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Original Article

Predictors of early growth failure in preterm, very low birth weight infants during hospitalization

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Abstract

Background Preterm, very low birth weight (VLBW) infants experience intrauterine nutritional deficits and perinatal comorbidities that may impair early growth parameters. Early growth failure has detrimental effects on later growth and neurodevelopment in childhood.

Objective To analyze predictors of early growth failure in preterm, VLBW infants and differences in early growth parameters between small-for-gestational age (SGA) and appropriate-for-gestational age (AGA) infants.

Methods This retrospective cohort study was conducted at Dr. Sardjito Hospital, Yogyakarta from 2011 to 2016. Subjects were preterm infants, with birth weights of 1,000-1,499 g. Twins, those who died during hospitalization, were discharged against medical advice, or had incomplete medical records were excluded. Adequate intrauterine growth was determined by the Lubchenco table criteria. Growth parameters and perinatal comorbidities were collected from medical records. Growth failure was defined as discharge weight less than 10th percentile of the Fenton growth curve. Bivariate and multivariate analysis were used to analyze potential predictive factors of early growth failure.

Results Of 646 preterm, VLBW infants during the study period, 398 were excluded. Respiratory distress and SGA were predictors of early growth failure (AOR 6.94; 95%CI 2.93 to 16.42 and AOR 34.44; 95%CI 7.79 to 152.4, respectively). Mean weight velocities in SGA and AGA infants were not significantly different [16.5 (SD 5.9) and 17.5 (SD 5.3) g/kg/day, respectively; (P=0.25)]. Median time to regain, time to reach full feeding, and time to reach 120 kcal/kg/day were also not significantly different between SGA and AGA infants.

Conclusions SGA and respiratory distress are predictors of early growth failure in preterm, VLBW infants during hospitalization. The SGA infants grow slower than AGA infants. **[Paediatr Indones. 2019;59:44-50; doi: http://dx.doi.org/10.14238/pi59.1.2019.44-50].**

Keywords: *SGA-AGA; growth failure; preterm; VLBW*

As the biggest proportion of the NICU population, preterm and VLBW infants are susceptible to perinatal comorbidities, as well as growth and neurodevelopmental impairment.[1] About 4.7% of all births are VLBW infants, and Indonesia is included in the top ten nations with the highest prevalence of LBW (10.2%).[2,3] Preterm, VLBW infants may be further described as either SGA or AGA. Most SGA infants experienced intrauterine growth restriction (IUGR) and nutritional deficits.[4,5] Due to metabolic and gastrointestinal immaturity, compromised immune function, and other complicating medical conditions, nutritional deficits may continue during the early weeks after birth, impairing the growth rate. Perinatal comorbidities, such as patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), respiratory distress, and anemia, aggravate the problem. Intrauterine chronic hypoxia in SGA infants results in maladaptation and ineffective energy utilization. Their thin, subcutaneous fat layer leads

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to higher energy reserve loss and hypothermic stress leads to higher basal metabolic rates.[5,6]

The early postnatal growth target of preterm infants is to reach a growth rate similar to intrauterine growth at the same gestational age.[7] Weight velocity, time to regain birth weight, time to reach full feeding, and time to reach 120 kcal/kg/day are some growth parameters that may be impaired in the early weeks, resulting in growth failure, defined as a discharge weight $<10^{th}$ percentile according to Fenton growth charts by chronological age.[8,9] The incidence and predictors of early postnatal growth failure among preterm, VLBW infants have not been well studied in Indonesia. Early postnatal growth failure may affect long term neurodevelopmental outcomes and cause persistent growth failure.[10,11] The aims of this study were to analyze potential predictive factors of early growth failure in the perinatal period of preterm, VLBW infants and to analyze differences in early growth parameters between SGA and AGA subjects.

Methods

A retrospective cohort study based on medical records was done in Perinatology Division of Dr. Sardjito General Hospital, Yogyakarta from 2011 until 2016. Subjects were infants with gestational age < 37 weeks, birth weight of 1,000-1,499 g weighed within 1 hour after birth for Sardjito deliveries and 24 hours for out-of-Sardjito deliveries. Gestational age was determined by calculating Dubowitz score, or Ballard score for very ill infants.[12] Twins, those who died during hospitalization, were discharged against medical advice, had gastrointestinal surgery, or syndromes were excluded from this study.

Sample size was calculated using an unpaired, categorical analysis formula, with 20% proportion considered to be significantly different between the affected and not affected groups. Adequate intrauterine growth was based on Lubchenco table criteria.[13] Subjects were subcategorized as SGA (birth weight $<10^{th}$ percentile) or AGA (birth weight between 10^{th} and 90^{th} percentiles), based on sex and gestational age. Recorded perinatal comorbidities, such as PDA, neonatal sepsis, respiratory distress, NEC, and anemia requiring transfusion were analyzed as possible predictors of postnatal growth failure. Echocardiography was done to assess for PDA. Neonatal sepsis was defined by fulfilling 4 of 7 clinical criteria (abnormal heart rate, abnormal respiration rate, lethargy, jaundice, feeding intolerance, thermoregulation instability, and abnormal laboratory finding). Respiratory distress was defined as needing mechanical ventilation in the first 24 hours, neonatal pneumonia, ventilator dependency of >72 hours, meconium aspiration syndrome, and/or oxygen dependence for more than 28 days. Necrotizing enterocolitis (NEC) was defined by the pertinent clinical symptoms and revealed by plain, abdominal X-ray. Anemia was defined as low hemoglobin level which caused hemodynamic instability and needed packed red cell (PRC) transfusion. Growth failure was defined as discharge weight based on chronological age and sex of $<10^{th}$ percentile on the Fenton curve.[8,13] Bivariate analysis with Chi-square test followed by multivariate analysis with logistic regression test were used to assess the main possible predictors of growth failure during hospitalization. Predictive factors from multivariate analysis with P values < 0.05 were used for making mathematic models to calculate probability. Relative risk was calculated by comparing each probability based on clinical characteristics in preterm, VLBW infants. This study was approved by the Ethics Committee of Universitas Gadjah Mada Medical School, Yogyakarta.

Results

There were 636 preterm, VLBW infants during the 6-year study period in the Perinatology Ward of Dr. Sardjito General Hospital, of whom 238 were eligible for analysis and 398 were excluded (301 died, 43 twins, 39 discharged against medical advice, 3 syndromes, 12 incomplete medical records). Baseline characteristics of subjects are described in **Table 1**.

The SGA subjects had median gestational age 3 weeks older than AGA infants. Both birth weight and discharge weight in SGA group were significantly lower than those of the AGA group (mean difference of birth weight was 42.2 g). Differences in growth parameters between SGA and AGA subjects are described in **Table 2**.

Incidence of growth failure was 84.5%. Only

Table 1. Baseline characteristics and growth parameters of preterm, VLBW infants

Characteristics and growth parameters	Preterm VLBW (N=238)
SGA, n (%)	120 (50.4)
Male sex, n (%)	122 (51.3)
Gestational age, n (%)	
< 32 weeks	105 (44,1)
≥ 32-36 weeks	133 (55.9)
Type of delivery, n (%)	
Vaginal	92 (38.7)
C-section	146 (61.3)
Mean birth weight (SD), g	1,271.7 (138.6)
Mean discharge weight (SD), g	1,682.5 (182.3)
Discharge weight, n (%)	
< 3rd percentile	183 (76.9)
Between 3rd and 10th percentile	18 (7.6)
≥10th percentile	37 (15.5)
Median length of stay (range), days	33 (13-95)
Neonatal asphyxia, n (%)	106 (44.5)
Perinatal comorbidities	
Neonatal sepsis, n (%)	224 (94.1)
Positive culture, n (%)	108 (48.2)
PDA, n (%)	24 (10.1)
Respiratory distress, n (%)	136 (57.1)
NEC, n (%)	18 (7,6)
Anemia, n (%)	109 (45.8
Maternal problems	
Preeclampsia/eclampsia, n (%)	109(45.8)
Hypertension, n (%)	67 (28.2)
HELLP/partial HELLP, n (%)	45 (18.9)
Diabetes melitus,n (%)	4 (1.7)
Cardiac problem, n (%)	17 (7.1)
Mean weight velocity (SD), g/kg/day	16.9 (5.3)
Median time to regain birth weight (range), days	11 (3-42)
Median time to reach full feeding (range), days	16 (5-57)
Median time to reach 120 kcal/kg/day (range), days	20 (8-53)

HELLP: hemolysis, elevated liver function, low platelet

1.7% of all SGA, preterm, VLBW subjects reached discharge weight ≥ 10th percentile, while the rest stayed in the < 3rd percentile of the Fenton growth curve according to their chronological age. Subjects without growth failure regained birth weight, reached full feeding, and reached 120 kcal/kg/day faster than subjects without growth failure. They also had significantly higher mean weight velocity than those with growth failure (**Table 3**).

Bivariate analysis followed by multivariate analysis was used to compare independent variables (SGA and perinatal comorbidities) that may contribute to postnatal growth failure during hospitalization (**Table 4**). Logistic regression revealed that SGA and respiratory distress were the significant predictors of growth failure in preterm VLBW infants. Based on probability comparison from a mathematic model/y (using constant from logistic regression for predictive study), the relative risk was calculated using the following formula:

$$y = -0.109 + (3{,}539 \times SGA) + (1{,}937 \times \text{respiratory distress})$$

$$\text{probability} = \frac{1}{1+\exp[-(y)]}$$

(SGA: Yes=score 1, No=score 0; respiratory distress: Yes=score 1, No=score 0)

The relative risk of preterm, SGA, VLBW infants with respiratory distress suffering growth failure when they were discharged was 2.1 times higher than in AGA, VLBW infants without respiratory distress.

Discussion

In this study, 301 (47.3%) infants died during hospitalization within 6 years period. Only 5% of SGA, VLBW infants with less than 32 weeks gestational age survived until discharge. The high mortality rate was caused by complex perinatal comorbidities and younger gestational age. Tsai et al. reported that the mortality rate of SGA, VLBW with less than 32 weeks gestational age was significantly increased (OR 1.89; 95%CI 1.39 to 2.58).[15]

Surviving preterm, VLBW infants who passed critical phase in early life created specific proportion. As expected, the AGA group was dominated by infants of 28 to 32 weeks gestational age, while the SGA group was predominantly infants of 34 to <37 weeks gestational age. This composition was similar to another Perinatology Unit/NICU of a tertiary hospital, with a high mortality rate (50%) and median birth weight of 1,540 g in VLBW infants >32 weeks gestational age.[13]

The most common maternal problems in our study were preeclampsia/eclampsia and hypertension. These conditions are related to placental insufficiency that cause intrauterine growth retardation, such that the SGA proportion are higher than that of AGA. In the general population, SGA is at about 10-15%, much

Table 2. Differences in early growth parameters between SGA and AGA subjects

Parameters	SGA (n=120)	AGA (n= 118)	P value
Median gestational age (range), weeks	33 (30-36)	30 (27-33)	0.01
Mean birth weight (SD), g	1,250.76 (143.22)	1,292.96 (130.93)	0.02
Male sex, n (%)	61 (50.8)	61 (52.1)	0.49
Median time to regain birth weight (range), days	11 (3-42)	12 (3-35)	0.18
Mean weight velocity (SD), g/kg/day	16.50 (5.99)	17.52 (5.32)	0.25
Median time to reach full feeding (range), days	16 (6-38)	16 (5-57)	0.49
Median time to reach 120 kcal/kg/day (range), days	20 (8-51)	21 (9-53)	0.43
Mean discharge weight (SD), g	1,642.52 (133.25)	1,723.05 (214.46)	0.01
Median length of stay (range), days	32 (13-79)	34 (13-95)	0.73

Table 3. Comparison of growth parameters in subjects with and without postnatal growth failure

Growth parameters	With growth failure (n=201)	Without growth failure (n=37)	P value
Mean time to regain birth weight (SD), days	12.6 (6.2)	10.2 (3.9)	0.04
Mean time to reach full feeding (SD), days	18.7 (8.2)	15.3 (4.7)	0.055
Mean time to reach 120 kcal/kg/day (SD), days	22.9 (9.4)	18.9 (5.9)	0.03
Mean weight velocity (SD), g/kg/day	16.5 (5.4)	18.8 (4.7)	0.02

Table 4. Predictive factors of early postnatal growth failure in preterm, VLBW infants

Predictor factors	Growth failure (n=201)				
	Bivariate analysis			Multivariate analysis	
	n (%)	OR (95% CI)	P value	adj OR (95% CI)	P value
SGA	118 (58.7)	24.88 (5.82 to 106.31)	0.001	34.44 (7.79 to 152.4)	0.001
Male sex	108 (53.7)	1.91 (0.93 to 3.92)	0.055	1.89 (0.81 to 4.42)	0.14
PDA	22 (10.9)	2.15 (0.48 to 9.56)	0.24	1.88 (0.35 to 10.03)	0.46
Neonatal sepsis	190 (94.5)	1.52 (0.40 to 5.75)	0.38		
Respiratory distress	126 (62.7)	4.54 (2.08 to 9.89)	0.001	6.94 (2.93 to 16.42)	0.001
Anemia	93 (46.3)	1.13 (0.56 to 2.29)	0.44		
NEC	16 (8.0)	1.51 (0.33 to 6.88)	0.45		
T120 > 14 days	161 (80.1)	0.78 (0.30 to 1.99)	0.39		

PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; T120: time to reach 120 kcal/kg/day

lower than our findings. Our high SGA proportion may have been because there were many referral cases to our hospital, due to maternal and perinatal complications.

The most common perinatal comorbidity in this study was neonatal sepsis (94.1%), much higher than studies by Lima *et al.*[16] (4.6%) and Shan *et al.* (56.8%).[17] Neonatal sepsis is caused by the interaction of internal factor (immature immune system) and external factors, such as inappropriate infectious

transmission/termination practices (deemed to be in part due to poor hand-washing compliance in the nursery, high room density, frequency of room fogging, and selection of definitive antibiotics.) In addition, a diagnosis of neonatal sepsis in this study required a minimum of 4 from 7 criteria. Blood culture was performed only in 73.9% of sepsis patients. About 40% of all neonatal sepsis cases had negative blood culture. These results are indicative of the difficulty of prescribing appropriate antibiotics due to the lack of a definitive cause of sepsis. Prolonged sepsis may affect infant growth rate during hospitalization.

In this study, subjects' mean weight velocity was 16.8 (SD 5.33) g/kg/day, which was similar to growth targets of NICUs worldwide.[18] Mean weight velocity in our subjects was higher than a Brazilian study [9.3 (SD 2.3) g/kg/day]. This result proved that Indonesian preterm VLBW infants had same potential growth rate as found in other developing country.[19] Mean of weight velocity in the subgroup without growth failure was 2.3 g/kg/day higher than the subgroup with growth velocity failure (P=0.015). Based on these findings, we have to evaluate weight velocity weekly from the time they regained their birth weight, so that we can recognize growth impairment earlier.

Median time to reach full feeding was 16 days for both SGA and AGA groups. A previous study reported that the mean time to reach full feeding in VLBW infants was 15 days.[20] Median time to reach 120 kcal/kg/day in SGA and AGA was 20 and 21 days, respectively, similar to Anchieta *et al*., who reported the highest growth rate in the third week of life.[21] There was no significant difference between time to regain birth weight, time to reach full feeding, or time to reach 120 kcal/kg/day between the SGA and AGA groups. This finding means that discharge weight was determined by adequate intrauterine growth and weight velocity in the early weeks of life.

The incidence of growth failure in this study (84.5%) was much higher than in studies by Lima *et al.*[16] (26%) and Marks *et al.* (10.6%).[22] This finding may have been due to the higher SGA proportion in our study than the previous ones, while growth failure was experienced mostly by SGA infants. Variations in growth failure incidence may also have been affected by study location, complexity of medical condition, gestational age, and applied nutritional management guidelines.[23] In our center, nutritional practices for SGA and AGA preterm, VLBW infants are not different.

Mean weight velocity of the SGA group was less lower than that of the AGA group (P=0.25). Ineffective energy utilization and energy deficit due to perinatal comorbidities in SGA infants are basic causes of growth impairment. In addition, basal metabolic rate in SGA is generally higher than in AGA infants. The minimal energy reserve in SGA infants is due to the thin layer of fat that increases heat loss and results in greater energy expenditure.[24] Postnatal growth failure is due to a complex interaction of comorbidities which lead to energy expenditure and endocrine function abnormalities, central nervous system impairment and immaturity, as well as immature sucking and swallowing reflexes. Ultimately, inadequate nutrition and energy deficit during the first weeks of life are considered to be most responsible for postnatal growth failure.[23]

Respiratory distress was a perinatal comorbidity that was significantly associated with postnatal growth failure during hospitalization. Infants with respiratory distress have trouble consuming liquids, including enteral feeding as their primary energy source. It also increases the basal metabolic rate, aggravating the total energy deficit in preterm, VLBW infants.[20,23] Other perinatal comorbidities, such as neonatal sepsis, PDA, anemia, and NEC were not significantly associated with growth failure in preterm, VLBW infants in our study. This finding was contrast to a previous study that reported anemia requiring transfusion related with delayed time to regain.[26] The lack of an association could have been due to an immediate hemoglobin correction to stabilize the hemodynamics at the time of diagnosis, hence, the growth parameter was just transiently impaired. In our study, the complexity and synergy of perinatal comorbidities caused a high incidence of growth failure, while single perinatal comorbidities were not significantly associated with growth failure.

The high incidence of postnatal growth failure may have also been influenced by low calorie intake during the transition period from parenteral to full enteral feeding. Based on our findings, calorie intake decreases about 10-20 kcal/day during the transition period. Energy deficits during the transition period may only maintain the status quo or even cause decreased growth rate. Inadequate energy and protein intake

during the transition period contribute to the risk of growth failure during hospitalization.[27] The time interval from regaining birth weight until reaching full feeding and nutrition for growth at 120 kcal/kg/day was longer in our subjects than in a previous study.[28] Prolonged energy and calorie deficits in preterm, VLBW in that status quo interval (while they had already been ready for increasing body weight) cause higher growth failure in our study.

Other than SGA and respiratory distress, we need to study other factors that may contribute to growth failure in preterm, VLBW infants during hospitalization, such as early enteral feeding and monitoring the application of nutritional practices. Our study had several weakness as the retrospective design might have resulted in bias in data collection, and we only analyzed body weight to evaluate growth failure. Our study was the first in Indonesia to review detailed growth parameters in preterm, VLBW infants during early life. This study also reported on the difference in early growth parameters between SGA and AGA infants.

In conclusion, SGA and respiratory distress are significant predictors of early growth failure in preterm, VLBW infants during hospitalization. SGA infants grew less slower than AGA infants. These findings imply that low weight velocity in weekly monitoring was an appropriate warning sign of postnatal growth failure. We should optimize the interval between weight regain time, time to reach full feeding, and time to reach 120 kcal/kg/day, in order to prevent prolonged nutritional deficits. Early nutritional management targets in SGA, preterm, VLBW infants aim to maintain weight gain in parallel with the growth curve and prevent severe postnatal growth failure (discharge weight $<3^{rd}$ percentile).

Conflict of Interest

No conflict of interest.

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