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Comparisons of mortality and pre-discharge respiratory outcomes in small-for-gestational-age and appropriate-for-gestational-age premature infants

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Abstract

Background: There are differences in the literature regarding outcomes of premature small-for-gestational-age (SGA) and appropriate-for gestational-age (AGA) infants, possibly due to failure to take into account gestational age at birth.

Objective: To compare mortality and respiratory morbidity of SGA and AGA premature newborn infants.

Design/Methods: A retrospective study was done of the 2,487 infants born without congenital anomalies at ≤36 weeks of gestation and admitted to the neonatal intensive care unit (NICU) at John Dempsey Hospital, between Jan. 1992 and Dec. 1999. Recent (1994–96) U.S. birth weight percentiles for gestational age (GA), race and gender were used to classify neonates as SGA (<10th percentile for GA) or AGA (10th–90th percentile for GA). Using multivariate logistic regression and survival analyses to control for GA, SGA and AGA infants were compared for mortality and respiratory morbidity.

Results: Controlling for GA, premature SGA infants were at a higher risk for mortality (Odds ratio 3.1, P = 0.001) and at lower risk of respiratory distress syndrome (OR = 0.71, p = 0.02) than AGA infants. However multivariate logistic regression modeling found that the odds of having respiratory distress syndrome (RDS) varied between SGA and AGA infants by GA. There was no change in RDS risk in SGA infants at GA ≤ 32 wk (OR = 1.27, 95% CI 0.32 – 1.98) but significantly decreased risk for RDS at GA > 32 wk (OR = 0.41, 95% CI 0.27 – 0.63; p < 0.01). After controlling for GA, SGA infants were observed to be at a significantly higher risk for developing chronic lung disease as compared to AGA infants (OR = 2.2, 95% CI = 1.2 – 3.9, P = 0.01). There was no significant difference between SGA and AGA infants in total days on ventilator. Among infants who survived, mean length of hospital stay was significantly higher in SGA infants born between 26–36 wks GA than AGA infants.

Conclusions: Premature SGA infants have significantly higher mortality, significantly higher risk of developing chronic lung disease and longer hospital stay as compared to premature AGA infants. Even the reduced risk of RDS in infants born at ≥32 wk GA, (conferred possibly by intra-uterine stress leading to accelerated lung maturation) appears to be of transient effect and is counterbalanced by adverse effects of poor intrauterine growth on long term pulmonary outcomes such as chronic lung disease.

Background

Small for gestational age infants (SGA) represent a significant percentage of infants admitted to the Neonatal Intensive care units (NICU). There are a number of studies comparing premature small for gestational age (SGA) infants with appropriate for gestational age (AGA) infants, for differences in their mortality and morbidity [1-8] Although there is a consensus that premature SGA infants have higher mortality than AGA infants, the differences in outcomes regarding respiratory and non-respiratory morbidity are controversial. The discrepancies between different studies may partly be explained by variations in gestational age (GA) of the study populations and by the studies' failure to stratify the study population by GA. Moreover, several of these studies used birth weight percentile curves from older norms, to determine whether the infant is SGA or AGA [9-11] and/or did not take into account the racial differences in birth weight.

The aim of the present study was to compare the respiratory outcomes between premature SGA and AGA infants stratified by gestational age, using the most current US birth weight percentiles for gestational age by race and gender. [12]

Methods

This is a retrospective study involving 2,530 infants born at ≤36 weeks of gestational age and admitted to the NICU at University Of Connecticut Health Center, Farmington, CT, between January 1992 and December 1999. Forty-three infants born with congenital malformations or chromosomal aberrations were excluded from the study and the remaining 2,487 infants were included in the analyses.

Gestational age was determined based on maternal menstrual history and early fetal ultrasound. If, rarely, a difference of more than 2 weeks was observed using the physical exam based modified Ballard score, then the newly assessed GA was used. [13]*Infants were classified as* SGA (<10th percentile for gestational age), AGA (10th to 90th percentile for gestational age) and LGA (Large for gestational age) (>90th percentile for gestational age) based on US singleton birth weight percentiles for gestational age by race and gender. [12]*Mortality* was based on death prior to hospital discharge. *Respiratory Distress Syndrome* was diagnosed on the basis of clinical presentation and chest radiographs. [14] Long-term morbidity (Days on ventilator, BPD, Chronic lung disease and length of hospital stay) was studied only for the infants who survived ≥28 days of life. *Days on Ventilator* included total number of days on Bear 750 servo controlled ventilator, Sensor medics 3100 A High-frequency oscillator and/or Continuous Positive Airway Pressure. *BPD* was diagnosed based upon need for any amount of supplemental oxygen at 28 days of life. *Chronic lung disease* was based upon any supplemental oxygen need at 36 weeks postmenstrual age [GA at birth (wks) plus weeks after birth]. *Length of hospital stay* included total number of days that the infant was in the NICU before being discharged. The infants were discharged when they were at ≥35 weeks of postmenstrual age, able to maintain body temperature in open crib, free of apneic spells for ≥7 days and on full oral feeds. Infants who were transferred to another hospital were included and constituted <10% of the group.

Statistics

Univariate analyses, multivariate logistic regression analyses and survival analyses were performed and odds ratio with 95% confidence intervals were calculated for the major outcome variables. P value ≤ 0.05 was considered to be statistically significant.

Results

Patient demographics

Of the 2,487 neonates included in the study, 358 (14.4%) were classified as SGA, 2,008 (80.7%) were classified as AGA, 41 (1.6%) were classified as LGA and 80 (3.3%) could not be classified for incomplete data. The distributions of GA, birth weight, sex and race distribution along with maternal factors are shown in table 1. Table 2 shows distribution of population based on groups classified by GA at birth (wk).

Table 1: Distribution of study population based on gender and ethnicity

	SGA (n = 358)	AGA (n = 2008)
Gestational Age (wks)	33.2 ± 2.5	30.9 ± 3.5
Birth weight (gm)	1524.6 ± 466	1753.5 ± 683
Male Sex	197 (55%)	109 (55%)
Race		
Whites	270 (75%)	1620 (81%)
African-Americans	42 (12%)	192 (9%)
Hispanics	46 (13%)	196 (10%)
Maternal HTN	8 (2.3%)[a]	51 (2.6%)[b]
Antepartum Bleeding	59 (16.8%)[a]	389 (19.7%)[b]
Chorioamnionitis	70 (19.9%)[a]	315 (16.0%)[b]

Data shown as frequency (%) or mean ± sd a – missing data on 7 infants, b – missing data on 37 infants

Mortality

The relationship of mortality between SGA and AGA premature infants, stratified by GA, is shown in the figure 1. Controlling for GA, logistic regression analysis showed that premature SGA neonates were at a higher risk of mortality than premature AGA infants (Odds Ratio 3.1, p = 0.001). Among the 15 SGA infants who died 12 had RDS (80%), 5 developed pulmonary hemorrhage (33%), 2 suffered from perinatal asphyxia (13%), 2 developed sepsis

Table 2: Distribution of study population based on gestational age

GA	SGA (n = 358)	AGA (n = 2008)
22–25 weeks	8 (2.2%)	167 (10.4%)
26–28 weeks	11 (3.1 %)	312 (15.5%)
29–31 weeks	46 (12.8%)	447 (22.3%)
32–34 weeks	161 (45%)	731 (36.4%)
35–36 weeks	132 (36.9%)	307 (15.3%)

Data shown as frequency (%)

(13%) and 1 infant each developed intraventricular hemorrhage and pneumothorax (6.7%); an infant may have had more than one diagnosis. Among the 117 AGA infants who died 101 developed RDS (86.3%), 24 had pulmonary hemorrhage (20.5%), 5 suffered from perinatal asphyxia (4.3%), 26 had sepsis (22.2%), 31 developed IVH (26.5%) and 34 developed pneumothorax (29.1%). Among infants who died, the age of death was similar for SGA and AGA infants (SGA vs. AGA, mean ± sd; 17.1 ± 41.4 days vs. 14.3 ± 32.9 days, p = 0.6).

Respiratory distress syndrome

The relationship of RDS between SGA and AGA premature infants is shown in the figure 2. Controlling for GA, multivariate logistic regression analysis showed that premature SGA infants are at a lower risk for RDS than premature AGA infants (Odds ratio = 0.71, 95% CI = 0.53 – 0.94; P = 0.02). As shown in table 3, at the lower gestational age groups (24 – 31 weeks), the incidence of RDS was not significantly different between the two groups. At GA 32–34 weeks, SGA infants were observed to be at a lower risk for having RDS and this difference approached significance (p = 0.09). However at GA > 34 weeks, the incidence of RDS in SGA infants was significantly lower than AGA infants (p < 0.002). Overall, there was no change in RDS risk in SGA infants at GA ≤ 32 wk (OR = 1.27, 95% CI 0.32 – 1.98) but significantly decreased risk for RDS at GA > 32 wk (OR = 0.41, 95% CI 0.27 – 0.63; p < 0.01).

Days on ventilator

After controlling for GA, among the SGA and AGA infants who survived till discharge, there was no significant difference in the number of days on ventilator (RR = 0.94, 95% CI = 0.87 – 1.02; P = 0.13).

Broncho-pulmonary dysplasia

After controlling for GA, among infants who survived until 28 days of life, SGA infants were observed to be at a slightly higher risk for developing BPD. This difference was not significant statistically (OR = 1.09, 95% CI = 0.64 – 1.8; P = 0.73).

Chronic lung disease (defined as continuing need for supplemental oxygen at 36 wk corrected age)

After controlling for GA, among infants who survived until 28 days of life, SGA infants were observed to be at a significantly higher risk for developing chronic lung disease as compared to AGA infants (OR = 2.2, 95% CI = 1.2 – 3.9; P = 0.01).

Length of hospital stay

Among the infants who survived till discharge from the hospital, SGA infants had a significantly longer hospital stay than AGA infants (RR 1.29, 95% CI = 1.22 – 1.37, P < 0.0001). The relationship of length of hospital stay between SGA and AGA premature infants, stratified by GA, is shown in the Figure 3 and Table 4.

Discussion

It is a commonly held assumption that growth restricted fetuses are "stressed" by unfavourable *in-utero* environment and have accelerated lung maturation and thus lower incidence of pulmonary complications when compared to appropriately grown infants. [15,16] However different studies have conflicting reports on outcomes of premature SGA infants when compared to premature AGA infants with some reporting an increased mortality and morbidity [1,3,4,7,8], some reporting decreased [5] and some reporting no change in the mortality and morbidity of SGA preterm infants when compared to AGA infants. [17-19]

Regarding mortality, our study confirmed that premature SGA neonates were at a higher risk of mortality than premature AGA infants (Odds Ratio 3.1, p = 0.001) and most of the risk of mortality was in the lower gestational age groups (23 – 31 weeks) as shown in the figure 1. These findings are consistent with those observed in some of the previous studies [3,8,20-22]. One study by Bardin et al [1] however did not observe any significant difference in mortality between the two groups. This study's population however was limited to 24 – 26 weeks of GA with only 41 SGA infants enrolled and did not represent the complete spectrum of premature infants. A recent report from Lal et al from a geographically defined population has confirmed that SGA preterm infants are at higher risk for chronic lung disease and death before 28 days of birth and 36 weeks post-menstrual age. [23]

In our study, the premature SGA infants were observed to be at a lower risk for RDS than premature AGA infants (Odds ratio = 0.71, P = 0.02). Procianoy et al [5] had also shown the incidence of RDS to be lower in SGA infants as compared to AGA infants born ≤32 weeks of GA. However other studies have found either no difference between the two groups [1,3,8] or an increased incidence and severity of RDS in premature SGA infants [7,24]. The concept of

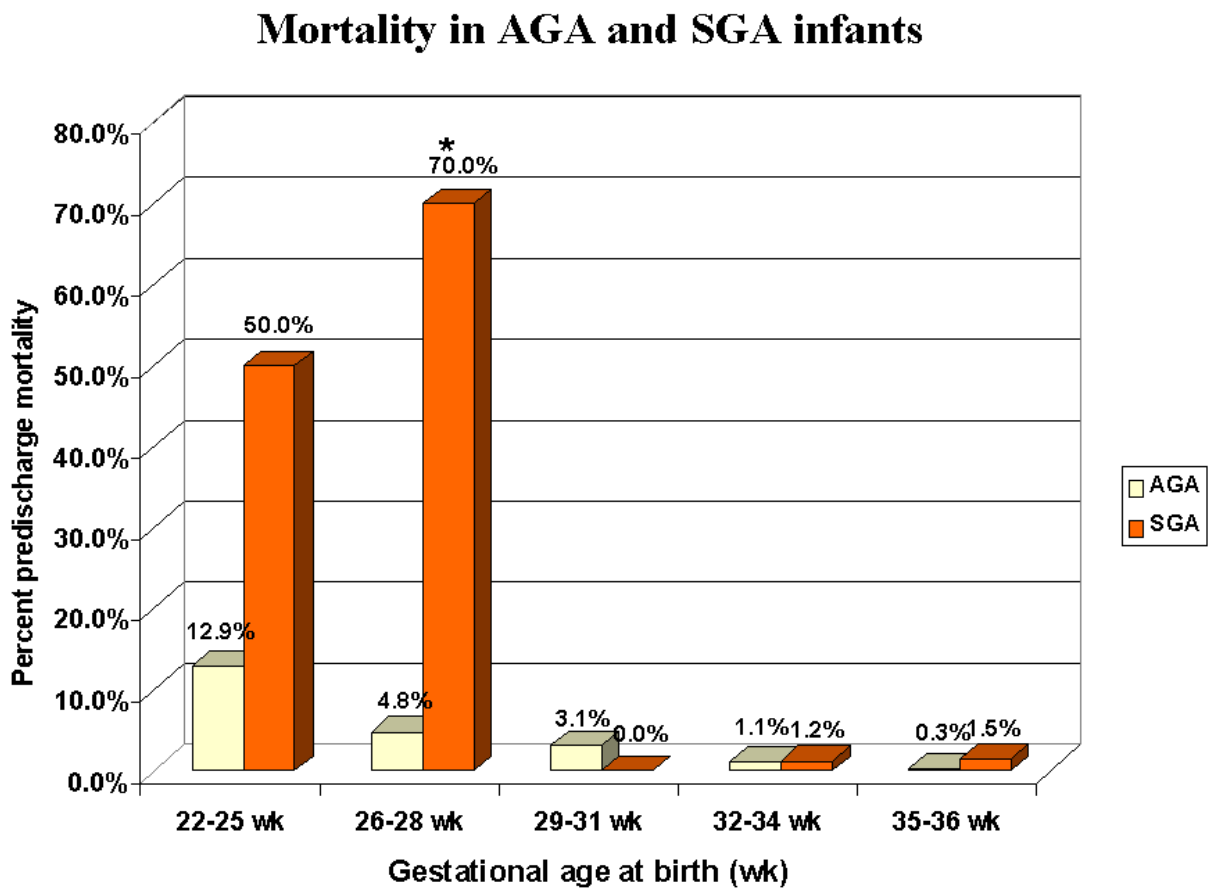

Figure 1
Mortality by gestational age The figure represents percent of infants that died in each gestational age group. AGA infants are represented by the lighter bars and SGA infants are represented by the darker bars.

accelerated lung maturation in response to stress was initially proposed in 1980s [16]. The concept was supported by data demonstrating improved biochemical pulmonary profile in growth restricted babies [25,26]. However postulated benefits of accelerated lung maturation may be counterbalanced by fetal hypoxemia and acidosis secondary to decreased utero-placental perfusion [27]. In our population, there appears to be is a distinct GA (>32 wks) where this balance appears to be shifted in favor of accelerated lung maturation and lower incidence of RDS (Figure 2).

The analysis for days on ventilator represents the severity of initial lung disease. From our study it is clear that despite the lower incidence of RDS in SGA infants as compared to AGA infants, the total number of days on ventilator in both groups is not different suggesting that the advantage of "stressed" lung is transient.

We found that SGA infants were at a slightly higher risk for developing BPD and at a significantly higher risk of developing chronic lung disease defined at 36 wk post-menstrual age. These findings are consistent with previous studies [1,3,28,29] which showed premature SGA infants to have increased incidence of BPD and/or chronic lung disease. It needs to be emphasized that the stratification by GA of these outcomes had not been done in these earlier studies and some were limited in the population studied, by GA ≤ 32 wk [28] or by birth weight ≤ 1500 gm [29]. Etiology of chronic lung disease is multifactorial, with var-

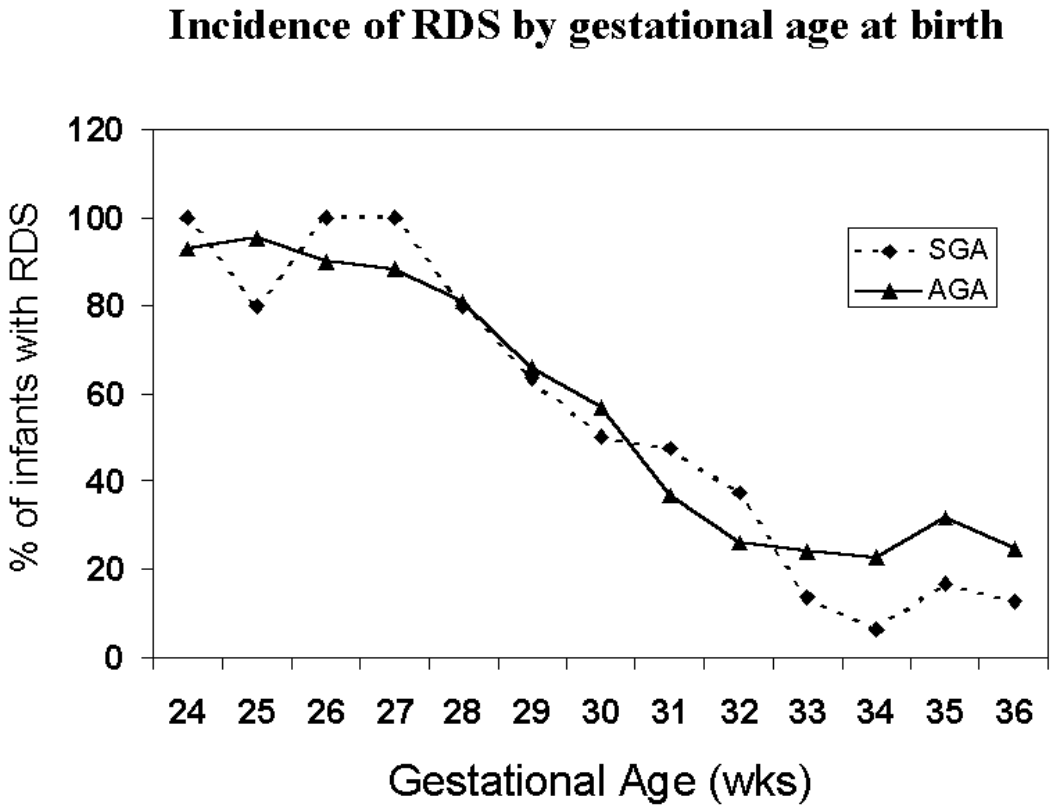

Figure 2
RDS by gestational age The figure represents percent of infants who developed RDS at each gestational age. SGA infants are represented by dotted line and AGA infants are represented by continuous line.

Table 3: Odds of RDS in SGA/AGA infants

GA groups	Odds ratio	95% CI	P Value
22–25 wks	0.38	0.06 – 7.6	0.44
26–28 wks	1.55	0.28 – 29	0.66
29–31 wks	0.99	0.54 – 1.83	0.98
32–34 wks	0.62	0.44 – 1.06	0.09
35–36 wks	0.45	0.25 – 0.73	0.002*

* Statistically significant

ious factors such as RDS, duration and degree of ventilator support, higher oxygen concentration exposure of the infant and chronic malnutrition, playing significant roles. Chronic undernutrition, as in case of intrauterine growth retardation, can aggravate the deficiency of antioxidants which might predispose the infant to chronic lung disease or make it worse [30]. Moreover, pulmonary alveolarization has been shown to be reduced by nutritional deprivation in experimental animals [31]. The hypoxemia and acidosis experienced by the fetus due to factors that induce restricted growth may be involved in the release of pro-inflammatory factors like Tumor Necrosis Factor-alpha [32]. Fetal exposure to Tumor Necrosis Factor-alpha has been shown to increase RDS and chronic lung disease in infants [33,34].

Length of hospital stay reflects severity of illness and morbidity among survivors. Our study showed that the SGA infants had a significantly longer hospital stay than AGA infants. This is consistent with observation made in other studies [1-3] and can be explained by increased complexity and severity of medical problems faced by premature SGA infants as compared to AGA infants.

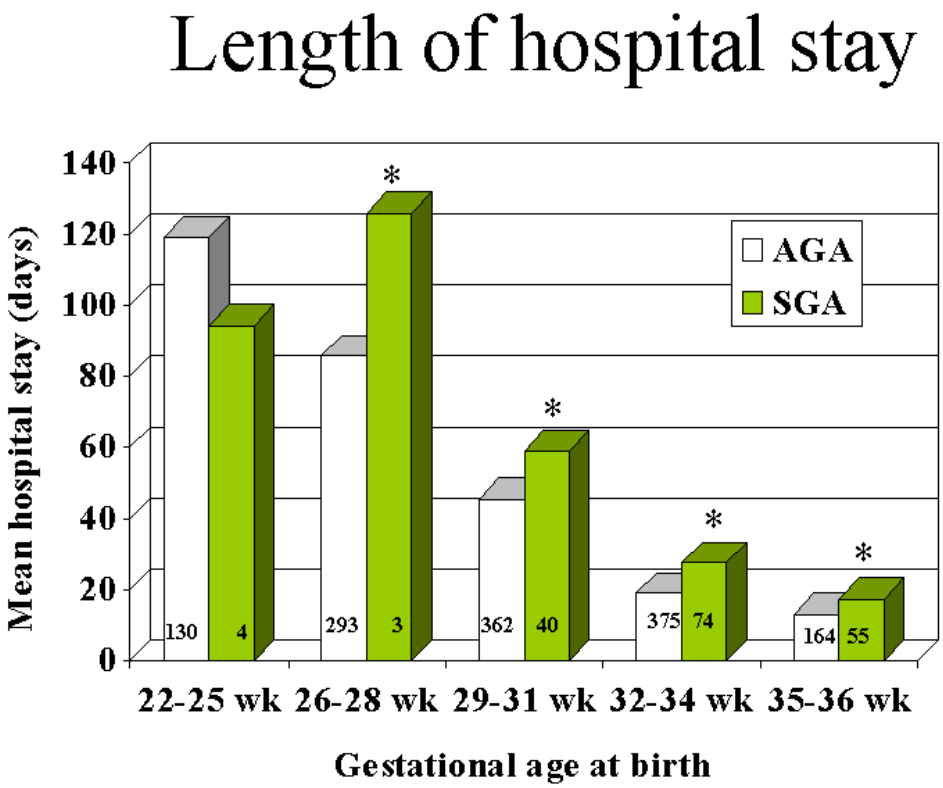

Figure 3
Length of hospital stay The figure represents the total length of stay in the hospital among infants who survived to 28 days. AGA infants are represented by the lighter bars and SGA infants are represented by darker bars. Total numbers of infants in each gestational age group are shown within the bars. * indicates $p < 0.05$.

Table 4: Relative risk of length of hospital stay in SGA/AGA infants

GA groups	Relative Risk	95% CI	P Value
22–25 wks	0.98	0.64–1.78	0.95
26–28 wks	1.77	1.09–3.57	0.02*
29–31 wks	1.28	1.1–1.5	0.0008*
32–34 wks	1.35	0.24–1.47	<0.0001*
35–36 wks	1.21	1.1–1.35	0.0002*

* Statistically significant

Conclusions

In conclusion, our study showed that when compared to premature AGA infants, premature SGA infants have significantly higher risk of mortality, significantly lower risk of RDS (though most of this benefit appears to be at GA 32–36 wks), significantly higher risk of developing chronic lung disease and a significantly longer hospital stay.

This study is unique in that it has utilized newer United States gender and race specific norms to classify infants as SGA and AGA. Also of note is that the lower incidence of RDS in SGA infants was observed to be most significant at the gestational ages 32–36 wks, but not at <32 wks, this may partly explain the discrepancies observed with some of the previous studies which studied premature infants as a single group and/or failed to look at the outcomes at different gestational ages. Transient benefit of accelerated lung maturity in premature SGA infants, as seen by lower incidence of RDS, does not appear to influence other pulmonary outcomes such as days on ventilator and BPD. On the other hand compromised nutrition [30] and intrauterine growth appears to play a more important role in determining long-term pulmonary morbidity such as chronic lung disease.

Competing interests
None declared.

Abbreviations
GA, gestational age;

SGA, Small for gestational age;

AGA, Appropriate for gestational age;

RDS, respiratory distress syndrome,

BPD, bronchopulmonary dysplasia;

CLD, chronic lung disease;

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