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Birth-weight differences at term are explained by placental dysfunction and not by maternal ethnicity

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KEYWORDS: birth weight; cerebroplacental ratio; ethnicity; fetal Doppler; fetal growth; fetal nutrition

ABSTRACT

Objective *To investigate the influence of ethnicity, fetal gender and placental dysfunction on birth weight (BW) in term fetuses of South Asian and Caucasian origin.*

Methods *This was a retrospective study of 627 term pregnancies assessed at two public tertiary hospitals in Spain and Sri Lanka. All fetuses underwent biometry and Doppler examinations within 2 weeks of delivery. The influences of fetal gender and ethnicity, gestational age (GA) at delivery, cerebroplacental ratio (CPR) and maternal age, height, weight and parity on BW were evaluated by multivariable regression analysis.*

Results *Fetuses born in Sri Lanka were smaller than those born in Spain (mean BW = 3026 ± 449 g vs 3295 ± 444 g; P < 0.001). Multivariable regression analysis demonstrated that GA at delivery, maternal weight, CPR, maternal height and fetal gender (estimates = 0.168, P < 0.001; 0.006, P < 0.001; 0.092, P = 0.003; 0.009, P = 0.002; 0.081, P = 0.01, respectively) were associated significantly with BW. Conversely, no significant association was noted for maternal ethnicity, age or parity (estimates = −0.010, P = 0.831; 0.005, P = 0.127; 0.035, P = 0.086, respectively). The findings were unchanged when the analysis was repeated using INTERGROWTH-21st fetal weight centiles instead of BW (log odds, −0.175, P = 0.170 and 0.321, P < 0.001, respectively for ethnicity and CPR).*

Conclusion *Fetal BW variation at term is less dependent on ethnic origin and better explained by placental dysfunction. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

A considerable debate regarding whether different ethnicities exhibit different birth-weight (BW) patterns is ongoing[1–3]. While some researchers think that these differences are genetic or constitutional, supporting the use of customized charts to adjust fetal growth to particular patient attributes such as maternal ethnicity, parity, pre-pregnancy weight and height [4–6], others, such as the INTERGROWTH-21st consortium (IG-21st), have proposed the use of universal charts on the basis that the influence of factors used in customization is redundant when fetal growth occurs in optimal environmental conditions[7]. The controversy surrounding this issue has increased following recent publications suggesting that prescriptive fetal growth standards would be less sensitive in identifying small-for-gestational-age (SGA) fetuses and adverse perinatal outcome than the corresponding locally-developed fetal growth charts[8,9]. In contrast, other studies have reported that the use of locally developed fetal growth standards was associated with a disproportionate number of fetuses being classified as SGA, resulting in unnecessary fetal surveillance[10].

A potential means to clarify this debate would be to compare the influence on BW of patient characteristics used in customization with those related to placental insufficiency. This would, in effect, allow quantification of the relative influence of constitutional factors and fetal environment restriction on fetal growth. Although patient characteristics are recorded routinely, assessing the extent of placental insufficiency has been, until recently, more difficult to quantify. In this regard, the cerebroplacental ratio (CPR), a Doppler index of fetal cerebral arterial redistribution, has been proposed recently as a marker of failure to reach growth potential

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at term. Abnormal CPR values are associated with adverse perinatal outcome, including Cesarean section for fetal compromise, abnormal intrapartum monitoring, admission to the neonatal unit and perinatal mortality. A consequence of these associations is that fetuses affected by placental insufficiency at term may present with low CPR values regardless of their weight centile[11–16].

The main aim of this study was to evaluate the relative influence of fetal CPR (a marker of placental insufficiency) and customization factors (representing maternal/fetal constitution) on BW in a Caucasian *vs* Asian population.

METHODS

This was a retrospective cohort study of 627 singleton pregnancies undergoing routine ultrasound examinations in Spanish and Sri Lankan public hospitals. Fetuses were examined at the Hospital Universitario y Politécnico La Fe and Colombo North Teaching Hospital, during 1 year (January 2016 to December 2016). All fetuses underwent biometry and estimated fetal weight assessment as well as Doppler examination of the umbilical artery (UA) and middle cerebral artery (MCA) from 37 + 0 weeks, as described previously[17,18]. In brief, Doppler examinations were performed using GE Voluson® (E8/E6/730, GE Medical Systems, Zipf, Austria) and Alpinion e-cube 15® ± Alpinion Medical Systems, Seoul, Korea) ultrasound machines equipped with 1–8-MHz convex probes, during fetal quiescence, in the absence of fetal tachycardia, and keeping the insonation angle with the examined vessels as small as possible. All examinations were performed by consultants who were trained to assess CPR using the same technique and were certified as experts by The Fetal Medicine Foundation or the Spanish Ultrasound in Obstetrics and Gynecology Society. CPR was calculated as the ratio between the MCA and UA pulsatility indices[17,19]. Only the last Doppler examination, undertaken within 2 weeks of birth, was included in the analysis. Gestational age (GA) was determined according to crown–rump length in the first trimester. Although the population was unselected, pregnancies complicated by congenital fetal abnormalities, stillbirths and multiple pregnancies were excluded. Data concerning BW, mode of delivery and Apgar score were recorded after birth and also collected for the analysis.

Statistical analysis

Descriptive statistics were produced evaluating ethnicity (Sri Lankan/Spanish), maternal age, height and weight, BW, gravidity (defined as the total number of pregnancies including the current pregnancy and all previous miscarriages), parity (defined as the total number of previous vaginal deliveries and Cesarean sections), fetal gender, GA at examination, GA at delivery, the interval between ultrasound examination and delivery, mode of delivery (spontaneous vaginal, instrumental or emergency or elective Cesarean section), and Apgar scores at 1 and 5 min. Mean ± SD and median (interquartile range) were calculated for continuous variables, and absolute and relative frequencies were calculated for categorical variables. Subsequently, in order to explain BW differences between the Sri Lankan and Spanish populations, a multivariable linear regression analysis was performed with the abovementioned variables, selecting the informative parameters and describing their estimates with their 95% CI and *P*-values. A multivariable beta regression model with link logit was repeated using IG-21st centiles instead of BW, after converting values using the calculator provided on the IG-21st website[20]. IG-21st BW centiles were used to prove the validity of the approach using centiles instead of BW, and IG-21st centiles were chosen as they were developed to be universally applicable and could therefore be used for evaluation of both countries in the same model. This type of multivariable regression may be used when the response variable lies between 0 and 1, as is the case with the centiles. The estimates of this model can be interpreted as log odds. Then, their exponent can be used to evaluate the association of the parameter in the explanation of the response variable as an odds ratio (OR)[21]. If it is > 1, the variable is associated positively with the response variable, while it is associated negatively with the response variable when it is < 1.

Some of these variables, such as mode of delivery and Apgar scores at 1 and 5 min, were not included in the analysis because they were not considered predictive variables but rather delivery outcomes. The Akaike Information Criterion (AIC) was used to select the most parsimonious model. The partial determination coefficient for each predictive variable was calculated in order to measure the proportional reduction in sums of squares once the variable was introduced into a model, as a way of quantifying the importance. Statistical analysis[22] was performed and graphs produced using R-software® (version 3.4.3). Comparisons between the Sri Lankan and Spanish fetuses were performed using the chi-square test for fetal gender and mode of delivery. The other parameters were analyzed using the Wilcoxon test. Significance was considered if $P < 0.05$.

RESULTS

The study included 627 pregnancies, of which 160 (25.5%) were Sri Lankan and 467 (74.5%) were Spanish and of Caucasian origin. The patient and pregnancy characteristics of the study population are shown and compared between the Spanish and Sri Lankan fetuses in Table 1. There were significant differences between the two groups in several maternal characteristics (age, weight, height and parity), GA at birth, ultrasound examination to birth interval, BW (Figure 1) and CPR.

A multivariable linear regression was performed using these variables (AIC = 607.3). However, given that GA at examination and gravidity were correlated with GA at birth and parity, respectively, we used the AIC as a method to obtain a more parsimonious model. Considering that there were statistically significant

Table 1 Descriptive analysis of study population of term pregnancies, overall and compared between ethnicities

Parameter	*All* (n = *627*)	*Spanish** (n = *467*)	*Sri Lankan*† (n = *160*)	P
Continuous data				
Maternal age (years)	31.6 ± 5.7 32 (28–36)	32.7 ± 5.2 33 (29–37)	28.2 ± 5.9 28 (24–32)	< 0.001
Gravidity	2.01 ± 1.24 2 (1–2)	2.02 ± 1.3 2 (1–2)	1.97 ± 1.08 2 (1–2)	0.79
Parity	0.65 ± 0.83 0 (0–1)	0.59 ± 0.79 0 (0–1)	0.82 ± 0.92 1 (0–1)	0.004
CPR	1.73 ± 0.52 1.70 (1.38–2.01)	1.79 ± 0.46 1.79 (1.46–2.05)	1.58 ± 0.66 1.50 (1.22–1.77)	< 0.001
GA at US (weeks)	39.1 ± 1 39.3 (38.1–40.0)	39.1 ± 0.99 39.3 (38.1–40.0)	39.0 ± 1.04 39.1 (38.1–40.0)	0.99
GA at delivery (weeks)	39.9 ± 0.98 40.1 (39.3–40.7)	40.1 ± 0.91 40.3 (39.6–40.9)	39.5 ± 1.0 39.6 (38.6–40.3)	< 0.001
Interval between US and delivery (days)	6.13 ± 5.3 5 (2–8)	7.2 ± 5.5 6 (3–9)	3.1 ± 3.1 2 (1–5)	< 0.001
Birth weight (g)	3226.7 ± 460.3 3200 (2920–3500)	3295.3 ± 444.3 3300 (3000–3567.5)	3026.5 ± 448.8 2990 (2760–3280)	< 0.001
1-min Apgar score	9.1 ± 1.04 9 (9–10)	9.13 ± 1.06 9 (9–10)	8.93 ± 0.95 9 (9–9)	< 0.001
5-min Apgar score	9.9 ± 0.5 10 (10–10)	9.9 ± 0.42 10 (10–10)	9.87 ± 0.57 10 (10–10)	0.59
Maternal weight (kg)	60.1 ± 12.4 58.5 (52.3–66.0)	62.1 ± 11.9 60.0 (54.0–68.0)	54.1 ± 12.0 54.0 (44.0–61.6)	< 0.001
Maternal height (cm)	160.9 ± 7.2 161 (156–165.5)	163.1 ± 6.0 163 (159–167)	154.4 ± 6.3 154 (150–159)	< 0.001
Categorical data				
Fetal gender (male)	335 (53.4)	257 (55.0)	78 (48.8)	0.19
Gravidity				0.83
1	267 (42.6)	203 (43.5)	64 (40.0)	
2	207 (33.0)	149 (31.9)	58 (36.2)	
3	81 (12.9)	57 (12.2)	24 (15.0)	
≥ 4	72 (11.5)	58 (12.4)	14 (8.8)	
Parity				0.005
0	331 (52.8)	258 (55.2)	73 (45.6)	
1	215 (34.3)	162 (34.7)	53 (33.1)	
≥ 2	81 (12.9)	47 (10.1)	34 (21.3)	
1-min Apgar score < 7	20 (3.2)	17 (3.6)	3 (1.9)	0.40
5-min Apgar score < 7	4 (0.6)	2 (0.4)	2 (1.2)	0.58
Mode of delivery				< 0.001
Cesarean section	177 (28.2)	121 (25.9)	56 (35.0)	
Instrumental labor	126 (20.1)	124 (26.6)	2 (1.2)	
Spontaneous labor	324 (51.7)	222 (47.5)	102 (63.8)	

Data are given as mean ± SD, median (interquartile range) or *n* (%). *All Spanish fetuses were of Caucasian origin. †All Sri Lankan fetuses were of South Asian origin. CPR, cerebroplacental ratio; GA, gestational age; US, ultrasound.

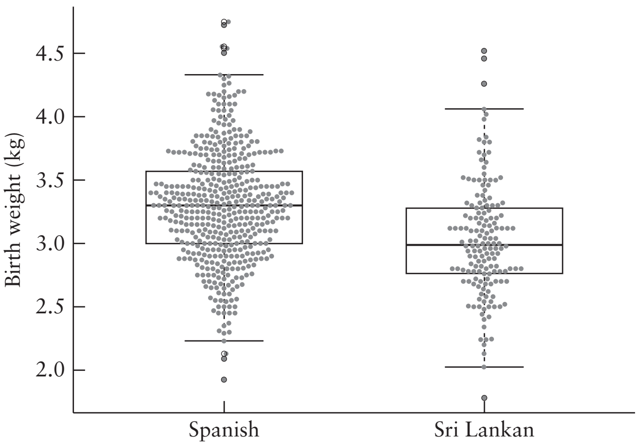

Figure 1 Box-and-whiskers plots comparing Spanish and Sri Lankan fetal birth weights ($P < 0.001$).

differences in parity and GA at birth between the two ethnicities, these variables were included in the final model. Thus, a second multivariable linear regression model explaining BW at term was developed excluding GA at examination and gravidity (AIC = 606.3). The final model including GA at delivery and parity is shown in Table 2 ($R^2 = 28.72\%$, adjusted $R^2 = 27.8\%$). In this model, GA at delivery (estimate = 0.168; 95% CI, 0.135–0.201; $P < 0.001$), CPR (0.092; 95% CI, 0.032–0.153; $P = 0.003$), fetal gender (0.081; 95% CI, 0.019–0.144; $P = 0.01$), maternal height (0.009; 95% CI, 0.003–0.014; $P = 0.002$) and maternal weight (0.006; 95% CI, 0.004–0.009; $P < 0.001$) influenced BW positively. However, there was not enough evidence to establish an influence of maternal ethnicity (−0.010; 95% CI, −0.101 to 0.081; $P = 0.831$), maternal age (0.005; 95% CI, −0.001 to 0.011;

Table 2 Multivariable linear regression analysis of studied parameters for prediction of birth weight in fetuses of Spanish and Sri Lankan ethnic origin

	Estimate	*95% CI*	P	*Partial* R^2
Intercept	−5.630	−7.204 to −4.057		
GA at delivery (in weeks)	0.168	0.135 to 0.201	< 0.001	0.144
Maternal weight (in kg)	0.006	0.004 to 0.009	< 0.001	0.029
CPR	0.092	0.032 to 0.153	0.003	0.016
Maternal height (in cm)	0.009	0.003 to 0.014	0.002	0.015
Fetal gender (male)	0.081	0.019 to 0.144	0.01	0.011
Parity	0.035	−0.005 to 0.074	0.086	0.005
Maternal age (in years)	0.005	−0.001 to 0.011	0.127	0.004
Ethnicity (Sri Lankan)	−0.010	−0.101 to 0.081	0.831	0.00005

Only parameters usually included in customized models plus cerebroplacental ratio (CPR), as well as gestational age (GA) at delivery, were analyzed. Parameters have been ordered according to their importance based on partial R^2. Akaike information criterion, AIC = 606.3, $R^2 = 28.72\%$, adjusted $R^2 = 27.8\%$.

Table 3 Multivariable beta regression analysis of studied parameters for prediction of INTERGROWTH-21st birth-weight centile in fetuses of Spanish and Sri Lankan ethnic origin

	Log odds	*Odds ratio*	*95% CI*	P
Intercept	−10.886	0	0.000–0.001	
CPR	0.321	1.379	1.168–1.628	< 0.001
GA at delivery (in weeks)	0.139	1.149	1.049–1.258	0.003
Maternal height (in cm)	0.021	1.022	1.006–1.037	0.005
Maternal weight (in kg)	0.015	1.015	1.008–1.023	< 0.001
Maternal age (in years)	0.017	1.017	1.000–1.033	0.046
Parity	0.074	1.077	0.967–1.199	0.178
Ethnicity (Sri Lankan)	−0.175	0.840	0.654–1.078	0.170
Fetal gender (male)	−0.092	0.912	0.768–1.082	0.289

Only parameters usually included in customized models plus cerebroplacental ratio (CPR), as well as gestational age (GA) at delivery, were analyzed. Parameters have been ordered according to their importance based on odds ratio. Akaike information criterion, AIC = −101.13, pseudo $R^2 = 16.7\%$.

$P = 0.127$) or parity (0.035; 95% CI, −0.005 to 0.074; $P = 0.086$).

The partial determination coefficient (partial R^2) was calculated for each predictive variable as a quantification method of its importance. The three most important parameters were GA at birth (partial $R^2 = 0.144$), maternal weight (partial $R^2 = 0.029$) and CPR (partial $R^2 = 0.016$), followed by maternal height (partial $R^2 = 0.015$), fetal gender (partial $R^2 = 0.011$), parity (partial $R^2 = 0.005$), maternal age (partial $R^2 = 0.004$) and maternal ethnicity (partial $R^2 = 0.00005$). The associations of BW with CPR, maternal age, fetal gender and maternal ethnicity, accounting for GA at delivery, are depicted using contour graphs in Figure S1.

An alternative multivariable beta regression model using the IG-21st BW centiles instead of BW is shown in Table 3 (AIC = −101.13, pseudo $R^2 = 16.7\%$). The results of the model show that CPR is associated positively with a higher BW (OR = 1.379; 95% CI, 1.168–1.628; $P < 0.001$), as are GA at delivery (OR = 1.149; 95% CI, 1.049–1.258; $P = 0.003$), and maternal height (OR = 1.022; 95% CI, 1.006–1.037; $P = 0.005$), weight (OR = 1.015; 95% CI, 1.008–1.023; $P < 0.001$), and age (1.017; 95% CI, 1.000–1.033; $P = 0.046$). Again, no statistically significant association was found with maternal ethnicity (OR = 0.840; 95% CI, 0.654–1.078; $P = 0.170$) or parity (OR = 1.077; 95% CI, 0.967–1.199; $P = 0.178$). In this case, the influence of fetal gender in the model was not significant (OR = 0.912; 95% CI, 0.768–1.082; $P = 0.289$), as the BW centiles were adjusted for each sex.

DISCUSSION

Summary of study findings

BW at term was determined by GA at delivery, fetal gender, and maternal height and weight. Conversely, some maternal characteristics, such as age, parity and ethnicity, did not demonstrate a statistically significant influence on BW variation[23–27]. Furthermore, the data demonstrated that CPR (a marker of fetal hypoxemia) was an independent and relevant factor contributing to BW variation. When the analysis was performed using IG-21st BW centiles instead of absolute BW, CPR remained a significant predictor, whilst ethnicity remained non-significant.

Interpretation of results and comparison with existing literature

The finding that BW differed between ethnicities due to either genetic or constitutional influences, prompted the use of customized charts in multiethnic populations[6,28].

Alternatively, data from IG-21st have suggested that ethnicity is an indirect marker of nutrition and is not a true or direct determinant of BW. As such, the IG-21st consortium suggests that all fetuses should be evaluated according to the same growth reference standard[7,29].

CPR at term is a marker of fetal hypoxemia secondary to placental dysfunction. If fetal smallness is due to placental dysfunction, we would expect to find a higher frequency of abnormal CPR values in the tested population. In contrast, CPR values would be expected to remain normal if fetuses were simply constitutionally small. CPR values at term may therefore be useful to distinguish whether BW differences are the consequence of maternal ethnicity or placental dysfunction[11–16]. The multivariable regression model in this bi-ethnic population demonstrated that CPR, but not ethnicity, was associated significantly with BW, which is in contrast to what was believed previously. This finding suggests that BW variation might not be due to constitutional factors such as ethnicity, but that it is the consequence of a failure to reach the fetal growth potential.

Several published studies have reported a higher incidence of low BW in fetuses in the Indian subcontinent[30,31], which could be attributed to ethnicity, higher incidence of placental insufficiency or nutritional restriction[32–34]. The supposition that low BW trends in certain ethnicities are due to placental dysfunction is in line with reports confirming a higher incidence of stillbirth and adverse perinatal outcome in Asian or Afro-Caribbean women[35,36]. Additionally, low BW in these populations varies according to educational status and hemoglobin level[37,38]. Furthermore, the rural and underprivileged newborns weigh less than their urban and privileged counterparts[39], suggesting that environmental factors also affect fetal growth and that ethnicity may be associated, by way of proxy, with placental dysfunction.

Clinical implications

If the environmental influences on fetal growth are responsible for BW variation in fetuses from different ethnic origins, this would support the use of IG-21st reference standards[7], and challenge the use of ethnicity-specific growth charts[1,2] or customization models[6,28]. Moreover, if indeed ethnicity is a risk factor for placental dysfunction, this should also preclude the inclusion of ethnicity in the customization models, as is the case for maternal age[40] and height[41]. Customization should be conducted for physiological factors, not for parameters that are related to adverse perinatal outcome.

The influence of CPR on BW variation has a significant bearing on the importance of the parameters used in customization. As expected, the most important parameter explaining BW was GA at delivery. However, CPR was also an important parameter as it had the greatest estimated effect for the explanation of IG-21st centiles. Finally, another interesting finding was that the BW prediction model showed notable importance of maternal prepregnancy weight. In addition, parity and maternal age were not associated significantly (although both models showed a positive estimated effect). This is a relevant finding given that these factors have been associated previously with BW[24,25] and have been used in different customization models[6,28]. Again, the most likely reason for this finding is that the influence of these parameters might be in part mediated by placental dysfunction[42,43], and might therefore be already represented in the model to some extent by CPR.

Our approach was retested using IG-21st BW centiles instead of absolute BW in order to evaluate its consistency. The results of this second analysis using odds ratios confirmed that the influence of CPR in the explanation of BW is robust. In the same way, there was also a lack of importance of ethnicity. As expected with using the IG-21st centiles, which are specific for male and female fetuses, the influence of fetal gender was residual.

Strengths and limitations

The main strengths of this study include the relatively large number of fetuses and the use of robust statistical analyses. Conversely, the main shortcoming is the retrospective nature, which hinders the collection of the complete set of perinatal data such as smoking habit or maternal weight gain throughout the pregnancy. Furthermore, the two study cohorts are not very similar. The fetuses of Sri Lankan origin delivered significantly earlier and had a higher incidence of Cesarean section and spontaneous delivery, and a much lower incidence of instrumental delivery. In this regard, although a shorter duration of pregnancy had been described previously in fetuses of the Indian subcontinent[44], it could also be the result of more intervention. Finally, despite the fact that the Sri Lankan mothers might not be representative of the whole Sri Lankan and Indian subcontinent population, we considered that, in rural settings, CPR differences may well have been even stronger.

Conclusions

In an ethnically and geographically heterogeneous population, BW differences are better explained by CPR as an index of placental dysfunction. The finding that maternal ethnicity had practically no influence on BW centile challenges the rationale for using this parameter in customized fetal growth models.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Contour graphs (multivariable regression) comparing association between birth weight (BW) and several predictive variables: CPR (a), maternal age (b), fetal gender (c) and ethnicity (d), taking into consideration gestational age (GA) at birth. Color scale displayed on right of each graph represents BW in kg. Scale of colors for different values of each predictive variable shows importance of parameter. For instance, maternal age is not an important parameter explaining BW because, in the color scale, BW changes mostly according to GA at delivery but very scarcely according to maternal age. Graphically, contour lines are seen to change mainly leftwards and not downwards. In contrast, CPR is an important parameter because, in the color scale, BW is seen to change according to both GA at delivery and CPR. Graphically, the contour lines are seen to change towards the left lower corner. On the other hand, fetal gender is an important parameter as, for the same GA at delivery, differences between male and female fetuses are important while the effect of ethnicity is small as, for the same GA at delivery, differences between Spanish and Sri Lankan fetuses are insignificant.

