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Effect of Antenatal Corticosteroids on Respiratory Morbidity in Singletons After Late-Preterm Birth

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Abstract

Objective—To evaluate whether neonates born to women who had previously received antenatal corticosteroids and then delivered a late-preterm birth neonate had less respiratory morbidity compared with those unexposed to antenatal corticosteroids.

Methods—This is a secondary analysis from a multicenter observational study regarding mode of delivery after prior cesarean delivery. We compared women who received one course of antenatal corticosteroids with unexposed parturients, and evaluated various respiratory outcomes among those having a singleton late-preterm birth neonate. We controlled for potential confounders including gestational age at delivery, diabetes, mode of delivery, and maternal race.

Results—Five thousand nine hundred twenty-four patients met the inclusion criteria; 550 received steroids, while 5,374 did not. In the univariable model, compared with unexposed women, those who received antenatal corticosteroids appeared more likely to have neonates who required ventilatory support (11.5% v. 8.6%, p=0.022), had respiratory distress syndrome (RDS) (17.1% v. 12.2%, p=0.001), developed transient tachypnea of the newborn (12.9% v. 9.8%, p=0.020), or required resuscitation in the delivery room (55.8% v. 49.7%, p=0.007). After controlling for confounding factors, we found no significant differences among the groups

*For a list of other members of the NICHD MFMU, see the Appendix online at http://links.lww.com/xxx.

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regarding all of the above outcomes with an odds ratio for RDS of 0.78 (95% CI 0.60–1.02) and ventilator support of 0.75 (95% CI 0.55–1.03).

Conclusion—Exposure to antenatal corticosteroids does not significantly affect respiratory outcomes among those with a subsequent late-preterm birth.

INTRODUCTION

Approximately 75% of preterm births in the United States occur in the "late-preterm" period between 34^0 and 36^6 weeks gestation(1). Since 1990, births in the late-preterm window increased by approximately 25% (2). Until recently, the prevailing belief has been that neonates born in the late-preterm period may have mild respiratory compromise requiring brief periods of oxygen support, but that more severe and costly complications are uncommon. This may have resulted in part by a statement made by the American Congress of Obstetricians and Gynecologists saying that survival for newborns at 34 weeks of gestation is within 1% of those born at 37 weeks or beyond(3). Although this remains true, we are increasingly aware of the higher risk of short and long term morbidities that are more frequent in this group when compared with neonates born at term (4–7).

The administration of antenatal corticosteroids (ACS) to women at risk for preterm delivery has been shown to decrease the rate of respiratory distress syndrome (RDS) in neonates of women who deliver between 24 and 34 weeks gestation (8–9). Although currently not recommended in the late-preterm period, the lack of demonstrated benefit at advanced gestations is thought to be due to the low incidence of RDS and the lack of adequately powered studies to address these outcomes in this group. A recent Cochrane review found less than 200 published cases of patients randomized to ACS or placebo between 35 and <37 weeks of gestation(9). Among these, there were only 6 cases of RDS. Given the evidence of respiratory compromise in late-preterm neonates, we sought to estimate whether exposure to ACS during pregnancy decreased the rate of respiratory morbidities if the pregnancy was delivered during the late-preterm period.

METHODS

This was a secondary analysis from a multicenter observational study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network from 1999–2002 regarding primary and repeat cesarean delivery. Full details of the methods and study design have been previously reported(10). This secondary analysis was approved by the IRB at Columbia University Medical Center.

Women with a singleton gestation resulting in late-preterm birth (LPTB) were identified. Late preterm birth was defined as delivery occurring between 34 0/7 to 36 6/7 weeks gestation. Gestational age was determined by best obstetric estimate in the parent study. Women with multiple gestations were excluded from the parent study. Neonatal data were collected up to discharge or 120 days post delivery, whichever came first, and data on ACS exposure was abstracted from maternal charts. Women were considered to have ACS exposure if they received corticosteroids for fetal lung maturity that cross the placenta in significant amounts. Women receiving prednisone or other steroids not for lung maturity were considered unexposed. Data on the specific corticosteroid received by each subject were not obtained. Women were included if they never received steroids or if they completed one course. Women who received multiple courses, partial dosing, or those for whom information was incomplete were not included. Although it is not common practice to administer ACS in the late-preterm period at the institutions that participated in the parent

study, we could not ascertain the gestational age at steroid administration from our records. Therefore, the time from ACS administration to delivery was not available in this dataset.

We compared women exposed to one course (2 or 4 doses) of ACS with unexposed parturients, and evaluated neonatal respiratory outcomes such as RDS, transient tachypnea of the newborn (TTN), ventilator use, and the need for resuscitation in the delivery room. In multivariable analyses we controlled for potential confounders that might influence respiratory outcomes. These include maternal diabetes (gestational and pregestational), race, prenatal care insurance, mode of delivery, presence of labor, gestational age (GA) at delivery, and congenital anomalies.

Our primary outcome was RDS. Secondary outcomes included TTN, ventilator use, and the need for resuscitation in the delivery room. Additionally, a composite of respiratory morbidities that included RDS, TTN, and ventilator support in the first 24 hours was analyzed between groups. Categorical variables were compared using the chi-square test for dichotomous variables, and the Wilcoxon rank-sum test was used for continuous variables. Multivariable logistic regression was performed to control for the confounders listed above. Odds ratios (OR) and 95% confidence intervals (CI) for various outcomes were determined. Nominal two-sided probability values are reported with statistical significance defined as $P<0.05$. No adjustments were made for multiple comparisons. Statistical analyses were performed using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

70,442 women were enrolled in the Cesarean Registry. Of these, 5924 met eligibility criteria for this secondary analysis; 550 received steroids and 5,374 did not (Figure 1). Maternal characteristics of the study population by ACS exposure are described in Table 1. The groups were similar in age and parity. Women who received ACS were more likely to be Caucasian, have private insurance, and to be delivered by cesarean compared with women who did not receive steroids. These women also delivered earlier, 34.9 (34.3–35.7) weeks gestation (median [IQR]), than patients who did not receive steroids, 36.0 (35.5–36.6) weeks, $p<0.001$.

Compared with unexposed women, those who were given ACS appeared more likely to have neonates with RDS (17.1% v. 12.2%, $p=0.001$). ACS exposure was also related to increased rates of TTN (12.9% v. 9.8%, $p=0.020$), increased need for ventilatory support (11.5% v. 8.6%, $p=0.022$), higher rates of the adverse respiratory composite (29.9% v. 22.2%, $p<0.001$), and higher rates of resuscitation in the delivery room (55.8% v. 49.7%, $p=0.007$). However, after controlling for the following confounders - maternal diabetes, race, prenatal care insurance, mode of delivery, labor, GA at delivery and congenital anomalies - women who received ACS had similar rates of all respiratory outcomes compared with controls [Table 2].

DISCUSSION

We found that exposure to antenatal corticosteroids during pregnancy did not appear to change the proportion of adverse respiratory outcomes in neonates born at 34 0/7 to 36 6/7 weeks when compared with offspring of unexposed parturients. Few prospective studies have evaluated respiratory outcomes in late-preterm neonates exposed to steroids. In the first randomized controlled trial of ACS to enhance fetal pulmonary maturation in 1972, Liggins and Howie found that exposure to betamethasone decreased the rate of RDS from 25.8% in controls to 9.0% in the treatment group, $p=0.003$(8). When they performed a subgroup analysis evaluating neonates delivered between 32 to <37 weeks gestation, they found a

lower rate of RDS from 6.9% in the control group to 4.7% in the treatment group; a similar risk reduction to that seen with delivery at earlier gestations, but statistical significance was not reached. Notably, there were only 4 cases of RDS in that cohort of 72 moderately preterm neonates. The most recent Cochrane systematic review evaluating the rates of RDS in fetuses exposed to steroids who delivered at 34 weeks gestation or beyond found a similar trend but significance was again not reached in control versus treatment groups, 4.7% versus 3.1%, Risk Ratio 0.66, 95% CI 0.38–1.16, p=0.15(9). Of 1,261 included subjects, there were only 49 cases of RDS. The risk ratio for RDS among 189 newborns delivered at 35–36 weeks gestation was similar (Risk Ratio 0.61, 95% CI 0.11–3.26). Like Liggins' study and this recent meta-analysis, our evaluation lacks the needed power to resolve this issue. However, it is reassuring that our multivariable analyses revealed similar results to those previously published.

Biologically, there is no good explanation supporting a cessation of benefit to ACS after 34 weeks gestation. Rather, it is more likely that a decrease in the disease burden makes demonstration of this benefit more difficult. Late-preterm neonates are less likely to have RDS than neonates born before 34 weeks; however, they are still at risk for respiratory morbidities from other causes. As a pregnancy approaches term, delivery is more likely to result in TTN than RDS. Rubaltelli et al, were one of the first groups to evaluate the etiologies of acute respiratory distress in the late-preterm cohort(11). They found that the rate of TTN at 34 to 36 weeks was higher than that of babies born beyond 36 weeks, 6.2% versus 0.4%. Escobar and colleagues evaluated the need for respiratory support among late-preterm neonates compared with those delivered between 38 and 40 weeks gestation(6). They found that babies born at 34, 35, and 36 weeks were 19.8-, 9.0-, and 5.2-fold more likely respectively to require assisted ventilation compared with the reference group born at 38 to 40 weeks. Other groups have also demonstrated higher respiratory morbidity in late-preterm compared with term neonates(4, 7). These data validate the suggestion that late-preterm neonates are at risk for serious respiratory morbidities other than RDS which impact their early neonatal management. What is currently unknown is whether ACS administration can decrease these other respiratory morbidities.

A limitation to our study is that we do not know the gestational age at which the steroids were given, and thus the time interval between ACS administration and delivery. This is an important confounder as the effects of ACS administration are believed to be of limited duration. None of the participating clinical centers in the parent study routinely administer ACS after 34 weeks gestation, so it is likely that the majority of exposed newborns had been exposed to ACS remote from delivery; and it is unlikely that ACS were administered beyond 34 weeks. Additionally, this secondary analysis evaluates the impact of ACS administration on those delivering at 34–36 weeks rather than the impact of steroids administered at 34–36 weeks on those delivering thereafter. Recently, a group of investigators evaluated the role of ACS to decrease respiratory morbidities including, but not limited to, RDS in a term population undergoing planned cesarean delivery(12). They randomized women over 37 weeks gestation to betamethasone versus routine management and evaluated rates of admission of their neonates to a special care unit for respiratory distress. They found that the newborns of women who received steroids were less likely to require admission to a special care unit compared with neonates of women who did not, 0.024 versus 0.051%, (Relative Risk (RR) 0.46, 95% CI 0.23–0.93). They also found a lower rate of RDS in the treated group, 0.002% versus 0.011%, but statistical significance was not reached,(RR 0.32, 95% CI 0.03– 1.32). Based on these findings, it is plausible that ACS administration at 34–36 weeks to women at risk for late-preterm birth could also result in improved pulmonary outcomes. Finally, this is a secondary analysis of a prior completed trial and therefore, our sample size is fixed and limited.. Perhaps this difference would have been detectable with a larger sample size.

Our findings regarding the effect of ACS in the late-preterm period are consistent with prior reports, but highlight that adequate power to make clinical recommendations based on these studies is lacking. These studies support the need for well-designed trials of adequate size to evaluate the impact of antenatal corticosteroid administration in the late-preterm period for reduction of newborn respiratory complications.

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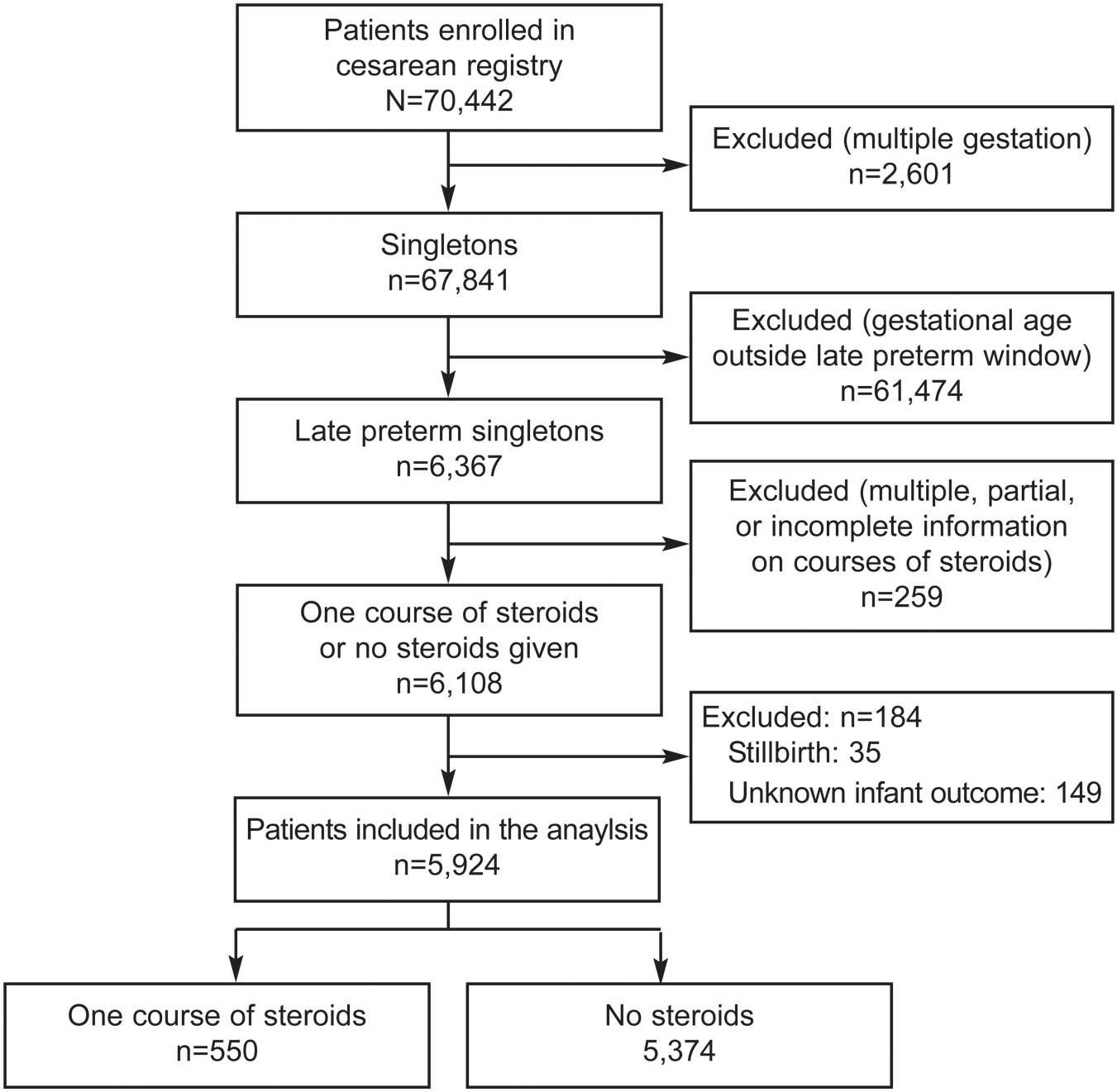

Figure 1.
Patients included in this study.

Table 1

Maternal Characteristics of the Study Population by Antenatal Steroid Exposure

Characteristic	**Antenatal Corticosteroids n = 550**	**No Antenatal Corticosteroids n = 5,374**	***P***
Race African American Caucasian Hispanic Asian Native American Other	167 (30.4) 312 (56.7) 48 (8.7) 6 (1.1) 1 (0.2) 16 (2.9)	1767 (32.9) 2154 (40.1) 1210 (22.5) 58 (1.1) 11 (0.2) 174 (3.2)	<0.001
Maternal age at delivery	28.9 ± 6.5	28.7 ± 6.4	0.55
Gestational age at delivery (median [IQR])	34.9 (34.3–35.7)	36.0 (35.5–36.6)	<0.001
Nulliparous	121 (22.2)	1112 (20.8)	0.47
Cesarean delivery	470 (85.5)	4406 (82.0)	0.042
Diabetes	82 (14.9)	827 (15.4)	0.76
Labor	273 (49.6)	3076 (57.2)	<0.001
Insurance for prenatal care Government	256 (49.4)	2891 (58.3)	<0.001
Private	262 (50.6)	2068 (41.7)	
Congenital anomalies	22 (4.0)	231 (4.3)	0.74

IQR interquartile range.

Data are n (%) or mean ± standard deviation.

Data on prenatal care insurance were missing for 32 (5.8%) women in the antenatal corticosteroids group and 415 (7.7%) of women in the no antenatal corticosteroids group, or 447 (7.5%) overall.

Table 2

Adjusted and Unadjusted Odds of Each Outcome Related to Antenatal Steroid Exposure

Outcome	Antenatal Corticosteroids n (%)	No Antenatal Corticosteroids n (%)	Unadjusted Odds Ratio	Adjusted Odds Ratio*
Respiratory distress syndrome	94 (17.1)	652 (12.2)	1.49 (1.18–1.89)	0.78 (0.60–1.02)
Ventilatory support	63 (11.5)	459 (8.6)	1.38 (1.05–1.83)	0.75 (0.55–1.03)
Transient tachypnea of the newborn	71 (12.9)	525 (9.8)	1.37 (1.05–1.78)	1.10 (0.83–1.47)
Resuscitation in the delivery room	307 (55.8)	2672 (49.7)	1.28 (1.07–1.52)	0.89 (0.73–1.09)
Composite (RDS, TTN, ventilatory support)	164 (29.9)	1188 (22.2)	1.50 (1.23–1.82)	0.88 (0.71–1.10)

RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.

*Adjusted for maternal diabetes, race, prenatal care insurance, mode of delivery, labor, gestational age at delivery, and congenital anomalies.