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Vitamin A Supplementation in Extremely Low- Birth-Weight Infants: Subgroup Analysis in Small-for-Gestational-Age Infants

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Abstract

Objective—Preterm infants with intrauterine growth restriction are at increased risk of respiratory distress syndrome and bronchopulmonary dysplasia (BPD). A randomized clinical trial by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network demonstrated that vitamin A supplementation in extremely low-birth-weight (ELBW) preterm infants requiring early respiratory support decreased the risk of developing BPD.

Study Design—A subgroup analysis of small-for-gestational-age (SGA) infants from the original NICHD trial was performed to test the hypothesis that in infants requiring early respiratory support, vitamin A supplementation decreases the relative risk of BPD or death in premature SGA infants to a greater extent than in gestational age-equivalent vitamin A-treated appropriate-for-gestational-age (AGA) infants.

Results—Although vitamin A supplementation significantly increased serum retinol concentrations in AGA ELBW infants (median [5th percentile, 95th percentile]: 16.3 [–7.0, 68.8] versus 2.4 [–13.9, 55.1]; $p < 0.001$), no increases were noted in SGA ELBW infants.

Conclusions—Given the limited power of this analysis due to a low number of SGA infants, these data did not provide evidence to support the hypothesis that vitamin A supplementation in preterm SGA infants requiring early respiratory support decreases the relative risk of BPD or death as compared with preterm AGA infants.

Keywords

vitamin A; IUGR—intrauterine growth restriction; BPD—bronchopulmonary dysplasia; SGA—small for gestational age; AGA—appropriate for gestational age

Infants who are exposed to calorie-restricted environments prenatally often experience intrauterine growth restriction (IUGR) and are at risk of developing significant metabolic alterations of critical organs such as brain, liver, cardiac muscle, and lungs.¹ Contrary to conventional wisdom, IUGR fetal stress causes delayed lung maturation² with affected infants showing abnormalities in alveolar formation. Premature infants born small for gestational age (SGA; a frequent hallmark of IUGR) have additional caloric limitations extending into the early postnatal period and are at increased risk of developing pulmonary sequelae such as respiratory distress syndrome and bronchopulmonary dysplasia (BPD).¹ As these infants grow, they often develop more wheezing and respiratory infections as compared with very low-birth-weight infants who are appropriate for gestational age (AGA).³ Diminished airway function in these infants may persist into adulthood, suggesting the possibility that adverse events during “fetal programming” result in lifelong respiratory compromise.³

Two postulated mechanisms linking IUGR to BPD include systemic fetal inflammatory response due to underlying chronic hypoxia or delayed metabolic adaptation with lack of essential micronutrients (e.g., vitamin A) necessary for optimal organogenesis. A previous report from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network clinical trial demonstrated that intramuscular injection of 5,000 IU vitamin A (retinoic acid) three times per week for 4 weeks reduced biochemical evidence of vitamin A deficiency and decreased the risk of chronic lung disease in extremely low-birth-weight (ELBW) infants requiring early respiratory support.⁴ Although there were no differences in mortality, the primary outcome—death or chronic lung disease at 36 weeks postmenstrual age—occurred in significantly fewer infants in the vitamin A group than in controls (55% versus 62%; relative risk, 0.89, 95% confidence interval, 0.80 to 0.99). Overall, for every 14 to 15 infants who received vitamin A, one additional infant survived without chronic lung disease. Furthermore, no increases in mortality or neurodevelopmental impairment were associated with the reduction of BPD at 18 to 22 months’ follow-up.⁵ Although the study population included approximately 15% SGA infants, further data analysis has not been performed to determine the extent of this improvement within the premature SGA/IUGR infant subgroup alone. The question of whether vitamin A supplementation preferentially improves pulmonary outcomes in ELBW infants who are SGA thus remains unanswered.

The purpose of the current subgroup analysis was to test the hypothesis that in infants requiring early respiratory support, vitamin A supplementation decreases the relative risk of BPD or death in premature SGA infants to a greater extent than in gestational age–equivalent vitamin A–treated AGA infants. This premise is based on the possibility that the slight improvement in risk of developing BPD observed among ELBW infants in the original study (prevention of BPD in 1 of every 14 to 15 infants treated) may represent a diluted effect. A separate analysis of each subgroup (SGA versus AGA) could thus reveal a greater effect of vitamin A intervention in SGA ELBW infants and lead to a more targeted strategy for vitamin A supplementation to prevent BPD in this population.

Materials and Methods

Study Population

The vitamin A supplementation trial was a multicenter, masked, randomized trial to assess the effectiveness and safety of vitamin A supplementation as compared with a sham procedure in 807 infants with ongoing need of respiratory support 24 hours after birth.⁴ We used prospectively collected data from this trial to determine if vitamin A supplementation decreases relative risk of BPD or death in the subset of infants who were SGA and if that decrease is greater than in AGA infants of the same gestational age group. Vitamin A was

given intramuscularly at a dose of 5,000 IU on Mondays, Wednesdays, and Fridays for 4 weeks where the procedure occurred behind a screen and the injection site was covered by an adhesive bandage. For control subjects, the sham procedure was the same with the exception that an actual injection was not given. BPD (referred to as “chronic lung disease” in the original study) was defined as the need for oxygen or mechanical ventilation at 36 weeks’ postmenstrual age.

This retrospective secondary analysis included all 807 infants divided into 4 subgroups: SGA (birth weight < 10th percentile on birth weight nomogram⁶) infants randomized to vitamin A ($n = 50$); SGA infants randomized to control ($n = 54$); AGA infants randomized to vitamin A ($n = 355$); and AGA infants randomized to control ($n = 348$). The original NICHD study was only powered to formally test the primary hypothesis of treatment effect on BPD or death for the entire study population combined (SGA and AGA infants analyzed together). As such, all analyses in this article are exploratory in nature and all p values presented are descriptive and do not represent formal tests of hypotheses.

Statistical Analysis

Baseline and demographic characteristics were compared between SGA and AGA infants using Wilcoxon rank sum tests for continuous outcomes and Cochran Mantel Haenszel tests for categorical variables. Because BPD at 36 weeks may be censored by death, the primary end point was BPD or death by 36 weeks’ postmenstrual age. Secondary end points assessed in the original study were also analyzed including the categorical outcomes of death (prior to 36 weeks’ postmenstrual age and prior to discharge); survival with BPD (overall and with ventilation); oxygen usage (overall and with ventilation); sepsis (treated with antibiotics 5 days); intraventricular hemorrhage (overall and grade 3); periventricular leukomalacia; necrotizing enterocolitis; and patent ductus arteriosus (overall and treated with indomethacin or requiring surgery). Continuous outcomes included fraction of inspired oxygen (FIO₂), days of hospitalization, and concentrations of serum retinol (μg/dL), serum retinol-binding protein (mg/dL), and serum retinyl esters (μg/dL). Categorical end points were assessed by obtaining relative risk (RR) estimates for treated versus control groups within the SGA and AGA subgroups based on a Poisson model with explanatory variables of treatment group, growth status, and their interaction. Gestational age and center (for primary outcome only) were included as covariates. Continuous end points were assessed by obtaining median (5th, 95th) percentile estimates for treated and control groups within the SGA and AGA subgroups and comparing treatment groups within these subgroups using p values obtained from rank analysis of covariance controlling for gestational age (an extension of Wilcoxon rank sum test that allows for covariate adjustment).⁷

Results

Premature SGA Infants Demonstrated Lower Serum Retinol Concentrations at Baseline

Of the 807 infants enrolled in the original study, we identified 104 (13%) as SGA (defined as birth weight below 10th percentile for gestational age⁶); 50 received intramuscular vitamin A and 54 received sham injections. Comparison of baseline characteristics showed evidence of differences in birth weight (695 ± 149 g versus 781 ± 131 g), gestational age (27.9 ± 2.2 weeks versus 26.6 ± 1.7 weeks), and serum retinol concentrations at baseline (average 2.6 days of age; 13.1 ± 5.7 μg/dL versus 16.7 ± 6.1 μg/dL) between SGA and AGA groups, respectively (► Table 1; $p < 0.05$). No differences were noted in regard to race/ethnicity, gender, exposure to antenatal glucocorticoids, Apgar scores, delivery room resuscitation, surfactant administration, initial respiratory status, FIO₂ need, or time from birth to randomization and time from birth to vitamin A treatment.

Vitamin A Treatment Increased Serum Retinol Concentrations

Measurement of serum retinol concentrations on day 28 (at completion of vitamin A supplementation) revealed increases in serum retinol change from baseline in vitamin A–treated AGA infants as compared with AGA controls (median [5th percentile, 95th percentile]: 16.3 [–7.0, 68.8] versus 2.4 [–13.9, 55.1], respectively; ► Table 2; $p < 0.001$). Median serum retinol concentration increased in both the SGA and AGA vitamin A groups regardless of history of postnatal glucocorticoid therapy within 2 weeks before sampling. Similar differences were also noted in day 28 concentrations of serum retinol binding protein (2.5 [1.0, 6.10] versus 1.8 [0.7, 6.4]) and serum retinyl esters (26.5 [4.9, 103.4] versus 6.0 [0.0, 41.0]) for vitamin A–treated AGA and AGA controls, respectively. For SGA subjects, the differences in treatment groups for these outcomes follow the same general trends as AGA subjects, although in most cases the difference in median values for SGA control versus vitamin A is smaller than the difference for AGA subjects and not statistically significant. The largest finding in the SGA infants was an increase in serum retinyl esters (36.7 [8.8, 117.4] versus 8.5 [2.7, 86.6]) in vitamin A–treated SGA infants as compared with SGA controls, respectively, including infants who did and did not receive postnatal glucocorticoids within 2 weeks prior to sampling.

Effect of Vitamin A Treatment on Relative Risk of BPD or Death and Select Secondary Outcomes

To determine whether vitamin A supplementation decreases the relative risk of BPD or death in premature SGA infants to a greater degree than in gestational age–equivalent vitamin A–treated AGA infants, we examined the statistical interaction between SGA status and vitamin A supplementation to calculate the relative risk of experiencing these outcomes as well as other binary outcomes reported in the original vitamin A study.⁴ Based on the limited sample size, although the difference in proportion of infants with BPD or death in vitamin A versus control was greater in the SGA compared with AGA group (BPD and death: 52% versus 61% for vitamin A versus control for SGA and 55% versus 62% for vitamin A versus control AGA), the relative risks were similar and the confidence interval included 1. The analysis thus provided no evidence of a potential difference in treatment effect between SGA and AGA infants (RR = 0.91; 95% confidence interval [CI] 0.66 to 1.26 and RR 0.90; 95% CI 0.80 to 1.00 for SGA and AGA respectively; p value for interaction = 0.91; ► Fig. 1). As reported in the primary report, BPD or death occurred significantly less frequently in the vitamin A versus control (55% versus 62%; RR = 0.89; 95% CI 0.80 to 0.99). Analysis of treatment effect on BPD or death in the AGA subgroup alone revealed consistent results, though barely statistically significant (RR = 0.90; 95% CI 0.80 to 1.00), and similar trends were observed for survival with BPD at 36 weeks' postmenstrual age (RR = 0.86; 95% CI 0.73 to 1.00) in vitamin A–treated infants as compared with sham controls. Although point estimates of treatment effect in the SGA subgroup were similar to those of AGA, the confidence intervals were wider due to the smaller sample size. Interestingly, the relative risk of patent ductus arteriosus requiring surgery was lower in vitamin A–treated AGA infants (RR 0.62; 95% CI 0.40 to 0.97) as compared with AGA controls. No differences were noted in any of the other measured secondary outcomes including binomial outcomes of sepsis, intraventricular hemorrhage, periventricular leukomalacia, or necrotizing enterocolitis and continuous outcomes of median FIO₂ or length of hospitalization (► Table 3).

Discussion

The combined diagnoses of prematurity and IUGR place this population of vulnerable infants at very high risk of developing adverse pulmonary sequelae including BPD. Despite significant advances in perinatal and neonatal care, strategies to prevent BPD remain

limited.⁸ In preterm ELBW infants requiring early respiratory support, Tyson et al demonstrated a decreased risk of developing BPD following vitamin A supplementation.⁴ The study determined that the number of infants needing vitamin A supplementation to effectively prevent BPD in a single infant was about 14 to 15. Despite this modest but proven benefit, vitamin A is not routinely used to prevent BPD in many neonatal intensive care units.^{9,10} The purpose of the current subgroup analysis of SGA infants from the original trial was to determine whether vitamin A supplementation decreases the relative risk of BPD or death in premature SGA infants to a greater extent than in gestational age–equivalent vitamin A–treated AGA infants. Results showed that although vitamin A supplementation increased concentrations of serum retinol, retinol-binding protein, and retinyl esters in premature AGA infants, only retinyl esters were increased to the same extent in age-matched SGA controls. These data do not provide any evidence that vitamin A supplementation in infants requiring early respiratory support decreases the relative risk of BPD or death to a greater extent in preterm SGA infants than in preterm AGA infants. Importantly, the findings of the current study do not contradict the original study by Tyson et al and thus provide no reason not to continue to treat both SGA as well as AGA premature infants with vitamin A as originally suggested.

Previous studies exploring the effects of vitamin A on lung development and function have largely focused on newborn infant populations without specifically accounting for the underlying nutritional status (i.e., IUGR). Two observational studies in older children demonstrated a positive functional association between vitamin A status and lung function.^{11,12} Recently, a large, longitudinal placebo-controlled, double-blind, cluster-randomized trial in a chronically undernourished population of Nepali children demonstrated that maternal supplementation with vitamin A before, during, and after pregnancy improved lung function in their offspring.¹³ Similar to the study by Tyson et al, this study did not specifically differentiate outcomes between infants with and without a history of IUGR status, although it is likely that the Nepali cohort included a substantial number of SGA infants.^{14,15} The impact of calorie restriction on lung function has been long recognized. At least two studies have reported that infants born at term or near term with a low birth weight had lower lung function than controls of normal birth weight.^{16,17} A recent study reported that school-aged children who specifically met the criteria for IUGR as newborns based on birth weight and Ponderal index also showed poorer lung function as compared with age-matched controls.¹⁸

In contrast to the limited number of human studies, a considerable body of evidence from animal models, utilizing rats and mice, provides a rationale for vitamin A supplementation in the context of rescuing altered lung development. Daily injections of vitamin A induced alveolar formation following dexamethasone pretreatment that initially inhibited alveolar septation in 1-month-old rats.¹⁹ Vitamin A treatment during the alveolar period of lung development (first 2 to 3 weeks) also accelerated alveolar numbers in otherwise untreated newborn rats.¹⁹ Similarly, vitamin A treatment restored alveolar numbers in 1- to 2-month-old mice with genetically defective alveolar formation.¹⁹ We recently reported, in a novel rat model of IUGR through maternal calorie restriction, that vitamin A supplementation was able to rescue alveolar development in both pre- and postnatally calorie restricted offspring.²⁰ Importantly, this rodent model has applicability to preterm human infants because term newborn rats are born with lung development equivalent to that of 26- to 28-week preterm human infants.¹⁹ These findings are thus highly relevant to the current subgroup analysis in exploring whether vitamin A supplementation demonstrates improved pulmonary outcomes in preterm human infants who are SGA (and possibly IUGR).

Several limitations of our subgroup analysis are important to consider. First, our results represent a retrospective secondary analysis of a previous study that was not specifically

designed to compare the SGA and AGA subgroups of infants. Although a preliminary power analysis suggested a minimum requirement of at least 30 infants per group (SGA/vitamin A; SGA/ control), we recognize that the power analysis may not have been straightforward due to unequal sample sizes of SGA and AGA infants at a given gestational age and the need to adjust for trial stratification factors such as study center in the analysis. Second, because prenatal information regarding true IUGR status was not available during the original study, SGA status based on initial birth weight was used as a surrogate marker for IUGR in determining the subgroups. The original study did not collect information on possible causes of growth restriction in the SGA subgroup, and it is important to note that some infants who were IUGR may not have met the definition of SGA and may have thus been grouped with controls in the current analysis. It is also possible that uncertainty of pregnancy dating could also have introduced bias within the small sample size of SGA infants. Thus, some percentage of the SGA infants may not share the same risk factors and/or may have additional risk factors as compared with those infants who are truly of IUGR status. Third, it is unknown whether vitamin A dosing at 5,000 IU or the dosing interval or length are optimal for SGA infants. Preliminary studies to determine optimal dosing did not specifically focus on SGA status.²¹ It is thus unknown whether a higher dose of vitamin A may be necessary to elicit a positive impact especially given that the concentrations of serum retinol and serum retinol binding protein did not change following vitamin A treatment in SGA groups. Possible explanations of why retinol concentrations did not change may include differences in liver function or vitamin A metabolism between SGA and AGA subgroups, although the details remain unknown. Finally, it is important to recognize that there have been ongoing improvements to available clinical treatment regimens for preterm infants and the potential benefits of vitamin A supplementation may be less clear today as compared with clinical practice during the original study, especially given the expanded definitions of mild, moderate, and severe BPD.

In summary, our analysis did not provide any evidence to indicate that vitamin A supplementation in infants requiring early respiratory support decreases the relative risk of BPD or death to a greater extent in preterm SGA infants than in preterm AGA infants. However, the trend toward increased BPD or death in the SGA versus AGA preterm infants may set the stage for future studies that have adequate power to address this question as the primary outcome measure. Furthermore, data suggesting less effective increases in serum retinol concentrations of vitamin A suggest that future studies with higher doses of vitamin A may be warranted that focus specifically on preterm SGA/IUGR infants.

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Fig. 1.

Relative risk of experiencing binary clinical outcomes for all study infants. A robust Poisson model assuming an interaction between treatment and gestational age group was used to obtain the p values and relative risk estimates. The model controlled for gestational age for all outcomes and also for center for the primary outcome. Abbreviations: AGA, average for gestational age; CLD, chronic lung disease; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PMA, postmenstrual age; PVL, periventricular leukomalacia; SGA, small for gestational age; Vit A, vitamin A.

Baseline Characteristics of all Infants Enrolled in Original Study

Characteristic		SGA			AGA			Total		
	Vitamin A (<i>n</i> = 50)	Control (<i>n</i> = 54)	<i>p</i> value	Vitamin A (<i>n</i> = 355)	Control (<i>n</i> = 348)	<i>p</i> value	SGA (<i>n</i> = 104)	AGA (<i>n</i> = 703)	<i>p</i> value	
Birth weight (g)	698 ± 147	692 ± 151	0.729	780 ± 130	781 ± 133	0.891	695 ± 149	781 ± 131	<0.001	
Gestational age (wk)	28.1 ± 2.5	27.6 ± 1.8	0.570	26.7 ± 1.7	26.5 ± 1.7	0.352	27.9 ± 2.2	26.6 ± 1.7	<0.001	
Race/ethnicity, <i>n</i> (%)										
Black	26 (52)	26 (48)	0.806	172 (49)	163 (47)	0.641	52 (50)	335 (48)	0.459	
White	20 (40)	22 (41)		113 (32)	114 (33)		42 (40)	227 (32)		
Hispanic	4 (8)	6 (11)		60 (17)	57 (16)		10 (10)	117 (17)		
Other	0 (0)	0 (0)		10 (3)	14 (4)		0 (0)	24 (3)		
Male, <i>n</i> (%)	31 (62)	27 (50)	0.221	171 (48)	162 (47)	0.668	58 (56)	333 (47)	0.110	
Antenatal glucocorticoid, <i>n</i> /total (%)	40/49 (82)	43/54 (80)	0.798	267/355 (75)	255/348 (73)	0.558	83/103 (81)	522/703 (74)	0.166	
Apgar score 3, <i>n</i> /total (%)										
1 min	20/49 (41)	24/54 (44)	0.711	156/351 (44)	124/344 (36)	0.024	44/103 (43)	280/695 (40)	0.639	
5 min	6/49 (12)	7/54 (13)	0.931	35/351 (10)	23/345 (7)	0.115	13/103 (13)	58/696 (8)	0.154	
Delivery room care, <i>n</i> (%)										
Intubation	41 (82)	48 (89)	0.320	323 (91)	315 (91)	0.830	89 (86)	638 (91)	0.099	
Drugs for resuscitation	5 (10)	8 (15)	0.460	37 (10)	32 (9)	0.585	13 (13)	69 (10)	0.398	
Surfactant administration, <i>n</i> (%)	43 (86)	47 (87)	0.878	294 (83)	282 (81)	0.539	90 (87)	576 (82)	0.249	
Respiratory status at 24 h										
Mechanical ventilation, <i>n</i> (%)	43 (86)	47 (87)	0.878	326 (92)	320 (92)	0.952	90 (87)	646 (92)	0.072	
Mean airway pressure (cm H ₂ O)	6.4 ± 1.9	7.1 ± 2.4	0.260	7.0 ± 2.7	6.9 ± 2.4	0.858	6.8 ± 2.2	7.0 ± 2.5	0.888	
Fraction of inspired oxygen	0.40 ± 0.14	0.42 ± 0.19	0.836	0.41 ± 0.20	0.41 ± 0.20	0.873	0.41 ± 0.17	0.41 ± 0.20	0.148	
Serum retinol (µg/dL)	12.8 ± 5.4	13.5 ± 6.0	0.689	16.8 ± 6.1	16.7 ± 6.1	0.939	13.1 ± 5.7	16.7 ± 6.1	<0.001	
Time from birth to randomization (h)	61.9 ± 22.0	61.1 ± 19.5	0.823	60.7 ± 21.0	60.5 ± 20.7	0.908	61.5 ± 20.6	60.6 ± 20.8	0.64	
Time from birth to first treatment (h)	65.6 ± 21.6	63.9 ± 19.9	0.629	64.2 ± 20.2	64.1 ± 19.7	0.943	64.7 ± 20.7	64.2 ± 20.0	0.759	

Abbreviations: AGA, average for gestational age; SGA, small for gestational age.

Note: Plus-minus values are means $\pm$ standard deviations. *p* values are based on Wilcoxon rank sum tests for continuous outcomes and Cochran Mantel Haenszel tests for categorical variables.

Table 2

Serum Concentrations of Retinol and its Analogs for all Study Infants

Outcome	SGA			AGA			<i>p</i> value for difference between SGA and AGA vitamin A groups	<i>p</i> value for difference between SGA and AGA control groups
	Vitamin A (<i>n</i> = 23)	Control (<i>n</i> = 22)	<i>p</i> value for treatment difference within SGA	Vitamin A (<i>n</i> = 135)	Control (<i>n</i> = 125)	<i>p</i> value for treatment difference within AGA		
Serum retinol (µg/dL)	22.9 (11.2, 58.8)	17.9 (7.6, 46.2)	0.073	33.5 (13.1, 87.4)	17.8 (7.4, 63.1)	<0.001	0.029	0.376
No postnatal glucocorticoid therapy within 2 wk before sampling	18.8 (10.2, 30.6)	11.9 (5.5, 35.9)	0.085	22.8 (11.8, 44.5)	14.8 (7.1, 28.3)	<0.001	0.169	0.445
Postnatal glucocorticoid therapy within 2 wk before sampling	49.9 (19.8, 66.2)	29.1 (19.3, 64.7)	0.292	43.6 (16.1, 87.9)	24.8 (8.0, 76.7)	<0.001	0.705	0.384
Serum retinol change from baseline (µg/dL)	10.7 (−3.0, 48.3)	4.7 (−9.5, 22.5)	0.124	16.3 (−7.0, 68.8)	2.4 (−13.9, 55.1)	<0.001	0.292	0.666
No postnatal glucocorticoid therapy within 2 wk before sampling	6.4 (−10.2, 16.8)	−0.5 (−10.3, 20.4)	0.177	6.1 (−11.7, 30.7)	−2.6 (−12.6, 15.6)	<0.001	0.762	0.243
Postnatal glucocorticoid therapy within 2 wk before sampling	40.5 (6.8, 56.4)	18.8 (6.6, 54.9)	0.242	25.4 (−3.7, 69.6)	8.5 (−13.9, 57.1)	<0.001	0.295	0.304
Serum retinol-binding protein (mg/dL)	1.9 (0.9, 4.7)	1.4 (0.7, 4.3)	0.141	2.5 (1.0, 6.10)	1.8 (0.7, 6.4)	0.003	0.128	0.104
No postnatal glucocorticoid therapy within 2 wk before sampling	1.7 (0.7, 2.3)	1.1 (0.7, 3.1)	0.102	1.6 (0.7, 2.7)	1.5 (0.7, 3.2)	0.330	0.912	0.169
Postnatal glucocorticoid therapy within 2 wk before sampling	4.4 (1.0, 5.1)	2.9 (1.3, 4.8)	0.451	3.5 (1.1, 6.5)	2.6 (0.8, 6.8)	0.021	0.423	0.601
Serum retinyl esters (µg/dL)	36.7 (8.8, 117.4)	8.5 (2.7, 86.6)	0.005	26.5 (4.9, 103.4)	6.0 (0.0, 41.0)	<0.001	0.330	0.015
No postnatal glucocorticoid therapy within 2 wk before sampling	24.0 (3.3, 180.7)	11.2 (1.2, 86.6)	0.047	22.7 (4.7, 88.8)	6.8 (0, 47.3)	<0.001	0.604	0.088
Postnatal glucocorticoid therapy within 2 wk before sampling	52.3 (16.2, 117.4)	8.2 (4.9, 108.0)	0.089	30.6 (7.3, 113.2)	5.3 (0, 31.9)	<0.001	0.117	0.113

Abbreviations: AGA, average for gestational age; SGA, small for gestational age.

Note: *p* values are based on Wilcoxon rank sum tests.

Table 3

Relative Risk for Continuous Clinical Outcomes of all Study Infants

	SGA			AGA				
Continuous outcomes	Vitamin A (<i>n</i> = 50)	Control (<i>n</i> = 54)	<i>p</i> value for treatment difference within SGA	Vitamin A (<i>n</i> = 355)	Control (<i>n</i> = 348)	<i>p</i> value for treatment difference within AGA	<i>p</i> value for GA group and treatment interaction	<i>p</i> -value for difference between SGA and AGA groups
Fraction of inspired oxygen, median (5th, 95th percentiles)								
36 wk	0.21 (0.21, 1.0)	0.26 (0.21, 1.0)	0.50	0.23 (0.21, 1.0)	0.25 (0.21, 1.0)	0.98		0.48
28 d	0.30 (0.21, 0.58)	0.32 (0.21, 0.75)	0.14	0.34 (0.21, 0.87)	0.32 (0.21, 0.80)	0.74		0.64
Length of hospitalization, median (5th, 95th percentiles)								
Infants who survived	91 (54, 176)	90 (55, 242)	0.85	95 (62, 168)	94 (57, 166)	0.40	0.07	0.13
Infants who died	20 (6, 213)	20 (5, 141)	0.56	20 (3, 226)	19 (5, 152)	0.37	0.09	0.51

Abbreviations: AGA, average for gestational age; GA, gestational age; SGA, small for gestational age.

Note: For FIO₂, *p* values were obtained using Wilcoxon rank sum tests adjusting for gestational age. For length of hospitalization, a Poisson model assuming an interaction between treatment and GA group was used to obtain *p* values. The model controlled for GA.