Birth weight differences at term are explained by placental dysfunction, but not by maternal ethnicity

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SHORT TITLE

CPR explains ethnicity birth weight differences

KEY WORDS

Cerebroplacental ratio, fetal Doppler, fetal growth, fetal nutrition, birth weight, ethnicity.

ABSTRACT

Objective

The main aim of this study was 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 in two public tertiary hospitals in Spain and Sri Lanka. All fetuses underwent a scan and Doppler examination within two weeks of delivery. The influences of fetal gender,

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ethnicity, gestational age (GA) at delivery, cerebroplacental ratio (CPR), 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= 3026g±449g versus 3295g±444g, 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) were significantly associated with BW. Conversely, no significant association was noted with maternal ethnicity, age and parity (estimates= -0.010, p=0.831; 0.005, p=0.127; 0.035, p=0.086). The findings were unchanged when the analysis was repeated using IG21 EFW instead of BW centile (-0.175, p=0.170; 0.321, p<0.001).

Conclusions

Fetal BW variation at term is less dependent on ethnic origin and better explained by placental dysfunction.

INTRODUCTION

A considerable debate regarding whether different ethnicities exhibit different birth weight (BW) patterns is ongoing[1-3]. While some researchers think these differences are genetic or constitutional, supporting the use of customized charts to adjust the 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 the factors used in customization is redundant when fetal growth occurs in optimal environmental conditions[7]. The controversy surrounding this issue has increased following the recent publications suggesting that the latter 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 excess of fetal surveillance[10].

A potential means to clarify this debate would be to compare the influence of patient characteristics used in customization, with those related with placental insufficiency on BW. This would, in effect, allow quantification of the relative influence of constitutional factors and fetal environment restriction on fetal growth. Although the patient characteristics are routinely recorded, 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 recently been proposed as a marker of failure to reach growth potential 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 with placental insufficiency at term, may present with low CPR values regardless of their fetal 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 versus Asian population.

MATERIAL AND METHODS

This was a retrospective cohort study of 627 singleton pregnancies undergoing routine ultrasound scans from 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 201-December 2016. All fetuses underwent a biometry with an estimated fetal weight plus Doppler examination of the umbilical artery (UA) and middle cerebral artery (MCA) at and beyond 37+0 weeks as previously described[17-18]. In brief, Doppler examinations were performed with General Electric Voluson® (E8/E6/730) and Alpinion e-cube 15® ultrasound machines using 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 trained to assess the CPR using the same technique and were certified as experts by the Fetal Medicine Foundation or the Spanish Ultrasound in Obstetrics and Gynecology Society. The CPR was calculated as the ratio between the MCA and the UA pulsatility index (PI)[17,19]. Only the last Doppler examination, undertaken within two weeks of birth, was included in the analysis. The gestational age (GA) was determined according to the 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 was recorded after birth and also collected for the analysis.

Statistical analysis

Descriptive statistics were performed 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 examination and delivery, mode of delivery (spontaneous vaginal delivery, instrumental delivery and emergency or elective cesarean section), and Apgar scores at 1 and 5 minutes. Mean (SD) and median (plus 1st, 3rd Quartiles) were calculated in case of continuous variables and absolute and relative frequencies were calculated in case of 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 above-mentioned variables, selecting the informative parameters and describing their estimates with their 95% confidence intervals 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]. 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[21]. If it is >1, the variable is positively associated with the response variable, while it is negatively associated with the response variable when it is <1.

Some of these variables such as the mode of delivery and the Apgar at 1 and 5 minutes 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] and graphs were performed with R-software® (version 3.4.3). Comparisons between the Sri Lankan and Spanish fetuses were performed with the Chi-square test in case of the fetal gender and mode of delivery. The other parameters were analyzed using the Wilcoxon Test. Significance was considered with a $p<0.05$.

RESULTS

The study included 627 pregnancies, of which 160 (25.5%) were Sri Lankan and 467 (74.5%) were Spanish of Caucasian origin. The patient and pregnancy characteristics of the study population are shown Table 1. The characteristics of the Spanish and Sri Lankan fetuses are compared in Table 2. 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.

Firstly, a multivariable linear regression was performed with formerly mentioned variables (AIC=607.3). However, given that GA at examination and gravidity were respectively correlated with GA at birth and parity, we used the AIC as a method to obtain a more parsimonious model. Considering that there were statistically significant differences in parity and GA at birth between both ethnicities, these variables were finally included in the model. Thus, a second multivariable linear regression model explaining BW at term was carried out dismissing the variables GA at examination and gravidity (AIC=606.3). The final model including GA at delivery and parity is shown in Table 3 (R^2 = 28.7%, 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) were the parameters that influenced positively BW, while there was not enough evidence to establish an influence from ethnicity, maternal age and parity (-0.010, 95% CI [-0.101, 0.081], p=0.831; 0.005, 95% CI [-0.001, 0.011], p=0.127; 0.035, 95% CI [-0.005, 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 (0.144), maternal weight (0.029), and CPR (0.016) followed by maternal height (0.015), fetal gender (0.011), parity (0.005), maternal age (0.004), and ethnicity (0.00005). The associations between CPR, GA at delivery, maternal age, fetal gender, ethnicity, and BW are depicted using contour graphs in supplementary figure 1.

An alternative multivariable beta regression model using the IG-21st BW centiles instead of BW is shown in Table 4 (AIC= -101.13, pseudo R^2 = 16.7%). The results of the model show that the parameter CPR is positively associated with a higher BW (OR=1.379, 95% CI [1.168, 1.628], p<0.001), as well as the GA at delivery (OR=1.149, 95% CI [1.049, 1.258], p=0.003), 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), and 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.

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DISCUSSION

Summary of the study findings

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

Interpretation of the results and comparison with existing literature

The finding that BW was noted to differ 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 has suggested that the ethnicity is an indirect marker of nutrition and not a true or direct determinant of BW. As such, the IG-21st consortium suggest that all fetuses should be evaluated according to the same growth reference standard[7,29].

The 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 population tested. 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 ethnically diverse population demonstrated that the CPR, but not ethnicity, was significantly associated with BW, in contrast to what was previously believed. This finding suggests that BW variation might not be due to constitutional factors such as ethnicity, but the consequence of a failure to reach the fetal growth potential.

Several published studies have reported the higher incidence of low BW in fetuses of 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]. Finally, low BW in these populations varies according to the educational status and hemoglobin level[37,38]. Furthermore, the rural and underprivileged newborns weigh less than their urban and privileged counterparts[39], suggesting the environmental factors also affect fetal growth and that ethnicity may me associated by way of proxy for 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 ethnic-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 the CPR on the BW variation has a significant bearing on the importance of the parameters used in customization. As expected, the most important parameter explaining BW was the GA at delivery. However, the CPR was also an important parameter and the greatest estimated effect for the explanation of the IG-21st centiles. Finally, another notable finding was that the BW prediction model gave maternal pre-pregnancy weight a notable importance. In addition, parity and maternal age were not significantly associated (although both models showed a positive estimated effect). This is a relevant finding given that these factors have previously been associated 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 the 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 the Odds-Ratios confirmed that the influence of CPR in the explanation of BW was a robust one. In the same way, there was 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 analysis. Conversely, the main shortcoming is the retrospective nature, which hinders the collection of the complete set of perinatal data such as the smoking habit or the 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 sections and spontaneous delivery, and a much lower incidence of instrumental delivery. In this regard, although a shorter duration of pregnancy had been earlier described 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, the CPR differences may well have been even stronger.

Conclusions

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

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FIGURES (Legends)

Figure 1

Box and whiskers graph comparing the birth weight of the Spanish and Sri-Lankan fetuses.

Supplementary figure 1

Contour graphs (multivariable regression) comparing the association between BW and several predictive variables: CPR (upper left graph), maternal age (upper right graph), fetal gender (lower left graph) and ethnicity (lower right graph), taking in consideration GA at birth.

The color scale displayed on the right side of each graph represents the BW in Kg. The scale of colors for the different values of each predictive variable shows the importance of the 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, the 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, we can see that fetal gender is an important parameter: for the same GA at delivery differences between male and female fetuses are important while the effect of ethnicity is small: for the same GA at delivery differences between Spanish and Sri-Lankan fetuses are insignificant.

Table 1. Study population descriptive analysis.

Parameter	Mean (SD)	Median (1st Q, 3rd Q)
Maternal age	31.6 (5.7)	32 (28, 36)
Gravidity	2.01 (1.24)	2 (1, 2)
Parity	0.65 (0.83)	0 (0, 1)
CPR	1.73 (0.52)	1.70 (1.38, 2.01)
GA at ultrasound in weeks	39.1 (1)	39.3 (38.1, 40.0)
GA at delivery in weeks	39.9 (0.98)	40.1 (39.3, 40.7)
Interval between the ultrasound examination and delivery in days	6.13 (5.3)	5 (2, 8)
Birthweight in grams	3226.7 (460.3)	3200 (2920, 3500)
Apgar score at 1 minute	9.1 (1.04)	9 (9, 10)
Apgar score at 5 minutes	9.9 (0.5)	10 (10, 10)
Maternal Weight in kg	60.1 (12.4)	58.5 (52.3, 66)
Maternal Height in cm	160.9 (7.2)	161 (16, 165.5)
Parameter (categorical data)		**N (%)**
Fetal gender (male)		292 (46.6%)
Gravidity 1		267 (42.6%)
Gravidity 2		207 (33%)
Gravidity 3		81 (12.9%)
Gravidity 4 or more		72 (11.5%)
Nulliparity		331 (52.8%)
Parity 1		215 (34.3%)
Parity 2 or more		81 (12.9%)
Apgar <7 at 1 minute		20 (3.2%)
Apgar <7 at 5 minutes		4 (0.6%)
Cesarean section		177 (28.2%)
Instrumental labor		126 (20.1%)
Spontaneous labor		324 (51.7%)

Notes: CPR: cerebroplacental ratio, GA: gestational age, SD: standard deviation, 1st and 3rd Quartiles. Concerning ethnicity, all Spanish fetuses were of Caucasian origin.

Table 2. Comparisons between the Sri Lankan and Spanish study populations.

Variable	Ethnicity Spanish (N=467)	Ethnicity Sri Lankan (N=160)	
	Mean (SD) Median (1st, 3rd Q)	Mean (SD) Median (1st, 3rd Q)	p-value
Maternal age in years	32.7 (5.2) 33 (29, 37)	28.2 (5.9) 28 (24, 32)	P<0.001
Gravidity	2.02 (1.3) 2 (1, 2)	1.97 (1.08) 2 (1, 2)	P=0.79
Parity	0.59 (0.79) 0 (0, 1)	0.82 (0.92) 1 (0, 1)	P=0.004
Cerebroplacental ratio	1.79 (0.46) 1.79 (1.46, 2.05)	1.58 (0.66) 1.5 (1.22, 1.77)	P<0.001
GA at ultrasound in weeks	39.1 (0.99) 39.3 (38.1, 40)	39.0 (1.04) 39.14 (38.14, 40)	P=0.99
GA at delivery in weeks	40.1 (0.91) 40.3 (39.6, 40.9)	39.5 (1.0) 39.6 (38.6, 40.3)	P<0.001
Interval between the ultrasound and delivery in days	7.2 (5.5) 6 (3, 9)	3.1 (3.1) 2 (1, 5)	P<0.001
Birthweight in grams	3295.3 (444.3) 3300 (3000, 3567.5)	3026.5 (448.8) 2990 (2760, 3280)	P<0.001
Apgar score at 1 minute	9.13 (1.06) 9 (9, 10)	8.93 (0.95) 9 (9, 9)	P<0.001
Apgar score at 5 minutes	9.9 (0.42) 10 (10, 10)	9.87 (0.57) 10 (10, 10)	P=0.59
Maternal Weight in kg	62.1 (11.9) 60 (54, 68)	54.1 (12.0) 54 (44, 61.6)	P<0.001
Maternal Height in cm	163.1 (6.0) 163 (159, 167)	154.4 (6.3) 154 (150, 159)	P<0.001
Categorical data	**N (%)**	**N (%)**	**P-value**
Fetal gender (male)	257 (55%)	78 (48.8%)	P=0.19
Gravidity 1 Gravidity 2 Gravidity 3 Gravidity 4 or more	203 (43.5%) 149 (31.9%) 57 (12.2%) 58 (12.4%)	64 (40%) 58 (36.2%) 24 (15%) 14 (8.8%)	P=0.83
Nulliparity Parity 1 Parity 2 or more	258 (55.2%) 162 (34.7%) 47 (10.1%)	73 (45.6%) 53 (33.1%) 34 (21.3)	P=0.005
Apgar <7 at 1 minute	17 (3.6%)	3 (1.9%)	P=0.40
Apgar <7 at 5 minutes	2 (0.4%)	2 (1.2%)	P=0.58
Mode of delivery Cesarean section Instrumental Spontaneous vaginal	 121 (25.9%) 124 (26.6%) 222 (47.5%)	 56 (35%) 2 (1.2%) 102 (63.7%)	P<0.001

Notes: GA: gestational age, SD: standard deviation, 1st, 3rd Q: 1^{st} and 3^{rd} Quartiles. Concerning ethnicity, all Spanish fetuses were of Caucasian origin.

Table 3.

Multivariable regression linear analysis of the studied parameters for the prediction of birth weight. Only those parameters usually included in customized models plus the cerebroplacental ratio (CPR), as well as the gestational age (GA) at delivery were analyzed. Parameters have been ordered according to their importance based on the partial R^2.

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

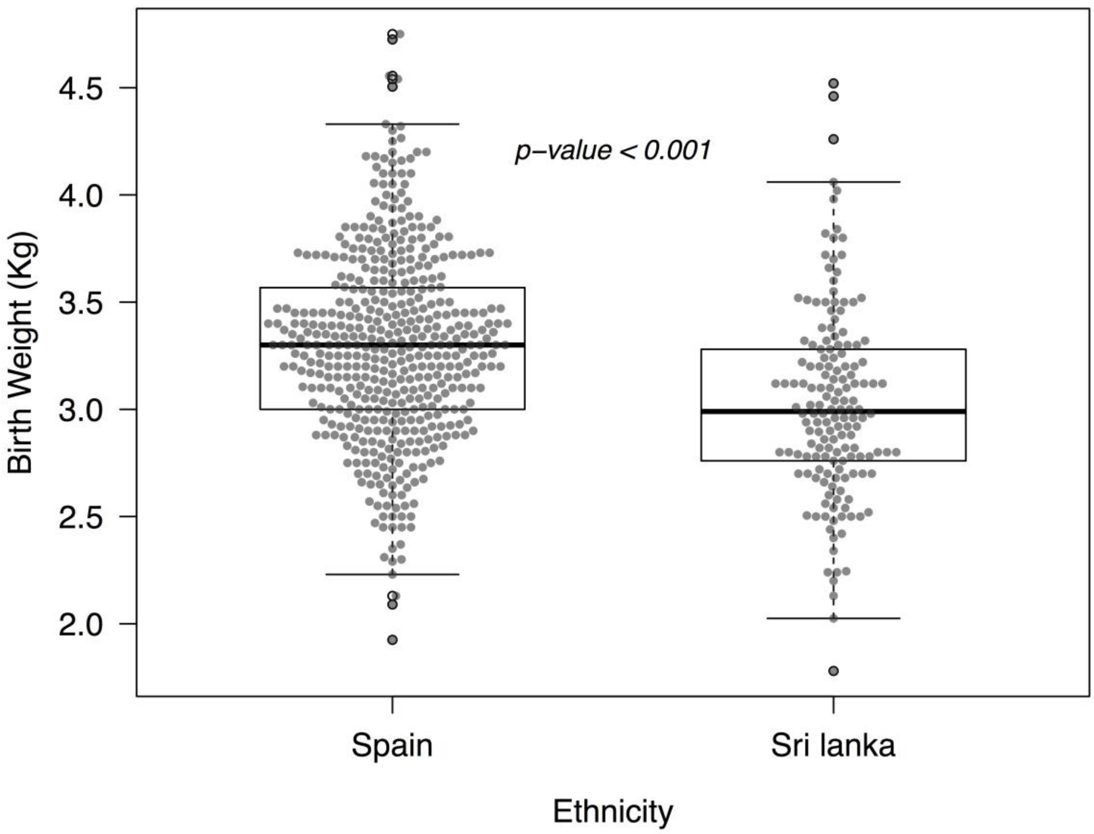
AIC= 606.3, R^2 = 28.72%, adjusted R^2 = 27.8%, 95% CI: 95% confidence interval.

Table 4.

Multivariable beta regression analysis of the studied parameters, for the prediction of Intergrowth-21st centiles. Only those parameters usually included in customized models plus the cerebroplacental ratio (CPR), as well as the gestational age (GA) at delivery were analyzed. Parameters have been ordered according to their importance based on the Odds Ratio.

	Log Odds	Odds Ratio	95% CI	P-value
(Intercept)	-10.886	0	[0.000, 0.001]	
CPR	0.321	1.379	[1.168, 1.628]	<0.001
GA at delivery (weeks)	0.139	1.149	[1.049, 1.258]	0.003
Maternal height (cm)	0.021	1.022	[1.006, 1.037]	0.005
Maternal weight (kg)	0.015	1.015	[1.008, 1.023]	<0.001
Maternal age (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

95% CI: 95% Confidence interval. AIC= -101.13, Pseudo R^2 = 16.7%.


4.5
4.0
3.5
3.0
2.5
2.0
Birth Weight (Kg)
p−value < 0.001
Spain
Sri lanka
Ethnicity