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

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

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 antenatal steroids and 25 matched infants who did not receive antenatal steroids. 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 ($P = .007$) or >24 hours of supplemental oxygen ($P = .046$). There was no difference in surfactant therapy.

Conclusions Respiratory compliance was significantly increased in this cohort of late preterm infants born at $34^{0/7}$-$34^{6/7}$ weeks who received antenatal steroids compared with matched infants who did not receive antenatal steroids. Although not randomized, these data provide physiologic support for the possible beneficial effects of antenatal steroids in late preterm infants. *(J Pediatr 2018;■■:■■-■■).*

Late preterm infants born at $34^{0/7}$-$36^{6/7}$ weeks of gestation make up about 70% of all preterm deliveries and accounted for 6.9 % of all births in the US 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 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 of gestation, initial randomized trials of antenatal steroid 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 3 different time epochs, Joseph et al concluded that failure to provide adequate treatment with antenatal steroids 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 trial[11] of antenatal steroids given at 34-36 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 antenatal steroids on newborn pulmonary function.[14-16] These physiologic measurements correlate with clinical respiratory outcomes. We reported[14] that infants who remained undelivered greater than 14 days after a course of antenatal steroids, and who were then randomized to a single rescue course of antenatal steroids vs 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 antenatal steroids.[17] The purpose of our present study was to test the hypothesis that late preterm infants born at $34^{0/7}$-$34^{6/7}$ weeks of gestation after treatment with antenatal steroids would have significantly increased Crs compared with matched late preterm infants who had not received antenatal steroids prior to delivery.

CPAP	Continuous positive airway pressure
Crs	Passive respiratory system compliance
FRC	Functional residual capacity
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
TTN	Transient tachypnea of the newborn

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Methods

This prospective cohort study was done in the Neonatal Intensive Care Unit at Oregon Health and Science University 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 $34^{0/7}$-$34^{6/7}$ weeks treated with antenatal steroids as part of clinical care; (2) maternal treatment with 2 doses of betamethasone (12 mg intramuscular injection/dose, Celestone Soluspan; Merck and Co, Inc, Whitehouse Station, New Jersey) 24 hours apart with the first dose given within 7 days of delivery, or treatment with at least 1 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 antenatal steroids 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, and 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 as secondary outcomes.

Infant pulmonary function tests were measured with a computerized infant pulmonary function cart (SensorMedics 2600; SensorMedics Inc, Yorba Linda, California). 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 nonintubated 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 ms; (3) plateau pressure varying by < ±0.125 cm H_2O; (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 of 5 cm H_2O.

For the nitrogen washout technique,[14,16,19,22] calibration was performed with 2 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; and (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 fractional inspired oxygen concentration (FiO_2) to maintain adequate pulse oximeter oxygen saturation (SpO_2), had a pH <7.25, and/or had increased work of breathing despite adequate CPAP. In addition, oxygen supplementation was initiated if the SpO_2 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 antenatal steroids 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 antenatal steroid therapy. Epidemiologic data show late preterm infants have increased respiratory morbidity compared with term infants because of increased RDS and TTN. For our present study, we hypothesized that late preterm infants $34^{0/7}$-$34^{6/7}$ weeks of gestation treated with antenatal steroids 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 χ^2 tests and Fisher exact tests where appropriate. Data are expressed as mean ±SD unless otherwise indicated.

We matched 25 infants who did not receive antenatal steroids before delivery as closely as possible to the 25 antenatal steroids-treated late preterm infants on the basis of gestational age at delivery, birth weight, race, and sex. This approach

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