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Placental measurements and their association with birth weight in a Brazilian cohort

Medidas placentárias e sua associação com o peso ao nascer em uma coorte brasileira

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ABSTRACT: ***Introduction:*** Epidemiological studies have shown associations between placental measurements and perinatal and later life outcomes. ***Objectives:*** To report placental measurements and evaluate their association with birth weight in a Brazilian birth cohort. ***Methods:*** Retrospective cohort study with 958 mothers, placentas, and newborns delivered at the Ribeirão Preto Medical School Hospital, Universidade de São Paulo, Brazil, in 2010 and 2011. The information was collected from interviews, medical records, and pathology reports. The placental measurements were: weight, largest and smallest diameters, eccentricity, thickness, shape, area, and birth weight/placental weight and placental weight/birth weight ratios. We analyzed the associations between birth weight and placental measurements using multiple linear regression. ***Results:*** Placental weight alone accounted for 48% of birth weight variability ($p < 0.001$), whereas placental measurements combined (placental weight, largest and smallest diameters, and thickness) were responsible for 50% ($p < 0.001$). When adjusted for maternal and neonatal characteristics, placental measurements explained 74% of birth weight variability ($p < 0.001$). ***Conclusion:*** Placental measurements are powerful independent predictors of birth weight. Placental weight is the most predictive of them, followed by the smallest diameter.

Keywords: Placenta. Birth weight. Perinatology. Anthropometry. Body weights and measures. Observational study.

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RESUMO: ***Introdução:*** Estudos epidemiológicos demonstraram associações entre medidas placentárias, resultados perinatais e futuros. ***Objetivos:*** Descrever medidas placentárias e avaliar suas associações com peso ao nascer numa coorte de nascimentos brasileira. ***Metodologia:*** Estudo de coorte retrospectiva de 958 mães, placentas e recém-nascidos no Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Brasil, em 2010 e 2011. As informações foram coletadas por entrevistas, prontuários médicos e laudos de patologia. As medidas placentárias foram: peso, diâmetros maior e menor, excentricidade, espessura, forma, área, relações peso ao nascer/ peso da placenta e peso da placenta/ peso ao nascer. As associações entre peso ao nascer e medidas placentárias foram examinadas por meio de regressão linear múltipla. ***Resultados:*** O peso da placenta foi responsável por 48% da variabilidade do peso ao nascer ($p < 0,001$), enquanto o conjunto de medidas placentárias (peso, diâmetros maior e menor e espessura) foi responsável por 50% ($p < 0,001$). Quando ajustadas pelas características maternas e neonatais, as medidas placentárias explicaram 74% da variabilidade do peso ao nascer ($p < 0,001$). ***Conclusão:*** medidas placentárias são preditores independentes do peso ao nascer. O peso placentário é o mais forte preditor dentre elas, seguido pelo diâmetro menor.

Palavras-chave: Placenta. Peso ao nascer. Perinatologia. Antropometria. Pesos e medidas corporais. Estudo observacional.

INTRODUCTION

The placenta remains an under-researched and poorly understood human organ. It is the interface between the pregnant woman and the fetus; the source of oxygen and nutrients to the latter, so deficits in its function impair fetal development[1]. The placenta is subject to the same intrauterine environment as the fetus; thus, maternal diseases and inadequate nutrition limit the growth of both. Consequently, understanding placental growth and function is essential to clarify the mechanisms through which different exposures affect the developing fetus[2].

Placental measurements (PMs) have been studied as indicators of its growth and function. Epidemiological studies have shown associations between PMs and perinatal and later life outcomes[3]. Placental weight (PW), for instance, relates to the risk of stillbirth, 5-minute Apgar score lower than 7, neonatal seizures, and ventilation for more than 3 minutes after birth[4]. PMs are also associated with adult diseases, namely hypertension[5], diabetes[6], coronary heart disease, stroke[7], and colorectal cancer[8]. Studies on the developmental origins of health and disease postulate that PMs signal fetal and placental adaptations to environmental insults[9].

The main PMs under investigation are weight, largest diameter, smallest diameter, thickness, eccentricity, and surface area. Each of them has a critical period of development and respond differently to negative stimuli[3]. The surface area is proportional to the number of uterine spiral arteries available for fetal nutrition; thickness reflects the level of villous ramification; and changes in eccentricity signal uterine constraint of placental growth[10].

Small placentas are more likely to be dysfunctional, and PW is closely correlated to birth weight (BW). Studies conducted in populations from various geographic and historic backgrounds confirm such association[11-13]. Besides, placental to birth weight ratio (PW/BW) is an important marker of fetal growth and a proxy of placental efficiency. Other ratios of interest to estimate placental efficiency are the largest and smallest diameter to BW[14].

Placental morphometry has been extensively explored in developed countries, where PW percentile curves have been reported[15,16]. However, there is limited data from Latin American populations, including Brazilian ones[13,17,18].

The present study aimed to describe the placental morphometry of a Brazilian birth cohort and investigate its relationship with BW.

METHODS

This was an observational study conducted at the Ribeirão Preto Medical School Hospital, Universidade de São Paulo, Brazil, in 2010 and 2011. It is part of the project "Etiological factors of preterm birth and consequences of perinatal factors in child health: birth cohorts in two Brazilian cities," known as BRISA (*Brazilian Ribeirão Preto and São Luís Birth Cohort*). Exclusion criteria were gestational age (GA) under 22^{+0} weeks or over 42^{+6} weeks, multiple gestation, and PW under 100 g or over 2500 g, which were considered implausible values.

Trained personnel interviewed 1067 consecutive women to trace their demographic, social, and health profile. Pediatricians examined the newborns after birth. Pathologists evaluated the placentas according to standard procedures[1], blinded from maternal and neonatal data. All information was collected from the interview questionnaires, medical records, and pathology reports. Education level was estimated by the years of school attendance, whereas the socioeconomic status was assessed by the occupation of the main income earner in the household[19]. Body mass index (BMI) was calculated using the formula weight/height^2. GA was calculated by the most reliable information available, either the last menstrual period or early obstetric ultrasound[20]. BW was classified as very low (VLBW, $< 1{,}500$ g) and low (LBW, $< 2{,}500$ g). Weight for GA and ponderal index (weight/length^3) were also assessed[21,22].

The placentas were weighed in grams on an electronic scale after cutting the cord and membranes. Length was considered the largest diameter measured with a transparent ruler in cm, whereas the diameter perpendicular to the length was defined as the smallest diameter (breadth), measured in the same way[1]. Thickness was measured at the center of the placenta by a graduated needle, in millimeters. Eccentricity was estimated by the ratio of the largest to the smallest diameter, measuring the relative asymmetry of placental growth. Placental area (cm^2) was calculated assuming an elliptical surface by the formula largest diameter $\times$ smallest diameter $\times \pi/4$[5]. Placental shape was obtained by the difference between the largest and smallest diameters: A difference of 3 cm or more characterized an oval placenta, whereas a difference of less than 3 cm characterized a round placenta[23].

PW was compared in different GA groups (22–28 weeks; 29–32 weeks; 33–36 weeks; and 37–42 weeks). Also, the placental weight Z scores of term and preterm neonates were established according to Thompson et al.[15].

BW (g) to PW (g) ratio (BW/PW) indicated the adequacy of fetal nutrition[24]. PW (g) to BW (g) ratio (PW/BW), a proxy of placental efficiency ("efficiency 1"), was expressed as percentage [(PW/BW) × 100]. Finally, two other measurements of placental efficiency were calculated using the ratios of length ("efficiency 2") and breadth ("efficiency 3") to BW[23].

The descriptive statistics included the mean, proportion, standard deviation (SD), and 95% confidence interval (CI). Student's *t*-test and analysis of variance (ANOVA) compared the means. Pearson correlation coefficients explored the relationship between PW and four outcomes of fetal growth: BW, birth length, head circumference, and ponderal index.

We found no strong correlations among the PMs, so we fitted unadjusted and multiple linear equations to explore the prediction of BW by them. The effect point estimates with 95%CI and R^2 were obtained. When a PM included the dependent variable (BW) as well as any other predictor, it was excluded from the adjusted models. The goodness of fit of each regression model was assessed according to Royston and Wright[25], leaving four PMs (PW, largest and smallest diameters, and disc thickness) as predictors. Three models were then defined:

- an *unadjusted* model of each of these four PMs as predictors of BW (bivariate);
- a *multivariate* model, in which the four PMs were considered together as predictors of BW;
- a *full* model, also with the four PMs as predictors and further adjusted for maternal characteristics (parity, BMI before pregnancy, gestational diabetes mellitus, hypertension, and tobacco use), GA, and gender.

Type of delivery (cesarean or vaginal) was not firstly taken into consideration because it could be a downstream consequence of maternal risk factors and placental size (e.g., preeclampsia may result in a small placenta, and fetal compromise resulting from the small placenta can increase the risk of cesarean delivery). However, since cesarean delivery could affect PW through mechanisms independent of underlying pathological processes, secondary analyses were conducted so that models could be additionally adjusted for this factor[26].

The sample size calculation determined that 51 subjects were necessary to obtain a statistical power of 80%, with α set at 0.05 and an expected adjusted coefficient of determination (R^2) of 0.40. Stata 13.0® (College Station, Texas, USA) and SAS/STAT® (SAS Institute Inc., Cary, NC, 2010) performed all statistical calculations, and significance was set at 0.05 level.

The presentation of research results followed the STROBE international guidelines for observational studies in epidemiology[27].

The Research Ethics Committee approved this project (process number 11,157/2008). The women were informed about the study protocol and signed an informed consent form.

RESULTS

From the original 1067 subjects, 77 were excluded for lack of placental data, 1 for hydropic placenta, and 31 for multiple pregnancy, resulting in a final study population of 958 trios of mothers, placentas, and newborns.

Tables 1, 2, and 3 present the maternal, neonatal, and placental characteristics, respectively.

Table 1. Maternal characteristics during pregnancy.

Characteristic	n / N (%)[a]
Age (years)	
≤ 19	122 / 958 (12.7)
20–34	696 / 958 (72.7)
≥ 35	140 / 958 (14.6)
Ethnicity	
White	455 / 949 (48.0)
Other	494 / 949 (52.0)
Parity	
1	379 / 957 (39.6)
2 or 3	443 / 957 (46.3)
≥ 4	135 / 957 (14.1)
BMI before pregnancy (kg/m^2)	
≤ 18.4 (underweight)	42 / 840 (5.0)
18.5–24.9 (adequate)	392 / 840 (46.7)
25–29.9 (overweight)	210 / 840 (25.0)
≥ 30 (obese)	196 / 840 (23.3)
Hypertension during pregnancy	262 / 955 (27.4)
Diabetes during pregnancy	165 / 955 (17.3)
Consumed alcohol during pregnancy	261 / 957 (27.3)
Smoked during pregnancy	178 / 957 (18.6)
Six or more antenatal visits	681 / 773 (88.1)
Type of delivery	
Vaginal	548 / 958 (57.2)
Cesarean	410 / 958 (42.8)

[a]The denominator, when specified, indicates that there were some missing values; BMI: body mass index.

Adolescent mothers corresponded to 12.7% of the sample, while 14.6% were 35 years old or older. About half of them were white, which is compatible with the Brazilian ethnic distribution. Despite 98.3% having attended school, only 8.8% reached higher education. Most families were headed by manual workers, who have low incomes, and most women used the Brazilian public health system; only 5.7% paid for private medical care. Nearly 20% of the women did not live with a partner.

The frequency of primiparity was 39.6%. Approximately half of the women were overweight or obese. The frequencies of hypertension, diabetes, alcohol consumption, and tobacco use during pregnancy were high — 27.4, 17.3, 27.3, and 18.6%, respectively. Besides, 42.8% had cesarean deliveries (Table 1).

Mean GA was 38 weeks, and 25.6% of the births were preterm; 50.5% of the newborns were female. Mean BW was 3,047 g, 6.2% had a VLBW, and 15.6% were small for gestational age (SGA)[21], which occurred with a similar frequency among term (13.5%) and preterm infants (13.8%). The mean ponderal index was 2.8 g/cm^3 (Table 2).

Table 2. Neonatal characteristics.

Characteristic	Mean (SD)	n / N (%)[a]
Gestational age (weeks)	38.0 (3.5)	
Preterm birth		246 / 958 (25.6)
Stillborn		7 / 958 (0.7)
Gender		
Female		483 / 957 (50.5)
Male		474 / 957 (49.5)
Birth weight (g)	3047 (789)	
< 1,500 (VLBW)		59 / 958 (6.2)
< 2,500 (LBW)		168 / 958 (17.5)
Weight for gestational age		
SGA (< 10th percentile)		144 / 926 (15.6)
AGA (10th to 90th percentile)		690 / 926 (74.5)
LGA (> 90th percentile)		92 / 926 (9.9)
Birth length (cm)	48.1 (3.5)	
Head circumference at birth (cm)	34.3 (2.0)	
Ponderal index (g/cm^3)	2.8 (0.4)	

SD: standard deviation; VLBW: very low birth weight; LBW: low birth weight; SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age; [a]the denominator, when specified, indicates that there were some missing values

Mean PW was 579 g, mean largest diameter was 17 cm, mean smallest diameter was 15.1 cm, and mean thickness was 2.5 cm. Mean eccentricity was 1.1, and mean surface area was 205 cm^2. The shape of 77.4% of the placentas was round. Mean BW/PW was 5.3, and mean PW/BW was 19.8 (Table 3). All PMs except PW/BW were consistently higher in males than females, without statistical significance (data not shown).

Table 3. Placental characteristics.

Characteristic	n[a]	Mean	SD	95%CI
Weight (g)	940	579	155	315 – 840
Gestational age (w)				
22–28	33	316	126 **	135 – 565
29–32	65	456	163	210 – 800
33–36	148	504	144	240 – 760
37–42	694	612	138	410 – 850
Weight Z score	904	-0.34	1.1	-1.9 – -1.5
Term neonates	714	-0.40	1.0	-1.8 – -1.3*
Preterm neonates	190	-0.14	1.2	-2.1 – 2.4*
Largest diameter (cm)	952	17.0	2.2	14.0 – 21.0
Smallest diameter (cm)	952	15.1	2.1	12.0 – 18.0
Eccentricity	952	1.1	0.1	1.0 – 1.3
Disc thickness (cm)	952	2.5	0.6	1.5 – 3.5
Area (cm^2)	952	204.9	55.8	127 – 283
Placental shape	952	1.9	1.5	0.1 – -5.0
Oval (≥ 3 cm)	215	22.5%		20.0 – 25.3
Round (< 3 cm)	737	77.4%		74.6 – 79.9
BW/PW	940	5.3	1.3	3.6 – 7.3
Term neonates	714	5.6	1.2	4.1 – 7.5*
Preterm neonates	198	4.5	1.2	2.3 – 6.6*
PW/BW (Efficiency 1)	940	19.8	6.2	13.6 – 27.8
Efficiency 2	952	6.1	2.9	4.2 – 10.8
Efficiency 3	952	0.9	0.5	0.5 – 1.9

SD: standard deviation; 95%CI: confidence interval of 95%; w: weeks; BW/PW: birth weight/placental weight ratio; PW/BW: placental weight/birth weight ratio; [a]the denominator, when specified, indicates that there were some missing values; **t* test, $p < 0.001$; **ANOVA, $p < 0.001$.

Correlation coefficients of PW with BW, birth length, head circumference, and ponderal index were 0.67, 0.49, 0.48, and 0.24, respectively, all statistically significant. Indices of placental efficiency showed no significance.

BW was weakly correlated with length ($r = 0.464$, $R^2 = 0.215$, $p < 0.001$), breadth ($r = 0.421$, $R^2 = 0.177$, $p < 0.001$), and placental surface area ($r = 0.476$, $R^2 = 0.226$, $p < 0.001$).

Table 4 displays the results of the regression models of BW. Model 1(unadjusted) with PW, largest diameter, smallest diameter, and thickness as single predictors had an R^2 of 0.48, 0.24, 0.27, and 0.02, respectively; all of them were significant at the 0.001 level. Model 2 (multivariate) considered these four PMs together as predictors, without other adjustments, and its R^2 was 0.50, but only the effects of PW and smallest diameter were statistically relevant. Finally, model 3 (full multivariate), which was further adjusted for maternal variables (parity, BMI before pregnancy, gestational diabetes, hypertension, and tobacco use), GA, and gender, resulted in an R^2 of 0.74. Again, only PW and smallest diameter had statistically relevant effects on BW in opposition to largest diameter and thickness.

In a secondary analysis conducted to explore the main results further, PMs explained 50% of BW variability among preterm births compared with 37% at term, and maternal characteristics explained 64.8% of the BW variance after adjustment for GA and gender ($p < 0.001$). The additional adjustment of the full model for type of delivery had a minimal impact on the R^2, and we found no significant association between cesarean delivery and BW.

Table 4. Linear regression models of placental measurements predicting birth weight.

Placental measurements	Model 1 (unadjusted)		Model 2 (multivariate)[a]		Model 3 (full multivariate)[b]	
	Point estimate (95%CI)	R^2	Point estimate (95%CI)	R^2	Point estimate (95%CI)	R^2
Weight (g)	3.5 (3.3 – 3.7)	0.48*	2.9 (2.6 – 3.3)*	0.50*	1.7 (1.4 – 1.9)*	0.74*
Largest diameter (cm)	171.6 (152 – 190)	0.24*	19.3 (-5.08 – 43.7)		17.0 (-1.3 – 35.5)	
Smallest diameter (cm)	196.6 (176 – 217)	0.27*	46.9 (20.0 – 73.8)*		30.1 (9.8 – 50.4)*	
Thickness (cm)	194.7 (122 – 266)	0.02*	10.3 (-43.8 – 64.6)		17.9 (-23.1 – 58.9)	

a: four placental measurements (weight, largest diameter, smallest diameter, thickness) considered together as predictors of BW; b: four placental measurements (weight, largest diameter, smallest diameter, thickness) considered together as predictors of BW and further adjusted for maternal characteristics (parity, BMI before pregnancy, gestational diabetes mellitus, hypertension, and tobacco use), gestational age, and gender; 95%CI: confidence interval of 95%; *significant at the 0.001 level.

DISCUSSION

As expected, weight, largest diameter, smallest diameter, and thickness of the placenta were positively associated with BW. In addition, four PMs explained 50% of the BW variability, yet only PW and smallest diameter showed statistical significance. After adjustment for maternal and infant factors, R^2 raised to 74%. This result is in agreement with previous Argentinian findings[13]. In contrast, an American study with a similar methodology found that the adjustment for covariates diminished the power of association between PM and BW[28].

PW had the strongest bivariate association with BW (R^2 48%). However, in the multivariate models (2 and 3), PW point estimates declined significantly from four to six times, while in the three models, the smallest diameter presented the highest BW gain for each unit (cm) increase.

The mean PW *Z* score was lower than that of a previous population study[26]; this might be attributable to the high-risk population of the investigation.

Although BW was correlated with PW, Figure 1 shows a wide variation in PW for any given BW; e.g., infants weighing around 3000 g had placentas ranging from 300 to 900 g. This finding suggests a wide variation in placental efficiency, which corroborates previous data[13].

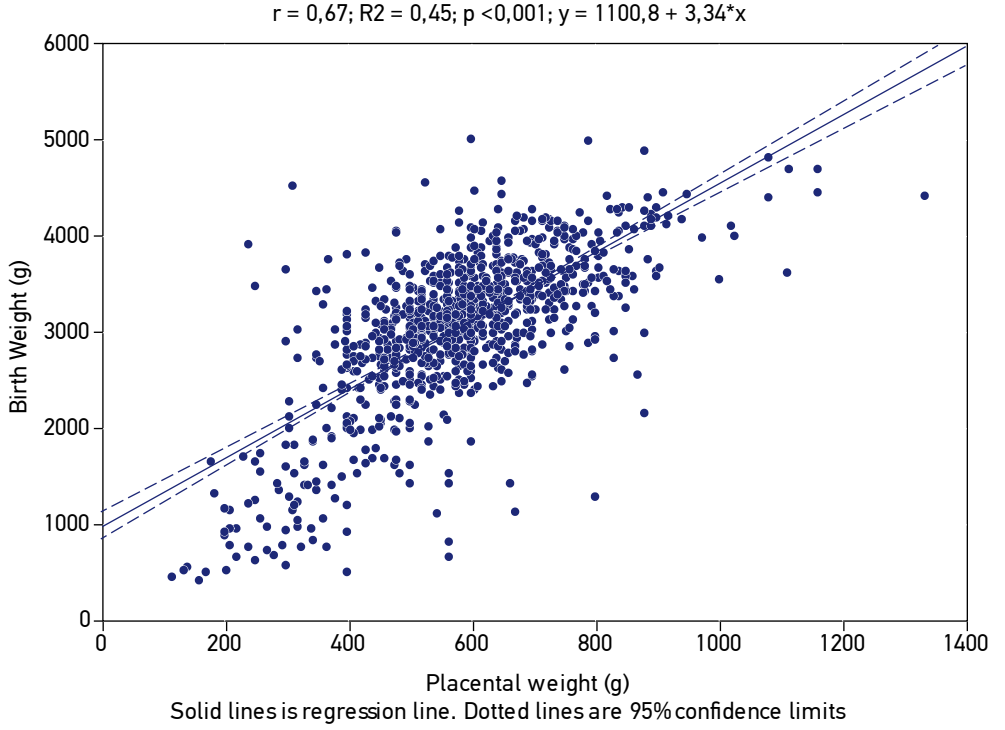

Figure 1. Birth weight according to placental weight.

The caloric intake and dietary composition during pregnancy affect the size of the human placenta at term[29]. It is positively related to maternal BMI across the normal spectrum. In the adjusted model[3], BMI before pregnancy was positively associated with PW; on average, PW increased 4.5 g per 1 Kg/m^2 increment in BMI ($p < 0.001$) (data not shown).

The smallest diameter was more strongly correlated to BW than the largest diameter in the three models. Other studies have also found this difference[28]. Previous research has concluded that the smallest diameter is more sensitive to the pregnancy nutritional status than the largest one[30]. Barker et al. identified that placental growth along the major axis is qualitatively different from growth along the minor axis. They postulated that the minor axis is more important for nutrient transfer to the fetus, partially explaining current results[5].

A previous study revealed that neonatal ponderal index, head, chest, abdomen, and thigh circumferences are all highly associated with placental breadth, while none of them are related to placental length[30].

Freedman et al. found that the surface area had more impact on BW than other PM[28]. However, this study did not include surface area in its regression models for it being a composite measurement derived from the largest and smallest diameters.

The surface area of the maternal-fetal interface increases in line with PW during pregnancy due to the growing length and branching of the fetal villi[31]. Besides, the mean chorionic plate eccentricity could explain the round placental shape predominance (77%). In addition, this may have contributed to 74.5% of the newborns being classified as appropriate for gestational age (AGA). This is also consistent with the hypothesis that tissue along the smallest diameter plays a key role in nutrient transfer from mother to fetus[32].

At present, data show that elliptical placentas tend to be less efficient than circular ones, yet more research is necessary to understand the underlying biological reasons. The degree to which a placenta deviates from being perfectly round has a predictive value for specific diseases. A suitable explanation is that placental shape is a proxy indicator of placentation processes related to its transport and other physiological functions[33].

Previous studies conclude that a placenta with a low average thickness has decreased functional efficiency, leading to a smaller newborn for a given PW[15,23,28]. However, this and another Latin American study have found a low explanatory power of BW by placental thickness[13]. The speculated reason is that this measurement incompletely captures the variability that characterizes the human placenta.

Fetal growth restriction (FGR) has been associated not only to PW and length but also to other gross morphological changes such as type of placental cord insertion and presence of knots in the umbilical cord[34,35].

Placental efficiency, defined as the amount of fetal body mass accumulated per gram of placenta, is a key indicator of the resilience and susceptibility of the offspring to chronic diseases in later life. It also provides an overview of placental function[36]. This index is simple to calculate in epidemiological studies. Moreover, it encapsulates numerous factors, such as placental exchange surface area, transporter density and activity, and blood flow

rates, which all require more detailed individual stereological, molecular, and physiological research. In the present study, the BW/PW ratio was higher in term than preterm, reflecting the high demand of the fetus across the entire pregnancy[37].

Among the three proxies of placental efficiency, PW/BW ratio showed the greatest value and was higher in preterm than term infants, demonstrating that it can be a useful tool to evaluate the placenta functionality.

The main strength of the current study is its population size, one of the largest among recent Latin American investigations into placental morphometry. On the other hand, a limitation is that it took place at a high-complexity maternity ward, which mainly treats unhealthy pregnancies. The main conditions observed were chronic diseases, such as hypertension and diabetes, and obstetric complications, such as preterm labor and fetal malformations. Another potential drawback is the information bias, since the data about gestational exposure were self-declared by the mothers, instead of checked in medical records. Although random measurement error in an outcome variable (BW) should not influence the point estimates of regression models, bias could have been introduced if placentas of complicated pregnancies were prepared for measuring with more scrutiny than those of uncomplicated pregnancies[38].

More comprehensive placental phenotyping is necessary to expand the current knowledge: sequential PMs during pregnancy by ultrasound, calculation of structural parameters, such as surface area and internal distance; characterization of maternal and fetal circulations; analysis of the expression and activity of different transporters; measurement of endocrine function and enzyme activities; assessment of placental metabolism and regulatory signaling pathways; and, ideally, investigation into single-cell transcriptomics and epigenetics[31].

CONCLUSION

PMs are powerful independent predictors of BW. PW is the most predictive of them, followed by the smallest diameter. PMs should be estimated during pregnancy and at the time of birth to assess the nutritional status of the fetus.

Since distinct environmental insults affect each PM differently, studying them may contribute to understanding both perinatal outcomes and maternal-placental programming of chronic diseases.

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