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Respiratory Compliance in Late Preterm Infants (34^{0/7} to 34^{6/7} Weeks) after Antenatal Steroid Therapy

Mitzi Go, MD, MCR¹, Diane Schilling, RRT¹, Thuan Nguyen, PhD², Manuel Durand, MD³, and Cindy T. McEvoy, MD, MCR¹

¹Division of Neonatology, Department of Pediatrics, Oregon Health & Science University, Portland, Oregon

²Oregon Health & Science University - Portland State University School of Public Health

³Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California

Abstract

Objective: To compare respiratory compliance in late preterm infants (34^{0/7} to 34^{6/7} weeks) who received antenatal steroids versus matched late preterm infants who did not receive AS.

Study design: This was a single-center prospective cohort study. Patients were matched for birth weight, gestational age, race and sex. Respiratory compliance was the primary outcome measured with the single breath occlusion technique.

Results: We studied 25 late preterm infants treated with AS and 25 matched infants who did not receive AS. The treated infants had a significantly increased respiratory compliance/kg (adjusted 95% CI 0.05, 0.49; $P = .016$) and fewer required continuous positive airway pressure ($p = 0.007$) or >24 hours of supplemental oxygen ($p = 0.046$). There was no difference in surfactant therapy.

Conclusions: Respiratory compliance was significantly increased in this cohort of late preterm infants born at 34^{0/7} to 34^{6/7} weeks who received AS compared with matched infants who did not receive AS. Although not randomized, these data provide physiologic support for the possible beneficial effects of AS in late preterm infants.

Keywords

Antenatal corticosteroids; betamethasone; premature infants; pulmonary function; respiratory compliance

Corresponding author: (Reprints not available from authors), Cindy McEvoy, MD, MCR, Department of Pediatrics, Oregon Health & Science University, 707 SW Gaines Road (CDRC-P), Portland, Oregon 97239 Phone (503) 494-0085/ Fax (503) 494-1542/ mcevoyc@ohsu.edu.

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Late preterm infants born at 34^{0/7} to 36^{6/7} weeks of gestation make up about 70% of all preterm deliveries and accounted for 6.9 % of all births in the United States in 2015.¹⁻⁴ Although this group of infants often appear mature, increasing epidemiologic evidence demonstrates they are at greater risk than term infants for mortality and morbidities including respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN).^{2,5,6} These newborns have a large impact on healthcare utilization compared with full term infants.⁷

Meta-analyses have demonstrated that a single course of antenatal steroids (AS) significantly reduces mortality and RDS in preterm infants delivered before 34 weeks of gestation,⁸⁻¹⁰ and is the standard of care for threatened deliveries at these gestations.^{9,10} Because the incidence of RDS is lower after 33 weeks gestation, initial randomized trials of AS therapy included few patients more than 33 weeks. Therefore until recently,¹¹ there were few data available regarding the response or effectiveness of this intervention in late preterm infants. Examining gestational age birth data for three different time epochs, Joseph et al concluded that failure to provide adequate treatment with AS at late preterm gestation may be partly responsible for the absence of a reduction in infant deaths associated with respiratory distress between 1995–1997 and 2002–2004.¹² The recent multicenter, randomized trial¹¹ of AS given at 34 to 36 weeks of gestation found a significant reduction in the rate of neonatal respiratory complications in treated infants. These findings have been endorsed by the Society for Maternal-Fetal Medicine.¹³

We have used measurements of pulmonary function, specifically passive respiratory compliance (Crs), or lung distensibility, and functional residual capacity (FRC), or lung volume at the end of a normal expiration, as an objective and reproducible way of quantifying the effects of AS on newborn pulmonary function.¹⁴⁻¹⁶ These physiologic measurements correlate with clinical respiratory outcomes. We reported¹⁴ that infants who remained undelivered greater than 14 days after a course of AS, and who were then randomized to a single rescue course of AS versus placebo, had significantly increased Crs. This provided physiologic support for the large trial from Garite et al that demonstrated improved respiratory outcomes after a rescue course of AS.¹⁷ The purpose of our present study was to test the hypothesis that late preterm infants born at 34^{0/7} to 34^{6/7} weeks after treatment with AS would have significantly increased Crs compared with matched late preterm infants who had not received AS prior to delivery.

METHODS

This prospective cohort study was done in the Neonatal Intensive Care Unit at Oregon Health & Science University (OHSU) in Portland, Oregon. The study was approved by the Institutional Review Board of the hospital and informed consent was obtained from the parents. Patients were enrolled between September 2009 and March 2010. Inclusion criteria for the study group included: 1) infants born at a gestational age 34^{0/7} to 34^{6/7} weeks treated with AS as part of clinical care; 2) maternal treatment with two doses of betamethasone (12 mg intramuscular injection/dose, Celestone Soluspan, Merck & Co, Inc, Whitehouse Station, NJ) 24 hours apart with the first dose given within 7 days of delivery, or treatment with at least one dose of betamethasone at least 6 hours prior to delivery; and 3)

pulmonary function test done within the first 72 hours of life and prior to surfactant therapy if required for clinical care. The comparison group was comprised of infants whose mothers had not received AS before delivery (because of late arrival to the hospital or maternal conditions requiring imminent delivery) and who were matched as closely as possible to the study group for birth weight, gestational age, race, sex. We excluded patients born to mothers with insulin dependent diabetes, multiple gestation greater than twins, clinical chorioamnionitis, major congenital anomalies or chromosomal abnormalities. Gestational age was defined according to the date of the mother's last menstrual period, if known and reliable, or by ultrasound if done before 20 weeks of pregnancy.

Our primary outcome was comparison of respiratory compliance between the 2 groups. We also measured FRC in the 2 groups of patients and monitored other pertinent clinical respiratory outcomes were monitored as secondary outcomes.

Infant pulmonary function tests were measured with a computerized infant pulmonary function cart (SensorMedics 2600, SensorMedics Inc, Yorba Linda, CA). Crs was measured with the single-breath occlusion technique and FRC with the nitrogen washout method.^{14,18-22} These measurements can be performed in non-intubated and intubated infants.

Crs was measured with the single-breath occlusion technique^{14-16,18,21} while the patient was supine and quietly asleep. During this test, the airway was briefly occluded at end inspiration until an airway pressure plateau was observed, invoking the Hering Breuer reflex.

Respiratory system compliance and resistance were calculated from the passive flow-volume curve and total Crs was related to body weight. Acceptance criteria as per the American Thoracic Society and European Respiratory Society included: 1) stable end-expiratory baseline; 2) plateau pressure lasting >100 msec; 3) plateau pressure varying by ± 0.125 cm H₂O; 4) acceptable flow-volume curve by visual inspection, with linear data segment identified; and 5) at least 10 breaths accepted with a coefficient of variation <20%.^{18,23,24} For intubated infants, testing was done prior to surfactant therapy on ventilator settings to give tidal volumes of 4-6 mL/kg and on a positive end expiratory pressure (PEEP) of 5 cm H₂O.

For the nitrogen washout technique,^{14,16,19,22} calibration was performed with two known volumes, and a calibration line was constructed for the system at the specific flow rate. The calibration curve was then used to correlate the nitrogen washed out to the infant's FRC. The system corrected for dead space present and corrected the FRC to body temperature, pressure, and water-saturated conditions. Total FRC was related to body weight. Acceptance criteria included: 1) infant supine and quietly asleep; 2) test initiated at end expiration; 3) no evidence of leak on tracing of the washout; 4) consistent tracings; 5) at least 3 measurements with a coefficient of variation of <10%.^{18,23,24}

Clinical respiratory outcome measures including need for continuous positive airway pressure (CPAP), need for oxygen supplementation, surfactant administration, hours on CPAP, and hours on oxygen supplementation were also monitored. CPAP was initiated for grunting, increased work of breathing, and tachypnea. Surfactant was given to patients with moderate to severe RDS. Surfactant was administered within the first 24 hours of life if the

patient required > 0.40 FiO₂ to maintain adequate pulse oximeter oxygen saturation (SpO₂), had a pH < 7.25 , and/or had increased work of breathing despite adequate CPAP. In addition, oxygen supplementation was initiated if the SpO₂ was lower than 90% in our late preterm infants.

Statistical Analyses

We have previously reported a 50% increase in Crs and FRC in preterm infants (about 30 weeks of gestation) treated with AS within 7 days of delivery compared with matched untreated controls,¹⁶ reflecting both the biochemical (surfactant induction as reflected in increased Crs measurements) and structural benefits (as reflected in the increased FRC or lung volume measurements) of AS therapy. Epidemiologic data show late preterm infants have increased respiratory morbidity compared with term infants due to increased RDS and TTN. For our present study we hypothesized that late preterm infants 34^{0/7} to 34^{6/7} weeks treated with AS would have significantly higher Crs compared with matched untreated infants. Given the more mature gestational age of the late preterm infant compared with the patients in our previous study (about 30 weeks),¹⁶ we estimated that to show at least a 25% difference in Crs between groups we would need to study about 25 patients in each group to reject the null hypothesis with a type I error of 0.05 and a power of 80%.

Differences in continuous variables, including respiratory compliance between the 2 groups were analyzed by 2-tailed, Student t-tests, Mann-Whitney U test, and Wilcoxon signed ranks test were used where appropriate (for data not normally distributed). Categorical variables were evaluated with Chi-Square tests and Fisher exact tests where appropriate. Data are expressed as mean $\pm$ SD, unless otherwise indicated.

We matched 25 infants who did not receive AS before delivery as closely as possible to the 25 AS treated late preterm infants on the basis of gestational age at delivery, birth weight, race, and sex. This approach increased the homogeneity between the treated and untreated groups. In addition, mixed linear modeling²⁵ was used to compare respiratory compliance/kg and total respiratory compliance in the treated and untreated groups (primary outcome). Mixed linear modeling for continuous variables and mixed logistic modeling for categorical variables were also used to compare differences in secondary outcomes between the groups. This approach accounts for the correlation (non-independence) between twins, and allows for adjustment for additional covariates and potential confounders. Our model included the important covariates of maternal smoking, mode of delivery, and twin gestation. Other potential covariates included in the analyses were gestational age, birth weight, race, sex, the primary etiology of the preterm delivery, and rupture of membranes. We used SPSS for Windows, Version 22.0, Chicago, IL and SAS 9.4, SAS Institute Inc, Cary, NC for analyses.

RESULTS

The primary reason for preterm delivery in both groups was preterm labor, followed by hypertension / preeclampsia and antepartum hemorrhage (Table I). The AS treated group included 7 sets of twins and the untreated group included 5 sets of twins. Both groups had the same percent of Caucasians and females, and similar birth weights. The mean gestational

age of the treated group was 34.1 weeks versus 34.3 weeks in the untreated group. This was statistically different due to the very narrow gestational age range in the treated group (34.0 to 34.1 weeks) but had no significant effect on outcome when added to the statistical model. There was no significant difference in maternal smoking, mode of delivery, twin gestation, the primary etiology of the preterm delivery, or rupture of membranes between the groups (Table I).

The late preterm infants who received AS had significantly increased respiratory compliance, normalized for both body weight and total respiratory compliance (Table II) when compared with the untreated infants. These differences remained significant after accounting for the correlation between twins, and using mixed linear modeling to adjust for the confounding variables of maternal smoking, mode of delivery and twin gestation. The mean Crs normalized per kg in the AS treated group was 25% higher than in the untreated group: 1.33 versus 1.06 mL/cm H₂O/kg (adjusted 95% CI for difference 0.05, 0.49; $p = 0.016$). Mixed linear modeling showed that the variables of birth weight, gestational age, race, sex, primary etiology of the preterm delivery, and rupture of membranes were not statistically significant when added to the model containing only treatment group.

These outcomes were also compared accounting for the association between twins, and using mixed linear modeling (continuous variables) and mixed logistic modeling (categorical variables) to adjust for the potential confounders of maternal smoking, mode of delivery, and twin gestation. Although the study was not powered to detect differences in FRC between groups, FRC was measured (at the same time as Crs) in 24 of 25 of the treated and 20 of the 25 untreated infants. Measurement failures were due to inability to meet standard testing acceptance criteria. There was no significant difference in FRC with both groups having mid normal values (27.8 mL/kg in the AS treated group versus 25.4 mL/kg in the untreated group; adjusted p value = 0.260; Table III). There was no difference in respiratory resistance between groups. Respiratory compliance per mL of FRC (specific compliance) was higher in the treated compared with the control group (0.0480 versus 0.0410; $p = 0.093$). However, our study was not powered for differences in FRC and there were some missing FRC values. Although the study was also not powered for clinical secondary outcomes, there was a significant difference in the need for CPAP, with 16% in the treated group requiring CPAP versus 68% in the untreated group ($p = 0.007$). Also, 12% of the patients in the treated group required >24 hours of supplemental oxygen versus 48% in the untreated group ($p = 0.046$; Table III). There was no significant difference in surfactant therapy (8% versus 12%), RDS, hours on CPAP (median values 0 versus 11 hours), or hours on oxygen (median 0 versus 18 hours) between the groups.

DISCUSSION

This prospective cohort study demonstrates that late preterm infants (34^{0/7} to 34^{6/7} weeks) treated with AS as part of clinical care prior to delivery had significantly increased Crs (25% higher) compared with matched infants who did not receive AS therapy. This increased Crs also correlated with improved clinical respiratory outcomes, as significantly less of the AS treated infants required any CPAP and significantly less required more than 24 hours of

oxygen therapy. This study suggests that infants delivering as late preterm infants could benefit from AS treatment with an increased Crs after delivery.

Our study is limited by the fact that it is not a randomized trial and it was completed prior to the publication of the recent randomized controlled trial (RCT)¹¹ of AS versus placebo to women at risk for LPI deliveries conducted by the NICHD Maternal-Fetal Medicine Units Network. Therefore at the time of our study, it was still standard obstetrical practice to limit use of AS to women at risk for preterm delivery at <34 weeks of gestation and we report data on infants born at the beginning ($34^{0/7}$ to $34^{6/7}$ weeks) of the late preterm gestational age range. The study would have been strengthened by measurements of biomarkers for lung maturity²⁶ to help further define the mechanism of benefit of AS on respiratory compliance in the late preterm infant. Also, six of the 25 AS treated infants delivered less than 24 hours after initial AS dosing, so they may not have received the maximum clinical benefit from the AS therapy. However, studies in preterm lambs²⁷ have shown that changes in postnatal pulmonary function and decreases in pulmonary edema occur after about 8 hours of exposure to AS, thus Crs measurements in these six patients should still reflect partial benefit of AS therapy. Despite these limitations, this study adds important physiologic data for late preterm infants born at 34–35 weeks gestation and after AS therapy.

The strengths of our study include patient populations well matched for factors known to affect pulmonary function including birth weight, gestational age, race, and sex and also the adjustment for the correlation between twins. There were also no significant differences between groups in other important covariates that can affect pulmonary function testing such as cesarean section delivery or maternal smoking during pregnancy,^{18,28} and our results were adjusted for maternal smoking, mode of delivery and twin gestation with mixed linear modeling or mixed logistic modeling. In addition, our study reaffirms that pulmonary function tests, and specifically Crs measurements, can reproducibly quantify pulmonary responses to AS and these measurements correlate with clinical outcomes. Our data provide physiologic support to the recent large randomized trial of AS in late preterm infants.¹¹

Initial randomized trials of AS^{8–10} included few patients treated after 33 weeks due to accepted dogma that beyond 33 weeks the premature lung had achieved both biochemical / surfactant and structural maturity with the establishment of alveoli during the saccular phase of lung development.²⁹ Current data show that late preterm infants have increased respiratory morbidity compared with term infants. In a contemporary cohort of 233,844 deliveries, the odds of RDS were increased 40 fold for newborns born at 34 weeks and decreased with each advancing week until 38 weeks.³⁰ That study included 19,334 LPI and demonstrated differences in the incidence of respiratory distress between 34, 35, and 36 weeks as a whole, as well as a range of maturation within each gestational age.³⁰ There is increasing appreciation that lung maturation is a complex and dynamic process, and developmentally the late preterm lung is more similar to the more premature lung than the term lung.²⁹

Even in the absence of initial clinical respiratory disease, late preterm infants have increased wheezing and asthma, and altered pulmonary function tests that remain decreased over time compared with those of term infants.²⁹ In addition, lung maturity does not assure adequate

fluid reabsorption after delivery, and retained lung fluid can also lead to respiratory distress and need for support. AS could work by induction of the surfactant system, induction of structural lung maturity, and/or by stimulation of the epithelial sodium channel, an important determinant of fluid reabsorption after delivery.³¹ The increased Crs demonstrated in the infants treated with AS in our study could have been due to decreased RDS and/or TTN, entities that can sometimes be difficult to differentiate in the late preterm infant. Based on our physiologic measurements of FRC and on the comparable surfactant dosing between the 2 groups of patients, we speculate that the increased Crs was primarily due to decreased TTN. Although not powered for FRC measurements, there was not a significant difference in FRC between our groups which would be more consistent with TTN.

The large RCT¹¹ conducted by the NICHD Maternal-Fetal Medicine Units Network randomized women at high risk for late preterm delivery (34–36 weeks) to a course of AS (betamethasone) versus placebo. They reported a significant reduction in the need for respiratory support within 72 hours after birth (primary outcome) in the AS treated group (n=1427) compared with the control group (n=1400). The rates of severe neonatal respiratory complications, TTN, and surfactant use were also significantly lower in the AS group.¹¹ Neonatal hypoglycemia was significantly more common in the AS group than in the placebo group, although the rates of hypoglycemia in the AS group were similar to those expected in late preterm infants.^{11,13} The need for CPAP in our study was 16% in the AS treated group versus 68% in the untreated group. The primary outcome of our study, physiologic data of increased Crs in the AS group, supports the results of the RCT for decreased rate of neonatal respiratory complications in LPI, although we included twin gestations and patients with antepartum hemorrhage in our study. Of interest, two trials included in the Cochrane Systematic Review showed a significant reduction in RDS in babies exposed to AS between 33^{0/7} and 34^{6/7} weeks' gestation.^{8,32,33} There was no difference in the use of surfactant (RDS) in our patients (8% versus 12%), but this rate of RDS is comparable with the 10.4% incidence reported at 34 weeks in a recent large review.³⁰ Other smaller RCTs involving antenatal corticosteroids at 34–36 weeks of gestation have been published,^{34–36} although these studies were inconclusive, because they had substantial loss to neonatal follow-up³⁴ and had exclusions after randomization.³⁵ A recently updated Cochrane Review has included these randomized studies of AS in late preterm infants.³⁶

Respiratory compliance is significantly increased in late preterm infants (34^{0/7} to 34^{6/7} weeks of gestation) who received AS prior to delivery compared with matched untreated infants. Although not randomized, these pulmonary function data support the possible beneficial effects of AS in late preterm infants. We speculate that the increased Crs could be secondary to enhanced lung fluid reabsorption and/or to decreased RDS.

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ABBREVIATIONS

CPAP	Continuous positive airway pressure
Cr_s	Passive respiratory system compliance
FiO₂	Fractional inspired oxygen concentration
RDS	Respiratory distress syndrome
TTN	Transient tachypnea of the newborn

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Table I.**Maternal and Infant Demographics**

	<u>AS</u> (n = 25)	<u>No AS</u> (n = 25)	<u>P Value</u>
Maternal age (years) ^a	28.0 ±7.3	29.4 ±7.5	NS
Preterm labor (%)	14 (56)	17 (68)	NS
Hypertension/Preeclampsia (%)	5 (20)	7 (28)	NS
Antepartum hemorrhage (%)	6 (24)	1 (4)	NS
Maternal smoking (%)	3 (12)	3 (12)	NS
Rupture of membranes (hr) ^b	0 (0–0.5)	0 (0–2.4)	NS
Rupture of membranes >24 hr (%)	0	0	NS
Cesarean section (%)	15 (60)	11 (44)	NS
Gestational age at birth (wks) ^a	34.1 ±0.1	34.3 ±0.6	<0.05
Birth weight (g) ^a	2118 ±377	2177 ±323	NS
Caucasian (%)	22 (88)	22 (88)	NS
Female (%)	11 (44)	11 (44)	NS
1-minute Apgar ^b	8 (7–8)	7 (4–8)	NS
5-minute Apgar ^b	9 (9–9)	8 (7–9)	NS

AS, antenatal steroids; NS, not significant.

^aMean ± SD

^bMedian (25th – 75th percentiles).

Rupture of membranes is for 24 AS treated and 24 untreated patients. The AS group included 7 sets of twins and the untreated group 5 sets of twins (NS).

Table II.

Primary Outcome: Measurements of Respiratory System Compliance

	AS treated (n=25)	No AS (n=25)	Unadjusted Mean Difference (95% CI)	Unadjusted P value	Adjusted Mean Difference (95% CI) ^a	Adjusted P value ^a
Crs/kg (mL/cmH2O/kg)	1.33 ± 0.44	1.06 ± 0.32	0.27 (0.05, 0.49)	0.018	0.27 (0.05, 0.49)	0.016
Total Crs (mL/cmH2O)	2.82 ± 1.07	2.28 ± 0.62	0.54 (0.04, 1.04)	0.035	0.56 (0.06, 1.06)	0.030

AS, antenatal steroids; Crs, respiratory compliance.

Values are mean ± SD, mean difference (95% confidence intervals) and P values.

^a Adjusted for correlation between twins and maternal smoking, mode of delivery, and twin gestation with mixed linear modeling.

Table III.**Pulmonary Function and Respiratory Outcomes in Late Preterm Infants**

	AS treated (n=25)	No AS (n=25)	Unadjusted Mean Difference (95% CI)	Unadjusted P value	Adjusted Mean Difference (95% CI) ^a	Adjusted P value ^a
FRC/kg (mL/kg) ^c	27.8 ± 7.1	25.4 ± 6.3	2.40 (−1.72, 6.52)	0.247	2.25 (−1.73, 6.23)	0.260
Total FRC (mL) ^c	57.7 ± 16.5	54.3 ± 13.0	3.43 (−5.76, 12.63)	0.455	3.04 (−6.29, 12.37)	0.513
Rrs (cmH2O/mL/sec)	0.055 ± 0.020	0.056 ± 0.025	− 0.001 (− 0.014, 0.012)	0.889	− 0.001 (− 0.015, 0.013)	0.877
	AS treated (n=25)	No AS (n=25)	Unadjusted Odds Ratio (95% CI)	Unadjusted P value	Adjusted Odds Ratio (95% CI) ^b	Adjusted P value ^b
Surfactant (%) ^d	2 (8)	3 (12)	0.64 (0.09, 4.40)	0.642	0.64 (0.09, 4.40)	0.642
RDS (%) ^d	2 (8)	3 (12)	0.64 (0.09, 4.40)	0.642	0.64 (0.09, 4.40)	0.642
Needing CPAP (%)	4 (16)	17 (68)	0.08 (0.01, 0.45)	0.005	0.07 (0.01, 0.46)	0.007
Needing >24 hours of oxygen (%)	3 (12)	12 (48)	0.20 (0.04, 0.95)	0.043	0.18 (0.03, 0.97)	0.046

AS, antenatal steroids; FRC, functional residual capacity; Rrs, respiratory resistance; RDS, respiratory distress syndrome; CPAP, continuous positive airway pressure.

Values are mean ± SD, mean difference (95% confidence intervals) and P values for continuous variables; and number (%), odds ratio (95% confidence intervals) and P values for categorical variables.

^aAdjusted for correlation between twins and maternal smoking, mode of delivery, and twin gestation with mixed linear modeling for continuous variables

^bAdjusted for correlation between twins and maternal smoking, mode of delivery, and twin gestation with mixed logistic modeling for categorical variables.

^cFRC obtained in 24 AS treated and 20 untreated patients.

^dUnadjusted odds ratio and P values because model would not converge for these variables.