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Practice patterns in the administration of late preterm antenatal corticosteroids

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Condensation

Delivery between 2-7 days after late preterm antenatal corticosteroid administration was more likely in women at risk for medically indicated compared to spontaneous preterm birth.

Short Title

Practice patterns of late preterm antenatal corticosteroids

AJOG at a Glance

A. Why was this study conducted?

- Data from neonates born in the early preterm period suggest that administration of antenatal corticosteroids between 2-7 days prior to delivery is optimal. We set out to evaluate the likelihood of delivery between 2-7 days after late preterm antenatal corticosteroid administration, and whether this differs based on indication for corticosteroid administration.

B. What are the key findings?

- Regardless of the indication for late preterm antenatal corticosteroid administration, the likelihood of delivery between 2-7 days later is low, as only 13.3% of our study cohort delivered between that time interval.
- Delivery between 2-7 days after late preterm antenatal corticosteroid administration was more likely in women at risk for medically indicated late preterm birth compared to spontaneous late preterm birth.

C. What does this study add to what is already known?

- Current practice patterns of late preterm antenatal corticosteroids suggest that delivery between the desired time interval of administration (2-7 days) is more common in women at risk for medically indicated preterm birth compared to those at risk for spontaneous preterm birth.

Keywords: preterm birth, late preterm birth, spontaneous preterm birth, medically indicated preterm birth, corticosteroids, betamethasone, optimal timing, time interval

Abstract

Background: Given the unpredictable nature of preterm birth and the short-term impact of antenatal corticosteroids on neonatal outcomes, optimal timing of antenatal corticosteroid administration (2-7 days from expected birth) remains challenging.

Objective: We set out to evaluate the likelihood of delivery between 2-7 days after antenatal corticosteroid administration in the late preterm period, and whether this differs based on indication for corticosteroid administration.

Study Design: Retrospective cohort of all singletons that received antenatal corticosteroids in the late preterm period (34 0/7-36 6/7 weeks) and delivered within a large health system between November 2017 and March 2020. Women who received antenatal corticosteroids prior to the late preterm period, major fetal structural malformations, and cases with missing data were excluded. Cases were stratified based on the indication for antenatal corticosteroid administration i.e. anticipated spontaneous late preterm birth or medically indicated late preterm birth. The primary outcome was delivery between 2 and 7 days after administration of the first dose of antenatal corticosteroids. Secondary outcomes included time interval from antenatal corticosteroid administration to delivery, as well as delivery during the first 2 or later than 7 days after antenatal corticosteroid administration. Multivariable logistic regression was performed to evaluate factors associated with optimal timing, while adjusting for potential confounders.

Results: Of the 1,238 patients included, 656 (53%) delivered within the first day after antenatal corticosteroid administration and thus, received only the first of two doses. Regardless of the indication for late preterm antenatal corticosteroid administration, the likelihood of delivery between 2-7 days later was 13.3% (165/1,238). Moreover, it was more common (23.4% vs 5%, *P* = <0.001; Table 2), and more likely (adjusted OR 5.88, 95% CI 4-9.09) in women at risk for

medically indicated preterm birth compared to those with anticipated spontaneous preterm birth. Furthermore, women with anticipated spontaneous preterm birth had a shorter time interval from antenatal corticosteroid administration to delivery (10.7 hrs vs. 49.71 hrs, P = <0.001).

Conclusions: Regardless of the indication for late preterm antenatal corticosteroid administration, the likelihood of delivery between 2-7 days later is low. Nevertheless, our data suggest that delivery within the desired time interval of antenatal corticosteroid administration is more common in women at risk for medically indicated late preterm birth compared to those at risk for spontaneous late preterm birth.

Introduction

Late preterm birth, defined as birth between 34 0/7 and 36 6/7 weeks of gestation, accounts for over 70% of all preterm births in the United States.[1-3] While the majority of late preterm newborns appear well at birth, have short hospital stays, and favorable long-term outcomes, they are at increased risk of morbidity and mortality compared to their term counterparts.[4-11] With the recent reported rise in the United States preterm birth rate largely reflective of the increase in late preterm births,[1,2] and the known associated risk for adverse outcomes in this cohort,[4-11] management strategies have been investigated for women at risk for late preterm birth to reduce the likelihood of such adverse outcomes.[12-14]

Antenatal corticosteroid administration for pregnant women at risk for early preterm birth (24 0/7 to 33 6/7 weeks' gestation) represents one of the most important antenatal therapies available to improve neonatal outcomes.[15,16] When timed appropriately (delivery between 2 to 7 days after administration), antenatal corticosteroids have been associated with a significant reduction in neonatal morbidity and mortality in several randomized clinical trials.[16-23] A lack of supportive data and the underappreciated risks associated with late preterm infants had initially limited the recommendation of corticosteroid use to extend to women at risk for late preterm delivery.[18,24] However, in a recent multi-center, randomized, double-blind, placebo-controlled trial, antenatal corticosteroid administration (intended as 12 mg of betamethasone given 24 hours apart) was associated with a decrease in neonatal respiratory morbidities in singleton pregnancies at risk for late preterm birth.[14] These benefits were found despite the challenges in predicting the timing of delivery, which resulted in only 60% of the study participants receiving the full course of antenatal corticosteroids.[14]

Given the unpredictable nature of preterm birth and the short-term impact of antenatal corticosteroids on neonatal outcomes, optimal timing of antenatal corticosteroid administration remains challenging.[25-27] We set out to evaluate the likelihood of delivery between 2-7 days after antenatal corticosteroid administration in the late preterm period, and whether this differs based on indication for corticosteroid administration.

Materials and Methods

This was a retrospective cohort study of all women with singleton pregnancies who were prescribed antenatal corticosteroids in the late preterm period (34 0/7-36 6/7 weeks) and delivered within a multi-center health system between November 2017 and March 2020. Prior to the study period, our institutional guidelines suggested consideration for administration of antenatal corticosteroids, defined as two doses of betamethasone 12mg given intramuscularly 24 hours apart, in women with a singleton pregnancy in the late preterm period who were at high risk for preterm birth within the next 7 days. These guidelines also suggested that antenatal corticosteroids be avoided in women with chorioamnionitis, pregestational diabetes, those who received corticosteroids prior to the late preterm period in the same pregnancy, and that tocolysis should not be used to allow for corticosteroid administration. The decision to administer antenatal corticosteroids was left for the discretion of the obstetrician, with Maternal-Fetal Medicine consultation available as needed.

All women with singleton pregnancies who were prescribed antenatal corticosteroids during the late preterm period, and received at least one of the two doses were included. Exclusion criteria included administration of antenatal corticosteroids prior to the late preterm period in the same pregnancy, major fetal structural malformations, and cases with missing data regarding the

indication for antenatal corticosteroid administration. Maternal characteristics such as age, body mass index (BMI), race/ethnicity and parity were collected. In addition, a detailed review of each medical record was performed in order to obtain data regarding the presence or absence of pregnancy-related complications and/or risk factors for preterm birth, as well as the indication for antenatal corticosteroid administration.

Cases were stratified into two groups based on the indication for antenatal corticosteroid administration: either anticipated spontaneous late preterm birth (i.e. preterm labor with intact membranes based on evaluation by the managing obstetrician, which was suspected to result in preterm birth within the next 7 days, or preterm prelabor rupture of membranes) or medically indicated late preterm birth (i.e. hypertensive disorders of pregnancy, fetal growth restriction, oligohydramnios, intrahepatic cholestasis of pregnancy, non-reassuring fetal status, placental abruption, placenta previa, placenta accreta, vasa previa, or other [i.e. history of classical cesarean section or uterine rupture, poor maternal or obstetric history, alloimmunization]). The primary outcome was delivery between 2 and 7 days after the first dose of betamethasone administration. We considered 2-7 days as an optimal time interval, extrapolated from data on the use of antenatal corticosteroids in women with preterm birth < 34 weeks,[28] as corticosteroid administration is dosed on a 48-hour schedule, and neonatal benefit may diminish with a latency period > 7 days.[29-32] Secondary outcomes included time interval from antenatal corticosteroid administration to delivery, delivery prior to 2 or later than 7 days after antenatal corticosteroid administration, gestational age at delivery and delivery < 37 weeks. Demographic data, baseline characteristics, and outcome data were compared between the two groups using Chi-squared and Wilcoxon rank sum testing with statistical significance set at $P < 0.05$. Multivariable logistic regression was also performed to evaluate factors associated with optimal timing of antenatal

corticosteroid administration, while adjusting for potential confounders such as maternal age, race/ethnicity, BMI, parity, gestational age at antenatal corticosteroid administration, gestational diabetes, and history of preterm birth. Data were presented as adjusted Odds Ratios (aOR) with 95% confidence intervals (95% CI).

An institutional review board approval was obtained.

Results

During the study period, there were approximately 45,060 deliveries that took place at the study centers included. Our population included a total of 1,272 (2.8%) women with singleton gestations who were prescribed antenatal corticosteroids during the late preterm period and received at least one of the two doses of betamethasone. Women who received antenatal corticosteroids prior to the late preterm period in the same pregnancy (5), major fetal structural malformations (3), and cases with missing data regarding the indication for antenatal corticosteroid administration (26) were excluded. After applying our exclusion criteria, 1,238 patients comprised the study cohort and were further analyzed. Of those, 679 (54.8%) presented with anticipated spontaneous late preterm birth, whereas 559 (45.2%) were at risk for medically indicated late preterm birth. The distribution of the various indications for late preterm antenatal corticosteroid administration in each group is displayed in Table 1. Furthermore, of the 1,238 patients included, 656 (53%) delivered less than 24 hours from administration and thus, received only the first dose of betamethasone.

Women at risk for medically indicated late preterm birth had a higher mean maternal age (34 years vs. 32 years, $P = <0.001$) and BMI (31.4 kg/m^2 vs. 29 kg/m^2, $P = <0.001$), and were more likely to be of non-Hispanic black race and Hispanic ethnicity (20% vs. 15%, and 14.7% vs.

10.6%; *P* = <0.001), compared to women with anticipated spontaneous late preterm birth (Table 2). Women at risk for medically indicated late preterm birth also had higher rates of gestational diabetes (8.4% vs. 3.8%, *P* = 0.001) and prior pregnancy with medically indicated preterm birth (7.9% vs. 2.5%, *P* = <0.001), compared to women with anticipated spontaneous late preterm birth (Table 2). The median gestational age at antenatal corticosteroid administration was similar between the two groups (Table 2).

Regardless of the indication for late preterm antenatal corticosteroid administration, the likelihood of delivery between 2-7 days later was 13.3% (165/1,238). Moreover, delivery between 2-7 days after corticosteroid administration was more common in women at risk for medically indicated late preterm birth compared to anticipated spontaneous late preterm birth (23.4% vs 5%, *P* = <0.001; Table 3). The rate of delivery > 7 days after corticosteroid administration and median time interval from corticosteroid administration to delivery were higher in women at risk for medically indicated late preterm birth (28.6% vs. 19.7%, *P* = <0.001, and 49.7 hours vs. 10.7 hours, *P* = <0.001), while delivery prior to 2 days after corticosteroid administration and preterm birth < 37 weeks were more common in women at risk for spontaneous late preterm birth (75.3% vs. 47.9%, *P* = <0.001, and 80% vs. 69.8%, *P* = <0.001) (Table 3).

On multivariable analysis, the likelihood of delivery between 2-7 days after corticosteroid administration was significantly higher in women at risk for medically indicated late preterm birth compared to anticipated spontaneous late preterm birth (adjusted OR 5.88, 95% CI 4-9.09; Table 4). In addition, later gestational age at corticosteroid administration, within the late preterm period, was associated with an increased likelihood of optimal timing (aOR 1.33, 95% CI 1.06-1.68; Table 4).

Discussion

Principal Findings

The results of our study illustrate two main findings. First, the likelihood of delivery between 2-7 days after late preterm antenatal corticosteroid administration is low, as only 13.3% (165/1,238) of our study cohort delivered between that time interval. Second, delivery between 2-7 days after antenatal corticosteroid administration was more likely in women at risk for medically indicated late preterm birth compared to anticipated spontaneous late preterm birth, suggesting that delivery between that desired time interval is more common in that group of patients.

Results

This study highlights the clinical challenge of timing antenatal corticosteroids appropriately in women before anticipated preterm birth. It is known that the benefit of corticosteroid administration is greatest between 2 and 7 days after the initial dose,[28] and that corticosteroids should not be administered unless there substantial clinical concern for imminent preterm birth,[16] yet the timing of corticosteroid administration remains suboptimal.[25-27] This has been demonstrated in women at risk for both spontaneous and medically indicated preterm birth < 34 weeks. For example, in a cohort of 345 singleton and twin gestations who received betamethasone for threated spontaneous preterm birth with intact or ruptured membranes between 24 and 34 weeks of gestation, Adams et al. reported that the likelihood of optimally timed corticosteroids (defined in their study as delivery within 7 days of administration) was 20%.[25] In efforts to determine whether timing was more optimal in a separate cohort of 193 singleton and twin gestations at risk for medically indicated preterm birth between 24 and 34

weeks of gestation, Adams el al. reported that only 48% of women who received corticosteroids prior to anticipated indicated preterm delivery actually delivered within 7 days of its administration and that optimal timing was more likely when delivery was due to maternal indications (i.e. preeclampsia) rather than fetal indication (i.e. fetal growth restriction). Our findings of improved corticosteroid timing in women with medically indicated preterm birth compared to those with anticipated spontaneous preterm birth were similar to the studies by Adams et al.[25,26] Lastly, a single center cohort study of singleton preterm births between 24 and 35 weeks of gestation by Levin et al. demonstrated that the likelihood of optimally timed corticosteroids (defined in their sensitivity analysis as delivery between 2-7 days after administration) was 27.5%.[27]

Clinical Implications

Despite the general similarity of prior studies in the early preterm period, indicating that corticosteroid timing is often suboptimal, we suggest caution when comparing these studies to ours for several reasons. First, preterm birth becomes more likely as gestational age increases,[33] and thus, only 23.7% (294/1,238) of our study cohort delivered > 7 days after corticosteroid administration, a lower rate compared to the studies reported by Adams et al.[25,26] This was also reflective in our finding that a later gestational age at corticosteroid administration was associated with a higher likelihood of optimal timing. Second, preterm prelabor rupture of membranes was the most common indication for corticosteroid administration in our study, where delivery is usually recommended in the late preterm period rather than expectant management (as in cases prior to 34 weeks),[34] increasing the likelihood of delivery within 48 hours after corticosteroid administration, which may be suboptimal. Lastly, our cohort of

medically indicated late preterm births included patients with scheduled deliveries prior to 37 weeks, a more common event than scheduled delivery < 34 weeks, which may allow for practitioners to time corticosteroid administration more appropriately.

Research Implications

The number of patients that completed the course of antenatal corticosteroids prior to delivery in our cohort was lower compared to that reported by Gyamfi-Bannerman et al. (47% vs. 60%) in their randomized trial evaluating the neonatal benefit of corticosteroids in women at risk for late preterm delivery.[14] This may have reflected the eagerness of practitioners to use this intervention in every day practice, which led to suboptimal timing. Furthermore, our cohort included over 70% of patients who presented with anticipated spontaneous late preterm birth and progressed rapidly to delivery within 48 hours after the first dose of corticosteroid administration, which emphasizes the challenge in predicting spontaneous preterm birth that may contribute to suboptimal corticosteroid timing. Nevertheless, future studies investigating the utility of possible predictors of preterm birth, particularly in the late preterm period, and identifying improved clinical criteria that may lead to improved timing of antenatal corticosteroids are needed.

Strengths and Limitations

Our study has several strengths. To our knowledge, and after review of the literature, this is the first study investigating the likelihood of delivery in the assumed optimal time interval (between 2-7 days) after late preterm antenatal corticosteroid administration, which was also stratified by indication to compare women with anticipated spontaneous late preterm birth to those at risk for medically indicated late preterm birth. Our sample size was robust, including over 1,200

singleton pregnancies from 3 different hospitals within a large health system in New York. Moreover, our population is diversified in terms of maternal race, ethnicity and demographics, making our findings generalizable.

This study, however, has several limitations. First, we defined administration of late preterm antenatal corticosteroids between 2-7 days prior to delivery as an optimal time interval based on data from corticosteroid use in women at risk for preterm delivery < 34 weeks. Currently, there are no data confirming the optimal time interval for corticosteroid administration for neonates born in the late preterm period, so it remains unclear whether the 2-7 day interval indeed carries the greatest benefit to this select population. Nevertheless, this time interval is generally accepted in clinical practice. Additionally, the indication for corticosteroid administration was at the provider's discretion in each hospital and extracted from the medical record retrospectively. While institutional guidelines and consultation with Maternal-Fetal Medicine were present and available to guide practitioners with respect to selecting the appropriate candidates for corticosteroid administration, practice patterns may have varied slightly among the three hospitals. Neonatal outcomes were not compared between the two groups of late preterm neonates (medically indicated versus spontaneous) as these are impacted by multiple confounding factors. Finally, despite our large sample size, several of the medical indications that applied to corticosteroid administration in our cohort, i.e. fetal growth restriction, oligohydramnios, abnormal placentation and non-reassuring fetal status, were relatively rare, limiting our ability to evaluate the likelihood of optimal timing of each individual indication within our regression analysis.

Conclusions

In conclusion, we have demonstrated that the likelihood of delivery between 2-7 days after antenatal corticosteroid administration in women at risk for late preterm birth is low and that delivery between that time interval was more likely in women at risk for medically indicated late preterm birth compared to anticipated spontaneous late preterm birth. Although any duration of dose exposure has been proven beneficial in reducing short-term neonatal morbidities for this select cohort,[14] the long-term implications of corticosteroid exposure in this time period is not fully understood, and recent evidence has suggested possible harm.[35] Thus, selecting the appropriate patient population for whom corticosteroid administration in the late preterm period would be timed appropriately and result in neonatal benefit is essential in order to optimize benefits from antenatal corticosteroids, while limiting the risks associated with such intervention.

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Table 1. Indications for late preterm steroid administration within the study cohort

	ACS administered (n=1238)
Risk for spontaneous late preterm birth	
Suspected preterm labor with intact membranes	316 (25.5)
Ruptured membranes	363 (29.3)
Risk for medically indicated late preterm birth	
Hypertensive disorders of pregnancy	281 (22.7)
Fetal growth restriction	21 (1.7)
Oligohydramnios	71 (5.7)
Intrahepatic cholestasis of pregnancy	23 (1.9)
Non-reassuring fetal status	49 (4)
Placenta previa, accreta, or vasa previa	32 (2.6)
Placental abruption	44 (3.6)
Other	38 (3.1)

Data presented as n (%).
ACS, antenatal corticosteroids.

Table 2. Comparison of baseline characteristics between study groups

	Risk for spontaneous late-preterm birth (n=679)	Risk for medically indicated late-preterm birth (n=559)	*P* value
Maternal age (year) – median	32 (29,36)	34 (31,37)	<0.001

(IQR)			
BMI (kg/m^2) – median (IQR)	29 (25.9,32.7)	31.4 (27.5,35.9)	<0.001
Gestational age at ACS administration (weeks) – median (IQR)	35.7 (35,36.3)	35.6 (35,36.2)	0.89
Race or ethnic group – n (%)			
Non-Hispanic white	257 (37.8)	205 (36.7)	<0.001
Non-Hispanic black	102 (15.0)	112 (20.0)	
Hispanic	72 (10.6)	82 (14.7)	
Asian	131 (19.3)	76 (13.6)	
Other	80 (11.8)	41 (7.3)	
Unknown	37 (5.4)	43 (7.7)	
Nulliparous – n (%)	318 (46.8)	287 (51.3)	0.32
History of preterm birth – n (%)			
Spontaneous	77 (11.3)	28 (5)	<0.001
Medically indicated	17 (2.5)	44 (7.9)	
Gestational diabetes – n (%)	26 (3.8)	47 (8.4)	0.001

IQR, interquartile range; *BMI*, body mass index; *ACS*, antenatal corticosteroids.

Table 3. Primary and secondary outcomes

	Risk for spontaneous late-preterm birth (n=679)	Risk for medically indicated late-preterm birth (n=559)	*P* value
Delivered 2-7 days after ACS	34 (5)	131 (23.4)	<0.001
Delivered < 2 days after ACS	511 (75.3)	268 (47.9)	<0.001
Delivered > 7 days after ACS	134 (19.7)	160 (28.6)	<0.001
Time interval from ACS to delivery (hours) – median (IQR)	10.7 (5.23,44.6)	49.71 (20.1,96.2)	<0.001
Delivered < 37 weeks – n (%)	543 (80)	390 (69.8)	<0.001
Gestational age at delivery (weeks) – median (IQR)	36.1 (35.3,36.7)	36.4 (35.7,37)	0.049

IQR, interquartile range; *ACS*, antenatal corticosteroids.

Table 4. Multivariable logistic regression to evaluate factors associated with optimal timing of ACS administration

	Adjusted Odds Ratio	95% Confidence Interval	*P* value
Indication for ACS administration – anticipated spontaneous vs. medically indicated late preterm birth	0.17	0.11-0.26	<0.0001
Gestational age at ACS administration	1.33	1.05-1.68	0.02
Maternal age	1.00	0.97-1.04	0.9
Body mass index	0.98	0.95-1.01	0.2
Race/ethnicity: non-Hispanic black	1.14	0.71-1.84	0.6
Race/ethnicity: Hispanic	1.09	0.63-1.90	0.7
Race/ethnicity: Asian	1.19	0.72-1.98	0.5
Race/ethnicity: Other	1.13	0.59-2.14	0.7
Nulliparous	0.69	0.47-1.02	0.06
History of spontaneous preterm birth	1.13	0.50-2.55	0.8
History of medically indicated preterm birth	1.63	0.80-3.31	0.2
Gestational diabetes	1.04	0.53-2.07	0.9

ACS, antenatal corticosteroids.
Reference group for race/ethnicity is non-Hispanic white.
Maternal age, body mass index and gestational age at ACS administration were entered into the model as continuous variables.