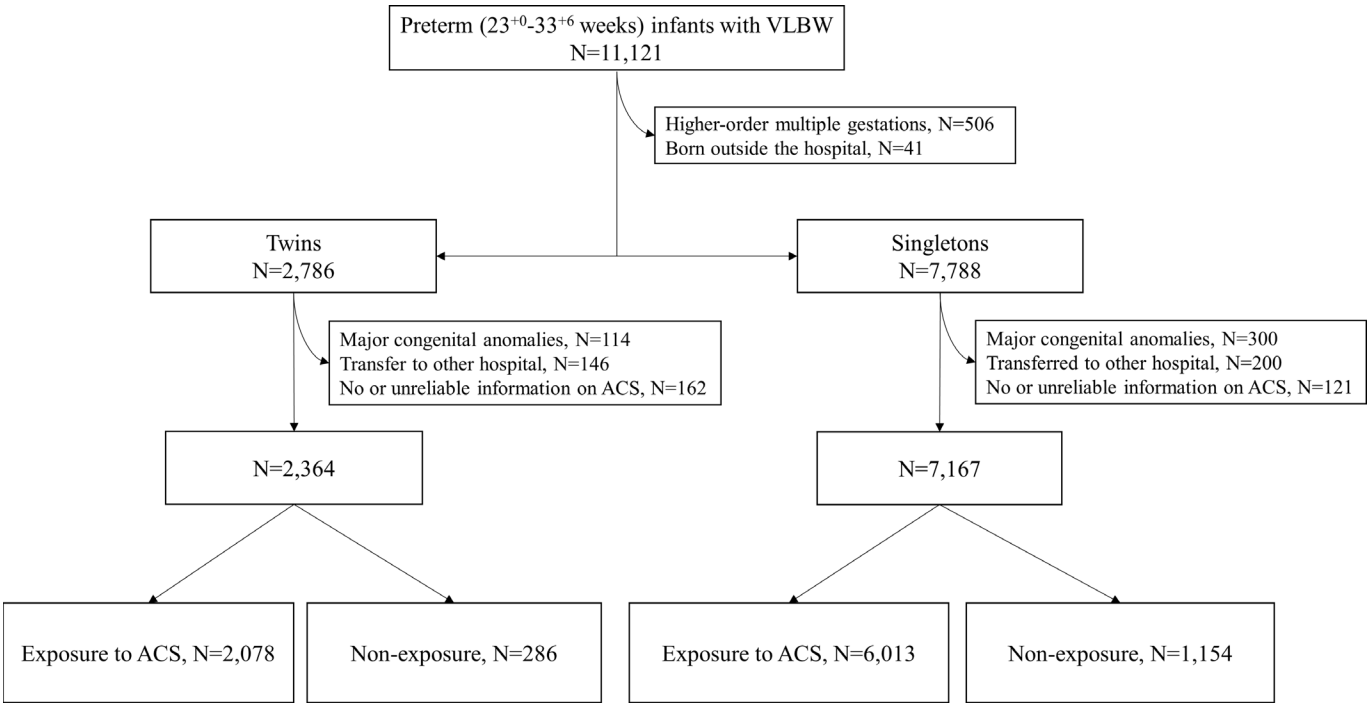

Figure 1 Flow chart showing the selection of study population. ACS, antenatal corticosteroid; VLBW, very low birth weight.

with multiple pregnancies may result in adverse perinatal outcomes.[9–11]

Recently, the mortality of extreme preterm multiplets has decreased to a level comparable with that of singletons born at the same gestational age along with increased use of ACS therapy.[12] However, many studies have reported conflicting results regarding equivalent effects of ACS on neonatal outcomes of twins and singletons.[3 13–18] To date, there have been no clinical trials designed to investigate the effect of ACS in twins. A meta-analysis on ACS therapy has also highlighted the need for additional studies on multiple pregnancies.[4]

Thus, the purpose of this study was to investigate whether effects of ACS administered before preterm delivery on neonatal outcomes of twins and singletons were comparable.

MATERIALS AND METHODS

Study design and participants

Information on the study population is presented in figure 1. Data collected prospectively through the Korean Neonatal Network (KNN), a nationwide very low birthweight (VLBW, <1500 g) infant registry participated by 61 neonatal intensive care units across South Korea,[19] were used for this study. A total of 11 121 infants with VLBW born preterm (between 23^{+0} and 33^{+6} weeks of gestation) between January 2014 and December 2019 were enrolled. Exclusion criteria were: high-order multiple gestations (≥triplets), birth outside the hospital, major congenital anomalies, transfer to other hospitals, no or unreliable information on ACS. Finally, 2364 twins and 7167 singletons were analysed. ACS therapy was defined if the pregnant women had received at least one dose of any kind of corticosteroids before preterm delivery. Variables collected included gestational age, birth weight, small for gestational age, sex, maternal age, maternal diabetes mellitus (DM), maternal hypertension, chorioamnionitis, premature rupture of membrane, caesarean section, in vitro fertilisation (IVF), surfactant use, sepsis, high-grade intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL), surgically treated patent ductus arteriosus, bronchopulmonary dysplasia (BPD), advanced retinopathy of prematurity (ROP) and mortality. Definitions for different variables are provided in online supplemental materials. The analysis of neonatal morbidity was performed for infants who survived before discharge, while the analysis of mortality was performed for the total population.

Patient and public involvement

Patient and/or the public were not involved in the design, or recruitment, or conduct, or reporting, or dissemination of plans of the study.

Statistical methods

Rates of neonatal outcomes between infants exposed to ACS and infants without such exposure are presented along with risk difference and 95% CIs. To investigate whether associations between ACS and neonatal outcomes were altered by plurality (twins vs singletons), the interaction effect between ACS and twin pregnancies on neonatal outcomes was evaluated by adding interaction terms (ACS×twins) in Poisson regression models. The crude and adjusted relative risks (aRRs) and 95% CI

for the individual effects of ACS and twins were obtained in the second model without the interaction term.

All models were fitted with generalised estimating equations approach for the correlation between a pair of twins from a mother. Covariables in regression models were gestational age, birth weight, sex, maternal age, maternal DM, maternal hypertension, premature rupture of membrane, caesarean section and IVF. Chorioamnionitis was excluded from the analyses due to substantial missing values (17.6% in twins and 14.5% in singletons).

For each outcome, a backward-stepwise method was used to remove the variable with the highest p value, and variables in final model were selected that showed minimal quasi-likelihood under the independence model criterion value.[20–22] To confirm multicollinearity, variance inflation factor values were checked for all covariates, which were all less than 5, indicating no significant multicollinearity (1.002~2.989). The level of significance was set at p<0.05. All statistical analyses were performed using SPSS V.25.0 (IBM Corp) and 'geepack' and 'car' package R V.4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Exposure to ACS

Among 2364 twins, 2078 (87.9%) infants were exposed to at least one dose of ACS before preterm delivery. Among 7167 singletons, 6013 (83.9%) infants were exposed to at least one dose of ACS before preterm delivery (figure 1).

Comparisons of perinatal baseline characteristics between infants exposed to ACS and infants without ACS exposure

Twins exposed to ACS were born at a later gestational age (mean (SD), 28.08 (2.19) vs 27.75 (2.50) weeks) compared with those without ACS exposure (table 1). However, there was no difference in gestational age (mean (SD), 28.49 (2.52) vs 28.39 (2.78) weeks) or birth weight (mean (SD), 1060 (281) vs 1073 (289) g) between singletons exposed to ACS and those without ACS exposure. Singletons exposed to ACS had higher rates of maternal DM (9.9% vs 7.7%; p=0.019), maternal hypertension (29.1% vs 24.8%; p=0.003) and caesarean section (77.1% vs 69.9%; p<0.001) than those without exposure. In both twins and singletons, infants exposed to ACS were more likely to have higher rates of premature rupture of membrane and be conceived through IVF from older mothers than those without exposure.

Interaction between ACS and twin pregnancies on neonatal outcomes

We investigated whether effects of ACS on neonatal outcomes differed between twins and singletons. Because neonatal outcomes are substantially dependent on gestational age, comparison of ACS effects on neonatal outcomes by plurality was performed by stratifying the

Table 1 Comparisons of perinatal baseline characteristics between infants exposed to ACS and infants without ACS exposure

	Twins (n=2364)			Singletons (n=7167)		
	ACS exposed (n=2078)	ACS unexposed (n=286)	P value*	ACS exposed (n=6013)	ACS unexposed (n=1154)	P value*
Infant						
Gestational age (weeks), mean (SD)	28.08 (2.19)	27.75 (2.50)	0.034	28.49 (2.52)	28.39 (2.78)	0.256
Birth weight (g), mean (SD)	1059 (274)	1034 (301)	0.186	1060 (281)	1073 (289)	0.138
SGA, n (%)	147 (7.1)	22 (7.7)	0.704	1080 (18.0)	199 (17.2)	0.560
Male, n (%)	1079 (51.9)	143 (50.0)	0.541	3074 (51.1)	597 (51.7)	0.708
Maternal						
Maternal age (years), mean (SD)	33.41 (3.80)	31.91 (4.66)	<0.001	33.44 (4.43)	32.82 (4.92)	<0.001
Maternal diabetes mellitus, n (%)	238 (11.5)	26 (9.1)	0.221	597 (9.9)	89 (7.7)	0.019
Maternal hypertension, n (%)	196 (9.5)	22 (7.7)	0.329	1749 (29.1)	286 (24.8)	0.003
Chorioamnionitis†, n (%)	516 (29.9)	63 (28.0)	0.551	2084 (40.2)	351 (37.0)	0.064
Premature rupture of membrane, n (%)	787 (38.1)	84 (29.9)	0.007	2334 (38.9)	312 (27.5)	<0.001
Caesarean section, n (%)	1837 (88.4)	244 (85.3)	0.132	4634 (77.1)	807 (69.9)	<0.001
In vitro fertilisation, n (%)	1152 (56.6)	128 (45.1)	<0.001	494 (8.2)	51 (4.4)	<0.001

Data are presented as mean (SD) or n (%).
*P value obtained from X^2 test for categorical variables and Student's t-test for continuous variables.
†Values were missing for 415 infants in the group of twins and 1039 infants in the group of singletons.
ACS, antenatal corticosteroid; SGA, small for gestational age.

study population into two gestational age groups: an gestational age group of 23–28 weeks and an gestational age group of 29–33 weeks.

Interaction analyses within 23–28 weeks (table 2) and 29–33 weeks (table 3) gestational age groups found no significant difference in the association of ACS therapy with any neonatal outcomes between twins and singletons (p>0.1 for all).

Independent effects of ACS and twins on neonatal outcomes

In the second model excluding the interaction term, we calculated aRR and 95% CI for individual effects of ACS and twins on each neonatal outcome. In the gestational age group of 23–28 weeks, exposure to ACS was significantly associated with a lower risk of surfactant use (aRR: 0.972 (95% CI: 0.961 to 0.984)), high-grade IVH (aRR: 0.621 (95% CI: 0.487 to 0.794)), PVL (aRR: 0.728 (95% CI: 0.556 to 0.954)) and mortality (aRR: 0.758 (95% CI: 0.679 to 0.846)) (figure 2A). Twins were associated with higher risks of high-grade IVH (aRR: 1.466 (95% CI: 1.178 to 1.825)) and advanced ROP (aRR: 1.193 (95% CI: 1.069 to 1.331)) than singletons.

In the gestational age group of 29–33 weeks, exposure to ACS was significantly associated with lower risks of surfactant use (aRR: 0.914 (95% CI: 0.862 to 0.970)) and mortality (aRR: 0.409 (95% CI: 0.269 to 0.624)), but a higher risk of sepsis (aRR: 1.416 (95% CI: 1.018 to 1.969)) (figure 2B). Twins showed a lower risk of BPD (aRR: 0.798 (95% CI: 0.648 to 0.982)), but a higher risk of PVL (aRR: 1.735 (95% CI: 1.256 to 2.396)) than singletons.

DISCUSSION

In this nationwide cohort study, we demonstrated that effects of ACS therapy administered before preterm birth on neonatal outcomes were not significantly different by plurality. Mortality and surfactant use were reduced by ACS exposure in both gestational age groups. ACS exposure was associated with decreased risks of high-grade IVH and PVL in infants born at 23–28 weeks of gestation, but increased the risk of sepsis in infants born at 29–33 weeks of gestation.

ACS therapy for mothers at risk of impending preterm delivery is the most effective evidence-based strategy to reduce the mortality and morbidity of their preterm offspring. However, previous studies that investigated the association between ACS therapy and neonatal outcomes in twin pregnancies not only reported conflicting results but also lacked quantity.

A recent meta-analysis has reported that ACS therapy is associated with decreased neonatal death, respiratory distress syndrome (RDS) and IVH in singleton pregnancies, but not in multiple pregnancies.[4] Furthermore, a randomised controlled trial on 311 twin infants who were delivered before 34 weeks of gestation showed that ACS therapy had no association with RDS or composite neonatal morbidity.[23] However, large population-based cohort studies from the mid-2000s reported positive ACS effects in multiple pregnancies.[24–26] A study of 750 twin infants from France has reported that a complete course of ACS therapy administered within 7 days before birth is associated with decreased rates of brain injury and mortality.[24] Another study of 8274 multiplets from Italian Neonatal Network reported that ACS therapy reduced the risk of severe IVH and mortality, although it was less effective in multiple pregnancies than in singleton pregnancies.[25] A study of 2516 twin infants from Canadian Neonatal Network has reported that twins can benefit from a complete course of ACS therapy as good as singletons in short-term respiratory morbidity, severe brain injury and mortality.[26] Consistent with results of these large cohort studies, our study, using the latest data from KNN, revealed that the effectiveness of ACS therapy in twins was comparable with that of singletons. Moreover, its benefits on mortality and morbidity were shown to be different by gestational age groups.

Additionally, we found that twins had a higher rate of morbidity than singletons in this study. Twins were associated with higher risks of high-grade IVH and advanced ROP in infants born at 23–28 weeks of gestation and PVL in infants born at 29–33 weeks of gestation than singletons. Although twins are more likely to be delivered preterm than singletons, whether twin pregnancy alone has such adverse effects on neonatal outcomes in preterm infants remains unknown.[27] In a large study of infants born between 23 and 35 weeks of gestation, twins and singletons had comparable average birth weights up to 32 weeks of gestation and similar neonatal outcomes.[28] One study from Australian and New Zealand Neonatal Network has found higher mortality, but not morbidities, in twins than in singletons.[12] Furthermore, two national cohort studies have reported comparable risks for neonatal outcomes except for RDS between twins and singletons.[29 30] However, a population-based European cohort study showed that twins had higher risk of mortality and high-grade IVH in infants born at 24–27 weeks of gestation.[14] Other studies have revealed disparities in the rate of morbidity such as BPD and ROP between twins and singletons.[8 31]

Possible reasons for conflicting findings in twins include study design and changes in population characteristics over time.[32] We found that twins had lower rates of antenatal complications such as maternal hypertension and chorioamnionitis, and higher rates of obstetric interventions, including IVF, ACS and caesarean section than singletons in both gestational age groups (online supplemental file 2). This trend has also been observed across other recent studies.[12 33] The higher rate of IVF in twins reflects the current trend of childbirth in Korea.[5] The reason for higher ACS exposure in twins is currently unclear. However, more medical attention for twin pregnancies might be one possible cause.[34] One noteworthy result was that the caesarean section rate for twins born between 23 and 28 weeks of gestation was 87.2% in our study, which was higher than that in other countries. For

Table 2 Comparisons of neonatal outcomes between infants exposed to ACS and infants without ACS exposure born at 23–28 weeks of gestation

Infants who survived before discharge (n=4160)	ACS exposed (n=3606)	ACS unexposed (n=554)	Risk difference, % (95% CI)	P value*	P value for interaction†
Surfactant use, n (%)					
Total	3468/3606 (96.2)	546/554 (98.6)	−2.4 (−3.6 to −1.2)	0.005	
Twin	952/991 (96.1)	108/109 (99.1)	−3.0 (−5.2 to −0.9)	0.006	0.199
Singleton	2516/2615 (96.2)	438/445 (98.4)	−2.2 (−3.6 to −0.8)	0.018	
Sepsis, n (%)					
Total	985/3606 (27.3)	166/554 (30.0)	−2.7 (−6.7 to 1.4)	0.195	
By numbers of fetus					
Twin	273/991 (27.5)	32/109 (29.4)	−1.8 (−10.8 to 7.2)	0.689	0.706
Singleton	712/2615 (27.2)	134/445 (30.1)	−2.9 (−7.5 to 1.7)	0.209	
High-grade IVH, n (%)					
Total	313/3606 (8.7)	79/554 (14.3)	−5.6 (−8.6 to −2.5)	<0.001	
By numbers of fetus					
Twin	115/991 (11.6)	15/109 (13.8)	−2.2 (−8.9 to 4.6)	0.508	0.224
Singleton	198/2615 (7.6)	64/445 (14.4)	−6.8 (−10.2 to −3.4)	<0.001	
Periventricular leucomalacia, n (%)					
Total	327/3606 (9.1)	74/554 (13.4)	−4.3 (−7.3 to −1.3)	0.001	
By numbers of fetus					
Twin	86/991 (8.7)	14/109 (12.8)	−4.2 (−10.7 to 2.4)	0.151	0.749
Singleton	241/2615 (9.2)	60/445 (13.5)	−4.3 (−7.6 to −0.9)	0.005	
Surgically treated PDA, n (%)					
Total	616/3606 (17.1)	99/554 (17.9)	−0.8 (−4.2 to 2.6)	0.647	
By numbers of fetus					
Twin	175/991 (17.7)	23/109 (21.1)	−3.4 (−11.5 to 4.6)	0.375	0.400
Singleton	441/2615 (16.9)	76/445 (17.1)	−0.2 (−4.0 to 3.6)	0.911	
Necrotising enterocolitis, n (%)					
Total	268/3606 (7.4)	36/554 (6.5)	0.9 (−1.3 to 3.2)	0.432	
By numbers of fetus					
Twin	72/991 (7.3)	8/109 (7.3)	−0.07 (−5.2 to 5.1)	0.978	0.479
Singleton	196/2615 (7.5)	28/445 (6.3)	1.2 (−1.3 to 3.7)	0.368	
Bronchopulmonary dysplasia, n (%)					
Total	1664/3606 (46.1)	269/554 (48.6)	−2.4 (−6.9 to 2.1)	0.290	
By numbers of fetus					
Twin	437/991 (44.1)	51/109 (46.8)	−2.7 (−12.6 to 7.2)	0.591	0.986
Singleton	1227/2615 (46.9)	218/445 (49.0)	−2.1 (−7.1 to 3.0)	0.419	
Advanced ROP, n (%)					
Total	957/3604 (26.6)	131/554 (23.6)	2.9 (−0.9 to 6.7)	0.147	
By numbers of fetus					
Twin	285/991 (28.8)	33/109 (30.3)	−1.5 (−10.6 to 7.6)	0.740	0.158
Singleton	672/2613 (25.7)	98/445 (22.0)	3.7 (−0.5 to 7.9)	0.097	
All infants (n=5407)	**ACS (n=4587)**	**No ACS (n=820)**	**Risk difference, % (95% CI)**	**P value***	**P value for interaction†**
Mortality, n (%)					
Total	981/4587 (21.4)	266/820 (32.4)	−11.1 (−14.5 to −7.6)	<0.001	
By numbers of fetus					
Twin	265/1256 (21.1)	65/174 (37.4)	−16.3 (−23.8 to −8.7)	<0.001	0.458
Singleton	716/3331 (21.5)	201/646 (31.1)	−9.6 (−13.5 to −5.8)	<0.001	

Data are presented as n (%).
*Tests for risk difference within each subgroup.
†Tests for interaction between ACS and twin pregnancies on each outcome. P values for interaction were obtained from multivariable Poisson regression models using the generalised estimating equations.
ACS, antenatal corticosteroid; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

Table 3 Comparisons of neonatal outcomes between infants exposed to ACS and infants without ACS exposure born at 29–33 weeks of gestation

Infants who survived before discharge (n=4019)	ACS exposed (n=3428)	ACS unexposed (n=591)	Risk difference, % (95% CI)	P value*	P value for interaction†
Surfactant use, n (%)					
Total	2240/3428 (65.3)	402/591 (68.0)	−2.7 (−6.8 to 1.4)	0.206	
By numbers of fetus					
Twin	583/801 (72.8)	86/104 (82.7)	−9.9 (−17.8 to −2.0)	0.030	0.243
Singleton	1657/2627 (63.1)	316/487 (64.9)	−1.8 (−6.4 to 2.8)	0.446	
Sepsis, n (%)					
Total	376/3428 (11.0)	41/591 (6.9)	4.0 (1.7 to 6.3)	0.003	
By numbers of fetus					
Twin	90/801 (11.2)	8/104 (7.7)	3.5 (−2.0 to 9.1)	0.274	0.966
Singleton	286/2627 (10.9)	33/487 (6.8)	4.1 (1.6 to 6.6)	0.006	
High-grade IVH, n (%)					
Total	53/3426 (1.5)	14/591 (2.4)	−0.8 (−2.1 to 0.5)	0.150	
By numbers of fetus					
Twin	10/801 (1.2)	2/104 (1.9)	−0.7 (−3.4 to 2.1)	0.572	0.742
Singleton	43/2625 (1.6)	12/487 (2.5)	−0.8 (−2.3 to 0.6)	0.204	
Periventricular leucomalacia, n (%)					
Total	179/3427 (5.2)	30/591 (5.1)	0.2 (−1.8 to 2.1)	0.882	
By numbers of fetus					
Twin	71/801 (8.9)	6/104 (5.8)	3.1 (−1.8 to 8.0)	0.287	0.492
Singleton	108/2626 (4.1)	24/487 (4.9)	−0.8 (−2.9 to 1.3)	0.412	
Surgically treated PDA, n (%)					
Total	95/3428 (2.8)	18/591 (3.0)	−0.3 (−1.8 to 1.2)	0.709	
By numbers of fetus					
Twin	19/801 (2.4)	4/104 (3.8)	−1.5 (−5.3 to 2.4)	0.369	0.955
Singleton	76/2627 (2.9)	14/487 (2.9)	0.02 (−1.6 to 1.6)	0.982	
Necrotising enterocolitis, n (%)					
Total	85/3427 (2.5)	11/591 (1.9)	0.6 (−0.6 to 1.8)	0.363	
By numbers of fetus					
Twin	21/801 (2.6)	4/104 (3.8)	−1.2 (−5.1 to 2.6)	0.474	0.492
Singleton	64/2626 (2.4)	7/487 (1.4)	1 (−0.2 to 2.2)	0.175	
Bronchopulmonary dysplasia, n (%)					
Total	524/3423 (15.3)	93/591 (15.7)	−0.4 (−3.6 to 2.8)	0.790	
By numbers of fetus					
Twin	114/797 (14.3)	16/104 (15.4)	−1.1 (−8.4 to 6.3)	0.768	0.834
Singleton	410/2626 (15.6)	77/487 (15.8)	−0.2 (−3.7 to 3.3)	0.912	
Advanced ROP, n (%)					
Total	74/3428 (2.2)	11/591 (1.9)	0.3 (−0.9 to 1.5)	0.643	
By numbers of fetus					
Twin	20/801 (2.5)	4/104 (3.8)	−1.4 (−5.2 to 2.5)	0.420	0.202
Singleton	54/2627 (2.1)	7/487 (1.4)	0.6 (−0.6 to 1.8)	0.366	
All infants (n=4124)	**ACS (n=3504)**	**No ACS (n=620)**	**Risk difference, % (95% CI)**	**P value***	**P value for interaction†**
Mortality, n (%)					
Total	76/3504 (2.2)	29/620 (4.7)	−2.5 (−4.2 to −0.8)	<0.001	

Continued

Table 3 Continued

Infants who survived before discharge (n=4019)	ACS exposed (n=3428)	ACS unexposed (n=591)	Risk difference, % (95% CI)	P value*	P value for interaction†
By numbers of fetus					
Twin	21/822 (2.6)	8/112 (7.1)	−4.6 (−9.5 to 0.3)	0.066	0.722
Singleton	55/2682 (2.1)	21/508 (4.1)	−2.1 (−3.9 to -0.3)	0.005	

Data are presented as n (%).
*Tests for risk difference within each subgroup.
†Tests for interaction between ACS and twin pregnancies on each outcome. P values for interaction were obtained from multivariable Poisson regression models using the generalised estimating equations.
ACS, antenatal corticosteroid; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

similar gestational age, the caesarean section rate for twins was 74.4% in the USA and 61.8% in Australia and New Zealand.[12 15]

Despite the fact that these differences in characteristics between twins and singletons are observed in other studies, an increase in the proportion of the population exposed to ACS along with variation in practice of neonatal care in each country might have complexly contributed to the interaction between ACS and plurality as well as the inherent risk of a twin pregnancy.[35] Although we adjusted potential confounders which were different between twins and singletons in the analyses, different population characteristics between twins and singletons and/or between studies should be considered when interpreting our results.

Our study has several limitations. First, the KNN registry had no information about chorionicity in multiple pregnancies. Thus, we were unable to investigate the difference in the effect of ACS therapy on neonatal outcomes according to chorionicity in twins. Second, although we used prospective cohort data of preterm infants with VLBW for this study, antenatal information including ACS administration was collected retrospectively because preterm infants were enrolled after they were born. Therefore, it was unknown why ACS was not or incompletely administered in infants who did not receive a

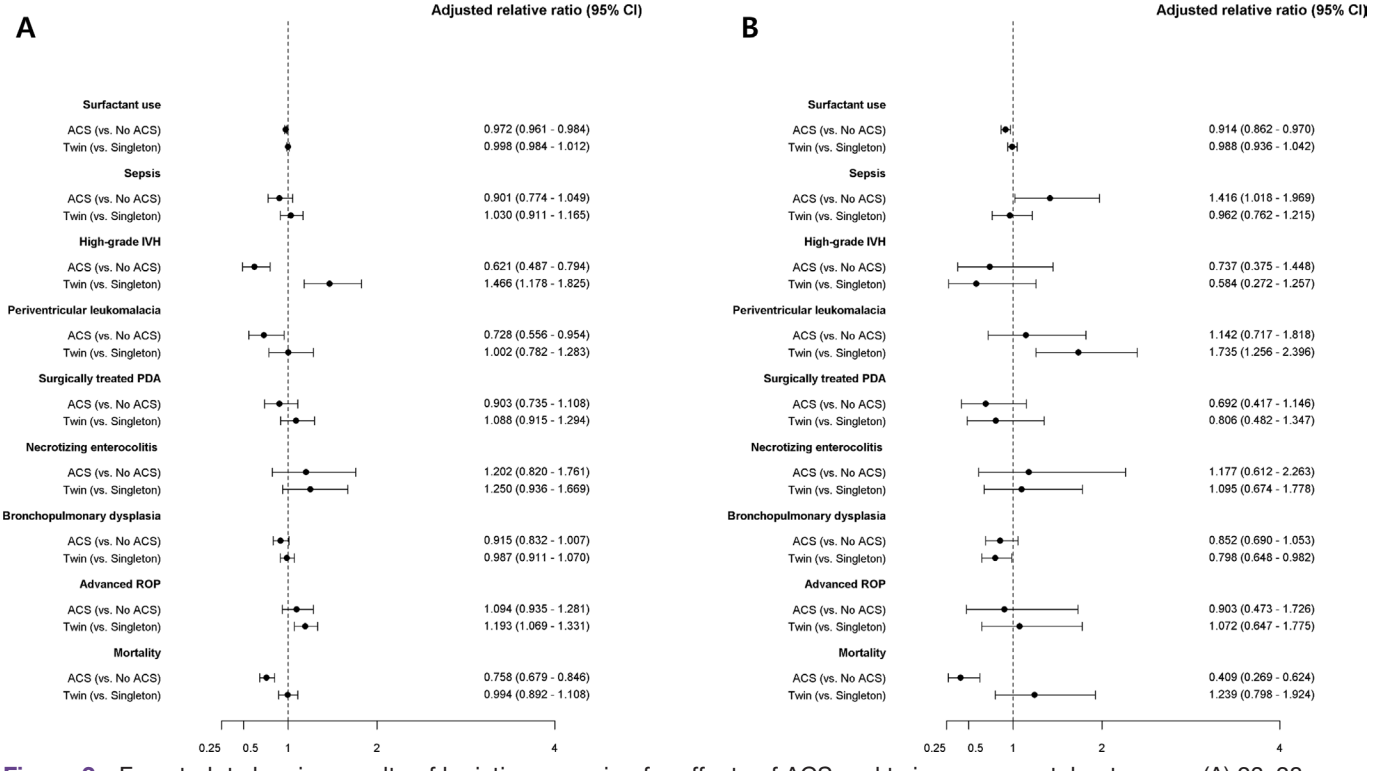

Figure 2 Forest plot showing results of logistic regression for effects of ACS and twins on neonatal outcomes: (A) 23–28 weeks of gestation; (B) 29–33 weeks of gestation. For each neonatal outcome, solid dots represent the adjusted OR and lateral lines represent the 95% CI. Adjusted relative risk and 95% CI were obtained from multivariable Poisson regression models using generalised estimating equations. ACS, antenatal corticosteroid; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

complete course of ACS therapy. Notably, the percentage of singletons without exposure to ACS was higher in this study than in other studies.[36 37] Moreover, information on the total amount of ACS administered was not available in the KNN registry database. Information on total amount of ACS administered will enable a more quantitative analysis of effects of ACS therapy on neonatal outcomes. Lastly, in our cohort, 56.6% of twins were conceived via IVF whereas only 7.1% of singletons were conceived via IVF. Although preterm infants conceived via IVF are known to have comparable morbidity and mortality with their peers conceived via natural pregnancy,[38] higher proportion of IVF cases among twins should be taken into account when interpreting our results.

CONCLUSION

Despite differences in demographic and clinical characteristics according to plurality, ACS therapy administered before birth had comparable positive effects on neonatal outcomes of preterm infants with VLBW regardless of plurality.

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Data availability statement Data are available upon reasonable request. The Korean Neonatal Network (KNN) Publication Ethics Policy adheres to the following research data management and access guidelines: all information about patients and participating NICUs is confidential and may be used by individuals for approved research purposes. If an individual or institution that is not affiliated with KNN wants to use the data, it must make an official request to the KNN publication-Ethics Committee and obtain approval from the network.

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Supplemental text 1. The definition of variables

Small for gestational age (SGA) was defined as birth weight below the 10th percentile for gestational age according to the Fenton growth chart.[1] Sepsis was defined as a case of positive blood culture and requiring systemic antibiotics treatment for more than five days. Chorioamnionitis was defined as histologic findings of acute inflammation in the chorion-decidua, amnion, umbilical cord, and chorionic plate by pathologist at each participating facility using the criteria of Salafia et al.[2] modified by Yoon et al.[3] Maternal hypertension included pre-existing hypertension and/or pregnancy-induced hypertension. Maternal diabetes mellitus (DM) included pre-existing and/or pregnancy-induced DM. High-grade intraventricular hemorrhage (IVH) was defined as grade 3 or 4 IVH according to Papile's criteria.[4] Periventricular leukomalacia (PVL) was diagnosed based on brain ultrasound or magnetic resonance imaging obtained at term-equivalent age. Only cystic lesions were counted. Surgically treated patent ductus arteriosus (PDA) was defined as surgical ligation or division of symptomatic PDA. Necrotizing enterocolitis (NEC) was diagnosed and staged according to modified Bell's criteria.[5] Only NEC of stage 2 or higher was counted. Bronchopulmonary dysplasia (BPD) was defined as a need for supplementary oxygen at 36 weeks postmenstrual age (PMA) or discharge according to the National Institute of Child Health and Human Development, the National Heart, Lung and Blood Institute, and the Office of Rare Diseases workshop definition.[6] Advanced retinopathy of prematurity (ROP) was defined as stage 3 or higher according to the International Classification for Retinopathy of Prematurity[7] or having an operation (cryotherapy, laser photocoagulation, or vitrectomy), or intravitreal injection with anti-vascular endothelial growth factor.[8]

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Supplemental Table 1. Comparison of baseline characteristics between twins and singletons

	23 – 28 weeks of gestational age			29 – 33 weeks of gestational age		
	Twin (n = 1,430)	Singleton (n = 3,977)	*P* value	Twin (n = 934)	Singleton (n = 3,190)	*P* value
Infant						
Gestational age (weeks), mean (SD)	26.63 (1.64)	26.60 (1.58)	0.471	30.19 (0.91)	30.80 (1.34)	0.001<
Birth weight (g), mean (SD)	917 (235)	913 (246)	0.581	1,268 (188)	1,248 (203)	0.005
SGA, n (%)	75 (5.2)	380 (9.6)	0.001<	94 (10.1)	899 (28.2)	0.001<
Male, n (%)	775 (54.2)	2,107 (53.0)	0.434	447 (47.9)	1,564 (49.0)	0.529
Maternal						
Maternal age (years), mean (SD)	33.05 (4.04)	33.33 (4.51)	0.031	33.51 (3.79)	33.36 (4.52)	0.305
Maternal diabetes mellitus, n (%)	138 (9.7)	348 (8.8)	0.268	126 (13.5)	338 (10.6)	0.013
Maternal hypertension, n (%)	74 (5.2)	678 (17.0)	0.001<	144 (15.5)	1357 (42.5)	0.001<
Chorioamnionitis[a], n (%)	446 (37.2)	1701 (49.9)	0.001<	133 (17.7)	734 (27.0)	0.001<
Premature rupture of membrane, n (%)	524 (37.0)	1770 (44.8)	0.001<	347 (37.4)	876 (27.6)	0.001<
Cesarean section, n (%)	1247 (87.2)	2823 (71.0)	0.001<	834 (89.3)	2618 (82.1)	0.001<
In vitro fertilization, n (%)	768 (54.8)	348 (8.8)	0.001<	512 (55.8)	197 (6.2)	0.001<
Antenatal corticosteroid, n (%)	1256 (87.8)	3331 (83.8)	0.001<	822 (88.0)	2,682 (84.1)	0.003

Data are presented as mean (SD) or n (%).

Abbreviations: ACS, antenatal corticosteroid; SGA, small for gestational age; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

[a] Values were missing for 797 infants in the group with 23 to 28 weeks of gestational age and 657 infants in the group with 29 to 33 weeks of gestational age.