Respiratory Function in Healthy Late Preterm Infants Delivered at 33-36 Weeks of Gestation

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Objective To compare pulmonary function testing including respiratory compliance (Crs) and time to peak tidal expiratory flow to expiratory time (TPTEF:TE) at term corrected age in healthy infants born at 33-36 weeks of gestation versus healthy infants delivered at term.

Study design We performed a prospective cohort study of late preterm infants born at 33-36 weeks without clinical respiratory disease (<12 hours of >0.21 fraction of inspired oxygen) and studied at term corrected age. The comparison group was term infants matched for race and sex to the preterm infants and studied within 72 hours of delivery. Crs was measured with the single breath occlusion technique. A minimum of 50 flow-volume loops were collected to estimate TPTEF:TE.

Results Late preterm infants (n = 31; mean gestational age 34.1 weeks, birth weight 2150 g) and 31 term infants were studied at term corrected age. The late preterm infants had decreased Crs (1.14 vs 1.32 mL/cm H_2O/kg; $P < .02$) and decreased TPTEF:TE (0.308 vs 0.423; $P < .01$) when compared with the term infants. Late preterm infants also had an increased respiratory resistance (0.064 vs 0.043 cm H_2O/mL/s; $P < .01$).

Conclusions Healthy late preterm infants (33-36 weeks of gestation) studied at term corrected age have altered pulmonary function when compared with healthy term infants. *(J Pediatr 2013;162:464-9)*.

See editorial, p 443

Human lung development is a vulnerable process that can be significantly affected by multiple factors, particularly premature delivery. The rate of preterm births in the US has increased over the last 20 years. Of these preterm births, about 70% are born late preterm (34 0/7-36 6/7 weeks' gestation) with the rate of late preterm births increasing at a faster pace than the overall rate of preterm birth.[1-3] Infants born at late preterm gestations are at increased risk for morbidities in the immediate newborn period including a higher rate of respiratory distress syndrome and transient tachypnea of the newborn when compared with term infants.[1]

Alveolarization in the human lung occurs in the third trimester of gestation and, therefore, preterm delivery, and without any clinical signs of respiratory distress, may affect lung structure and development. Histologic studies of the lungs of premature infants, including infants without respiratory disease, have shown pulmonary structural changes with increased bronchial muscle, collagen, and elastin.[4] Recent studies examining premature infants born at a wide range of gestational ages (25-36 weeks), but without signs of respiratory distress, have demonstrated these infants to have altered airway and alveolar development[5,6] in the first few years of life. Prematurity is considered a risk factor for subsequent airway dysfunction, respiratory morbidity, and asthma in childhood. Little is known about the evolution of pulmonary function in the extra-uterine environment of the subgroup of healthy late preterm infants.

Our objective was to measure and compare pulmonary function tests (PFTs) including respiratory compliance (Crs) and flow volume characteristics including time to peak tidal expiratory flow to expiratory time (TPTEF:TE) in healthy late preterm infants versus healthy term infants matched for race and sex. We hypothesized that the late preterm infants without clinical lung disease would have decreased pulmonary function compared with healthy term infants studied at the same corrected age.

Methods

This study was conducted in the Neonatal Intensive Care Unit and the normal newborn nursery at Oregon Health and Science University (OHSU). The protocol was reviewed and approved by the Institutional

CPAP	Continuous positive airway pressure
Crs	Passive respiratory system compliance
FRC	Functional residual capacity
PFTs	Pulmonary function tests
Rrs	Respiratory resistance
TPTEF:TE	Time to peak tidal expiratory flow to expiratory time

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Review Board at OHSU. Informed consent was obtained for all enrolled patients. Infants were enrolled if they met the following inclusion criteria: (1) born at a gestational age 33 0/7-36 6/7 weeks for the late preterm infants and 38 0/7 weeks or more in the comparison group (term infants); (2) appropriate weight for gestational age; (3) without or requiring less than 12 hours of supplemental oxygen (including nasal cannula) or continuous positive airway pressure (CPAP) to maintain an adequate oxygen saturation; and (4) signed informed consent. Exclusion criteria included: (1) infants delivered to mothers who gave a history of smoking; (2) documented sepsis; (3) multiple congenital anomalies; (4) history of oligohydramnios; (5) congenital heart disease; and (6) evidence of respiratory distress syndrome by chest radiograph or need for surfactant therapy. Gestational age was calculated using the date of last menstrual period confirmed by first trimester ultrasound, or if unavailable by the Ballard exam of the neonatologist or pediatrician.[7] Late preterm infants had to be free of respiratory symptoms for at least 4 weeks prior to the outpatient testing at term corrected age.

A prospective cohort study design was used. Infants were studied in the supine position while quietly asleep, behaviorally determined by a stable body posture, regular respirations, and a lack of eye movements. No sedation was used. The term infants in the comparison group were matched for race and sex to the late preterm infants. Pulmonary function was measured at 40 weeks of corrected age for both groups of infants. Late preterm infants had been discharged prior to this age, so they were tested in the infant pulmonary function laboratory as outpatients. Term infants in the comparison group were studied prior to discharge, within 72 hours of life, in a room designated for pulmonary function testing on the Mother Baby Unit at OHSU. One respiratory therapist performed all of the tests.

Measurements

PFTs were measured with computerized infant pulmonary function carts (SensorMedics 2600; SensorMedics Inc, Yorba Linda, California and Jaeger/Viasys Master Screen BabyBody; Yorba Linda, California). The measurements were done with the infants breathing through a face mask that was connected to a 3-way valve.[8-10] Crs was measured with the single-breath occlusion technique. The airway was briefly occluded at end inspiration until an airway pressure plateau was observed and the Hering–Breuer reflex was invoked. The linear portion of the passive flow-volume curve was identified, and a regression line was drawn for the best fit. From the intercepts on the flow and volume axes, Crs and respiratory resistance (Rrs) were calculated. Acceptance criteria included: (1) stable end expiratory baseline; (2) plateau pressure lasting >100 ms; (3) plateau pressure varying by $\pm$ 0.125 cm H_2O or less; (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 of <20%.[9-11]

The functional residual capacity (FRC) was measured by the nitrogen washout technique. Calibration was done with 2 known volumes, and a calibration line was constructed for the system at the specific flow rate. The infant was switched in at end expiration from his/her baseline fraction of inspired oxygen (21%) to 100% oxygen at the flow rate used for calibration. 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 also related to body weight. Acceptance criteria included: (1) baby 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 <10%.[8,9,12] A minimum of 50 flow-volume loops with inspiratory and expiratory volumes within 15% were collected to estimate tidal volumes and the expiratory flow ratio of TPTEF:TE (Jaeger/Viasys Master Screen BabyBody).[13,14] These loops were collected during behaviorally determined quiet sleep and customarily collected in epochs of 20-30 breaths. Clinical outcome variables including time on CPAP and time on oxygen supplementation were also monitored.

Statistical Analyses

Our primary outcome was the difference in Crs measurements between the late preterm infants and the term infants. Hjalmarson et al[15] reported an approximate 40% difference in Crs between 32 "healthy" preterm infants born at a mean gestational age of 29.5 weeks (range of 25-33 weeks) compared with term infants. We hypothesized that the Crs in healthy infants born at 33-36 completed weeks of gestation would be approximately 30% different than the Crs in healthy term infants, when both groups were tested at term corrected age. We estimated a sample size of approximately 30 infants in each group to demonstrate a 30% difference in Crs between the groups with an 80% power and a type I error of 0.05.

The late preterm infants and term infants were matched for race and sex, and studied as closely as possible to 40 weeks of corrected gestational age. Both groups of infants were healthy with no clinical signs of respiratory disease.

Differences in continuous variables between the 2 groups were analyzed by Student t tests (2-tailed) and categorical variables were evaluated by the χ^2 test or Fisher exact test where appropriate. To account for confounders, the pulmonary function data was further adjusted using general linear modeling[16] for: socioeconomic status based on insurance coverage; family history of asthma; the z score for the infant's length at the time of study; and the corrected age of the infant at the time of study. These factors are all well known confounders of lung function and preterm delivery. In addition, the infant's weight at time of study, and important perinatal factors such as gestational age at delivery, birth weight, multiple gestation, antenatal steroid therapy, and pre-eclampsia were investigated. The infant's Z scores for anthropometric measurements were calculated from 2000 Centers for Disease Control and Prevention growth charts (Epi Info v. 3.3.2; Centers for Disease Control and Prevention, Atlanta, Georgia) for the term group[17] and Fenton's preterm infant growth