Rate of weight gain in very-low birth weight Puerto Rican neonates

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Background: **Small for gestational age neonates have a higher risk of growth delay. The purpose of the study is to determine if there are differences in their early weight gain patterns that persist after adjusting for confounding variables.**

***Methods*: Two-hundred sixteen neonates born between 1999 and 2003 were included. The group for analysis was derived by matching all the SGA infants with AGA infants by sex, year of birth, and birth weight. The period of observation was from birth to date of discharge. Weight gain rate was defined as grams gained per kilogram of birth weight per day. Two sample T-test was used to determine the difference in growth rate between the groups. Simple regression was used to establish the effect of morbidities on weight gain rate.**

***Results*: The total mean birth weight was 1105 g (± 223 g), the mean gestational age was 30 weeks (± 2.7 weeks), and the mean weight gain rate was 13.4 g/kg/d (± 6.8 g/kg/d). The mean weight gain rate for the adequate for gestational age group was lower (11.9 g/kg/d ± 7.6g versus 14.9 g/kg/d ± 5.5g) (P<0.001). When all variables were analyzed using the lineal regression model, only having a low APGAR score (P=0.02) and being small for gestational age (P=0.0004) were significant.**

***Conclusions*: We conclude that the growth patterns of very low birth weight neonates are different based on the adequacy of their birth weight, and that the disparity in growth rate is not explained by the differences in the incidence of morbidities that affect growth.**

Key words: Very Low Birth Weight, Weight gain, Small for Gestational Age.

Small for gestational age infants are at risk of poor post-natal growth. Growth failure may lead to neurodevelopmental delay (1-4). Morley and colleagues as well as others have proven that nutritional interventions improve growth in small for gestational age (SGA) term newborns; but long term follow up revealed that there was no improvement on the neurodevelopmental outcomes of SGA term neonates that received nutrient supplementation (5). However, breastfed infants had significantly higher Bailey scores suggesting that small for gestational age infants have increased benefits from breast feeding. This finding has been confirmed in other studies (6). On the other hand, the recommendation of exclusive breastfeeding might not comply with the caloric density that is currently targeted to achieve catch up growth in premature SGA. Breastfeeding might be particularly difficult in small for gestational age infants born premature, who may require fluid restriction and high caloric intake. Although there have been multiple epidemiological studies demonstrating the impact that being born small for gestational age has on lifelong health (7-9), there is still no clear recommendations with regards to nutritional management of small for gestational age infants. Fetal programming engendered by exposure to an intrauterine nutrient restricted environment has been proposed to explain the higher rate of chronic diseases observed in adults that were born small for gestational age (10-12). However, the potential for a multifactor etiology continues to grow, as there have been reports on the relationship between early hyper caloric nutrition and increased risk of chronic disease both in childhood and adulthood (13-14) The effect of ethnicity on the risk of chronic disease has not been evaluated for SGA infants.

We have previously reported on the weight gain patterns of a cohort of very low birth weight Puerto Rican neonates with a mean weight gain rate of 13.6 g/kg/d ± 6 grams and mean gestational age of 30 ± 2.3 weeks (15). Of the multiple morbidity elements that might affect weight gain rate, the

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following were found to have a significant impact: bronchopulmonary dysplasia, necrotizing enterocolitis, low APGAR, fungal sepsis, and gender. We also observed a trend of increasing mean weight gain rate from the year 1999 to 2003. This finding correlates with changes in the nutritional interventions used due to the earlier use of total parenteral nutrition. Enteral feeding protocols remained the same. A particularly important finding was that SGA neonates demonstrated a higher weight gain rate. The purpose of this study is to evaluate if the observed differences in the weight gain rate of SGA neonates is maintained after comparing a matched cohort of SGA and adequate for gestational age (AGA) neonates. If the initially observed differences persist, this evidence would support the models of fetal programming demonstrated on animal models.

Methods

A retrospective study of a nested matched cohort was performed using data from the Vermont Oxford Network forms. Weight gain rate was defined as grams gained per kilogram of birth weight per day.

Inclusion criteria: All patients with birth weight less than 1500 grams admitted at the Neonatal Units of the University Pediatric Hospital from 1999 to 2003 who survived to discharge; including SGA and AGA infants. SGA was defined as birth weight < 10th percentile for gestational age using the Lubchenko growth curves.

Exclusion criteria: Patients with gastrointestinal conditions that would cause a discontinuation of enteral feedings for more than two weeks, birth defects, and those who were transferred to another Institution during the first week of life.

The study was approved by the University of Puerto Rico Medical Sciences Campus Institutional Review Board. Cohort A was derived from the original data by matching all SGA infants with AGA infants using the following criteria: sex, year of birth, and birth weight (within 100 g). A confirmatory Cohort B was derived by matching for the following criteria: sex, year of birth, and gestational age.

Statistics: Analysis was performed of the two matched cohort of patients independently. Descriptive statistics including mean, mode, standard deviation, median, and range were computed using STATA 9.0 software. Two sample T test was used to determine the difference in weight gain rate between groups.

Chi square was used to evaluate the association between categorical variables: bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), necrotizing enterocolitis (NEC), low APGAR, and sepsis. Bronchopulmonary dysplasia was defined as oxygen requirement at 28 days of life. Chronic lung disease was defined as oxygen requirement at 36 weeks postmenstrual age. Necrotizing enterocolitis was reported as present in cases of patients with NEC grade II or higher following Bell's classification criteria. The presence of patent ductus arteriosus (PDA) was documented based on echocardiographic findings. History of retinopathy of prematurity (ROP) was reported in cases with completed retinal evaluation prior to hospital discharge, and evidence of retinopathy stage 1 or higher. The differences between the grades of severity of ROP have been reported elsewhere (16). Odds ratio with a 95% confidence interval was determined to estimate magnitude of these associations.

Non parametric tests were used to determine the effect of the categorical variables over the growth rate. A generalized regression model was used to determine the impact of the morbidity elements over the growth rate. A secondary analysis of the weight gain rate was performed using the exponential model reported by Patel and colleagues, $GV = [1000 \times \ln(W_n/W_1)]/(D_n - D_1)$; where GV is growth velocity, W_n = weight at discharge, W_1 = birth weight, D_n = day of life at discharge, and D_1=0 (17) We decided to proceed with the use of the exponential model to account for the exponential characteristics of the rate of weight gain in biological models, which could prove to be a more accurate comparison of the rate of weight gain observed versus the two point evaluation model that was originally used in our study. A p value of less than 0.05 was considered statistically significant.

Results

A total of 108 SGA neonates included in the original study were matched with 108 AGA neonates for Cohort A. When we evaluated the complete cohort, the total mean birth weight was 1105 g (± 223 g), mean gestational age was 30 weeks (± 2.7 weeks), and mean weight gain rate was 13.4 g/kg/d (± 6.8 g/kg/d). The trend of increasing rate of weight gain based on the year of birth was also observed within the cohort (Figure 1). As expected, the mean birth weight was similar between AGA and SGA infants (Table 1). However, we also observed a similarity in the mean gestational age of AGA and SGA neonates which suggest that the AGA neonates included in the study might be in the lower percentile range of what is expected for their gestational age. In spite of the similarities identified, neonates that were classified as SGA had a significantly higher rate of weight gain (14.9 g/kg/d ± 5.5 g) than their AGA counterparts (11.9 g/kg/d ± 7.6g) (P=<0.001). When we evaluated the comparison of the rate of complications between SGA and AGA, we found that AGA neonates had a higher risk of developing many of the complications

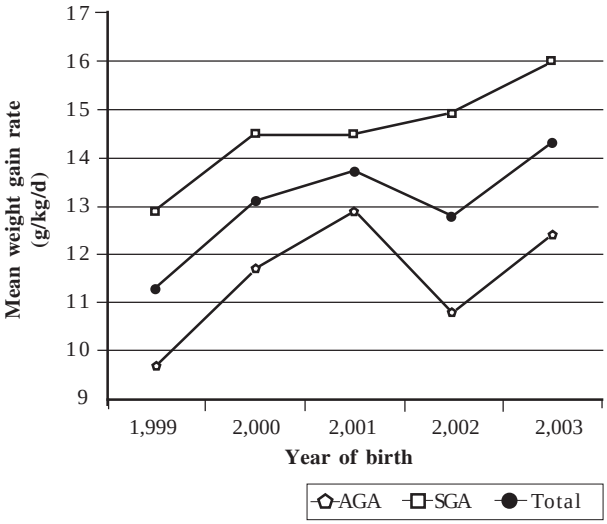

Figure 1. Trends in the weight gain rate per year of birth in each AGA, SGA and Total cohort of patients.

Table 1. Comparison between adequate for gestational age and small for gestational age infants paired by birth weight.

	AGA	SGA	P
Mean birth weight	1103 g ± 232 g	1106 ± 232 g	NS
Mean gestational age	30 wks ± 3 wks	31 wks ± 3 wks	NS
PDA	32 (30%)	23 (21%)	NS
IVH (n=206)	24 (23%)	9 (9%)	0.01
ROP (n=126)	26 (37%)	11 (20%)	NS
Discharge weight	1867 g ± 369 g	1787 ± 218 g	0.053
Length of stay	59 days ± 35 d	46 days ± 26 d	0.001

evaluated with exception of NEC, PDA and ROP which did not demonstrate a significant difference between the groups (Tables 1 and 2). After evaluating the possibility of interaction between variables, we analyzed whether the differences observed could be secondary to the differences in the rate of complications. Our logistic regression model revealed that the only variables that affected the rate of weight gain was having a low Apgar score (P=0.04) and being born SGA (P=0.01).

During the next phase of our analysis Cohort B was paired to eliminate the effect of gestational age over the observation in the weight gain rate differences. As can be noted in Table 3, the observed differences in mean weight gain rate of SGA neonates having a higher rate than AGA neonates is sustained. Another important observation is that in both cohorts we observed statistically significant differences in the length of stay of these patients where SGA had shorter hospitalizations (Average of 13 days for Cohort A and 7 days for Cohort B).

To overcome the limitation of the differences in the period of observation, we analyzed our data using the exponential method proposed by Patel. When we used the exponential model to evaluate the rate of weight gain and the effects of morbidity elements, we found that the mean rate of weight gain in Cohort A for SGA was 11.16 g/kg/d ± 8.1 g and for AGA was 8.25 g/kg/d ± 6 g. For the evaluation of Cohort B, the mean rate of weight gain was 11.16 ± 3.81 g for SGA and 8.5 g/kg/d ± 5.18 g for AGA. As observed in the two point technique, the only clinically significant element found to affect the rate of weight gain was SGA, confirming that the differences in the rate of complications identified does not account for the differences in the rate of weight gain.

Table 2. Risk evaluation for various comorbid conditions between SGA and AGA neonates and determination of their effect on the mean weight gain rate.

	AGA	SGA	OR	95% CI	P value	Effect on Weight Gain
BPD	42.6%	19.4%	0.3	0.2 – 0.6	0.04	NS
CLD	22.2%	12.0%	0.5	0.2 – 0.1	0.07	NS
Sepsis	40.7%	21.3%	0.4	0.2 – 0.7	0.003	NS
Low APGAR	25.7%	12.1%	0.4	0.2 – 0.8	0.01	0.04
NEC	13.9%	13.0%	0.9	0.4 – 0.2	1.00	NS
SGA						0.01

Discussion

As previously mentioned, the targets for optimal nutritional interventions in small for gestational age neonates are currently under debate. Factors that highlight the need for particular treatment strategies for these infants include evidence of fetal programming as well as neonatal programming that results from nutritional interventions. The long term effects of induced changes in the metabolic demands of the fetus in the presence of abundant nutritional supplementation during the neonatal period have been demonstrated to result in chronic disease in adulthood. Evaluation of the differences in the growth rate of a selected group of SGA premature neonates has demonstrated that these infants have a higher capacity for weight gain than those classified as AGA. We expect that the selection criteria used for this cohort of patients can shed light to the controversy of which SGA infants would benefit or should avoid sustained hyper caloric diets to avoid long term complications.

We concluded that patterns of early extra uterine growth rate of SGA and AGA infants are different. For the group we analyzed, being SGA provided an advantage not only in the rate of weight gain

Table 3. Comparison between Cohort A derived by matching for birth weight versus Cohort B derived by matching for gestational age.

	Cohort A		Cohort B	
Mean weight gain in SGA	14.9 g/kg/d ± 5.5 g		14.9 g/kg/d ± 5.5 g	
Mean weight gain in AGA	11.9 g/kg/d ± 7.6 g		11.5 g/kg/d ± 6.8 g	
Difference	3 g/kg/d		3.4 g/kg/d	
	SGA	**AGA**	**SGA**	**AGA**
Mean gestational age (SD)	31 w (3)	30 w (3)	30 w (2)	30 w (2)
Mean birth weight (SD)	1106 g (232)	1103 g (369)	1096 g (228)	1171 g (221)
Mean discharge weight (SD)	1787 g (218)	1867 g (369)	1788 g (221)	1863 g (333)
Mean length of stay (SD)	46 d (26)	59 d (35)	46 d (26)	53 d (30)

observed, but also in the risk of complications reported. These findings contrast with other reports of higher risk of complications in SGA neonates. However, we have to recognize that this group of SGA neonates is not representative of all subjects at risk for the condition, since it excludes many of the main causes for being born SGA such as chromosomal and structural congenital anomalies. As a result of the selection criteria, this cohort is mostly representative of neonates born to mothers with pre eclampsia or other causes of placental insufficiency. Based on the findings of increased weight gain rate observed in all the cohorts analyzed and sustained by all the methods used, we propose that the etiology of the fetal growth restriction should be taken into consideration when establishing a nutritional intervention plan. Based on the results of animal models, when exposed to a nutrient restricted environment prenatally, our SGA neonates would have a greater capacity for nutrient utilization that should provide them with the mechanisms to achieve catch up growth. Another important observation is that in both cohorts the differences in weight gain were expected to have an important contributing factor to the differences in the length of stay observed in the Table 3. On the other hand, the risk benefit analysis between catch up growth and later development of chronic diseases in childhood or adulthood remains to be determined (18). Especially when we consider that this cohort of infants is all Hispanic, which in itself places them at a higher risk of developing chronic diseases in adulthood.

An important limitation that we had to overcome was basing the gestational age determination mostly on the calculation according to the date of the last menstrual period, but the data collection forms had strict instructions to use the gestational age based on the physical examination if a discrepancy of one week or more was identified. We also observed a similarity in the average gestational age of Cohort A that could result from the percentile distribution among either of the compared groups or could emerge from the limitations of using the Lubchenko curves in our population. García and colleagues have found that when observed growth curves of premature Puerto Rican neonates are compared to the Lubchenko curves, our population is 50 grams lighter, and that the Puerto Rican 50th percentile corresponds with the Lubchenko 35th to 40th percentile (Unpublished data). This emphasizes the need for the development of ethnic specific growth curves to aid our goal of establishing early nutritional interventions for very low birth weight infants in our population.

In the future, we plan to evaluate how the differences in growth patterns persist later in life and how this affects the development of chronic illness in adulthood. This goal is of particular interest in this cohort, since early intervention plans were modified during the period of study, and follow up of the complete cohort is expected to bridge the gap between what has been observed in animal models with regards to neonatal programming and the human model. Furthermore, the information provided would also define the characteristics, both physiological and socio-demographic; of a group of mainly low income Hispanic subjects, which could aide in the evaluation of other contributing elements such as: education, quality of post discharge nutrition, access to health care, among others.

Resumen

Los neonatos que nacen pequeños para la edad gestacional tienen un mayor riesgo de rezago en el crecimiento. Evaluamos la taza de aumento de peso durante el período de hospitalización al nacer, de un cohorte pareado de neonatos de bien bajo peso al nacer nacidos en Puerto Rico, que recibieron tratamiento en el Hospital Pediátrico Universitario entre los años 1999 y 2003. Se parearon en dos grupos adecuados para la edad gestacional y pequeños para la edad gestacional basado en el género, el año de nacimiento y el peso al nacer. La tasa de aumento de peso se reportó como gramos ganados por kilogramo de peso de nacimiento por día. La ganancia de peso promedio de los neonatos adecuados para la edad gestacional fue menor que la de los pequeños para la edad gestacional (11.9 g/Kg/d ±7.6 g versus 14.9 g/Kg/d ±5.5 g) (P<0.001). Al considerar todas las potenciales variables

de confusión, encontramos que los únicos elementos que resultaban significativos para explicar esta diferencia fueron el tener una puntuación baja de APGAR (P=0.02) y ser pequeño para la edad gestacional (P=0.0004). Concluimos que los patrones de aumento de peso de los neonatos de bien bajo peso al nacer son diferentes a base de su clasificación por edad gestacional. La diferencia observada no puede ser explicada por los diferentes patrones de morbilidad entre los grupos.

References

1. Gutbrod T, Wolke D, et al. Effects of gestation and birth weight on the growth and development of very low birth weight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed 2000;82:208-214.
2. Bloom B, Mulligan J, et al. Improving Growth of Very Low Birth Weight Infants in the First 28 Days. Pediatrics 2003;112:14.
3. Fewtrell MS, Morley R, et al. Catch-up growth in small- for-gestational-age term infants: a randomized trial. Am J Clin Nutr 2001;74:516-523.
4. Robertson C. Catch-up growth among very-low-birth-weight preterm infants: a historical perspective. Pediatrics 2003;143.
5. Morley R, Fewtrell MS, et al. Neurodevelopment in Children Born Small for Gestational Age: A Randomized Trial of Nutrient-Enriched Versus Standard Formula and Comparison with a Reference Breastfed Group. Pediatrics 2004;113: 515-521.
6. Rao MR, Hediger ML, et al. Effect of breastfeeding on cognitive development of infants born small for gestational age. Acta Paediatr 2002;91:267-274.
7. Barker DJP, The Developmental Origins of Adult Disease. J Am Coll Nutr 2004;23(6 Suppl):588S-595S.
8. Thornburg K, Fetal Origins of Cardiovascular Disease. NeoReviews 2004;5:527-533.
9. Forsén T, Eriksson JG, Tuomilehto J, Osmond C and Barker D J P. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. BMJ 1999;319:1403-1407.
10. Srinivasan M, Aalinkeel R, et al. Maternal hyperinsulinemia predisposes rat fetuses for hyperinsulinemia, and adult-onset obesity and maternal mild food restriction reverses this phenotype. Am J Physiol Edocrinol Metab 2006;290:129-134.
11. Williams SJ, Hemmings JM, et al. effects of maternal hypoxia or nutrient restriction during pregnancy o endothelial function in adult male rat offspring. J Physiol 2005;565: 125-135.
12. Khan OA, Torrens C, et al. Effects of pre-natal and early post-natal undernutrition on adult internal thoracic artery function. Eur J Cardiothorac Surg 2005;28:811-815.
13. Lucas A, Sampson HA (eds): Primary Prevention by Nutrition Intervention in Infancy and Childhood. Nestlé Nutr Workshop Ser Pediatr Program. 57:1-13, Nestec Ltd. Vevey/S. Karger AG, Basel; 2006.
14. Labayen I, Moreno LA, et al. Early Programming of Body Composition and Fat Distribution in Adolescents. J Nutr 2006;136:147-152.
15. Arce S, Campos M, García I, García L, and Valcárcel M. Very Low Birth Weight Infants Growth in the Neonatal Intensive Care Unit. Abstract publication at: J Perinatol 2004;24:571-609.
16. Vélez N, Reyes G, Campos M, Arce S, Valcárcel M, and Pérez R: Impact of Intrauterine Growth Restriction (IUGR) on the Incidence and Severity of Retinopathy of Prematurity (ROP). Abstract publication at the XXVI Annual Research and Education Forum Proceedings UPR Medical Sciences Campus; 2006.
17. Patel AL, Engstrom JL, Meier PP, and Kimura RE. Accuracy of Methods for Calculating Postnatal Growth Velocity for Extremely Low Birth Weight Infants. Pediatrics 2005;116:1466-1473.
18. Victora CG, Barros FC, et al. Short-term benefits of catch-up growth for small-for-gestational-age infants. Int J Epidemiol 2001;30:1325-1330.