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An assessment of the severity, proportionality and risk of mortality of very low birth weight infants with fetal growth restriction. A multicenter South American analysis

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Abstract

Objectives: To evaluate the clinical severity and proportionality of small for gestational age, very low birth weight neonates (< 1,500 g) and to estimate the neonatal mortality risk associated with the condition of being small for gestational age according to the degree of severity and proportionality.

Methods: Observational design. All of the NEOCOSUR Collaborative Group's very low birth weight infants (25-36 weeks' gestation) were included (n = 1,518). Anthropometric indices: birth weight < 3rd and 10th percentile. Severity (fetal growth ratio = observed weight/mean birth weight for gestational age); no growth restriction: fetal growth ratio 0.90-1.10, mild: fetal growth ratio 0.80-0.89, moderate: fetal growth ratio 0.75-0.79 and severe: fetal growth ratio < 0.75. Proportionality: coefficient of bimodality and z score for ponderal index (PI = g/cm^3 x 100). Neonatal mortality until discharge.

Results: < 3rd percentile: 13.5% (p < 0.001); < 10th percentile: 31% (p < 0.001); fetal growth ratio: 0.90±0.21 (p < 0.001), mild restriction: 20.8%, moderate restriction: 8.7% and severe restriction: 32.6%. Coefficient of bimodality: 0.53; PI z score < -1: 8%. Maternal hypertensive disease was systematically associated with being small for gestational age (aOR 1.20, 95% CI 0.86-1.67), fetal growth ratio $\leq$ 0.89 (aOR 1.71, 1.24-2.36) and PI z score < -1 (aOR 1.60, 1.03-2.41). Adjusted odds ratios for neonatal mortality were: 2.64 (95% CI 1.71-3.92) for being small for gestational age, 2.76 (95% CI 1.85-4.10) for fetal growth ratio $\leq$ 0.89, and 1.37 (95% CI 0.80-2.32) for z score PI < -1.

Conclusions: Small for gestational age, mostly symmetric and severe restriction is a frequent condition in < 1,500 g neonates and is associated with higher mortality rates.

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Introduction

Intrauterine growth restriction (IGR) is defined as insufficient expression of genetic fetal growth potential. In general, any newborn infant (NI) whose birth weight is below the 10th percentile for the weight that corresponds to their gestational age is included. Such NI are classified as small for gestational age (SGA).

The importance of IGR is that those affected exhibited greater perinatal morbidity and mortality,[1-3] reduced postnatal growth and an increased risk of compromised intellectual development[4,5] and stillbirth during the next pregnancy.[6] Furthermore, IGR has recently been linked to an increased probability of developing chronic diseases during adulthood, such as arterial hypertension, cardiovascular diseases and diabetes.[7]

A recent study of 11 neonatal intensive care units in four South American countries,[8] found that 33% of the 38 NI included whose birth weights were below 1,500 g were SGA.

In addition, SGA infants born live are also heterogeneous in terms of severity, i.e. the degree of growth restriction, and little is known about the impact on prognosis.

Considerable interest has recently been generated in subdividing SGA infants into asymmetrical (wasted: normal length and head circumference for gestational age, but with low weight for length) and symmetrical (stunted: symmetrical reductions in weight, length and head circumference). The main reason for this classification is that there is some evidence that these two subtypes of growth restriction represent different etiologies, operate in different stages during pregnancy and have different prognostic significance.[9,10]

In consequence, it is relevant to take account of the condition of SGA when analyzing the prognosis of NI with birth weights below 1,500 g in our region. All of these facts lead us to undertake wider-ranging studies with dependent variables being the condition of SGA, its severity and proportionality according to varying degrees of prematurity, which could be of use for establishing recommendations or interventions to better care for these NI.

The objectives of the present study were: 1) to evaluate the prevalence, severity and proportionality of NI weighing less than 1,500 g and SGA at varying degrees of prematurity and, 2) to estimate the risk of mortality according to SGA, degree of severity and proportionality.

Methods

Population

Between October 1997 and May 2003 all infants were prospectively enrolled if they were born weighing from 500 to 1,500 g at one of 16 neonatal units in South America (Argentina, Chile, Peru, Paraguay and Uruguay) that cooperate in a neonatal network (NEOCOSUR Collaborative Group). Data for the study was compiled at one of the centers which acts as a central database (Neonatology Department, *Universidad Católica*, Chile). Data is updated online via the Internet. Records include demographic characteristics, morbidity, mortality and interventions, permanently controlling the degree of data consistency. Cases involving transfers, the presence of lethal congenital malformations and chromosomal diseases were excluded.

This is an observational and analytical study of a historical cohort. Infants were defined as small for gestational age if birth weight was below the 10th percentile on a weight for postnatal gestational age curve from Argentina.[11] Gestational age was estimated (in completed weeks) from the first day of the last menstrual period and usually confirmed with ultrasound at the start of the second trimester. Prematurity, based on gestational age, was classed as extreme (24-28 weeks), moderate (29-32 weeks) and mild (33-36 weeks).

Pre-established outcome measurements

- Birth weight below the 3rd percentile.
- Birth weight below the 10th percentile (SGA).
- Severity: using the fetal growth ratio (FGR), defined as the ratio between the observed birth weight and the mean birth weight for each gestational age adapted from previously published standards.[12] Infants were classed as having no growth restriction if FGR was between 0.90 and 1.10. Growth restriction was classed as mild: FGR 0.80-0.89; moderate: FGR 0.75-0.79 (below percentile 4.3) and severe, FGR < 0.75 (percentile below 1.7).[13] The cutoff point for the group without restricted growth (which includes 10% of the mean – FGR 1.00), represents a similar relative weight to that commonly utilized for identifying the optimal nutritional status level in older children and adults. The cutoff point for the group *with* restricted growth ($\leq$ 0.89) is approximately comparable with the conventional definition (< 10th percentile). We used this approach because it provides important clinical information (weight percentage below the mean).[14]
- Proportionality: estimated by the z score for ponderal index (PI = g/cm^3 x 100) and the coefficient of bimodality.

  Ponderal index z-scores were computed as follows: the observed PI (x_i) for each NI is subtracted from the mean (X) and divided by the corresponding standard deviation (SD) of each gestational age from the curve adopted.[11] Therefore the z-score indicates the number of standard deviations by which the PI diverges from the mean. If the z-score was below -1 (PI 1 SD below the average) this was defined as asymmetrical growth restriction.[12] Due to the increasing variation in z-score, which theoretically could be caused by deviation (lack of symmetry), platykurtosis (flattened distribution curve) or bi or multimodality of frequency distribution, a coefficient of bimodality was calculated for PI for each gestational age using the ratio: 1 + deviation ^2/ kurtosis + 3. Values < 0.55 indicate unimodal distribution – equivalent to symmetrical growth restriction – and values $\geq$ 0.55 indicate bimodality – equivalent to asymmetrical growth restriction.[12-15]
- Neonatal mortality up to discharge: adjusted for gestational age. Potential confounding variables: gestational age, adolescence (mother younger than 18), control of pregnancy, multiple birth, hypertension induced by pregnancy (gestational hypertension and preeclampsia), diabetes and prenatal diagnosis of restricted growth (by two ultrasound fetal anthropometric indicators: rate of fetal abdominal circumference growth and ratio abdominal circumference/length of femur below the 10th percentile).

Any significant interaction between pregnancy-induced hypertension and intrauterine growth restriction would suggest that the effect of restriction on the results is modified by maternal hypertension.

Statistical analysis

Measures of central tendencies (mean, median or proportions, as applicable) and measures of distribution (standard deviation, first and third quartiles, 95% confidence interval). In order to compare means, the Student *t* tests and one way analysis of variance were used and to compare medians the Mann-Whitney test was employed.

The χ^2 test was utilized to compare proportions. Bivariate risk was calculated from the unadjusted odds ratio (OR) with 95% confidence interval. Finally, the population attributable risk (PAR) was calculated together with its 95% confidence interval.

The risks for a variety of adverse events, adjusted for potential confounding variables, was estimated using multiple logistic regression models (adjusted OR with 95% confidence intervals). The result of including birth weight in the models was colinearity.

Statistical significance was defined as $p < 0.05$ (two tailed). Sample sizes for certain variables may produce small differences due to lack of data.

For all statistic analyses, Statistica (Version 5.1, Statsoft, Tulsa, OK) and Epidat 2.0 (PAHO/WHO and *Xunta de Galicia*) were used.

Results

One hundred and twenty-nine (6.9%) of the 1,895 live births with weights below 1,500 g that had originally been included in the database were excluded because of lethal congenital anomalies or chromosomal syndromes, 77 (4.1%) were excluded because their gestational ages were less than 24 weeks, three (0.16%) because data on gestational age was missing and 132 (7.1%) because length at birth was unknown. Thus, 1,518 (81.6%) records made up the final sample and were included in the analysis.

The population's characteristics appear in Table 1. Two thirds of mothers had undergone prenatal control (64% received antenatal corticoids), with the elevated prevalence of arterial hypertension and IGR among mothers giving birth to SGA infants meriting special mention ($p < 0.001$). These infants were born more mature and lighter than those with appropriate weights ($p < 0.001$).

Two hundred and fourteen newborns (13.5%; 95% CI 11.8-15.3) presented birth weight below the 3rd percentile, while for birth weight below the 10th percentile this figure rose to 455 (30.7%; 95% CI 27.8-32.2), both positively correlated with increasing gestational age (χ^2 for linear trend, $p < 0.001$).

The mean FGR was 0.90 (SD = 0.21) and there was a significant ($p < 0.001$) tendency for FGR to reduce as gestational age increased (Figure 1). Fetal growth ratio values were below 0.76 in 32.6% (95% CI 30-35.3, n = 387) of cases while 63% (95% CI 60-66.4, n = 734) exhibited FGR $\leq$ 0.89 which correlated positively with increasing gestational age ($p < 0.001$; Figure 2).

The mean z-score was 0.007 (±1.01) and was lower for SGA (-0.188±0.88 versus 0.099±1.05; $p < 0.0010$). One hundred and twenty (8%, 95% CI 6.6-9.3) of the NI with weights below 1,500g presented PI z-scores below -1 (asymmetrical growth restriction), with this proportion being greater among SGA infants (63/467, 13.5%) when compared with children whose weights were appropriate (57/1,051; 5.42%) ($p < 0.001$). No differences in the rates of z-score <-1 were observed according to degree of prematurity ($p = 0.178$). Furthermore, those preterms suffering from asymmetrical restriction exhibited more severe restriction (FGR < 0.75) than did those with symmetrical restriction (OR 3.16, 95% CI 2.1-4.7).

The coefficient of bimodality oscillated between -0.27 and 0.78 (mean 0.53) with no relation to gestational age, while mean PI was 2.26 (SD = 0.39). When compared with appropriate for gestational age children, SGA infants exhibited lower PI (2.30±0.33 and 2.18±0.57, respectively, $p < 0.001$).

In Table 2 it will be observed that the coefficient of bimodality reduced in line with severity of restriction, while the proportion of asymmetry increases with severity of growth restriction ($p < 0.001$).

Prenatal diagnosis of restricted growth and maternal arterial hypertension were the only conditions linked to an

Table 1 - Population's characteristics

Characteristic	Total (n = 1,518)	SGA (n = 467)	Non SGA (n = 1,051)	p *
BW (g) mean (SD)	1,113 (260)	1,077 (290)	1,129 (244)	< 0.001
GA (weeks) mean (SD)	29.6 (2.6)	31.7 (2.2)	28.6 (1.3)	< 0.001
Male sex	819 (54%)	256 (55%)	557 (53%)	0.716
Mother's age (years) mean (SD)	27.3 (7.2)	27.7 (7.0)	27.1 (7.6)	0.130
Adolescent mother ($\leq$ 18 years)	124 (8.2%)	45 (9.6%)	142(13.5%)	0.013
Prenatal control	1,145 (75.4%)	344 (7.6%)	800 (76.2%)	0.278
Multiple birth	264 (17.4%)	90 (19.2%)	174 (16.5%)	0.199
Diabetes	35 (2.3%)	12 (2.5%)	22 (2.1%)	0.625
Hypertension	466 (30.7%)	208 (44.5%)	259 (24.6%)	< 0.001
IGR	559 (36.8%)	348 (74.5%)	211(20%)	< 0.001

* Comparison between SGA and non SGA.
SGA = small for gestational age (< 10^{th} percentile); BW = birth weight; SD = standard deviation; GA = gestational age; IGR = intrauterine growth restriction (diagnosis by prenatal ultrasound).

increased risk of being small for gestational age and having FGR ≤ 0.89, with elevated PAR values meriting attention (Tables 3 and 4), while the condition of adolescence revealed a mild protective effect, although not a statistically significant one. The slight increase in risk in the absence of prenatal control, while statistically significant, did not correlate with a transcendent impact at the population level.

Once more, maternal hypertension (aOR 1.60, 95% CI 1.03-2.04) and intrauterine growth restriction (aOR 1.80, 95% CI 1.16-2.82) were the only variables that remained statistically associated with the condition of asymmetrical growth restriction with a discrete repercussion at the population level (PAR = 17% [95% CI 4-30] and 24% [95% CI 9-39], respectively).

Small for gestational age or severely growth restricted infants born at weights below 1,500 g exhibited a risk of death more than double that of those who did not present these conditions (p < 0.05). No prenatal characteristic or pathology was associated with a biological risk and/or statistically altered risk of mortality, with the exception of the absence of prenatal, control, which exhibited a significantly elevated risk with similar magnitude for each of the three outcomes (p < 0.05), suggesting delayed detection and treatment of medical and/or obstetric complications during pregnancy (Table 5). As would be expected, for every extra week that pregnancy lasts the risk of death reduces by 30 to 40% (p <0.05).

When FGR was processed in a continuous manner, the risk of neonatal mortality increased by 0.027 times for every 0.10 units that FGR reduced (95% CI 0.009-0.07, p < 0.001).

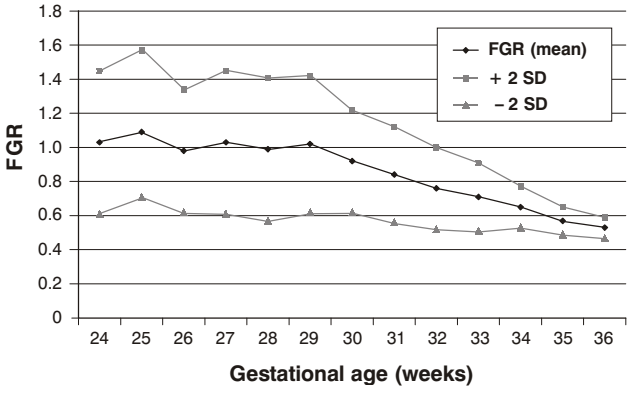
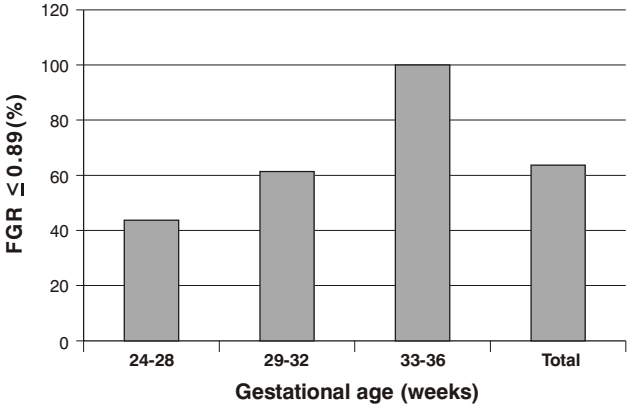


Figure 1 - Fetal growth ratio (FGR) according to gestational age



FGR: Fetal Growth Ratio.

Figure 2 - Severity of growth delay (FGR ≤ 0.89) according to prematurity levels

Discussion

The present study, based on a hospital sample from 16 neonatal units at 16 Latin American university hospital maternity units, demonstrates that the prevalence of the condition of being small for gestational is elevated among preterms born with weights below 1,500 g and that the condition is severe in a third of such infants. The condition is inversely related to gestational age and is linked with an elevated risk of mortality. The characteristic of asymmetry conferred little additional risk to that already generated by the degree of restriction severity.

Among the differentiating features of our study, it is worth mentioning that this is the first exploration of this problem in our region, describing FGR and PI in preterms and employing standardized data collection and accruing a large sample size. In contrast with other studies,[16] the sample was not limited by gestational age.

A number of limitations can be listed. Several different authors[17] have proposed that postnatal weight curves based on an estimate of gestational age calculated from the date of the last menstrual period overestimate gestational age and thus underestimate the prevalence and severity of compromised growth in preterms. Ott,[18] suggests that standards for birth weight based on fetal growth gauged by ultrasound and adjusted for maternal variables[19] offer better predictive value for abnormal outcomes. Until a local standard is developed by ultrasound we consider that the findings are sufficiently representative of the study population.

In view of the elevated prevalence of absent prenatal control and in the face of the possibility of selection bias, all of the logistic models were re-analyzed with cases where there was no prenatal control excluded with no changes in the OR resulting, and superimposed confidence intervals being observed (data not shown).

The absence of bimodality (coefficient < 0.55 and low prevalence of z-score < -1) is strong evidence against the existence of two different IGR subtypes (symmetrical *vs* asymmetrical), even in the most severe subsets.

Several different studies have linked fetal growth restriction with neonatal morbidity and mortality of preterms born weighing less than 1,500 g[1-5,13,20-22] although without contemplating, as does the present study, severity and

proportionality. Both the diagnosis and severity of growth restriction were associated (as expected) with a high risk of neonatal death, with absence of prenatal control being the only preceding factor that was potentially controllable to be systematically associated with death for the three outcomes investigated (SGA, FGR < 0.89 and z-score < -1).

Table 2 - Coefficient of bimodality and ponderal index z-score according to IGR severity (excluding multiple birth; n = 1,231)

IGR severity (FGR)	n	Coefficient of Bimodality	z-score		
			Mean *	< -1 †	
				%	CI 95%
0.90-1.10 (No)	501	0.53	0.19	5.1	3.3-7.6
0.80-0.89 (Mild)	335	0.48	0.02	6.4	3.8-10.4
0.75-0.79 (Moderate)	90	0.22	-0.26	13.4	7.7-21.8
< 0.75 (Severe)	305	0.20	-0.22	15.2	11.8-19.2

IGR = intrauterine growth restriction (IGR) evaluated by FGR (fetal growth ratio).
* Analysis of variance: F = 13.80 (p < 0,001).
† χ^2 for linear tendency = 29.4 (p < 0.001).

Table 3 - Unadjusted, adjusted, and population attributable risks of children small for gestational age according to maternal variables

Covariate	OR (CI 95%)	aOR (CI 95%) *	PAR (CI 95%)
Adolescent mother	0.68 (0.46-0.98)	0.62 (0.37-1.03)	-4 (-8 a 0)
Controlled pregnancy	1.26 (0.95-1.66)	1.40 (0.94-2.0)	4 (0 a 10)
Multiple birth	1.22 (0.91-1.63)	1.26 (0.84-1.88)	3 (-1 a 8)
Diabetes	1.17 (0.54-2.49)	1.80 (0.69-4.79)	0 (-1 a 2)
Mother's hypertension	2.27 (1.79-2.88)	1.20 (0.86-1.67)	25 (18 a 31)
IGR	12.47 (9.5-16.3)	7.41 (5.4-10.1)	70 (65 a 75)

OR = odds ratio; PAR = population attributable risk; IGR = intrauterine growth restriction (prenatal diagnosis by ultrasound).
* Adjusted risk for multiple logistic regression for the covariates listed and gestational age.
n = 1,387 -2 * log (likelihood) = 1081 χ^2 (7) = 634 (p < 0.001).
Correct predictive value of SGA = 65%.
No interaction between mother's hypertension and IGR was found. (p = 0.781)

Table 4 - Unadjusted, adjusted, and population attributable risks of the fetal growth ratio $\leq$ 0.89 according to maternal variables

Covariate	OR (CI 95%)	aOR (CI 95%) *	PAR (CI 95%)
Adolescent mother	0.86 (0.62-1.17)	0.77 (0.49-1.20)	-1 (-5 a 2)
Absence of prenatal control	1.41 (1.08-1.84)	1.85 (1.29-2.66)	6 (1 a 11)
Multiple birth	1.17 (0.88-1.54)	1.15 (0.80-1.17)	2 (-1 a 7)
Diabetes	0.54 (0.25-1.13)	0.43 (0.16-1.15)	-1 (-3 a 0)
Mother's hypertension	3.09 (2.43-3.93)	1.71 (1.24-2.36)	28 (23 a 33)
IGR	14.1 (11.2-19.5)	10.42 (7.5-14.4)	59 (55 a 62)

OR = odds ratio; PAR = population attributable risk; IGR = intrauterine growth restriction (prenatal diagnosis by ultrasound).
* Adjusted risk for multiple logistic regression for the covariates listed and gestational age.
n = 1,387 -2 * log (likelihood) = 1229 χ^2 (7) = 691 (p < 0.001)
Correct predictive value FGR $\leq$ 0.89 = 78%.
No interaction between mother's hypertension and IGR found. (p = 0.096).

Table 5 - Adjusted neonatal mortality risks (confidence interval of 95%) in SGA, FGR ≤ 0.89 and z-score for ponderal index < -1 (multivariate analysis by logistic regression)*

	Condition		
	SGA	**FGR ≤ 0.89**	**z-score < -1**
Exposition variable (1: Yes; 0: No)	2.64 (1.71-3.92)	2.76 (1.85-4.10)	1.37 (0.80-2.32)
Covariate			
Adolescent mother (1: Yes; 0: No)	1.44 (0.92 - 2.25)	1.45 (0.92-2.27)	1.30 (0.83-2.01)
Absence of prenatal control (1: Yes; 0: No)	2.66 (1.86-3.81)	2.56 (1.78-3.68)	2.74 (1.98-3.98)
Multiple birth (1: Yes; 0: No)	0.98 (0.63-1.52)	0.94 (0.61-1.45)	0.96 (0.63-1.46)
Diabetes (1: Yes; 0: No)	1.22 (0.48-3.10)	1.48 (0.58-3.76)	1.31 (0.51-3.32)
Mother's hypertension (1: Yes; 0: No)	0.80 (0.55-1.16)	0.72 (0.48-1.03)	0.80 (0.55-1.18)
IGR (1: Yes; 0: No)	1.20 (0.79-1.80)	1.04 (0.69-1.57)	1.65 (1.15-2.4)
Gestational age (weeks)	0.62 (0.58-0.67)	0.62 (0.58-0.69)	0.65 (0.60-0.69)

SGA = small for gestational age; FGR = fetal growth rate; z-score: ponderal index;
IGR = intrauterine growth restriction (prenatal diagnosis by ultrasound).
No interaction between mother's hypertension and IGR was found (p = 0.653, 0.953 and 0.660 for SGA, FGR ≤ 0.89 and z-score < -1, respectively).
Right predictive values of models = 24.1, 26.1 and 20.7% for SGA, FGR < 0.89 and z-score z < -1, respectively.

Maternal arterial hypertension and prenatal restricted growth diagnosis were the only maternal variables systematically and statistically associated with an increased risk for the three outcomes. It is important to point out the absence of interactions between these two variables, suggesting that each has an independent effect on the outcomes established. The magnitude of the PAR values associated with arterial hypertension and growth restriction are probably a reflection of the elevated prevalence of the two nosological entities among the study population (30.7 and 36.8%, respectively).

The etiology of premature delivery is plurifactorial, but the many different maternal diseases and pregnancy-related conditions that limit fetal growth and contribute to the chance of adverse events among more mature fetuses may also have an effect on the growth and birth weights of very premature infants.[20]

The pathophysiology of restricted growth in fetuses destined to be born preterm is explained by a reduction in uterine flow and placental perfusion. This would promote a reduction in hormones that induce fetal growth, increasing cortisol and stimulating the myometrium, with the consequent triggering of labor and premature delivery. The activation of compensatory mechanisms can lead two one of two outcomes: 1) if they fail then stillbirth occurs and 2) if they are successful, growth is restricted and adaptation takes place. If this is sufficient the result will be a small for gestational age fullterm infant and, if insufficient, the mechanisms of labor will be activated and the preterm may survive.[23]

Only one study[16] agrees with ours about the fact that SGA prevalence, and also severity, increase with advancing gestational age, in contrast with other authors. In a study that included 4,700 preterms, Zeitlin et al. concluded that the relationship between restricted growth and premature delivery was strongest before 34 weeks' gestation.[24] Another population study,[25] found that the prevalence of restriction increased up to the thirtieth week (12.3%) and then quickly decreased. Finally, in one study that enrolled 8,663 singleton infants, the proportion of SGA infants (< 2 SD from the mean) reduced from 21% between 26 and 30 weeks to 11.1% from 31 to 37 weeks.[26] These discrepancies may be the result of sample size, policies on inducing labor, gestational age estimation, SGA definition, cutoff points for weight or gestational age among those under 1,500 g and termination of pregnancy. Owen et al., in a contrastive article comparing spontaneous and induced premature deliveries did not find any significant difference in neonatal outcomes.[27]

Our values for PI agree with data published by other authors.[13,28] Employing this indicator, the most common type of growth restriction was symmetrical. In common with the majority of developing countries, this can be attributed to its association with greater severity and increased prevalence of certain risk factors (for example a very small mother).[29]

We conclude that the prevalence of the condition of small for gestational is elevated among preterm infants born with birth weights below 1,500 g and that when this is very severe, irrespective of the cause, there is a high risk of mortality. Asymmetric growth restriction confers very little additional risk to that already conferred by the degree of restriction severity. We suggest an early test for restricted growth during prenatal control.

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