

Placental Growth Measures in Relation to Birth Weight in a Latin American Population

Medidas de crescimento placentário em relação ao peso de nascimento em uma população latino-americana

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Abstract

Introduction The placenta, translates how the fetus experiences the maternal environment and is a principal influence on birth weight (BW).

Objective To explore the relationship between placental growth measures (PGMs) and BW in a public maternity hospital.

Methods Observational retrospective study of 870 singleton live born infants at Hospital Maternidad Sardá, Universidad de Buenos Aires, Argentina, between January 2011 and August 2012 with complete data of PGMs. Details of history, clinical and obstetrical maternal data, labor and delivery and neonatal outcome data, including placental measures derived from the records, were evaluated. The following manual measurements of the placenta according to standard methods were performed: placental weight (PW, g), larger and smaller diameters (cm), eccentricity, width (cm), shape, area (cm²), BW/PW ratio (BPR) and PW/BW ratio (PBR), and efficiency. Associations between BW and PGMs were examined using multiple linear regression.

Results Birth weight was correlated with placental weight ($R^2 = 0.49$, $p < 0.001$), whereas gestational age was moderately correlated with placental weight ($R^2 = 0.64$, $p < 0.001$). By gestational age, there was a positive trend for PW and BPR, but an inverse relationship with PBR ($p < 0.001$). Placental weight alone accounted for 49% of birth weight variability ($p < 0.001$), whereas all PGMs accounted for 52% ($p < 0.001$). Combined, PGMs, maternal characteristics (parity, pre-eclampsia, tobacco use), gestational age and gender explained 77.8% of BW variations ($p < 0.001$). Among preterm births, 59% of BW variances were accounted for by PGMs, compared with 44% at term. All placental measures except BPR were consistently higher in females than in

Keywords

- Placenta
- placental weight
- placental characteristics
- birth weight
- gestational age

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males, which was also not significant. Indices of placental efficiency showed weakly clinical relevance.

Conclusions Reliable measures of placental growth estimate 53.6% of BW variances and project this outcome to a greater degree in preterm births than at term. These findings would contribute to the understanding of the maternal-placental programming of chronic diseases.

Resumo

Introdução A placenta traduz como o feto experimenta o ambiente materno, além de ser a principal influência sobre o peso ao nascer (PN).

Objetivo Explorar a relação entre medidas de crescimento da placenta (MCPs) e PN em uma maternidade pública.

Métodos Estudo retrospectivo observacional de 870 recém-nascidos vivos únicos na Maternidade Sardá, Universidade de Buenos Aires, Argentina, entre janeiro de 2011 e agosto de 2012 com os dados completos das MCPs. Foram avaliados dados da história clínica e obstétrica materna, trabalho de parto e resultados neonatais, incluindo medidas da placenta derivadas dos registros médicos. Foram realizadas as seguintes medições manuais da placenta: peso da placenta (PP, g), diâmetros maior e menor (cm), excentricidade, espessura (cm), forma, área (cm²), razões PN/PP e PP/PN e eficiência. Associações entre PN e MCPs foram examinadas por meio de regressão linear múltipla.

Resultados Peso ao nascer foi correlacionado com peso placentário ($R^2 = 0,49$, $p < 0,001$), enquanto idade gestacional foi moderadamente correlacionada com peso placentário ($R^2 = 0,64$, $p < 0,001$). Por idade gestacional, houve uma tendência positiva para a relação PP e PN/PP, mas uma relação inversa com a razão PP/PN ($p < 0,001$). Somente peso da placenta respondeu por 49% da variabilidade do peso ao nascer ($p < 0,001$), ao passo que todas as MCPs foram responsáveis por 52% ($p < 0,001$). Combinados, MCPs, características maternas (paridade, pré-eclâmpsia, fumo), idade gestacional e sexo explicaram 77,8% da variação do peso ao nascer ($p < 0,001$). Entre nascimentos pré-termo, 59% da variância do PN foi contabilizada pelas MCPs, em comparação com 44% a termo. Todas as medidas placentárias, exceto a razão PN/PP, foram consistentemente maiores em mulheres do que em homens, mas não significativas. Índices de eficiência placentária mostraram fraca relevância clínica.

Conclusões medidas confiáveis de crescimento placentário estimam 53,6% da variância do peso ao nascer, e projetam esse resultado a um maior grau em nascimentos pré-termo do que a termo. Estes resultados contribuiriam para a compreensão da programação materno-placentária de doenças crônicas.

Palavras-chave

- Placenta
- peso da placenta
- características da placenta
- peso ao nascer
- idade gestacional

Introduction

Genetic, environmental and socioeconomic factors^{1,2} influence birth weight (BW), as well as illnesses that occur during pregnancy, such as infections, hypertensive disorders and diabetes mellitus.³

The placenta, to a large degree, translates how the fetus experiences the maternal environment, and genetic influences aside, is the main factor to influence BW. The growth of the placenta is directly related to its functional efficiency as the only fetal source of both nutrients and oxygen. Placental weight (PW) is one way to characterize placental size, but it is a collection of many dimensions of growth, including its surface area and its width.

The placental surface area reflects the laterally expanding growth of the chorionic disc (measured by disc shape

and chorionic disc diameters), whereas disc width reflects the arborization of the villous and vascular nutrient exchange surface. Placental weight and other placental growth measures (PGMs: larger and smaller diameters, disc width) are routinely collected in pathology laboratories across the world, but limited data regarding these placental dimensions in the Latin American population are available.

These PGMs were designed to capture different aspects of the placenta that, first of all, relate to placental function, theoretically influencing BW by different mechanisms; secondly, PGMs are conventionally considered to have different ‘critical periods of development’,⁴ and, finally, they are most relevant to the ‘fetal origins’ hypothesis, which posits that a wide variety of lifelong health risks are influenced by the fetal experience.

Additionally, PW and other PGMs were found to be predictive of maternal disease, obstetric outcome, perinatal morbidity and mortality and childhood growth and development.⁵

The aim of this study was to explore the relationships of PGMs with BW in a Latin American population.

Methods

This was an observational, retrospective study on 875 singleton live born infants at the Department of Obstetrics and Gynecology of Hospital Maternidad Sardá, Universidad of Buenos Aires, Argentina, between January 2011 and August 2012 with complete data for placental measures. Details of history, clinical and obstetrical maternal data, labor and delivery and neonatal outcome data, including placental measures derived from the records, were evaluated. Exclusion criteria were gestational age (GA) less than 22⁺⁰ weeks and over 42⁺⁶ weeks, twin gestation, PW lower than 100 g or higher than 2,500 g.

Chronic hypertension was defined as the presence of elevated blood pressure (> 140/90 mm Hg) before pregnancy or before the 20th week of gestation. Preeclampsia was defined as hypertension presenting beyond 20 weeks of gestation with > 300 mg protein in a 24-hour urine collection. Eclampsia was defined as the occurrence of seizures in a pregnant woman with preeclampsia.⁶ Women were diagnosed as having gestational diabetes according to the criteria of the World Health Organization (WHO) protocol.⁷ The diagnosis of clinical chorioamnionitis was based on a maternal temperature of > 38°C with or without uterine tenderness and/or foul vaginal discharge with no other cause of fever. Gestational age was ascertained by menstrual dates and early ultrasound measurements. Small for gestational age was defined when the BW for GA and sex were less than the ten percentile according to a local intrauterine growth chart.⁸

Preparation of the Placenta

After delivery, the placenta was placed in a self-sealing plastic bag and stored in a refrigerator; the date and time of birth were added to the label.⁹ A series of manual measurements of the placenta's gross structure were then made in accordance with standard methods used in pathology examinations.¹⁰

Placental weights (g) were taken using an electronic scale; cord and membranes were cut before weighing. Leary et al suggested that the fetal weight/placental weight correlation does not change when placentas are weighed trimmed compared when they are weighed untrimmed.¹¹ The longest diameter of the surface (length) was measured using a transparent plastic ruler placed on the surface and recorded in centimeters. The diameter perpendicular to the length was defined as the smallest diameter, and was measured in the same way. Chorionic plate eccentricity was calculated as the ratio of the largest to the smallest diameters of the chorionic plate. Eccentricity measures the relative asymmetry of normal placental growth, and may mark the uterine constraint of placental growth. Placental width at the center of the chorionic disc was measured by piercing the disc with a

needle onto which millimeter marks were inscribed, and analyzed in units of 0.1 cm.¹² Placental shape was defined as the difference between the larger and smaller diameters: oval placenta ≥ 3 cm; round placenta < 3 cm.¹³ Placental area (cm²) was calculated assuming an elliptical surface, using the formula length x breadth x $\pi/4$.¹⁴ The placental weight (g) to birth weight (g) ratio ([PW/BW], PBR), a proxy for placental efficiency ("efficiency 1"), was calculated as a percentage ([PW/BW] x 100).¹⁵ The birth weight (g) to placental weight (g) ratio ([BW/PW], BPR) has been used to indicate fetal nutrition adequacy.¹⁶ Finally, 2 other measures of placental efficiency were calculated using the ratios of length ("efficiency 2") and breadth ("efficiency 3") to BW.¹³

The placental measurements were obtained blinded from pregnancy and childbirth data.

Statistical Analysis

Sexual dimorphism and differences between term and pre-term were explored for all placental measures. As the PGMs are all measures of the same organ, they are necessarily interdependent. As there was no strong correlation among the PGMs (data not shown), unadjusted and multiple linear regression techniques explored the associations of PGMs to BW, and present the point estimates of effects with 95% confidence intervals (95%CI) and R-squared.

For the regression models, the following criteria were predefined. Firstly, when a PGM included the dependent variable (BW) as well as any other predictors, it was excluded from the adjusted models. Secondly, the goodness of fit of each regression model was carefully assessed according to Royston and Wright.¹⁷ This resulted in four placental predictors (placental weight, largest and smallest diameters and disc width). Thirdly, three models were predefined: a) unadjusted included each PGMs; b) model 1 adjusted for all PGMs, and c) the full model included PGMs, maternal characteristics (gestational age [weeks], parity, pre-eclampsia, tobacco use) and infant gender.

A sample size of 47 subjects to obtain a statistical power of 80% with α set at 0.05 and an expected adjusted coefficient of determination of 0.40 was calculated (as this seemed to possibly reveal a clinically relevant prediction of BW).

The Stata 12 software (College Station, Texas, USA) was used for all statistical calculations, and significance was set at a 0.05 level.

The study was submitted and approved by the Research Ethics Committee of Hospital Maternidad Sardá.

Results

None of the exclusion criteria were applied, leaving a final analytical sample of 870 mothers and their corresponding placentas for analysis. The mean maternal age was 24 years (range 13–45 years); the level of education, 10.1 years (standard deviation, SD, 3.0 years); primiparity, 24.5%; smoking during pregnancy, 12.6%; gestational diabetes, 4.9%; chronic hypertension, 3.3%; pre-eclampsia, 8.7%; eclampsia, 0.9%; clinical chorioamnionitis, 7.9%; and fetal growth restriction, 13.0%. Infants' characteristics included male gender (55.3%), a

mean GA at birth of 35.6 weeks (22.2–42.5 weeks), and a mean BW of 2,581 g (380–4,860 g); 6.3% ($n = 55$) of the infants were born at ≤ 28 gestational weeks; 8.7% ($n = 76$) at 29–32 weeks;

36.6% ($n = 319$) at 33–36 weeks; and 48.2% ($n = 420$) at ≥ 37 weeks. Small for gestational age represented 18.8% of the sample, and it was greater for term (31.2%) than preterm

Table 1 Placental characteristics

Characteristic	n ^a	Mean	SD	Range
Weight (g)	870	432	120	110–838
Gestational age (w):				
22–28	55	266	81.9**	
29–32	76	350	90.5	
33–36	319	428	101.4	
37–42	420	474	115.6	
Weight z score ^b	870	–1.1	0.9	–5.0–2.1
Term neonates	420	–1.4	0.9	–5.0–1.3*
Preterm neonates	450	–0.9	0.8	–4.3–2.1*
Largest diameter of placenta (cm)	862	16.6	2.5	5.0–29.0
Smallest diameter of placenta (cm)	862	12.4	2.9	3.0–23.0
Chorionic plate eccentricity ^c	862	1.4	0.4	0.8–5.6
Disc thickness (cm)	820	3.0	0.6	1.0–7.0
Chorionic plate area (cm ²)	862	164.8	55.8	15.7–397
Placental shape	870	4.1	2.6	–2–18
Oval (≥ 3 cm): 612/870 (70.4%)				
Round (< 3): 258/870 (29.6%)				
BPR	870	5.9	1.5	2.1–23.5
Term neonates	420	6.6	1.4	2.2–23.5*
Preterm neonates	450	5.4	1.3	2.1–10.8*
Gestational age (w):				
22–28	55	3.7	1.0**	
29–32	76	4.8	0.9	
33–36	319	5.8	1.1	
37–42	420	6.6	1.5	
PBR	870	17.6	5.1	4.2–46.0
Term neonates	420	15.5	3.5	4.1–44.6*
Preterm neonates	450	19.5	5.6	9.1–46.0*
Gestational age (w):				
22–28	55	28.4	6.8**	
29–32	76	21.5	4.3	
33–36	319	17.5	3.7	
37–42	420	15.5	3.5	
Efficiency 1 ^d	866	176.8	50.4	42.5–460
Efficiency 2 ^d	855	7.1	2.9	1.4–31.5
Efficiency 3 ^d	815	1.3	0.6	0.4–6.4

Abbreviations: BPR, birth weight to placental weight ratio; PBR, placental weight to birth weight ratio; SD, standard deviation; w, weeks.

^aThe denominator, when specified, indicates that there were some missing values.

^bSource: Thompson et al., 2007. There were no available values for 22–23 weeks of gestational age.

^cRatio of larger to smaller diameter.

^dRatio of placental weight (1), length (2) and breadth (3) to birth weight (efficiency).

*t-test, $p < 0.001$.

**ANOVA, $p < 0.001$.

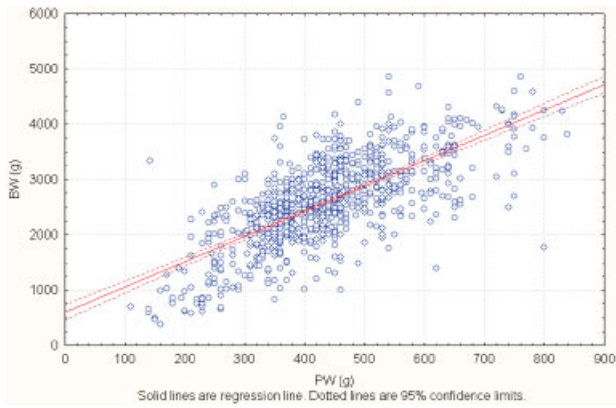


Fig. 1 Birth weight according to placental weight. $r = 0.704$ ($p < 0.001$), $BW = 569.63 + 4.57 \cdot PW$. Abbreviations: BW, birth weight; PW, placental weight.

neonates (8.3%), whereas congenital anomalies were present in 7.1%. The elective cesarean section rate was of 40.7%, and the vaginal birth rate, 43.2%; the remainder was induced labor.

A description of the placental variables is presented in ►Table 1. Birth weight was correlated with PW ($r = 0.70$, $R^2 = 0.49$, $p < 0.001$), but there was a wide variation in PW for any given BW, suggesting that there are large differences in placental efficiency. For example, babies weighing around 3,000 g had placentas ranging from 300 to 700 g in weight. (►Fig. 1) Birth weight was weakly correlated with other placental measures, ranging from -0.11 (efficiency 2) to 0.47 for the chorionic plate area (all $p < 0.001$).

Gestational age was strongly correlated with PW ($r = 0.80$, $R^2 = 0.64$, $p < 0.001$), but there was a wide varia-

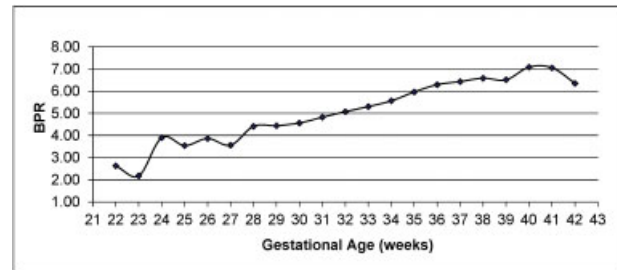


Fig. 2 Birth weight to placental weight ratio (BPR) according to gestational age. Mean BPR increases with gestational age. Results were obtained from all placentas submitted to the Department of Pathology at Hospital Maternidad Sardá in 2011–2012. Data are similar to those of a previously published study (Benirschke, Kaufmann; 2000).⁴ There appear to be three tiers of significantly increasing workload (relatively increased fetal demand based on weight). The interval between 28–37 weeks of gestation is the most pronounced, followed by a plateau until 39 weeks, and then another increase until 41 weeks of gestation.

tion in PW for any given GA. For example: babies around 36 weeks had placentas ranging from 200 to 700 g in weight. Combined, PW and GA reached 76.8% of BW variability ($p < 0.001$).

Significant differences between term and preterm placentas were only observed for weight z score, BPR and PBR (data not shown). When examined by GA intervals, there was a positive trend for BPR (►Fig. 2), but an inverse relationship with PBR (data not shown, all $p < 0.001$). Two-thirds of placental shapes were oval. Furthermore, all placental measures except BPR were consistently higher in females than in males, which was also not significant.

Comparing univariable and multivariable point estimates of effect (►Table 2) revealed important results: R-squared values increased steadily from the unadjusted model (5–

Table 2 Point estimates of effects for regression model of placental measures predicting birth weight (g)

	Unadjusted models		Multivariate models [#]			
	Point estimate (95%CI)	R-squared	Model 1 ^a		Full Model ^b	
			Point estimate (95%CI)	Adjusted R-squared	Point estimate (95%CI)	Adjusted R-squared
Placental weight (g)	4.5 (4.2–4.8)	0.49***	3.8 (3.4–4.3)***	0.52***	2.4 (2.1–2.7)***	0.78***
Largest diameter (cm)	142.4 (123.7–161.1)	0.21***	23.3 (3.4–43.2)**		16.4 (2.7–30.9)**	
Smallest diameter (cm)	115.8 (99.0–132.6)	0.18***	27.8 (11.6–44.1)***		5.1 (–6.0–16.3)	
Disc width (cm)	299.1 (210.7–387.5)	0.05***	61.3 (–7.9–130.5)		17.1 (–30.7–65.1)	

Abbreviation: 95%CI, 95% confidence interval.

[#]Predictors include placental measures (placental weight, largest diameter, smallest diameter and disc width), gestational age (weeks), parity, pre-eclampsia, tobacco use and infant gender.

^aModel 1: adjusted for all placental measures (no adjustments for maternal variables, gestational age and sex).

^bFull Model: adjusted for all placental measures, maternal variables, gestational age and sex.

**Significant at the 0.05 level.

***Significant at the 0.001 level.

Table 3 Point estimates of effects for regression model of placental measures predicting birth weight (g) according to gestational age

Measure	Gestational age					
	≤ 32 w (n = 131)		33–36 w (n = 319)		37–42 w (n = 420)	
	Point estimate (95%CI)	Adjusted R-squared*	Point estimate (95%CI)	Adjusted R-squared*	(95%CI)	Adjusted R-squared*
Placental weight (g)	2.20 (1.59–2.82)	0.84**	(1.72–2.62)	0.53**	2.65 (2.62–3.04)	0.49**
Large diameter (cm)	–17.90 (–39.14–3.32)		14.7 (–3.25–32.69)		15.27 (–4.52–35.06)	
Small diameter (cm)	19.55 (1.92–37.17)		5.85 (–9.74–21.46)		8.32 (–8.23–24.88)	
Disk width (cm)	–36.25 (–103.7–31.2)		–14.31 (–50.83–22.20)		–4.90 (–40.67–30.85)	

Abbreviation: 95%CI, 95% confidence interval.

*Predictors include placental measures, parity, preeclampsia, tobacco use and infant gender.

** $p < 0.001$.

49%) to 52% in the four placental growth models, whereas the multivariable model, including the maternal characteristics, GA, sex and the PGMs, accounted for 78% of BW variability (regression equation: $BW (g) = -3186.667 + 2.47 \cdot PW + 14.9 \cdot \text{largest diameter} + 5.52 \cdot \text{smallest diameter} + 17.19 \cdot \text{disc width}$ [$p < 0.001$]). In the full model, only placental weight and largest diameter retained an independent effect. Additionally, when excluding smallest diameter and disc width from the model, there was a minimal change in the adjusted R-squared value.

For preterm and term neonates, placental weight alone accounted for 52.5% and 37.4% of BW variances respectively ($p < 0.001$).

► **Table 3** shows regression models of placental measures predicting BW according to GA. Overall, an inverse relationship between GA and the adjusted R-squared of all placental measures were observed; the adjusted R-squared for the PGMs were smaller at or over 33 weeks of gestation compared with < 33 weeks.

Discussion

To our knowledge, this is the most comprehensive description of PGMs and their relation to BW in a selected population reported to date in Latin America, and it may provide a useful guide for future analyses of placental gross anatomy.

Although the BW of male neonates showed a marginal difference from that of females (58.3 g, $p = 0.499$), an opposite effect was observed for placental measures, suggesting that the growth of female placentas may not be the same as that of male placentas.

One hypothesis that explains this fact would be the “Feminine Eco-stability Hypothesis”, which holds that the female sex is less sensitive to external factors that modulate ontogenetic development; in contrast, the male sex would be more negatively affected by environmental factors.¹⁸

The ratio of fetal to placental weight (or its inverse) is used as an endpoint measure of placental nutrient transport

efficiency across species.¹⁹ A small BPR was associated with higher odds of small for gestational age (SGA) infants, and may serve as an indicator suggestive of adverse intra-uterine environment.²⁰ Our BPR findings increased with GA, suggesting a more dynamic growth during prematurity, in agreement with a previous study.²¹

The PBR has been associated with health throughout the lifespan, and has been shown to decrease with GA.²² The present study confirms these results and reveals values in a comparable range with other studies.^{15,23} Moreover, an elevated PBR may be an expression of a relatively inefficient placenta with reduced ability to maintain fetal growth, and thus can be used as a predictor of hypertension in adulthood for assumed lack of “placental functional efficiency”.²⁴

In our study, we also measured placental efficiency using the ratios of the length and breadth of the surface to BW in addition to the customary PBR.²⁵ Our findings are in agreement with a previous study,¹³ but in an attempt to define the mechanisms for this from our data, a subgroup analysis was run; in a multiple regression analysis, all indices were weakly associated with several maternal characteristics, GA and sex. Only the ratio of the length to BW showed clinical relevance, indicated by the adjusted R-squared (62%, $p < 0.001$). This suggests that when placental growth across the major axis in early pregnancy is adequate, there is increased thickening of the placenta, reflecting a different aspect of the control of the placental exchange surface.

In all regression analyses, we focused on the adjusted R-squared rather than on the magnitude of the β coefficients, because R-squared changes would be unaffected by collinearity.

Surprisingly, our results showed a higher R-squared for prediction of BW compared with other studies, although it was methodologically different.^{26–28}

After adjustment for maternal characteristics, GA and infant gender, 77% of BW variances were accounted for, suggesting ‘partial mediation’ of their effects on BW by the feature of the four placental measures.

–**Table 2** shows that only placental weight and largest diameter retained an independent effect on BW after adjustment for mother and infant conditions, in consonance with another study.²⁶ Barker et al¹⁴ observed that placental growth along the major axis (a proxy of volume) is qualitatively different from growth along the minor axis, and postulated that the minor axis is more important for nutrient transfer to the fetus, partially explaining our results.

We speculate that one of the main reasons for the comparatively low explanatory power of smallest diameter and disc thickness is that these measures have limitations, and incompletely capture the variability that characterizes the human placenta.

The difference in prediction of BW using PGMs in preterm versus term (80.8% versus 49.8% respectively) denotes different abilities of PGMs to account for BW across pregnancy, and suggests that PGMs are more powerful at gestational ages when they are considered to be more dynamic, which occurs prior to the third trimester.⁴ In other words, PGMs will have their strongest associations with BW variances when they themselves are changing.

Chorionic plate measures complement the ability of PW to account for BW variances.

These novels PGMs are related to both GA and BW at delivery, but their relations are not identical. In the present study, PGMs accounted for 25.8% of GA variances and 52.7% of BW variances. One explanation might be that growth parameters naturally change across gestation, independent of any environmental effectors.¹²

These measures are highly reproducible, and may clarify the complex interrelations among mother, placenta and fetus to maintain pregnancy and support fetal growth. The reliance on R-squared is sufficient to demonstrate the power of these novel measures.

While sample size was relatively large, the placental examinations were performed at the request of attending physicians. Consequently, our study was derived from a convenience sample in which preterm birth, SGA and congenital anomalies were overrepresented. Therefore, our findings may not be generalized to the general population. However, they do closely mirror the hospital registry because they present similar demographic, clinical and obstetrical maternal data.

Moreover, these data are cross-sectional, and longitudinal studies would be necessary to validate the results. However, longitudinal studies of a cohort of placentas to register morphometry in real time throughout pregnancy are very difficult to perform; they could be developed using ultrasound or magnetic resonance imaging, considering that their estimates have an error of 10 to 20%.²⁹ On the other hand, information on placental morphometry is rarely collected and evaluated in Latin America. These findings would contribute to the understanding of the maternal-placental programming of chronic disease.

As it was a retrospective analysis, a variety of health behaviors and environmental exposures has not been controlled for. Nevertheless, to ensure an accurate and complete report of this observational study, the Strengthening the

Reporting of Observational Studies in Epidemiology (STROBE) Statement was followed.³⁰

In conclusion, we have demonstrated that 52% of the variability of BW may be accounted for by the effects of four simple placental measures. In association with well-appreciated maternal and infant influences, this figure raised to 78%.

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