Time interval from late preterm antenatal corticosteroid administration to delivery and the impact on neonatal outcomes

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BACKGROUND: Although administration of antenatal corticosteroids has been shown to decrease neonatal respiratory morbidity when given to women at risk for late preterm birth, the time interval from antenatal corticosteroid administration to delivery that is associated with the greatest neonatal benefit remains unknown.

OBJECTIVE: This study aimed to evaluate whether the time interval from administration of late preterm antenatal corticosteroids to delivery is associated with a change in the likelihood of transient tachypnea of the newborn, respiratory distress syndrome, and hypoglycemia.

STUDY DESIGN: This was a retrospective cohort study of all singleton neonates who were exposed to 1 or 2 doses of antenatal corticosteroids in the late preterm period (34+0 to 36+6 weeks' gestation) within a large healthcare system between November 2017 and March 2020. Neonates exposed to antenatal corticosteroids before 34 weeks' gestation and those with major fetal structural malformations and chromosomal disorders were excluded. Cases were stratified into the following groups based on the time interval from the first dose of antenatal corticosteroid administration to delivery: <2 days, 2 to 7 days, and >7 days. The primary outcome of transient tachypnea of the newborn was compared among the 3 groups. Secondary outcomes included respiratory distress syndrome and hypoglycemia. A multivariable logistic regression was performed to evaluate the association between the time interval and neonatal outcomes while adjusting for potential confounders. For each outcome, delivery within 2 to 7 days from the first dose of betamethasone administration was defined as the reference group. Data were presented as adjusted odds ratios with 95% confidence intervals, and statistical significance was defined as $P < .05$.

RESULTS: The study cohort comprised 1248 neonates. Of those, 649 (52%) were exposed to 1 dose of antenatal corticosteroids. There were statistically significant differences in the maternal characteristics such as nulliparity, pregnancies complicated by hypertensive disorders and fetal growth restriction, gestational age at antenatal corticosteroid administration, gestational age at delivery, and mode of delivery among the 3 groups. There was a significantly increased risk for transient tachypnea of the newborn (adjusted odds ratio, 4.81; 95% confidence interval, 1.72–12.92) and respiratory distress syndrome (adjusted odds ratio, 9.86; 95% confidence interval, 1.15–84.24) associated with delivery <2 days of antenatal corticosteroid administration. The risk for hypoglycemia was highest in the delivery <2 days group (adjusted odds ratio, 3.44; 95% confidence interval, 2.10–5.63) and decreased as the time interval from antenatal corticosteroid administration to delivery increased (adjusted odds ratio, 0.32; 95% confidence interval, 0.20–0.51 for delivery >7 days).

CONCLUSION: Adverse neonatal outcomes such as transient tachypnea of the newborn, respiratory distress syndrome, and hypoglycemia are more common when late preterm birth occurs <2 days after antenatal corticosteroid administration when compared with birth 2 to 7 days after administration. In addition, delivery >7 days after antenatal corticosteroid administration is associated with a decreased risk for hypoglycemia. Understanding the impact of antenatal corticosteroid timing on neonatal outcomes is essential in caring for patients at risk for late preterm birth.

Key words: corticosteroids, hypoglycemia, late preterm birth, neonatal morbidity, preterm birth, respiratory distress syndrome, transient tachypnea of the newborn

Introduction

Despite advancements in the management of preterm neonates, preterm birth remains the leading cause of neonatal morbidity and mortality in the United States.[1–4] Recently, particular attention has been focused on investigating management strategies for optimizing care of neonates born in the late preterm period, defined as 34 to 36 weeks plus 6 days' gestation. The neonates born during this period represent the majority of preterm births and an increased risk for common prematurity-related complications such as hypoglycemia, hyperbilirubinemia, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), and sepsis have been observed despite the near-term gestational ages of the neonates.[5–14]

Antenatal corticosteroids have long been considered 1 of the most important interventions available for women at risk for imminent preterm birth based on the associated improved neonatal outcomes following their administration.[15–18] The timing of administration is key, and the benefit of antenatal corticosteroids is highest when delivery occurs within 2 to 7 days of administration.[18] Given the unpredictable nature of preterm birth, optimal timing of this intervention remains challenging in clinical practice. For example, suboptimal timing of antenatal corticosteroid administration has been demonstrated in women at risk for both spontaneous and medically indicated preterm birth before to 34 weeks' gestation.[19–21]

Recent recommendations have expanded the indication for antenatal corticosteroid administration to include women at risk for late preterm birth

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AJOG MFM at a Glance

Why was this study conducted?

Data collected from neonates born in the early preterm period suggest that the benefit of antenatal corticosteroids is greatest among those delivered 2 to 7 days after the initial dose. We set out to evaluate the impact of the time interval from late preterm antenatal corticosteroid administration to delivery on adverse neonatal outcomes.

Key findings

Neonates born within the first 2 days after late preterm antenatal corticosteroid administration were more likely to develop transient tachypnea of the newborn and respiratory distress syndrome than those born between 2 and 7 days after administration. Hypoglycemia was more likely to be present in neonates born within the first 2 days after administration of late preterm antenatal corticosteroids and the incidence thereof decreased as the time interval from antenatal corticosteroid administration to delivery increased.

What does this add to what is known?

A better understanding of the impact that appropriately timed late preterm antenatal corticosteroid administration has on neonatal outcomes is essential and may potentially improve neonatal outcomes in this select population.

based on the results of a large, multiple center randomized trial.[17,18,22] The authors demonstrated a reduction in several neonatal respiratory complications in singleton pregnancies when antenatal corticosteroids were administered to women at risk for late preterm birth.[22] These benefits were found despite 40% of the study participants being delivered before the administration of the second dose. In addition, neonatal hypoglycemia was more common in neonates exposed to antenatal corticosteroids. Although administration of antenatal corticosteroids before late preterm birth has been shown to decrease neonatal respiratory morbidity,[22] the time interval from late preterm antenatal corticosteroid administration to delivery that is associated with the greatest neonatal benefit remains unknown. Therefore, we set out to evaluate whether the time interval from late preterm antenatal corticosteroid administration to delivery is associated with a change in the likelihood of TTN, RDS, and hypoglycemia.

Materials and Methods

This was a retrospective cohort study of all singleton neonates who were exposed to 1 or 2 doses of antenatal corticosteroids in the late preterm period (34+0 to 36+6 weeks of gestation) within a multicenter healthcare system between November 2017 and March 2020. Exclusion criteria included newborn exposure to antenatal corticosteroids before 34+0 weeks of gestation, major fetal structural malformations (diagnosed in the antenatal or postnatal period) and confirmed chromosomal disorders (in the antenatal or postnatal period). Cases were stratified into the following 3 groups based on the time interval from the first dose of antenatal corticosteroid administration to delivery: <2 days, 2 to 7 days, and >7 days.

The primary outcome of TTN was compared among the 3 groups. Secondary outcomes included RDS and hypoglycemia. At our institution, TTN and RDS are diagnosed clinically by neonatologists based on guidelines from the American Academy of Pediatrics.[23,24] The diagnostic criteria for each adverse neonatal outcome is described in Table 1. All neonates diagnosed with hypoglycemia were subsequently treated using a regimen that included dextrose therapy and surveillance. We performed a detailed review of newborn medical records to confirm the clinical diagnosis of each adverse neonatal outcome.

Newborn exposure to antenatal corticosteroids was defined as the administration of at least 1 of the 2 doses of 12 mg betamethasone (Celestone Soluspan [betamethasone sodium phosphate and betamethasone acetate], American Regent, Shirley, NY), given intramuscularly 24 hours apart, as part of an antenatal corticosteroid course. This was

TABLE 1
Diagnostic criteria for each adverse neonatal outcome

Neonatal outcome	Diagnostic criteria
Transient tachypnea of the newborn	Tachypnea and increased work of breathing, which persists for 24–72 h, with or without chest radiography revealing prominent perihilar streaking, increased interstitial markings and fluid in the interlobar fissures.[23,24]
Respiratory distress syndrome	Marked respiratory distress (tachypnea, nasal flaring, grunting, and subcostal, intercostal and suprasternal retractions), requiring supplemental oxygen and chest radiography showing diffuse microatelectasis with resultant diminished overall lung volume or air bronchograms.[23,24]
Hypoglycemia	Serum glucose value of ≤45 mg/dL at routine screening (approximately 1 h of age) or within the first 24 h of life.

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administered to women with a singleton pregnancy in the late preterm period who were considered at high risk for preterm birth within the next 7 days. The guidelines outlining suggested criteria for the administration of antenatal corticosteroids in women at risk for late preterm birth were uniform at all participating sites and consistent with the published recommendations.[18,22] However, the decision to administer antenatal corticosteroids was ultimately left to the discretion of the obstetrician, with maternal-fetal medicine consultation available as needed.

Maternal characteristics such as age, body mass index (BMI), race and ethnicity, parity, gestational age at antenatal corticosteroid administration, gestational age at delivery, and mode of delivery were collected from review of medical records, and data regarding the presence or absence of various pregnancy-related complications and risk factors for preterm birth (ie, hypertensive disorders of pregnancy, fetal growth restriction, gestational diabetes) were also collected.

Statistical analysis included the use of Pearson's chi-square tests with statistical significance set at $P<.05$. Multivariable logistic regression analysis was performed to evaluate the association between the time interval and neonatal outcomes while adjusting for potential confounders such as nulliparity, hypertensive disorders of pregnancy, fetal growth restriction, gestational diabetes, number of antenatal corticosteroid doses (1 or 2), gestational age at first dose of antenatal corticosteroid administration (examined as continuous variables), and mode of delivery. For each outcome, delivery within 2 to 7 days from the first dose of betamethasone administration was defined as the reference group. We considered 2 to 7 days from administration of antenatal corticosteroids to late preterm birth as an optimal time interval based on data on the use of antenatal corticosteroids in women with preterm births before 34 weeks' gestation,[25] suggesting that neonatal benefit may diminish with a latency period of >7 days.[26−30] Data were presented as adjusted odds ratios (aORs) with 95% confidence intervals (95% CIs). An institutional review board approval was obtained.

Results

During the study period, there were a total of 1272 singleton neonates who were exposed to at least 1 of the 2 doses of antenatal corticosteroids in the late preterm period. Neonates exposed to antenatal corticosteroids before the late preterm period in the same pregnancy (n=5) or those with major fetal structural malformations (n=13) or confirmed chromosomal disorders (n=6) were excluded. After applying our exclusion criteria, the study cohort comprised 1248 neonates and were further analyzed. Of those, 772 (61.8%) delivered within 2 days of antenatal corticosteroid administration, 168 (13.5%) delivered within 2 to 7 days after antenatal corticosteroid administration, and 308 (24.7) delivered more than 7 days after antenatal corticosteroid administration. There were statistically significant differences in the maternal characteristics such as nulliparity, pregnancies complicated by hypertensive disorders and fetal growth restriction, gestational age at antenatal corticosteroid administration, gestational age at delivery, and mode of delivery among the 3 groups (Table 2). Maternal age, BMI, race and ethnicity, and prevalence of gestational diabetes were similar among the 3 groups (Table 2).

The baseline incidences of TTN, RDS, and hypoglycemia were 9.1% (113 of 1248), 6.2% (77 of 1248), and 39.3% (491 of 1248), respectively. Multivariable analysis showed a significantly increased risk for TTN (aOR, 4.81; 95% CI, 1.72−12.92) and RDS (aOR, 9.86; 95% CI, 1.15−84.24) associated with delivery within 2 days of antenatal corticosteroid administration when compared with delivery between 2 to 7 days after antenatal corticosteroid administration (Table 3). The associated risk for hypoglycemia was highest when delivery occurred within 2 days after antenatal corticosteroid administration (aOR, 3.44; 95% CI, 2.10−5.63) and decreased as the time interval from antenatal corticosteroid administration to delivery increased (aOR, 0.32; 95% CI, 0.20 −0.51 when delivery occurred >7 days after administration) (Table 3).

Of the 1248 neonates in our cohort, 649 (52%) were exposed to 1 dose of antenatal corticosteroids and 599 (48%) were exposed to 2 doses of antenatal corticosteroids. The incidences of TTN, RDS, and hypoglycemia were significantly higher among neonates exposed to only 1 dose of antenatal corticosteroids than among those exposed to 2 doses (Table 4). A comparison of neonatal outcomes by gestational age at first dose of antenatal corticosteroid administration is displayed in Table 5. The incidences of TTN and RDS were significantly lower as the gestational age at corticosteroid administration increased, whereas the incidences of hypoglycemia were similar among the 3 groups (Table 5).

Of the 772 neonates who were delivered within 2 days of antenatal corticosteroid administration, 642 were delivered within 24 hours and 130 were delivered between 24 and 48 hours after administration. The incidence of TTN was similar between the 2 groups (Table 6). The incidence of RDS was significantly higher (10.6% vs 4.6%; $P=.04$) among neonates who were delivered within 24 hours of antenatal corticosteroid administration than among those who were delivered between 24 and 48 hours after administration, whereas the incidence of hypoglycemia was significantly lower (46.3% vs 66.2%; $P=<.001$) among neonates who were delivered within 24 hours of antenatal corticosteroid administration than among those who were delivered between 24 and 48 hours after administration (Table 6).

Discussion

Principal findings

Neonates born within the first 2 days after late preterm antenatal corticosteroid administration were more likely to develop TTN, RDS, and hypoglycemia than those born between 2 to 7 days after administration. Furthermore, the likelihood of hypoglycemia decreased as time interval to delivery increased.

Results

The association between the time interval from antenatal corticosteroid

TABLE 2
Baseline maternal characteristics compared among the 3 groups

Characteristic	Delivered <2 d after ACS administration (n=772)	Delivered 2−7 d after ACS administration (n=168)	Delivered >7 d after ACS administration (n=308)	*P* value
Maternal age (y), mean±SD	32.8±0.19	33.4±0.43	33±0.29	.34
BMI (kg/m^2), mean±SD	30.8±0.22	31.2±0.52	30.7±0.34	.71
Race or ethnic group, n (%)				
Non-Hispanic White	278 (36)	61 (36.3)	143 (46.4)	.11
Non-Hispanic Black	140 (18.1)	35 (20.8)	46 (14.9)	
Hispanic	92 (11.9)	22 (13.1)	40 (13)	
Asian	135 (17.5)	27 (16.1)	46 (14.9)	
Other	81 (10.5)	13 (7.7)	22 (7.1)	
Unknown	46 (6)	10 (6)	11 (3.6)	
Nulliparity, n (%)	389 (50.4)	94 (56)	128 (41.6)	.005
Hypertensive disorder of pregnancy, n (%)	171 (22.2)	66 (39.3)	79 (25.6)	<.001
Intrauterine growth restriction, n (%)	34 (4.4)	18 (10.7)	22 (7.1)	.004
Gestational diabetes, n (%)	73 (9.5)	17 (10.1)	25 (8.1)	.72
Gestational age at ACS administration (wk), mean±SD	35.6±0.03	35.6±0.06	35.1±0.04	<.001
Gestational age at delivery (wk), mean±SD	35.7±0.03	36.2±0.06	38±0.07	<.001
Vaginal delivery, n (%)	460 (59.6)	76 (45.2)	201 (65.3)	<.001

ACS, antenatal corticosteroids; *BMI*, body mass index; *SD*, standard deviation.

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administration to delivery during early preterm birth (between 24 and 34 weeks of gestation) and adverse neonatal outcomes is well known.[18] Several contemporary studies have validated the initial observations described by Liggins and Howie in 1972 and demonstrated the transient effect of corticosteroids with their effectiveness most often limited to when administered within 7 days before birth.[16,25−30] Moreover, translational studies have also reported the time-dependent effectiveness of corticosteroid treatment on lung function, illustrating the importance of timing in application of this intervention.[31,32]

The impact of the time interval from late preterm corticosteroid administration to delivery on adverse neonatal outcomes, however, is unknown. This likely reflects the fact that administration of late preterm corticosteroids has only recently become widely adopted in clinical practice. In the randomized trial by Gyamfi-Bannerman et al[22] who evaluated the efficacy of late preterm corticosteroid administration in women at risk for late preterm birth, several respiratory complications including TTN were found to occur significantly less frequently in neonates exposed to antenatal corticosteroids than to a placebo. These benefits were observed despite administration of the full antenatal corticosteroid course to only 60% of the study participants and a median time interval from administration of corticosteroids to delivery of 33 hours.[22] The incidences of TTN, RDS, and hypoglycemia in neonates unexposed to corticosteroids in their trial were 9.9%, 6.4%, and 15%, respectively.[22] Furthermore, the reduced incidence of TTN in neonates exposed to corticosteroids in their trial was similar to the incidence reported in our cohort.[22] The association between the time interval from corticosteroid administration to delivery and neonatal complications was not evaluated in the trial, thus it remained unclear which time interval imparted the greatest benefit to the neonates. Our findings point to an increased likelihood of TTN in neonates born within 2 days of administration of late preterm antenatal corticosteroid than in those born between 2 and 7 days after administration, suggesting that birth between 2 and 7 days after administration may be an optimal time interval in the late preterm period as well. In a recent retrospective cohort of 216 neonates exposed to antenatal dexamethasone who were delivered from 23+5 to 36+6 weeks' gestation, Lau et al[33] reported that neonates born beyond 7 days after antenatal corticosteroid administration were significantly more likely to develop RDS than those born within 7 days (aOR, 7.02; 95% CI, 1.54−32.07).[33] Drawing conclusions when comparing the study by Lau et al[33] with ours is challenging because of the wide range of gestational ages and

TABLE 3
Association between time interval from antenatal corticosteroid administration and adverse neonatal outcomes

Outcome	Raten/N (%)	Adjusted OR (95% CI)	*P* value
Transient tachypnea of the newborn			
<2 d after ACS	97/772 (12.6)	4.81 (1.79−12.92)	.002
2−7 d after ACS	6/168 (3.6)	Ref	−−
>7 d after ACS	10/308 (3.2)	0.85 (0.30−2.45)	.8
Respiratory distress syndrome			
<2 d after ACS	74/772 (9.6)	9.86 (1.15−84.24)	.04
2−7 d after ACS	1/168 (0.6)	Ref	−−
>7 d after ACS	2/308 (0.6)	0.85 (0.08−9.56)	.9
Hypoglycemia			
<2 d after ACS	383/772 (49.6)	3.44 (2.10−5.63)	<.001
2−7 d after ACS	61/168 (36.3)	Ref	−−
>7 d after ACS	47/308 (15.3)	0.32 (0.20−0.51)	<.001

Odds ratios adjusted for nulliparity, hypertensive disorder of pregnancy, fetal growth restriction, gestational diabetes, number of ACS doses (1 or 2), gestational age at first dose of antenatal corticosteroid administration (as continuous variable), and mode of delivery.

ACS, antenatal corticosteroids; *CI*, confidence interval; *OR*, odds ratio; *Ref*, reference.

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corticosteroid types used in their cohort. Respiratory complications such as RDS are known to be more common after birth in the early preterm period and decrease as gestational age increases.[5]

Of note, the rate of neonatal hypoglycemia was significantly higher in the neonates exposed to antenatal corticosteroids (24% vs 15%; relative risk, 1.60; 95% CI, 1.37−1.87) in the study by Gyamfi-Bannerman et al.[22] The authors, however, reported no adverse events related to hypoglycemia.[22] The higher rate of hypoglycemia in our cohort (39%) was likely because of the lower threshold for diagnosis at our institution (45 mg/dL vs 40 mg/dL in the former study). The increased likelihood of hypoglycemia associated with late preterm antenatal corticosteroids was also reported in a recent study by Badreldin et al[34] who evaluated institutional adherence to late preterm corticosteroid administration and its impact on neonatal outcomes. To investigate whether this risk was associated with the time interval from corticosteroid administration to delivery, di Pasquo et al[35] performed a retrospective cohort study of 99 neonates exposed to antenatal corticosteroids before birth. They reported no association between the time interval from corticosteroid administration to delivery and the likelihood of neonatal hypoglycemia.[35] Notable differences in study design, which included their incorporation of neonates from a gestational age range of 24 weeks to 37 weeks and 6 days' gestation and evaluating time interval as a continuous variable, and the much smaller sample size likely contributed to their negative finding.[35] Although we observed an increased likelihood of neonatal hypoglycemia among neonates born within 2 days of late preterm antenatal corticosteroid administration, the effect was transient and diminished as the time interval from antenatal corticosteroid adminsitration to delivery increased.

Clinical implications

There are several clinical implications related to our findings. Our study highlights the importance of timing antenatal corticosteroid administration appropriately to optimize the neonatal benefit. The pharmacokinetic properties of corticosteroids, which have been demonstrated in basic science and animal studies, their known impact on lung maturation and function, and the metabolic changes that follow are mechanisms that likely contributed to our outcomes.[31,32,36−38] For example, serum evaluations of betamethasone in nonpregnant and pregnant women have demonstrated maternal hyperglycemia for up to 2 days after administration following prolonged exposure and detectable betamethasone levels in umbilical cord blood for at least a week after administration, which may impact the

TABLE 4
Comparison of neonatal outcomes between newborns exposed to 1 dose and 2 doses of antenatal corticosteroids

Neonatal outcome	Exposed to 1 dose of ACS(n=649)	Exposed to 2 doses of ACS(n=599)	*P* value
Transient tachypnea of the newborn, n (%)	80 (12.3)	33 (5.5)	<.001
Respiratory distress syndrome, n (%)	68 (10.5)	9 (1.5)	<.001
Hypoglycemia, n (%)	301 (46.4)	190 (31.7)	<.001

ACS, antenatal corticosteroids.

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TABLE 5
Comparison of neonatal outcomes by gestational age of antenatal corticosteroid administration

Neonatal outcome	Exposed to ACS from 34+0 to 34+6 wk of gestation(n=345)	Exposed to ACS from 35+0 to 35+6 wk of gestation(n=492)	Exposed to ACS from 36+0 to 36+6(n=411)	*P* value
Transient tachypnea of the newborn, n (%)	46 (13.3)	44 (8.9)	23 (5.6)	.001
Respiratory distress syndrome, n (%)	32 (9.3)	37 (7.5)	8 (1.9)	<.001
Hypoglycemia, n (%)	125 (36.2)	191 (38.8)	175 (42.6)	.2

ACS, antenatal corticosteroids.

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timing of neonatal hypoglycemia.[39,40] Suboptimal timing of corticosteroid administration in women at risk for preterm birth has been demonstrated to occur at high rates in women at risk for spontaneous and medically indicated preterm birth.[19–21] Thus, studies to better identify the appropriate patient population to maximize neonatal benefit from corticosteroid administration are needed. Our findings demonstrate that the risk for adverse neonatal outcomes such as TTN, RDS, and hypoglycemia is highest when late preterm birth occurs within the first 2 days of antenatal corticosteroid administration, irrespective of gestational age at corticosteroid administration. These implications are beneficial for obstetricians to optimally time the administration of late preterm antenatal corticosteroids and for neonatologists because these neonates can benefit from heightened respiratory surveillance and monitoring of blood glucose levels.

Research implications

Although our findings support the conclusion that antenatal corticosteroid administration between 2 and 7 days before late preterm birth is the optimal time interval for reducing the risk of TTN and RDS, future studies with large population cohorts may provide further confirmation of these results and determine whether the 2 to 7 day interval indeed also carries the greatest benefit with regards to other adverse neonatal outcomes in this select population. Furthermore, our results should not be interpreted as a recommendation to delay delivery to at least 2 days after late preterm corticosteroid administration. Given the multiple etiologies for late preterm birth (ie, spontaneous labor, preterm premature rupture of membranes, and medically indicated maternal or fetal conditions) and the complexity of weighing the maternal and fetal risks associated with delaying delivery against the benefits of improved neonatal outcomes, such decisions should be individualized and were not directly evaluated in this study.

Strengths and limitations

There are several strengths to this study. We address an important and understudied topic by evaluating the association between different time intervals from administration of late preterm corticosteroid to delivery and adverse neonatal outcomes. This intervention is now recommended as a standard of care for women at risk for late preterm birth in the United States and is widely incorporated into clinical practice.[18] Our sample size, which included nearly 1250 neonates from singleton pregnancies exposed to antenatal corticosteroids in the late preterm period, is among the largest reported in literature. Our multicenter cohort is also derived from a diverse New York urban population in

TABLE 6
Comparison of neonatal outcomes between newborns delivered within 24 hours and those delivery between 24 and 48 hours after late preterm antenatal corticosteroid administration

Neonatal outcome	Delivered <24 h after ACS administration (n=642)	Delivered 24–48 h after ACS administration(n=130)	*P* value
Transient tachypnea of the newborn, n (%)	78 (12.1)	19 (14.6)	.4
Respiratory distress syndrome, n (%)	68 (10.6)	6 (4.6)	.04
Hypoglycemia, n (%)	297 (46.3)	86 (66.2)	<.001

ACS, antenatal corticosteroids.

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terms of maternal demographics, which makes our findings more generalizable.

This study also has several limitations. Given the retrospective nature of our analysis, data regarding the neonatal outcomes of TTN and RDS were derived from chart review and clinical diagnoses of neonatologists. However, the clinical criteria for a diagnosis are uniform and homogenous within our healthcare system, and the incidence of each respiratory outcome was similar to previous literature in which neonates exposed to late preterm antenatal corticosteroids were evaluated.[22] Although adjusted for in our multivariable analyses, there were some significant differences in the maternal characteristics among the 3 study groups, including rates of hypertensive disorders, nulliparity, and mode of delivery, which have been independently associated with adverse neonatal outcomes and may have contributed to our findings. In addition, it may be challenging to elucidate the mechanism for the associations observed in this study. For example, it is possible that some of the associations may have been simply caused by differences in gestational age at delivery rather than the effect of corticosteroid timing. Finally, we do not have data on subsequent neonatal blood glucose levels over time or whether neonates diagnosed with hypoglycemia had any related adverse events. Nevertheless, it has suggested that hypoglycemia is a common and usually self-limiting condition in late preterm neonates.[22]

Conclusions

We have demonstrated that the likelihood of TTN and RDS was increased in neonates born within 2 days of late preterm antenatal corticosteroid administration than in those born between 2 and 7 days after administration. Moreover, the likelihood of hypoglycemia was highest among neonates born within the first 2 days of corticosteroid administration and diminished as the time interval to delivery increased. Predicting preterm birth continues to be challenging in both spontaneous and medically indicated preterm deliveries and thus the administration of antenatal corticosteroids has most commonly been suboptimal.[19–21] Nevertheless, an understanding of the impact of antenatal corticosteroid timing on neonatal outcomes is essential and has the potential to optimize neonatal surveillance and ultimately improve neonatal outcomes in this select population. ■

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