Short term outcomes of preterm infants following antenatal corticosteroid treatment for childbearing women at 34 (0/7) to 36 (6/7) weeks: do the advantages outweigh the disadvantages?

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Research article

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Abstract

Background The effects of maternal antenatal corticosteroid (ACS) treatment on the short-term outcome of late preterm infants are unclear.

Methods This is a retrospective cohort study. Data of pregnant women who gave birth between 34 (0/7) to 36 (6/7) weeks gestation from January 2014 to June 2019 were collected. Nine short-term outcomes of preterm infants from mothers who received ACS treatment were compared to preterm infants from mothers who did not receive ACS treatment.

Results The results were as follows: (1) ACS administration to pregnant women at high risk for giving birth between 34 (0/7) to 36 (6/7) weeks pregnancy, can decrease the cost and inpatient time of their infants; (2) lack of maternal ACS treatment is an independent risk factor for neonatal respiratory distress syndrome; (3) use of maternal ACS does not increase the risk of neonatal pneumonia, neonatal hypoglycemia, neonatal sepsis, necrotizing enterocolitis of newborns, neonatal intracranial hemorrhage, and hypoxic-ischemic encephalopathy in preterm infants.

Conclusions Use of ACS for pregnant women at risk for giving birth between 34 (0/7) to 36 (6/7) weeks pregnancy has more advantage than disadvantage. Our study provides evidence-based medicine for clinicians to make ACS treatment choices for pregnant women with risk of giving birth between 34 (0/7) to 36(6/7) weeks gestation.

Background

Preterm birth is the second cause of child death in children younger than 5 years [1]. In 2010, an estimated 14.9 million babies (uncertainty range 12.3–18.1 million) were born preterm, comprising 11.1% of all livebirths worldwide [2]. Late preterm birth is defined as infants born between 34(0/7)to 36 (6/7) weeks gestation and accounts for 70% of all preterm births [3]. Recent studies show that even babies born at late preterm have an increased risk of immediate complications [4], neonatal and infant death, cerebral palsy, and worse neurodevelopmental and school performance outcomes when compared with those born at term [5].

In the last few decades, antenatal corticosteroid (ACS) treatment has been administered to childbearing women who are at risk for giving birth before 34 weeks, and has achieved tremendous success in reducing adverse neonatal outcomes, especially for preventing respiratory morbidity in preterm neonates [6]. However, such treatment has not been extended to women during late preterm period, because of a lack of consensus concerning ACS treatment for women who are at risk for giving birth between 34 (0/7) to 36 (6/7) weeks gestation [7]. There are positive and negative views on ACS treatment for women at high risk of giving birth at 34 (0/7) to 36 (6/7) weeks. The positive view indicates that ACS treatment can decrease incidence of neonatal respiratory distress syndrome (NRDS) and neonatal hospitalization expenses in preterm infants between 34 (0/7) to 36 (6/7) weeks gestation [8–10]. The negative view indicates that this treatment does not reduce respiratory disease and wet lung in late preterm infants, but

increases incidence of neonatal hypoglycemia and neonatal sepsis [11, 12]. The purpose of this study is to compare the advantages and disadvantages of preterm infant short-term outcomes of ACS treatment for pregnant women of 34 (0/7) to 36 (6/7) weeks.

Methods

Setting and participants

This is a retrospective cohort study. The study protocol was approved by the research institute's committee of human research in the Second Affiliated Hospital of Shantou University Medical College (NO.2018-23) and abided by the standards of the Declaration of Helsinki. The data were anonymized in this study, so we did not use the consent to participate.

We collected data of pregnant women who gave birth at 34 (0/7) to 36 (6/7) weeks gestation from January 2014 to June 2019. The data were anonymized in this study. Data were excluded from this study if the pregnant women or preterm infants met the following criteria: (1) pregnant women had serious liver, kidney, lung or heart disease before or during pregnancy, (2) pregnant women received ACS treatment before 34 gestational weeks, (3) preterm infants had a congenital malformation or needed surgery.

Data collection

Variables included age of mother, gestational diabetes mellitus, pregnancy hypertension, method of delivery, premature rupture of membranes (PROM), condition of the placenta, meconium stained amniotic fluid, multiple gestation, gestational age, birth weight of preterm infants, asphyxia, pulmonary surfactant treatment for preterm infants, and mechanical ventilation for preterm infants. The short-term outcomes of preterm infants in this study included the length of neonatal hospital stay, hospitalization expenses for preterm infants, NRDS, neonatal pneumonia, neonatal hypoglycemia, neonatal sepsis, necrotizing enterocolitis of newborn, neonatal intracranial hemorrhage, and hypoxic-ischemic encephalopathy.

Exposure factor in this cohort is ACS treatment

According to the ACS treatment, this cohort was divided into two groups: the ACS group and the without-ACS group. Antenatal corticosteroid treatment consisted of four doses of dexamethasone (6 mg intramuscular) 12 hours apart [13].

Assessment short-term outcomes of preterm infants

We compared nine short-term outcomes of preterm infants between the ACS group and without-ACS group. Assessment methods of these outcomes were as follows. Neonatal hypoglycemia was defined as a glucose level less than 2.2 mmol per liter at any time [14].

The diagnosis of NRDS is based upon the findings of respiratory difficulty (cyanosis, grunting, nasal flaring, or tachypnea) that necessitated mechanical ventilation support, and is furthermore consistent with typical radiological findings of the lung (such as frosted glass-like changes, air bronchogram, and

white lung). Laboratory findings were characterized initially by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis. The clinical course, chest x-ray findings, and blood gas and acid-base values helped to establish the clinical diagnosis of NRDS [15].

Neonatal sepsis includes early-onset or late-onset, depending on the age of onset and timing of the sepsis episode. Both early-onset and late-onset neonatal sepsis were included in this study. Diagnosis of neonatal sepsis is based on symptoms and laboratory evidence. Initial symptoms might be few, and includes apnea, tachypnoea, or tachycardia. Late complications of neonatal sepsis might include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage or insufficiency, bone marrow dysfunction, and disseminated intravascular coagulation. Traditionally, neonatal sepsis can be diagnosed when the blood or other sterile body sites culture produces positive pathogenic bacteria or opportunistic pathogens. Other laboratory evidence that measure an inflammatory response including blood count, C-reactive protein, procalcitonin, interleukin 6, interleukin 8, and tumor necrosis factor. [16].

Necrotizing enterocolitis of newborn is one of the most serious complications for neonates [17]. Necrotizing enterocolitis of newborn often occurs in the first or second week of life in the late preterm infants. It is difficulty to be identified, because of the first symptoms of this disease is not typical. Gastrointestinal signs including feeding difficulty, gastric retention, abdominal distension, bilious vomiting, and stool with blood. Diagnosis of necrotizing enterocolitis of newborn is made according to plain abdominal radiographs. The finding of pneumatosis in the intestinal wall confirms the clinical suspicion of necrotizing enterocolitis of newborn and diagnosis.

Neonatal pneumonia is inflammation of the lung caused by infection. Diagnosis of neonatal pneumonia is made according to the risk factors, such as PROM, chorioamnionitis in the mother, and low birthweight, which predispose to pneumonia. Infants with respiratory distress usually require investigation to identify infection. A chest X ray picture can help diagnosis of neonatal pneumonia, which would show increased bronchovascular shadows with small patchy and macular shadows [18].

Intracranial hemorrhage is suspected basis of the history, clinical manifestations, and knowledge of the birthweight-specific risks for intravascular hemolysis. Ultrasonography is the preferred imaging technique for screening. All at-risk infants should undergo cranial ultrasonography within the 3–7 days of age [19].

The diagnosis of hypoxic-ischemic encephalopathy were made according to the PH value of the fetal umbilical artery, the Apgar score at 5 and 10 minutes, and multi-system organ failure including combined kidney damage, liver damage, blood abnormalities, heart dysfunction, metabolic disorders, and gastrointestinal tract injury [20]. Magnetic resonance imaging is a sensitive tool for evaluation of extensive periventricular injury. All at-risk preterm infants should undergo MRI within the first week of age.

Because this is a single center study, we compared the neonatal hospitalization expenses directly. Hospitalization expenses included the examination, drug, and nursing care costs. Length of hospital stay was counted from the day of admission to the day of discharge.

Statistical analysis

We used Shapiro-Wilk test to determine whether continuous variables are normally distributed, and the Wilcoxon-Mann-Whitney U-test was conducted for skewed distributions (presented as the median and the min-max range). Descriptive statistics for categorical variables were showed as frequency (percentage). Pearson chi-square test or Fisher's exact test were used to compare categorical variables, as appropriate. Collinearity among all covariates was assessed using the Spearman correlation test [21].

For binary variables, logistic regression was used to analyze the risk factors of neonatal short-term outcomes, and independent variables were chosen based on clinical knowledge. For continuous dependent variables, linear regression was used to analyze the relationship between independent variables. Regression analysis was performed by a forward stepwise method to identify the risk factors. Estimated slope and 95% confidence intervals (CI) were obtained. Statistical analyses were performed using SPSS 24.0 (SPSS, Chicago, IL). *P*-values of less than 0.05 were considered to be statistically significant.

Results

Population characteristics

In total, 1393 pregnant women and 1472 preterm infants were eligible for analysis. Two preterm triplets and 73 preterm twins were included in this study. Seven hundred fifty-seven out of the 1393 pregnant women accepted ACS treatment before giving birth. We analyzed the patient characteristics and clinical variables with and without maternal ACS treatment in this cohort (see Table 1). Women who were old, at low gestational age, developed PROM before delivery, or had parturition by cesarean section were more likely to receive ACS treatment.

Table 1
Patient characteristics and clinical variables with and without ACS in this cohort.

	Total	Without ACS	With ACS	*P*-value
N	1472	672	800	
Mother				
Age (years)	28(25–32)	28(25–31)	29(25–32)	0.008
Delivery				0.026
Vaginal	846	409 (48.35%)	437 (51.65%)	
Cesarean	626	263 (42.01%)	363 (57.99%)	
GDM				0.459
Yes	77	32 (41.56%)	45 (58.44%)	
No	1395	640(45.88%)	755 (54.12%)	
PROM				0.001
Yes	572	199 (34.79%)	373 (65.21%)	
No	900	473 (52.56%)	427 (47.44%)	
Placenta				0.795
Normal	1291	591 (45.78%)	700 (54.22%)	
Abnormal	181	81 (44.75%)	100 (55.250)	
MSAF				0.485
Yes	85	42 (49.41%)	43 (50.59%)	
No	1384	630 (45.52%)	754 (54.48%)	
MG				0.566
Yes	172	75 (43.60%)	97 (56.40%)	
No	1300	597 (45.92%)	703 (54.08%)	
Infants				

Results are shown as the median (min,max)] or n (%). P 0.05, indicates significant differences between the two groups. BW: Birth weight; DHC: Daily hospitalization cost; GA: Gestational age; GDM: gestational diabetes mellitus; HE: Hospitalization expenses; HIE: Hypoxic-ischemic encephalopathy; LHS: Length of hospital stay; MG: Multiple gestation; MSAF: Meconium stained amniotic fluid; NEC: Necrotizing enterocolitis of newborn; NH: Neonatal hypoglycemia; NICH: Neonatal intracranial hemorrhage; NP: Neonatal pneumonia; NS: Neonatal sepsis; PS: Pulmonary surfactant; RS: Respiratory support.

	Total	Without ACS	With ACS	*P*-value
Gender				0.356
Female	662	311 (46.98%)	351 (53.02%)	
Male	810	361 (44.57%)	449 (55.43%)	
GA	35.714 (34.857–36.286)	36 (35.286–36.571)	35.428 (34.714–36.142)	0.001
BW (kg)	2.37(2.1–2.6)	2.4(2.16–2.65)	2.35(2.1–2.55)	0.001
Asphyxia				0.138
Yes	123	64 (52.03%)	59 (47.97%)	
No	1349	608 (45.07%)	741 (54.93%)	
PS				0.113
Yes	88	33 (37.50%)	55 (62.50%)	
No	1384	639 (46.17%)	745 (53.83%)	
HIE				0.554
Yes	339	150 (44.25%)	189 (55.75%)	
No	1133	522 (46.07%)	611 (53.93%)	
NICH				0.576
Yes	40	20 (50.00%)	20 (50.00%)	
No	1432	652 (45.53%)	780 (54.47%)	
NRDS				0.730
Yes	136	64 (47.06%)	72 (52.94%)	
No	1336	608 (45.51%)	728 (54.49%)	
NEC				
Yes	22	9 (40.91%)	13 (59.09%)	0.653
No	1450	663 (45.72%)	787 (54.28%)	

Results are shown as the median (min,max)] or n (%). *P* 0.05, indicates significant differences between the two groups. BW: Birth weight; DHC: Daily hospitalization cost; GA: Gestational age; GDM: gestational diabetes mellitus; HE: Hospitalization expenses; HIE: Hypoxic-ischemic encephalopathy; LHS: Length of hospital stay; MG: Multiple gestation; MSAF: Meconium stained amniotic fluid; NEC: Necrotizing enterocolitis of newborn; NH: Neonatal hypoglycemia; NICH: Neonatal intracranial hemorrhage; NP: Neonatal pneumonia; NS: Neonatal sepsis; PS: Pulmonary surfactant; RS: Respiratory support.

	Total	Without ACS	With ACS	*P*-value
NS				0.228
Yes	276	117 (42.39%)	159 (57.61%)	
No	1196	555 (46.40%)	641 (53.60%)	
NP				0.329
Yes	107	44 (41.12%)	63 (58.88%)	
No	1365	628 (46.01%)	737 (53.99%)	
NH				0.037
Yes	307	124 (40.39%)	183 (59.61%)	
No	1165	548 (47.04%)	617 (52.96%)	
RS				0.664
Yes	107	51 (47.66%)	56 (52.34%)	
No	1365	621 (45.49%)	744 (54.51%)	
LHS (day)	10 (5–14)	9 (4–14)	10 (5–15)	0.001
HE	12083.96 (7049.11-17918.58)	11011.75 (5983.46-17032.46)	12830.16 (7684.90-18281.83)	0.002
DHC	1201.44 (980.19-1424.52)	1213.22 (969.45-1429.41)	1192.76 (986.5-1412.38)	0.778

Results are shown as the median (min,max)] or n (%). $P \leq 0.05$, indicates significant differences between the two groups. BW: Birth weight; DHC: Daily hospitalization cost; GA: Gestational age; GDM: gestational diabetes mellitus; HE: Hospitalization expenses; HIE: Hypoxic-ischemic encephalopathy; LHS: Length of hospital stay; MG: Multiple gestation; MSAF: Meconium stained amniotic fluid; NEC: Necrotizing enterocolitis of newborn; NH: Neonatal hypoglycemia; NICH: Neonatal intracranial hemorrhage; NP: Neonatal pneumonia; NS: Neonatal sepsis; PS: Pulmonary surfactant; RS: Respiratory support.

Advantages and disadvantages of preterm infant short-term outcomes of ACS treatment

In order to compare the advantages and disadvantages of preterm infant short-term outcomes of ACS treatment in pregnant women at 34 (0/7) to 36 (6/7) weeks, we analyzed the risk factors for short-term outcomes of preterm infants, including neonatal hypoglycemia, NRDS, neonatal sepsis, necrotizing enterocolitis of newborn, neonatal pneumonia, neonatal intracranial hemorrhage, hypoxic-ischemic encephalopathy, length of neonatal hospital stay, and hospitalization expenses of preterm infants (see Table 2).

Table 2
Logistic regression for the neonatal complications in late preterm infants (95%CI)

	NRDS	NH	NS	NP	HIE	NEC	NICH
Mother							
Age	0.950–1.045	1.002–1.054	0.960–1.016	1.009–1.091	0.978–1.032	0.938–1.109	0.967–1.096
ACS	0.332–0.906	0.812–1.393	0.726–1.327	0.635–1.514	0.895–1.581	0.356–2.241	0.478-1.800
Delivery	0.874–2.307	0.925–1.570	0.527–0.957	0.525–1.229	0.792–1.381	0.458–2.703	0.151–0.679
PROM	-	-	2.090–3.816	0.878–2.073	0.559–1.003	0.291–1.898	-
Placenta	-	-	-	-	-	-	0.261–2.495
AFMS	-	-	-	0.245–1.407	1.120–2.891	-	0.559–6.317
MS	-	-	-	0.704-4.300	0.667–2.141	-	0.234–4.628
MG	-	0.862–1.898	-			-	-
GDM	-	0.353–1.337	-	0.949–4.138	0.635–2.166	-	0.043–2.519
Infant							
Gender	-	-	-	0.749–1.705	0.937–1.615	-	0.769–3.032
GA	0.387–0.724	0.580–0.812	0.844–1.223	0.544–0.926	0.832–1.185	0.211–0.688	0.584–1.585
BW	0.539–1.831	0.552–1.071	0.380–0.772	0.641–1.740	0.584–1.134	0.540–4.871	1.155–5.379
Asphyxia	0.863–3.504	0.672–1.655	1.735–4.364	1.164–3.996	6.259–15.076	0.187–3.940	1.162–7.624
RS	-	-	0.587–2.339	0.360–2.072	-	-	-

ACS: antenatal corticosteroid; BW: Birth weight; DHC: Daily hospitalization cost; GA: Gestational age; HE: Hospitalization expenses; HIE: Hypoxic-ischemic encephalopathy; LHS: Length of hospital stay; MG: Multiple gestation; MSAF: Meconium stained amniotic fluid; NEC: Necrotizing enterocolitis of newborn; NH: Neonatal hypoglycemia; NICH: Neonatal intracranial hemorrhage; NP: Neonatal pneumonia; NS: Neonatal sepsis; PS: Pulmonary surfactant; RS: Respiratory support.

	NRDS	NH	NS	NP	HIE	NEC	NICH
PS	-	-	0.642–2.644	-	-	-	-
NRDS	-	-	1.780–5.763	1.005–4.558	1.749–3.948	-	1.441–7.029
NH	0.552–1.771	-	0.768–1.522	-	0.978–1.855	0.326–2.532	0.695–3.209
NS	-	-	-	-	-	1.023–6.420	-
NP	-	-	1.124–2.846	-	-	0.056–3.305	-
NEC	-	-	1.177–7.692	-	-	-	-

ACS: antenatal corticosteroid; BW: Birth weight; DHC: Daily hospitalization cost; GA: Gestational age; HE: Hospitalization expenses; HIE: Hypoxic-ischemic encephalopathy; LHS: Length of hospital stay; MG: Multiple gestation; MSAF: Meconium stained amniotic fluid; NEC: Necrotizing enterocolitis of newborn; NH: Neonatal hypoglycemia; NICH: Neonatal intracranial hemorrhage; NP: Neonatal pneumonia; NS: Neonatal sepsis; PS: Pulmonary surfactant; RS: Respiratory support.

The risk factors for neonatal hypoglycemia in this cohort were old maternal age (RR = 1.027, 95%CI = 1.002–1.054) and low gestational age (RR = 0.686, 95%CI = 0.580–0.812). The risk factors for neonatal sepsis in preterm infants were vaginal delivery (RR = 0.709, 95%CI = 0.848–1.233), low birth weight (RR = 0.541, 95%CI = 0.380–0.772), NRDS (RR = 3.203, 95%CI = 1.780–5.763), neonatal pneumonia (RR = 1.788, 95%CI = 1.124–2.846), necrotizing enterocolitis of newborn (RR = 3.009, 95%CI = 1.177–7.692), and the mother with PROM (RR = 2.824, 95%CI = 2.090–3.816). The risk factors for necrotizing enterocolitis of newborn in preterm infants were low gestational age (RR = 0.381, 95%CI = 0.211–0.688) and neonatal sepsis (RR = 2.562, 95%CI = 1.023–6.420). The risk factors for neonatal pneumonia in preterm infants were old maternal age (RR = 1.049, 95%CI = 1.009–1.091), low gestational age (RR = 0.381, 95%CI = 0.211–0.688), NRDS (RR = 2.140, 95%CI = 1.005–4.558), and asphyxia (RR = 2.157, 95%CI = 1.164–3.996). The risk factors for neonatal intracranial hemorrhage in preterm infants were vaginal delivery (RR = 0.320, 95%CI = 0.151–0.679), low birth weight (RR = 2.493, 95%CI = 1.155–5.379), NRDS (RR = 3.183, 95%CI = 1.441–7.029), and asphyxia (RR = 2.976, 95%CI = 1.162–7.624). The risk factors for hypoxic-ischemic encephalopathy in preterm infants were NRDS (RR = 2.628, 95%CI = 1.749–3.948) and asphyxia (RR = 9.714, 95%CI = 6.259–15.076). The above results show use of ACS treatment does not increase the incidence of neonatal hypoglycemia, necrotizing enterocolitis of newborn, neonatal sepsis, neonatal pneumonia, neonatal intracranial hemorrhage, and hypoxic-ischemic encephalopathy.

The risk factors for NRDS in preterm infants were low gestational age (RR = 0.529, 95%CI = 0.387–0.724) and lack of ACS treatment (RR = 0.548, 95%CI = 0.332–0.906), which shows that the incidence of NRDS in

preterm infants whose mother received ACS treatment before delivery, was about 50% that of preterm infants whose mothers did not use ACS (see Table 2).

Linear regression was used to analyze the length of hospital stay and the hospitalization expenses for preterm infants. According to linear regression analysis, a longer hospital stay of preterm infants was related to a lower gestational age, lack of maternal ACS treatment, mechanical ventilation for preterm infants, NRDS, neonatal hypoglycemia, neonatal pneumonia, neonatal sepsis, and hypoxic-ischemic encephalopathy (see Table 3). Longer hospital stay, the use of pneumonia surfactant, mechanical ventilation for preterm infants, lower birth weight, lower gestational age, NRDS, neonatal pneumonia, neonatal hypoxic-ischemic encephalopathy, and lack of maternal ACS treatment were correlation with more neonatal hospital expenses (see Table 4). Maternal ACS treatment was negatively correlated with the length of hospital stay and the hospitalization expenses of preterm infants (slope was − 0.784, P = 0.026 and − 933.173, P = 0.001, respectively). The above results suggest that ACS administration for pregnant women who had a high risk for giving birth at 34 (0/7) to 36(6/7) gestation can decrease the cost and inpatient time of their infants.

Table 3
Linear regression for the length of hospital stay in late preterm infants (days).

	Unstandardized B	Standardized coefficients beta	*P*-value	VIF	F
Age	0.096	0.057	0.005	1.053	105.354
ACS	-0.703	-0.041	0.047	1.091	
Delivery mode	1.312	0.077	0.001	1.075	
GA	-2.229	-0.218	0.001	1.069	
BW	-6.981	-0.351	0.001	1.178	
Asphyxia	3.299	0.106	0.001	1.069	
NRDS	4.919	0.165	0.001	1.087	
NH	2.063	0.097	0.001	1.031	
NS	4.565	0.207	0.001	1.082	
NP	3.110	0.094	0.001	1.027	
HIE	9.840	0.139	0.001	1.013	
* F 0.05 = 2.668.					
BW: Birth weight; GA: Gestational age; HIE: Hypoxic-ischemic encephalopathy; NH: Neonatal hypoglycemia; NP: Neonatal pneumonia; NS: Neonatal sepsis;					

Table 4
Linear regression for hospitalization expenses in late preterm infants (RMB).

	Unstandardized B	Standardized coefficients beta	*P*-value	VIF	F
ACS	-933.173	-0.036	0.001	1.08	790.98
GA	-496.615	-0.032	0.007	1.351	
BW	1877.452	0.063	0.001	1.37	
PS	10555.095	0.193	0.001	2.236	
RS	4379.518	0.088	0.001	2.407	
NRDS	3047.02	0.067	0.001	2.114	
NH	2.08	0.098	0.001	1.031	
NP	2106.388	0.042	0.001	1.048	
NS	2247.55	0.068	0.001	1.136	
HIE	833.192	0.027	0.014	1.139	
* F 0.05 = 2.668.					
ACS: antenatal corticosteroid; BW: Birth weight; GA: Gestational age; HIE: Hypoxic-ischemic encephalopathy; NH: Neonatal hypoglycemia; NP: Neonatal pneumonia; NS: Neonatal sepsis; PS: Pulmonary surfactant; RS: Respiratory support.					

Discussion

We found that ACS treatment decreases the incidence of NRDS, length of neonatal hospital stay, and neonatal hospital expenses, but has no influence on the incidence of neonatal short term complications, including neonatal hypoglycemia, neonatal pneumonia, neonatal sepsis, necrotizing enterocolitis of newborn, neonatal intracranial hemorrhage, and hypoxic-ischemic encephalopathy. Although some studies reported that administration of ACS in the late preterm period could decrease the incidence of NRDS or respiratory disease [8, 9], the sample sizes in those studies were smaller, some of these studies only used single factor analysis, and some of them did not consider the influence of asphyxia and neonatal hypoglycemia on the incidence of NRDS [9]. There is a prospective study concerning ACS treatment in the late preterm period that compares neonatal primary outcomes with and without ACS treatment, and includes NRDS, neonatal sepsis, respiratory morbidity, neonatal death, and neonatal hypoglycemia. It was found that ACS treatment could increase the incidence of neonatal hypoglycemia and neonatal sepsis [11]. Another RCT study found that use of ACS for pregnant women who gave birth at 34 (0/7) to 36 (6/7) gestation could increase the incidence of neonatal hypoglycemia [8]. However, there were only 74 pregnant women in the ACS group in the first study. Moreover, they did not consider the influence of birth weight of preterm infants on neonatal hypoglycemia, and asphyxia was not included in the study. In our study, ACS treatment for pregnant women at high risk of giving birth between 34 (0/7) to

36(6/7) gestation did not increase the risk of neonatal hypoglycemia and neonatal sepsis after controlling for other confounders and interactions between diseases. A large randomized trial study concerning ACS treatment, involving 1427 ACS-treated and 1400 placebo-treated pregnant women who gave birth at 34 (0/7) to 36 (6/7) gestation, found use of ACS for pregnant women, could decrease the incidence of severe respiratory complications of preterm infants, but had no influence on the use of mechanical ventilation for preterm infants and the incidence of neonatal sepsis. The above findings are consistent with our research [8, 10].

Maternal ACS treatment for pregnant women who gave birth at 34 (0/7) to 36(6/7) gestation is still controversial. The Society for Maternal-Fetal Medicine recommends ACS treatment, for women with a singleton pregnancy between 34 (0/7) to 36 (6/7) weeks gestation at high risk for giving birth, to decrease incidence of NRDS and use of mechanical ventilation for preterm infants [22]. The American College of Obstetricians and Gynecologists recommends a single course of betamethasone for pregnant women between 34 (0/7) to 36 (6/7) weeks of gestation, and at risk of giving birth within 7 days, who had not received a previous course of ACS treatment [23]. The Society of Obstetricians and Gynecologists of Canada suggests that possible neonatal benefit should be weighed against possible long-term harm when considering ACS at 35 to 36 weeks gestation [24]. In this cohort study, we found maternal ACS can decrease the incidence of NRDS, length of neonatal hospital stay, and neonatal hospital expenses. Although neonatal hospital stay and neonatal hospital expenses in the ACS group were higher than the without-ACS group, the ACS group had a higher cesarean section rate, a higher incidence of PROM, a lower gestational age of preterm, and a lower body weight of preterm infants, which may be the reason for the increased hospitalization time and hospitalization cost for the preterm infants. We then used linear regression to correct the effect of the above patient characteristics on the hospitalization time and hospitalization cost in the ACS group and without ACS group. The results showed that neonatal hospital stay and neonatal hospital expenses for the ACS group were lower than for the without-ACS group after controlling for the confounding factors. Moreover, we found use of ACS treatment for pregnant women who gave between 34 (0/7) to 36(6/7) gestation does not increase the risk of neonatal pneumonia, neonatal hypoglycemia, neonatal sepsis, necrotizing enterocolitis of newborn, neonatal intracranial hemorrhage, and hypoxic-ischemic encephalopathy in preterm infants. Therefore, we believe that use of ACS for pregnant women giving birth at 34 to 36(6/7) gestation has more advantages than disadvantages. However, this is a cohort study, which may be inherent bias within group allocation.

Conclusion

In this study, we found use of ACS for pregnant women who gave birth at 34 (0/7) to 36(6/7) gestation, can reduce the incidence of NRDS, length of neonatal hospital stay, and neonatal hospital expenses, but has no adverse effect on the incidence of neonatal complications, which are the major risk factors for the long-term outcomes of preterm infants. Because the possible neonatal benefit of maternal ACS treatment could weigh against the possible long-term harm for preterm infants, we suggest that pregnant women with late preterm labor should undergo ACS treatment. Our study provides evidence-based medicine for

clinicians to make ACS choices for pregnant women with high risk of giving birth at 34 (0/7) to 36(6/7) gestation.

Abbreviations

ACS
antenatal corticosteroids; GDM:gestational diabetes mellitus; NRDS:neonatal respiratory distress; PROM:premature rupture of membranes.

Declarations

Ethics approval and consent of participate

The study protocol was approved by the research institute's committee of human research in the Second Affiliated Hospital of Shantou University Medical College (NO.2018-23) and abided by the standards of the Declaration of Helsinki. This is a retrospective cohort study. The data were anonymized in this study, so we did not use the consent to participate.

Consent for publication

Not applicable.

Availability of data and material

The data in this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in our study.

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Author contributions

ZMH performed statistical analysis and wrote the manuscripts. XCD, HLL, LLX, and BWL collected the data of mother. JHY and XML collected the data of preterm infants. PSC and YJH contributed in

experiment design and reviewing the final manuscripts. The author read and approved the final manuscripts.

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References

1. Liu L, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. The Lancet. 2012;379(9832):2151–61. doi:10.1016/S0140-6736(12)60560-1.
2. Blencowe H, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet. 2012;379(9832):2162–72. doi:10.1016/S0140-6736(12)60820-4.
3. Russell Rebecca B, Green Nancy S, Steiner Claudia A, et al. Cost of hospitalization for preterm and low birth weight infants in the United States.[J].Pediatrics, 2007, 120: e1-9.doi: 10.1542/peds.2006-2386.
4. Consortium on Safe Labor,Hibbard Judith U,Wilkins Isabelle et al. Respiratory morbidity in late preterm births[J]JAMA. 2010;304:419 – 25. doi:10.1001/jama.2010.1015.
5. Petrini Joann R, Dias Todd,McCormick Marie C, et al. Increased risk of adverse neurological development for late preterm infants.[. J]J Pediatr. 2009;154:169 – 76. doi:10.1016/j.jpeds.2008.08.020.
6. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes.[J].JAMA, 1995, 273: 413–8.doi: 10.1001/jama.1995.03520290065031.
7. Shanks AL, et al. Controversies in antenatal corticosteroids. Semin Fetal Neonatal Med. 2019;24(3):182–8. doi:10.1016/j.siny.2019.05.002.
8. Gyamfi-Bannerman C, et al. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016;374(14):1311–20. doi:10.1056/NEJMc1605902.
9. Balci O, et al. The Effect of Antenatal Steroids on Fetal Lung Maturation between the 34th and 36th Week of Pregnancy. Gynecol Obstet Invest. 2010;70(2):95–9. doi:10.1159/000295898.
10. Gyamfi-Bannerman C, et al. Cost-effectiveness of Antenatal Corticosteroid Therapy vs No Therapy in Women at Risk of Late Preterm Delivery: A Secondary Analysis of a Randomized Clinical Trial. JAMA Pediatr. 2019;173(5):462–8. doi:10.1001/jamapediatrics.2019.0032.
11. Ramadan MK, et al. Antenatal corticosteroids in the late preterm period: A prospective cohort study. J Neonatal Perinatal Med. 2016;9(1):15–22. doi:10.3233/NPM-16915086.
12. Porto AM, et al. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ. 2011;342:d1696. doi:10.1136/bmj.d1696.

13. Huddleston JF, Sanchez-Ramos L, Huddleston KW. Acute management of preterm labor. Clin Perinatol. 2003;30(4):803–24. doi:10.1016/s0095-5108(03)00114-3.
14. Arya VB, Senniappan S. Maria Guemes… Neonatal Hypoglycemia[J]. Indian J Pediatr. 2014;81(1):58–65. doi:10.1007/s12098-013-1135-3.
15. Sweet DG, et al. European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update. Neonatology. 2013;103(4):353–68. doi:10.1136/archdischild-2014-306642.
16. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. The Lancet. 2017;390(10104):1770–80. doi:10.1016/S0140-6736(17)31002-4.
17. Berman Loren, Moss R, Lawrence. Necrotizing enterocolitis: an update.[J]. Semin Fetal Neonatal Med. 2011;16:145 – 50. doi:10.1016/j.siny.2011.02.002.
18. Duke T. Neonatal pneumonia in developing countries. Archives of Disease in Childhood - Fetal and Neonatal Edition, 2005. 90(3): p. F211-f219.doi: 10.1136/adc.2003.048108.
19. Fink S. Intraventricular Hemorrhage in the Term Infant[J]. Neonatal Network the Journal of Neonatal Nursing. 2000;19(7):13–8. 10.1891/0730-0832.19.7.13.
20. Lobmaier SM, Müller A. Huhn E, et al. HYPOXIC-ISCHEMIC ENCEPHALOPATHY[J]. Am J Perinatol. 2000;17(03):113–20. 10.1055/s-2000-9293.
21. 10.1155/2017/4827171
Salleh FHM, Zainudin S, Arif SM, Multiple Linear Regression for Reconstruction of Gene Regulatory Networks in Solving Cascade Error Problems. Advances in Bioinformatics, 2017. 2017: p. 1–14.doi: 10.1155/2017/4827171.
22. Implementation of the use. of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. Am J Obstet Gynecol, 2016. 215(2): p. B13-B15.doi:10.1016/j.ajog.2016.03.013.
23. Committee Opinion No
713 Summary: Antenatal Corticosteroid Therapy for Fetal Maturation.[
10.1097/AOG.0000000000002231
Committee Opinion No. 713 Summary: Antenatal Corticosteroid Therapy for Fetal Maturation. [J]Obstet Gynecol, 2017, 130: 493–4.doi:10.1097/AOG.0000000000002231.
24. Skoll A, et al. No. 364-Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes. J Obstet Gynaecol Can. 2018;40(9):1219–39. doi:10.1016/j.jogc.2018.04.018.