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Neonatal hypoglycemia after antenatal late preterm steroids in individuals with diabetes

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Abstract

Objective: To establish whether administration of antenatal late preterm steroids to pregnant people with diabetes resulted in higher risk of neonatal hypoglycemia.

Study design: This is a retrospective cohort study of individuals with pre-gestational or gestational diabetes admitted between 34 0/7-36 6/7 weeks' gestation before and after introduction of an antenatal late preterm steroids protocol. The primary outcome was any neonatal blood glucose ≤ 60 milligrams/deciliter in the first 24 hours of life.

Results: Of 123 mother-neonate pairs, 52.8% (N=65) delivered during the post-protocol period; 75.4% of those (N=49) received late preterm steroids. 59.7% (N=34) of the pre-protocol neonates and 81.5% (N=53) of the post-protocol neonates had hypoglycemia ($p = 0.008$). After controlling for gestational age at delivery and mode of delivery, neonates in the post-protocol group had increased odds of hypoglycemia (adjusted odds ratio 2.96, 95% confidence interval 1.29-6.82).

Conclusion: Neonates born to mothers with diabetes who received late preterm corticosteroids experienced greater odds of hypoglycemia.

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Introduction

The benefit of antenatal steroids in reducing neonatal respiratory and neurological morbidity and perinatal mortality is well established in early preterm birth (prior to 34 weeks' gestation).¹ More recently, the Antenatal Late Preterm Steroid (ALPS) trial demonstrated that the respiratory benefit of antenatal steroids extends to the neonates who are born in the late preterm period (34 weeks 0 days to 36 weeks 5 days gestation).² Accordingly, practitioners have begun routinely administering antenatal corticosteroids when managing individuals at risk of delivering during the late preterm period.³

Despite these benefits, concern has been raised regarding the risk of neonatal hypoglycemia, which was significantly higher in those neonates exposed to corticosteroids during the late preterm period in the initial ALPS trial.^{2,4} Neonates born to people with pre-gestational diabetes mellitus prior to 34 weeks gestation benefit similarly from antenatal corticosteroid treatment,⁵ and thus corticosteroid treatment for people with diabetes is recommended for individuals at risk of early preterm birth despite the potential increase in neonatal hypoglycemia.

In the late preterm period, however, less is known regarding the possible benefit of antenatal corticosteroid treatment in this population as individuals with pre-gestational diabetes were excluded from the ALPS trial, and patients with gestational diabetes comprised only about 10.8% of the overall sample from the ALPS trial. The neonates of people with pre-gestational diabetes are already at greater risk of hypoglycemia as a consequence of maternal hyperglycemia.⁶ Despite these unknown risks and benefits of late preterm corticosteroids for people with pre-existing diabetes, 55-80% of obstetrical providers report administering late preterm corticosteroids in this clinical scenario.⁷

Our objective was to evaluate neonatal hypoglycemia and neonatal outcomes associated with the administration of antenatal late preterm corticosteroids in pregnant people with diabetes.

Methods

This is a retrospective cohort study of all people with a diagnosis of pre-gestational (of any type) or gestational diabetes (diagnosed using a two-step process with a screening 50 gram glucose challenge test followed by a three hour 75 mg glucose tolerance test using Carpenter-Coustan criteria⁸). Patients with any diabetes diagnosis and singleton gestations admitted to Northwestern Memorial Hospital, a high-volume obstetric tertiary care center (approximately 12,000 deliveries per year), between 34 weeks 0 days and 36 weeks 6 days of gestation with concern for delivery before 37 weeks gestational age were included in this study. While not inclusive, common reasons for admission included blood pressure monitoring, preterm premature rupture of membranes, concern for preterm labor, or intrauterine growth restriction. Of note, individuals were included in this cohort even if delivery occurred after 36 weeks and 6 days of gestation, given the possibility of having received corticosteroids during the late preterm period.

The study period included a one year period before (pre-protocol: November 1, 2012 to October 31, 2013) and one year following (post-protocol: April 1, 2016 to March 30, 2017)

implementation of a late preterm corticosteroid administration protocol. The pre-protocol period was chosen to avoid possible overlap with recruitment for the ALPS study,² for which Northwestern served as a study site.⁹ Individuals were excluded from this study if they had received a prior course of antenatal corticosteroids, had a multiple gestation, had a contraindication to corticosteroids, experienced an antenatal or intrapartum stillbirth, or had a fetus with major anomalies. All data were abstracted from the electronic medical record used for clinical care, and data were reviewed by the research team for accuracy. The Northwestern Institutional Review Board approved the research protocol with a waiver of informed consent (# STU00204844).

The institution's antenatal late preterm corticosteroid protocol was implemented in March 2016 following publication of the ALPS study.² Based on the trial protocol, our institutional protocol recommends that individuals who present between 34 weeks and 0 days and 36 weeks and 5 days of gestation receive corticosteroids (12 mg of betamethasone acetate injected intramuscularly on 2 occasions 24 hours apart at this institution) if delivery is anticipated or if there is substantial risk for delivery prior to 37 weeks' gestation in people who have not previously received a course of corticosteroids. Notably, people with pre-gestational and gestational diabetes were included in the institutional protocol and were eligible for ALPS administration during the study period.

The new 2016 protocol was disseminated to all obstetric clinicians using education sessions, including grand rounds, resident and fellow lectures, labor and delivery unit lectures, and email reminders.⁹ Additionally, a member of the maternal fetal medicine division oversees the obstetrical units each day, and these faculty provided in-person re-education and reminders throughout the first year of implementation.

Our primary outcome was neonatal hypoglycemia, defined as any glucose < 60 mg/dL within the first 24 hours of life, which we chose as our threshold after consultation with the neonatologists at our institution as the threshold at which they become clinically concerned. Of note, the institutional protocol calls for screening all neonates at high risk for hypoglycemia, including all neonates born to patients with diabetes. Thus, all neonates in this study were screening for hypoglycemia.

Secondary outcomes included neonatal hypoglycemia defined as any glucose < 40 mg/dL in the first 24 hours of life (based on the threshold used in the ALPS trial²), 5-minute Apgar score less than 7, neonatal intensive care unit (NICU) admission, receipt of intravenous dextrose, transient tachypnea of the newborn, respiratory distress syndrome, surfactant administration, and hospital length of stay (days). Two values of neonatal blood glucose were used to define hypoglycemia as controversy exists as to the precise numerical threshold at which to intervene.¹⁰ Respiratory distress syndrome diagnosis was made based on chest x-ray findings of reticulogranular appearance and need for supplemental oxygen. A diagnosis of transient tachypnea of the newborn was made by chest x-ray finding of perihilar linear streaking. Those neonates requiring oxygen, but with normal chest x-ray findings, were individually reviewed for a diagnosis by a neonatologist.

Several variables were assessed as potential confounders, including maternal characteristics such as age, self-reported race and ethnicity, parity, and body mass index (BMI; defined as kg/m²) at delivery. Pregnancy characteristics examined included as gestational age at initial admission and delivery, mode of delivery (any vaginal delivery vs. any cesarean delivery), fetal sex, fetal birthweight (grams), and a diagnosis of chronic hypertension or a hypertensive disorder of pregnancy. We had an *a priori* plan to control for potential confounders in multivariable analysis if they were if they differed by protocol time period at the $p < 0.10$ level. In the final adjusted models, we also included gestational age at delivery as a possible confounder given its clinical importance to the outcomes examined.

In the primary analysis, we compared all eligible participants in each group. In a sensitivity analysis, we compared pre-protocol outcomes to only those of post-protocol neonates whose mothers actually received antenatal corticosteroids. For bivariable comparisons, we used student t, chi square, and Wilcoxon rank sum analyses. We used multivariable linear and logistic regression to control for potential confounders. A p-value of < 0.05 was otherwise used to define statistical significance and all tests were two-tailed. We did not adjust for multiple comparisons. The sample included all births in the study period given the quality aims of investigating implementation in the first year after the new protocol; as the sample size was constrained, no power analysis was performed for secondary outcomes. Statistical analyses were performed with Stata version 15.0 (StataCorp, College Station, TX). While the Stata code used to generate our analyses is available on request, the underlying data are not available without a formal data use agreement between Northwestern and another institution due to the nature of our IRB approval.

Results

Of 123 eligible mother-neonate pairs, 47.2% (N=58) delivered during the pre-protocol period and 52.8% (N=65) delivered during the post-protocol period. As compared to the pre-protocol period, people in the post-protocol period were similar in terms of age, nulliparity, or BMI, but neonates in the post-protocol period were more likely to be born via cesarean delivery (Table 1). There was no significant difference in self-reported racial or ethnic identity between the two groups; notably, the majority of participants identified as members of minority racial and ethnic groups. Additionally, there were no statistically significant differences the prevalence of pre-gestational diabetes (27.6% pre-protocol vs. 40.0% post-protocol; $p=0.15$) or the mean gestational age at delivery (35.9 weeks pre-protocol vs. 36.1 weeks post-protocol; $p=0.33$), between those in the post-protocol period compared to those in the pre-protocol period. In the post-protocol group, the average gestational age at receipt of steroids was 35.4 weeks.

Neonates in the post-protocol period experienced hypoglycemia in the first 24 hours of life at the level of ≤ 60 mg/dL significantly more frequently than neonates in the pre-protocol period (81.5% post-protocol vs. 59.7% pre-protocol; $p=0.008$) (Table 2). There was no significant difference in the frequencies of hypoglycemia ≤ 40 mg/dL (44.6% post-protocol vs. 29.3% pre-protocol; $p=0.08$) or in IV dextrose administration (35.4% post-protocol vs. 24.1% pre-protocol; $p=0.18$). Outcomes also did not differ between the two time periods in

terms of frequencies of Apgar scores < 7, NICU admission, transient tachypnea, respiratory distress syndrome, surfactant administration, or mean hospital length of stay (Table 2).

Neonates in the post-protocol period remained significantly more likely to experience hypoglycemia ≥ 60 mg/dL (aOR 2.96; 95% CI 1.29-6.82) in multivariable analysis adjusting for gestational age. No other findings differed significantly in multivariable analyses.

In the sensitivity analysis, 50 of 65 people eligible to receive corticosteroids in the post-protocol period (76.9%) actually received corticosteroids during the late preterm period; the other 15 people did not receive either dose of corticosteroid. Compared to people who delivered in the post-protocol period who did not receive corticosteroids, people who did receive corticosteroids were similarly likely to have pre-gestational diabetes. In this sensitivity analysis, the frequencies of hypoglycemia of both ≥ 60 mg/dL (79.6% post-protocol vs. 59.7% pre-protocol; $p=0.03$) and ≥ 40 mg/dL (51.0% post-protocol vs. 29.3% pre-protocol; $p=0.02$) were significantly greater in neonates in the post-protocol period (Table 3). The two groups did not differ in frequency of Apgar scores < 7, NICU admission, IV dextrose administration, transient tachypnea, respiratory distress syndrome, surfactant administration, or mean hospital length of stay. In multivariable models adjusting for gestational age, the odds of hypoglycemia of both ≥ 60 mg/dL (aOR 2.82; 95% CI 1.19-6.72) and ≥ 40 mg/dL (aOR 2.49; 95% CI 1.13-5.52) remained significantly greater in the post-protocol neonates exposed to late preterm corticosteroids compared to the pre-protocol group (Table 3).

Discussion

Our study shows evidence that corticosteroid administration in the late preterm period is associated with a higher risk of hypoglycemia among neonates born to people with pre-gestational or gestational diabetes. Our study, which included individuals with all types of diabetes (unlike the ALPS study, which included only people with gestational diabetes), did not show any significant difference in neonatal respiratory outcomes associated with late preterm corticosteroids in this population, although our study was not designed to show such differences.

Given the burden of prematurity and respiratory immaturity of neonates born to individuals with diabetes, this population may be the most likely to benefit from antenatal late preterm corticosteroids. Firstly, they are at higher risk of delivering during this time period, as they have a five-fold increase in preterm births compared to individuals without diabetes, with a majority of these occurring in the late preterm period.¹¹ Secondly, diabetes during pregnancy is associated with increased neonatal respiratory morbidities that are not fully explained by prematurity.¹² Thus, it is understandable that many practitioners began administering late preterm corticosteroids following publication of the ALPS trial.⁷ However, the ALPS trial also raised the possibility of unintended iatrogenic harm associated with late preterm corticosteroid use in people with diabetes: the ALPS trial reported an increased rate of neonatal hypoglycemia among newborns receiving corticosteroids in the late preterm period, with a relative risk of 1.6 and a prevalence of 24%.² Hypoglycemia is already a well-known

complication in neonates born to individuals with diabetes,^{6,13} which may be exacerbated by the administration of late preterm corticosteroids.

Because the ALPS study showed a significant benefit in terms of reduction of neonatal respiratory morbidity,² the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) both recommend administering antenatal corticosteroids in the late preterm period for individuals at high risk of delivery before 37 weeks' gestation.^{14,15} The ALPS study, however, explicitly excluded individuals with pre-gestational diabetes, and so potential benefits in this population are less clear. The SMFM and ACOG documents reflect this, stating benefits in this population remained unknown.^{14,15} However, data show that in clinical practice, more than half (55-80%) of surveyed obstetrical providers administer late preterm corticosteroids to people with pre-gestational and gestational diabetes.⁷ To date, there remain little existing data on neonatal outcomes following late preterm corticosteroid administration to people with diabetes. One study of people with pre-gestational diabetes showed no benefit of corticosteroids in terms of respiratory morbidity, but also no increased risk of neonatal hypoglycemia.¹⁶ This study, however, contained only 54 maternal-neonatal dyads. Our study, which contained more dyads and also includes individuals with gestational diabetes, does show some evidence of potential harm from hypoglycemia, although further study would be needed to determine whether this is a consistent effect.

At present, there is a wide variety of practice patterns with regard to corticosteroid administration to people with diabetes in the late preterm period, including in our study, where only 76.5% of participants with diabetes received corticosteroids in the post-protocol period. Recently, other authors have questioned whether antenatal corticosteroids yield unalloyed benefit, with Räikkönen et. al. recently showing an increased risk of behavioral disorders among children who received corticosteroids (at any gestational age) as compared to siblings who did not receive corticosteroids.¹⁷ Certainly, neonatal hypoglycemia can cause short- and long-term complications as well.¹⁸ Based on our study, there does seem to be emerging evidence of possible side effects from corticosteroid administration in the late preterm period among people with diabetes, without evidence of clear benefit, although our study was not necessarily powered to show a benefit. In tempering this interpretation, however, it should be noted that in the ALPS trial, even among those neonates who developed hypoglycemia, the hypoglycemia was transient (resolved within 24 hours) and mostly did not require treatment.⁴ Similarly, our study showed neonates had similar lengths of stay pre- and post-protocol, and thus any side effects of steroids were likely temporary. Studies specifically powered to show benefit in neonates born to individuals with diabetes could provide clearer guidance for whether corticosteroids should be considered in this population, and what the long-lasting effects, if any, of hypoglycemia may be.

This study has several strengths, including a relatively large, diverse population of participants with diabetes in pregnancy from both the pre-protocol and post-protocol period, as well as granular data on steroid administration and neonatal outcomes. This study also addresses a question about which relatively little is known, although our study has a relatively small sample size. There are several limitations that must be considered when interpreting results as well. First, the study was not powered to show neonatal benefit

of late preterm corticosteroids. Second, not all mothers received corticosteroids in the post-protocol period, and it is unknown if the lack of receipt of steroids was due to the diabetes diagnosis or other reasons; this may be due to unobserved characteristics that are associated with the risk of neonatal hypoglycemia. We also cannot observe whether deviation from the corticosteroid administration protocol occurred, either in terms of dosing or timing of administration. Third, we cannot account for maternal blood glucose during labor, which is associated with the risk of neonatal hypoglycemia. Fourth, there may remain residual confounding due to unobserved neonatal and maternal characteristics, as well as labor management and other obstetric complications. Finally, our sample size remains small, especially of patients with pre-existing diabetes, and thus it is hard to delineate whether the consequences of antenatal preterm corticosteroids for neonates differ by type of maternal diabetes.

Conclusion

After implementation of an antenatal late preterm steroid protocol, the majority of pregnant people with diabetes who were admitted in the late preterm period received steroids. Neonates born following protocol implementation experienced an increased frequency of hypoglycemia, with though no differences in other secondary outcomes.

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Table 1:

Group characteristics by antenatal late preterm steroid protocol status

	Pre-protocol group (11/1/12-10/1-13) (N=58) ¹	Post-protocol group (4/1/16-3/30/17) (N=65) ¹	P value ²
Age (years)	34.2 ± 5.8	34.6 ± 5.2	0.69
Nulliparity	26 (44.8)	32 (49.2)	0.63
Body mass index (kg/m ²)	35.3 ± 6.0	35.5 ± 7.5	0.87
Maternal race and ethnicity			0.26
White Non-Hispanic	22 (37.9)	17 (26.2)	
Black Non-Hispanic	12 (20.7)	10 (15.4)	
Hispanic	17 (29.3)	21 (32.3)	
Asian	5 (8.6)	14 (21.5)	
Other	2 (3.5)	3 (4.6)	
Pregestational diabetes	16 (27.6)	26 (40.0)	0.15
Chronic hypertension	6 (10.3)	12 (18.5)	0.20
Preeclampsia	3 (5.1)	4 (6.1)	1.00
Cesarean delivery	25 (42.1)	40 (61.5)	0.04
Female neonate	26 (44.8)	29 (44.6)	0.98
Neonatal birthweight (grams)	2844 ± 674	2962 ± 716	0.35
Gestational age at admission (weeks)	35.6 ± 0.8	35.7 ± 0.8	0.62
Gestational age at delivery (weeks)	35.9 ± 0.9	36.1 ± 0.8	0.33
Received late preterm antenatal corticosteroids between 34+0 and 36+6 weeks gestation		50 (76.9)	
Gestational age at corticosteroid administration (weeks)		35.4 ± 2.4	

¹Data are presented as N(%) for categorical variables, mean ± standard deviation for continuous variables.

²P values are for chi square tests for categorical variables, student t tests for continuous variables.

Table 2:

Neonatal outcomes before and after implementation of the late preterm antenatal corticosteroids protocol

	Pre-protocol group (N=58) ¹	Post-protocol group (N=65) ¹	P value ²	Multivariable analysis	
				Adjusted odds ratio or β coefficient ³	95% confidence interval
Primary Outcome					
Hypoglycemia (any blood glucose 60 mg/dL) ⁴	34 (59.7)	53 (81.5)	0.008	2.96	1.29-6.82
Secondary outcomes					
Hypoglycemia (any blood glucose 40 mg/dL) ⁴	17 (29.3)	29 (44.6)	0.08	1.76	0.81-3.79
5 minute Apgar < 7	3 (5.2)	4 (6.2)	0.82	1.43	0.29-7.06
NICU ⁵ admission	27 (46.6)	38 (58.5)	0.19	1.74	0.80-3.81
Intravenous dextrose administration	14 (24.1)	23 (35.4)	0.18	1.62	0.71-3.72
Transient tachypnea	7 (12.1)	8 (12.3)	0.97	1.04	0.31-3.43
Respiratory distress syndrome	3 (5.2)	4 (6.2)	0.82	1.03	0.22-4.97
Surfactant administration	2 (3.5)	2 (3.1)	0.91	0.73	0.10-5.54
Mean hospital length of stay (days)	7.3 ± 8.0	5.3 ± 4.1	0.10	-2.00	-4.0 to 0.02

¹. Data presented as N(%) for categorical variables, mean ± standard deviation or median (interquartile range) for continuous variables.

². P value is for chi square tests for categorical variables, student t test or Wilcoxon rank sum tests for continuous variables.

³. Logistic and linear regressions adjusting for gestational age at delivery and cesarean delivery; pre-protocol group as referent.

⁴. Any blood glucose value within the first 24 hours of life, expressed in milligrams/deciliter.

⁵. NICU – neonatal intensive care unit.

Table 3:

Neonatal outcomes of pre-protocol group versus neonates exposed to steroids in the post-protocol group

	Pre-protocol group (N=58) ¹	Post-protocol group ² (N=50) ¹	P value ³	Multivariable analysis	
				Adjusted odds ratio or β coefficient ⁴	95% confidence interval
Primary Outcome					
Hypoglycemia (any blood glucose 60 mg/dL) ⁵	34 (59.7)	39 (79.6)	0.03	2.82	1.19-6.72
Secondary outcomes					
Hypoglycemia (any blood glucose 40 mg/dL) ⁵	17 (29.3)	25 (51.0)	0.02	2.49	1.13-5.52
5 minute Apgar < 7	3 (5.2)	4 (8.2)	0.53	1.64	0.35-7.75
NICU ⁶ admission	27 (46.6)	30 (61.2)	0.13	1.87	0.83-4.20
Intravenous dextrose administration	14 (24.1)	19 (38.8)	0.10	2.00	0.87-4.60
Transient tachypnea	7 (12.1)	7 (14.3)	0.74	1.31	0.40-4.26
Respiratory distress syndrome	3 (5.2)	4 (8.2)	0.53	1.66	0.35-7.85
Surfactant administration	2 (3.5)	2 (4.1)	0.86	1.24	0.17-9.27
Mean hospital length of stay (days)	7.3 ± 8.0	5.5 ± 4.3	0.18	-1.91	-4.21-0.39

¹. Data presented as N(%) for categorical variables, mean ± standard deviation or median (interquartile range) for continuous variables.

². Includes only people who received late preterm steroids in the post-protocol group.

³. P value is for chi square tests for categorical variables, student t test or Wilcoxon rank sum tests for continuous variables.

⁴. Logistic and linear regressions adjusting for gestational age at delivery; pre-protocol group as referent.

⁵. Any blood glucose value within the first 24 hours of life, expressed in milligrams/deciliter.

⁶. NICU – neonatal intensive care unit.