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ANTENATAL CORTICOSTEROIDS DECREASE FORCED VITAL CAPACITY IN INFANTS BORN FULLTERM

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Abstract

Antenatal corticosteroids (ACS) administration to pregnant women for threatened preterm labor is standard obstetric care to reduce neonatal respiratory distress syndrome and the associated respiratory morbidity. While ACS stimulates surfactant production in the fetal lung, the effects of ACS upon the subsequent growth and development of the lung are unclear. Follow-up studies outside of the neonatal period have been primarily limited to spirometry, and most subjects evaluated were born prematurely. To our knowledge, no study has assessed both airway and parenchymal function in infants or adults following ACS exposure.

We hypothesized that ACS impairs lung growth and performed infant pulmonary function testing, which included spirometry, alveolar volume (V_A) and lung diffusion (D_L). As a pilot study, we limited our assessment to infants whose mothers received ACS for threatened preterm labor, but then proceeded to full term delivery. This approach evaluated a more homogenous population and eliminated the confounding effects of preterm birth.

We evaluated 36 full-term infants between 4–12 months of age; 17 infants had ACS exposure and 19 infants had no ACS exposure. Infants exposed to ACS had a significantly lower FVC compared to non-ACS exposed infants (250 vs. 313 ml; $p = 0.0075$). $FEV_{0.5}$ tended to be lower for the ACS exposed group (205 vs. 237 ml; $p = 0.075$). V_A and D_L did not differ between the two groups. These findings suggest that ACS may impair subsequent growth of the lung parenchyma.

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Keywords

lung growth; pulmonary function; spirometry; lung diffusion; lung volume

INTRODUCTION

Antenatal corticosteroids (ACS) administration to pregnant women for threatened preterm labor is standard obstetric care to reduce neonatal respiratory distress syndrome (RDS) and the respiratory morbidity associated with preterm birth[1]. While ACS stimulates surfactant production in the fetal lung, which reduces the incidence of RDS, the effects of ACS upon the subsequent growth and development of the lung are unclear. During late gestation, alveoli undergo secondary septation to increase alveolar surface area for gas exchange, the primary function of the lung. Based upon animal data, secondary septation and alveolarization may be impaired by ACS administration[2; 3].

Long-term pulmonary function follow-up studies of humans exposed to ACS have been limited. Among 6–8 year old children who were born preterm and exposed to ACS (N=9), neither spirometric measurements nor total lung volume (TLC) differed compared to non-ACS exposed children born preterm[4]. However, a follow-up study of 14-year old children born premature reported that ACS exposure was associated with an increased odds of having severe airways obstruction, FEV_1/FVC <5th percentile, particularly in those with birth weight <1000 gm[5]. The largest follow-up study evaluated 30-year old subjects who were part of a randomized control trial evaluating the efficacy of ACS to minimize neonatal RDS[6]. The investigators found no differences in FVC or FEV_1 comparing subjects exposed and non-exposed to ACS. A major limitation for lung growth and development studies is that the majority of the subjects evaluated were born prematurely, and often very premature. Therefore, the more direct effects of ACS upon the subsequent growth and development of the lung is difficult to separate from the adverse effects of premature birth itself, as well as the adverse effects from the oxygen and ventilator support required for premature infants. In addition, follow-up evaluation was many years after ACS exposure; post-natal environmental factors might be important confounders. Follow-up studies have been primarily limited to spirometry and not more direct assessment of the lung parenchyma, which may be more adversely affected by ACS than the airways.

Studies of infants following ACS exposure have also been very limited. When evaluated within days of delivery, McEvoy and colleagues reported that premature neonates whose mothers received ACS had a greater respiratory system compliance (C_{RS}) and functional residual capacity (FRC) compared to infants of non-treated mothers[7]. These results, which assessed the lung parenchyma, are consistent with the therapeutic goal for ACS to accelerate surfactant production in the neonatal lung. However, as measurements were obtained shortly after birth, the measurements probably reflect the relatively short-term benefits of ACS upon surfactant production, and not the potential longer-term adverse effects of ACS upon subsequent growth and development of the lung.

No study has assessed both airway and parenchymal function in infants or adults following ACS exposure to our knowledge. We hypothesized that ACS impairs lung growth and

development differentially, with a more negative impact on the lung parenchyma than the airways. We performed a detailed assessment of infant pulmonary function, which included spirometry, as well as alveolar volume (V_A) and lung diffusion (D_L), using state of the art methodology developed in our laboratory. As a pilot study, we limited our assessment to infants whose mothers received ACS for threatened preterm labor, but then proceeded to full term delivery. By eliminating infants born prematurely, we evaluated a more homogenous population and eliminated the confounding effects of preterm birth.

METHODS

Subjects

After discussion of risks and benefits, informed parental consent was obtained. Consent was obtained from both parents when possible, but single parent consent was acceptable when the other parent was not known or unable to be reached. The local governing Institutional Review Board approved this study and subjects were recruited between November 2015 and February 2020.

Term Infants - ACS exposed: Infants were considered exposed to ACS if their mother received one or more doses for threatened preterm labor, and then delivered full-term infants (> 37 weeks gestation). Subjects were recruited from either an ongoing research study on the pharmacokinetics of betamethasone therapy in threatened preterm birth (NCT02793700) or by mailing flyers to women who received ACS and delivered term within our health care system.

Term Infants – non-ACS exposed: Infants were recruited from either the normotensive full-term control population of an ongoing research study related to maternal preeclampsia (NCT02639676) or by mailing flyers to the women who did not receive ACS and delivered within our health care system.

Pulmonary Function

Pulmonary function testing was performed at James Whitcomb Riley Children's Hospital while sleeping after administration of oral chloral hydrate (50–100mg/kg). Oxygen saturation (SO_2) and heart rate were monitored during testing according to ATS guideline[8].

Spirometry: Forced expiratory maneuvers were measured using the Raised Volume-Rapid Thoracic Compression Technique, as previously described[9]. The primary outcome parameters were the forced vital capacity (FVC), forced expiratory flow at 75% expired volume (FEF_{75}), forced expiratory volume in 0.5 seconds ($FEV_{0.5}$), and FEF between 25% and 75% of FVC ($FEF_{25–75}$).

Diffusing Capacity and Alveolar Volume: D_L and V_A were measured using a single breath technique with an induced respiratory pause at an inflation pressure of 30 cm H_2O, as we have previously described[10; 11]. Gas concentrations of the test gas were continuously measured with a mass spectrometer (Perkin-Elmer). Results for D_L and V_A were expressed as the average of 2–3 values within 10%, and D_L was adjusted for hemoglobin.

Statistical Analysis

Demographic data for the two groups were compared using two sample t-tests for continuous variables and Fishers Exact test for categorical variables, due to low expected cell counts. For outcomes found to be non-linear, t results were verified by Wilcoxon rank-sum tests. Comparisons of the two groups were performed using ANCOVA, adjusting for body length at time of testing, gender, race, and gestational age at delivery. Within the group exposed to ACS, we performed a subgroup analysis of the pulmonary function outcomes based on gestational age at initial dose and number of doses of ACS received. All analytic assumptions were verified and all analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

We evaluated 36 full-term infants between 4–12 months of age; 17 infants had ACS exposure and 19 infants had no ACS exposure. The demographics for the mothers and the infants are summarized in Table 1. The maternal characteristics of age, as well as histories of asthma, tobacco smoking, preeclampsia, chorioamnionitis, and C-section delivery, did not differ for the two groups. The infants exposed to ACS delivered at a younger gestational age (39.8 vs. 38.0 weeks); however, they did not differ for birth weight, length, gender, or race. In addition, at the time of pulmonary function testing, the two groups did not differ in age, body length, or weight.

The comparison of pulmonary function is summarized in Table 2. The analysis adjusted for body length at testing, gender and race as covariates, as well as GA at birth. For spirometry, the infants exposed to ACS had a significantly lower FVC compared to Non-ACS exposed infants (250 vs. 313 ml; $p = 0.0075$). $FEV_{0.5}$ tended to be lower for the ACS exposed group (205 vs. 237 ml); however, the difference did not reach statistical significance ($p = 0.0751$). The forced expiratory flows (FEF_{75}, FEF_{50}, and $FEF_{25–75}$) did not differ for the two groups ($p > 0.68$). Similar results were obtained when GA at birth was excluded from the analysis. V_A and D_L did not differ between the two groups. Among those infants exposed to ACS, there were no differences in pulmonary function outcomes by subgroups of GA of the initial ACS dose or the number of doses. (data not shown)

DISCUSSION

Our study is the first, to our knowledge, to demonstrate that infants whose mothers received ACS for preterm labor, and subsequently delivered at full-term, have a lower FVC compared to infants born full-term whose mothers did not have preterm labor and did not receive ACS. In contrast to FVC, there were no differences in FEFs between the two groups. These findings suggest that ACS prescribed for preterm labor may impair subsequent growth of the lung parenchyma, but not adversely affect the airways. Our findings suggest that ACS for preterm labor may have adverse effects upon the subsequent growth and development of the lung parenchyma.

We found FVC to be on average 63 ml (20%) smaller in the group of infants that received ACS. The lung volume assessed by spirometry, FVC, is smaller than V_A; however, in the

absence of obstructive airways disease, these two lung volumes are highly correlated. There was a statistically significant difference in the GA at delivery for the two groups. We attempted to account for the difference by adjusting for GA at delivery in the ANCOVA model. We have previously reported that among infants following late preterm birth without significant respiratory morbidity, there was no difference in FVC compared to health full term controls when adjusting for body length at time of testing[12]Therefore, we do not believe that the difference in 2 weeks gestational age accounts for the observed difference in FVC observed in the ANS group of infants compared to controls. The ACS treated group had on average a V_A that was 70 ml (16%) smaller compared to the non-ACS group. Although this difference in V_A was not statistically significant, the similarity in magnitude for the decrement in both lung volumes measured by two very different techniques, is consistent with each other and suggests impaired lung parenchymal growth following ACS. The group mean D_L for the ACS treated group was 11% lower compared to the non-ACS infants; however, similar to V_A, this difference was not statistically significant. This likely reflects our limited sample size in this initial study for these outcomes. From the inter-subject variability in Table 2, estimated sample sizes for 80% power for differences in FVC, V_A and D_L are 18, 53, and 160 in each group, respectively.

The study most similar in design to ours was by Hjalmarson and Sandberg[13], who compared FRC for infants whose mothers received ACS for threatened preterm labor, but subsequently delivered full-term. At 40-weeks gestational age, FRC measurements were obtained by the nitrogen washout technique during tidal breathing, the investigators reported no difference for the ACS exposed, and full-term non-ACS exposed groups. FRC is dynamically controlled in neonates, so that the measured value is higher than the value obtained during an apnea or respiratory pause. In addition, FRC is less than 1/3 of V_A. Therefore, dynamic FRC is often not an effective lung volume to assess lung growth[14–16].

In contrast to the lower FVC in the ACS group of infants, we found no significant differences in forced expiratory flows (FEF_{75}, FEF_{50}, and $FEF_{25–75}$), which were lower by only 5, 4 and 3%, respectively. $FEV_{0.5}$ tended to be lower, but did not achieved statistical significance; however, this parameter is a timed expiratory volume in contrast to FEF, which are flows measured at specific expired lung volumes. The lower $FEV_{0.5}$ probably reflects the decrement in FVC, as the ratio, $FEV_{0.5}$/FVC, tended to be higher rather that lower in the ACS treated group.

Dalziel and colleagues evaluated the largest long-term spirometric follow-up of off-spring from mothers who were randomized to ACS versus placebo for preterm labor. At 30-years of age, approximately 200 subjects were evaluated and no differences were found in FVC or FEV_1. The adult study occurred decades after ACS exposure, which allows for other potential post-natal confounders to effect FEV_1 and FVC. In addition, the majority of the adult population (both ACS-exposed and controls) were born premature.

Our study has several strengths and limitations. An important strength of our study was restricting the evaluation to infants born full term. This approach minimized the heterogeneity in lung development that occurs following premature birth, as well as the lung injury potentially produced by the respiratory support and complications with premature

neonates. Another important strength of our study was the evaluation of the potential effect of antenatal glucocorticoids upon pulmonary function during infancy, outside of the neonatal period, but still relatively close to the ACS intervention. This limits the confounding of early childhood environmental exposures. Lastly, we evaluated both airway and parenchymal function using state of the art methodology for infants, and techniques similar to that routinely employed in older cooperative children. An important limitation of our study is the relatively small sample size. While we were able to detect differences in FVC, we were under-powered to detect potential differences in V_A and D_L, which are more direct measures of parenchymal function. Our small sample size limited our ability to detect a possible dose response relationship between ACS and altered fetal lung development influenced by GA at ACS exposure. Lastly, our study was not a randomized trial, which ethically cannot be performed at the current time, since ACS for preterm labor is the standard of care. The mothers of our non-ACS group did not experience preterm labor; however, the maternal histories otherwise did not differ for our two groups.

In summary, our study of infants whose mothers received ACS for premature labor and subsequently delivered at term had significantly lower FVC compared to infants born full-term whose mothers did not receive ACS. These findings suggest that ACS may impair growth and development of the lung parenchyma. Follow-up studies with a larger sample size are required to determine whether ACS impair more specific assessments of the lung parenchyma, such as alveolar volume and lung diffusion capacity.

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Table 1 –

Demographics

	Overall (n=36)	Non-ACS (n=19)	ACS (n=17)	p-value
Maternal				
Age (years)	27.69 (5.98)	28.26 (5.67)	27.06 (6.42)	.5540
Asthma	7 (19.4)	4 (21.1)	3 (17.7)	>.9999
Tobacco smoking during pregnancy	11 (30.6)	6 (31.6)	5 (29.4)	>.9999
Pre-eclampsia	2 (5.6)	0 (0)	2 (11.8)	.2159
Chorioamnionitis	1 (2.8)	0 (0)	1 (5.9)	.4722
GA at first steroid dosing	31.60 (3.81)	n/a	31.60 (3.81)	n/a
Number of steroid courses	0 (1)	n/a	1 (0)	n/a
Delivery cesarean	9 (25.0)	4 (21.1)	5 (29.4)	.7060
Infant				
GA at birth (weeks)	38.95 (1.20)	39.83 (0.66)	37.97 (0.84)	<.0001*
Gender (Female)	12 (33.3)	7 (36.8)	5 (29.4)	.7317
Birth weight (kg)	3.26 (0.53)	3.33 (0.49)	3.18 (0.57)	.3820
Birth length (cm)	50.17 (2.09)	50.49 (1.69)	49.81 (2.46)	.3378
Race (African-American)	13 (36.1)	6 (31.6)	7 (41.2)	.8592
Age at testing (months)	7.19 (2.57)	7.21 (2.30)	7.18 (2.92)	.9691
Length at testing (cm)	68.81 (5.45)	68.80 (5.58)	68.82 (5.48)	.9899
Weight at testing (kg)	8.63 (1.77)	8.62 (1.81)	8.64 (1.79)	.9764

Values are means (standard deviation) for continuous variables and frequencies (percentages) for categorical variables. P-values are from t-tests and Fisher's Exact tests, respectively. Due to some slight non-linearity, t-test results were verified with Wilcoxon rank-sum tests. Courses of steroids is given with median (IQR).

GA: gestational age

Table 2 –

Pulmonary Function Outcomes

	Non-Steroid (n=19)	Steroids (n=17)	p-value
Parameters			
Alveolar Volume and Diffusion			
V_A (ml) BTPS	448.0 (26.2)	377.6 (28.8)	.1316
D_L (mL/min/mmHg; STPD)	3.24 (0.22)	2.88 (0.24)	.3590
Spirometry			
FVC (ml)	313.0 (13.0)	249.6 (13.2)	.0075
$FEV_{0.5}$ (ml)	236.6 (10.1)	205.2 (10.2)	.0751
FEF_{75} (ml/s)	279.9 (22.8)	266.8 (23.1)	.7353
FEF_{50} (ml/s)	489.5 (30.9)	468.3 (31.2)	.6863
$FEF_{25–75}$ (ml/s)	450.6 (29.9)	438.6 (30.2)	.8126
$FEV_{0.5}$/FVC	0.77 (.278)	0.83 (.281)	.1984

Values are means (standard errors). P-values are from ANCOVA adjusted for body length at testing, gender, race, and GA at delivery. V_A – alveolar volume; D_L – lung diffusion; FVC – forced vital capacity; $FEV_{0.5}$ – forced expired volume in 0.5 seconds; FEF_{75} – forced expiratory flow at 75% FVC; FEF_{50} – forced expired flow at 50% FVC; $FEF_{25–75}$ – forced expiratory flow between 25% and 75% FVC.