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ORIGINAL ARTICLE

Birth-weight differences at term are explained by placental dysfunction and not by maternal ethnicity. Study in newborns of first generation immigrants

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ABSTRACT

Objective: The aim of the study was to investigate the influence of ethnicity and cerebroplacental ratio (CPR) on the birth weight (BW) of first generation Indo-Pakistan immigrants' newborns.

Methods: This was a retrospective study in a mixed population of 620 term Caucasian and Indo-Pakistan pregnancies, evaluated in two reference hospitals of Spain and Italy. All fetuses underwent a scan and Doppler examination within two weeks of delivery. The influence of fetal gender, ethnicity, GA at delivery, CPR, maternal age, height, weight and parity on BW was evaluated by multivariable regression analysis.

Results: Newborns of first generation Indo-Pakistan immigrants were smaller than local Caucasian newborns (mean BW mean= 3048 ± 435 g versus 3269 ± 437 g, $p < .001$). Multivariable regression analysis demonstrated that all studied parameters, but maternal age and ethnicity, were significantly associated with BW. The most important were GA at delivery (partial $R^2 = 0.175$, $p < .001$), CPR (partial $R^2 = 0.032$, $p < .001$), and fetal gender (partial $R^2 = 0{,}029$, $p < .001$).

Conclusions: The propensity to a lower BW, explained by placental dysfunction but not by maternal ethnicity is transmitted to newborns of first generation immigrants. Whatever are the factors implied they persist in the new residential setting.

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Cerebroplacental ratio; fetal Doppler; fetal growth; fetal nutrition; birth weight; ethnicity; first generation immigrants

Introduction

Different ethnicities present different birth weights (BW). However, it is still unclear whether these differences are due to the existence of different growth patterns or to presence of different environmental factors affecting placental function [1–3]. In this regard, while some researchers consider differences as constitutional and advocate for the use of customized charts to adjust fetal growth to the different maternal characteristics [4–6], others, postulate that all fetuses grow similarly under optimal environmental conditions and therefore should be evaluated with the same reference standards [7–10].

A way to clarify this controversy was recently proposed by us, comparing the influence on BW of customization parameters and cerebroplacental ratio (CPR), a marker of failure to reach growth potential [11–16]. Using this methodology we showed [17] that the influence of ethnicity was nearly eclipsed by CPR. However, because both ethnic groups lived in different countries, it could be argued that this mechanism occurred only when there were clear differences in the place of residence.

In order to study if these influences persisted in a new setting, we reevaluated those factors explaining BW in children of first generation immigrants living in Europe.

Material and methods

This was a retrospective cohort study of 620 singleton pregnancies of Indo-Pakistan and Caucasian origin undergoing routine ultrasound scans at Spanish and Italian reference hospitals. Fetuses were examined at Hospital Universitario y Politécnico La Fe (Valencia, Spain) and at Fondazione Policlinico Universitario Agostino Gemelli IRCSS (Rome, Italy). All fetuses underwent a biometry with an estimated fetal weight

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plus Doppler examination of the umbilical artery (UA) and middle cerebral artery (MCA) at and beyond 37 + 0 weeks as previously described [18,19]. In brief, Doppler examinations were performed with General Electric Voluson® (E8/E6/730) 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 Italian or Spanish Ultrasound in Obstetrics and Gynecology Societies. The gestational age (GA) was determined according to the crown-rump length in the first trimester. The CPR was calculated as the ratio between the MCA and the UA pulsatility index (PI) [18,20] and only the last Doppler examination obtained within two weeks of birth, was included in the analysis. All Indo-Pakistan fetuses were born to Indo-Pakistan citizens who were originally born in the Indian subcontinent and moved to Europe for socio-economic reasons. There were no second or third generation deliveries. Although the population was unselected, pregnancies complicated by significant maternal diseases, congenital fetal abnormalities, stillbirths and multiple pregnancies were excluded. Also, in order to avoid biases, both fetus and parents belonged to the same ethnicity and there were no gamete or embryo donations. 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 (Indo-Pakistan and Caucasian), 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 min. 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 Indo-Pakistan and Caucasian 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, p-values and partial R^2 as an estimate of their importance.

Some of these variables such as the mode of delivery and the Apgar 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 R^2 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 and graphs were performed with R-software® (version 3.4.3). Comparisons between the Indo-Pakistan and Caucasian fetuses were performed with the Chi-square test in case of categorical parameters, and the t-test in case of continuous parameters. Significance was considered with a $p < .05$.

Results

The study included 620 pregnancies, of which 87 (14%) were of Indo-Pakistan and 533 (86%) were of Caucasian origins. The patient and pregnancy characteristics of the study population are shown Table 1. The characteristics of the Caucasian and Indo-Pakistan fetuses are compared in Table 2. There were differences between the two groups in maternal age, height, GA at examination and especially in BW (Figure 1).

Table 1. Study population descriptive analysis, $N = 620$.

Parameter	Mean (SD)	Median (1st Q, 3rd Q)
Maternal age	32.52 (5.32)	33 (29, 36.25)
Gravidity	1.93 (1.21)	2 (1, 2)
MCA PI	1.43 (0.32)	1.4 (1.2, 1.61)
UA PI	0.83 (0.19)	0.8 (0.7, 0.92)
Parity	0.58 (0.81)	0 (0, 1)
CPR	1.8 (0.52)	1.79 (1.46, 2.1)
GA at ultrasound in weeks	39.15 (1)	39.29 (38.29, 40)
GA at delivery in weeks	39.85 (1)	40 (39.14, 40.71)
Interval*	4.94 (3.71)	4 (2, 8)
Birthweight in grams	3238.37 (442.95)	3212.5 (2950, 3500)
Apgar score at 1 minute	9 (1.13)	9 (9, 10)
Apgar score at 5 minutes	9.83 (0.58)	10 (10, 10)
Maternal Weight in kg	62.63 (11.73)	60 (54, 69)
Maternal Height in cm	162.63 (6.32)	162 (158, 167)
Parameter (categorical data)		***N*** **(%)**
Fetal gender (male)		323 (52.1%)
Apgar <7 at 5 minutes		4 (0.64%)
Cesarean section		157 (25.32%)
Instrumental vaginal delivery		133 (21.45%)
Spontaneous vaginal delivery		330 (53.23%)
Fetal ethnicity Indo-Pakistan		87 (14.03%)

Notes: CPR: cerebroplacental ratio, GA: gestational age, SD: standard deviation, 1st and 3rd Quartiles, *Interval between the ultrasound examination and delivery in days.

Table 2. Comparisons between the Indo-Pakistan and Caucasian study populations.

Variable	Ethnicity Spanish ($N = 533$) Mean (SD) Median (1st, 3rd Q)	Ethnicity Indo-Pakistan ($N = 87$) Mean (SD) Median (1st, 3rd Q)	p Value
Maternal age in years	33.04 (5.19) 33 (30, 37)	29.36 (5) 29 (26, 32.5)	$p < .001$
Gravidity	1.92 (1.23) 2 (1, 2)	2.05 (1.11) 2 (1, 3)	NS
Parity	0.56 (0.79) 0 (0, 1)	0.69 (0.91) 0 (0, 1)	NS
Cerebroplacental ratio	1.81 (0.5) 1.79 (1.49, 2.08)	1.7 (0.62) 1.65 (1.28, 2.13)	NS
GA at ultrasound in weeks	39.19 (0.97) 39.29 (38.43, 40)	38.88 (1.15) 38.86 (38, 40)	$p = .02$
GA at delivery in weeks	39.88 (0.98) 40 (39.14, 40.71)	39.66 (1.09) 39.71 (38.86, 40.57)	NS
Interval between the ultrasound and delivery in days	4.82 (3.55) 4 (2, 7)	5.68 (4.54) 5 (1, 9)	NS
Birth weight in grams	3269.42 (436.8) 3250 (2970, 3550)	3048.1 (435.19) 3070 (2790, 3315)	$p < .001$
Apgar score at 1 minute	9.02 (1.07) 9 (9, 10)	8.87 (1.45) 9 (9, 9)	NS
Apgar score at 5 minutes	9.84 (0.53) 10 (10, 10)	9.77 (0.8) 10 (10, 10)	NS
Maternal weight in kg	62.79 (11.88) 61 (54, 69)	61.64 (10.76) 60 (55, 67.5)	NS
Maternal height in cm	163.47 (6.07) 163 (160, 167)	157.54 (5.36) 157 (154, 160)	$p < .001$
Categorical data	***N*** **(%)**	***N*** **(%)**	***p*** **Value**
Fetal gender (male)	284 (53.28%)	39 (44.83%)	NS
Apgar <7 at 5 minutes	3 (0.56%)	1 (1.15%)	NS
Mode of delivery			
Cesarean section	130 (24.39%)	27 (31.03%)	
Instrumental vaginal delivery	118 (22.14%)	15 (17.24%)	NS
Spontaneous vaginal delivery	285 (53.47%)	45 (51.72%)	

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

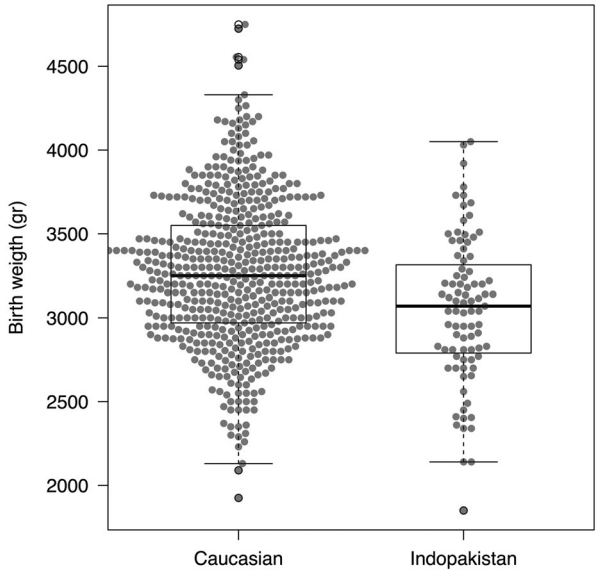

Figure 1. Box and whiskers graph comparing the birth weight of the Spanish and Indo-Pakistan fetuses.

A multivariable linear regression was performed with formerly mentioned variables in order to explain the true cause of BW differences between Caucasian and Indo-Pakistan fetuses. 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, which finally included those variables that were significantly different between both ethnic groups. The final model including GA at delivery and parity is shown in Table 3 ($R^2 = 27.3\%$, adjusted $R^2 = 26.3\%$).

In this model, GA at delivery (estimate = 178.078, 95% CI [147.366, 208.79], $p < .001$), CPR (estimate= 133.969, 95% CI [75.07, 192.868], $p < .001$), fetal gender (estimate= 132.971, 95% CI [72.364, 193.578], $p < .001$), maternal height (estimate = 11.155, 95% CI [5.763, 16.547], $p < .001$) Parity (estimate = 71.785, 95% CI [33.34, 110.23], $p < .001$) and maternal weight (estimate = 3.68, 95% CI [0.925, 6.435], $p = .009$) were the parameters that influenced positively BW, while there was not enough evidence to establish an influence from ethnicity (estimate = −83.28, 95% CI [−178.642, 12.082], $p = .087$) and maternal age (estimate = 2.936, 95% CI [−2.995, 8.866], $p = .331$).

As above indicated, the partial determination coefficient (partial R^2) was calculated for every predictive variable as a quantification method of its importance. The three most important parameters were GA at delivery (0,175), CPR (0.032) and fetal gender (0.029), followed by maternal height (0.026), parity (0.022),

Table 3. Multivariable regression linear analysis of the studied parameters for the prediction of birth weight.

	Estimate	95% CI	*p* Value	Partial R^2
(Intercept)	−6338.01	[−7899.16, −4776.86]	<.001	–
GA at delivery (weeks)	178.078	[147.366, 208.79]	<.001	0.175
CPR	133.969	[75.07, 192.868]	<.001	0.032
Fetal gender (male)	132.971	[72.364, 193.578]	<.001	0.029
Maternal height (cm)	11.155	[5.763, 16.547]	<.001	0.026
Parity	71.785	[33.34, 110.23]	<.001	0.022
Maternal weight (kg)	3.68	[0.925, 6.435]	.009	0.011
Ethnicity (Sri Lankan)	−83.28	[−178.642, 12.082]	.087	0.005
Maternal age (years)	2.936	[−2.995, 8.866]	.331	0.002

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. R^2 = 27.3%, adjusted R^2 = 26.3%.

and (maternal weight 0.011). Ethnicity (0.005), and Maternal age (0.002) showed a very poor coefficient in accordance with their lack of significance.

Discussion

Summary of the study findings

Children born to first generation immigrants presented lower BW values at term than their Caucasian counterparts. The difference was explained by GA at delivery, fetal gender, parity, maternal height, maternal weight and CPR, while maternal age and ethnicity had no influence. The tendency to a lower BW, explained by placental dysfunction and unrelated with ethnicity [17] persisted even when the residential setting was changed.

Interpretation of the results and comparison with existing literature

In order to discern the controversy between customization [6,21], and Intergrowth [7,22], we evaluated the effect of CPR on BW [17]. According to this approach if differences in BW were caused by placental dysfunction, we would expect to find low CPR values in fetuses with low BW. In contrast, if fetuses were constitutionally small, we would expect CPR values to be normal. Therefore, we used the CPR to score the influence of ethnicity and placental dysfunction upon BW [11–16]. The current study demonstrates that the predominance of CPR over ethnicity, earlier described [17], persisted in the first generation of immigrants when both ethnicities shared the same residential setting.

The possible reasons for the lack of influence of ethnicity and the importance of CPR in fetuses living in their respective continent were already addressed in our last work and could be related to poverty and nutritional factors [17,23–32]. However, the current results showed that moving to another country did not modify a scenario that seemed to be carried by immigrants to the new residential setting.

Concerning earlier research, two approaches have been considered. Some of the previous research suggested that children of first-generation immigrants were smaller than their local counterparts [33–36]. Several causes have been proposed. First, nutrition: immigrants adapt their diet to the new setting [37], increasing energy and fat intake and reducing carbohydrate intake, ending up with a higher risk of obesity, diabetes and cardiovascular disease. However, our patients were healthy and it is improbable that nutritional variations could account for fetal hypoxia and low CPR. Second, prenatal care: It has been also published that immigrant pregnant women are prone to a poorer follow-up and this might increase the possibility of adverse perinatal outcome [38]. However, our patients followed a standard protocol and it is unlikely that in our immigrant cohort paucity of follow-up could explain smallness. Third, a biological mechanism: improvements in the quality of life is frequently translated into better fenotypes after several generations [39]. Biologically, the primordial germ cells giving rise to the third generation are nourished as part of a second generation blastocyte by an uterus belonging to the first generation. In this scheme, the uterus (nourishing organ) belongs to the first generation, the embryo (nourished structure) belongs to the second and the primordial germ cells (part of the embryo) to the third generation [40]. This might be an interesting biological approach to understand how any improvement may take generations to be expressed in the individual phenotype and is supported by clinical works that show the persistence of health effects in the second or third generation (although progressively with less magnitude) [41–43], and by experimental works showing the persistence of epigenetic changes in the descendants of those who suffered famines decades ago in the second word war [44,45].

In other cases previous research found that immigrant children presented higher BW, supporting the so

called "healthy immigrant paradox" [46–48], a phenomenon by which health complications in immigrants are less frequent than in the locals population. This apparently contradictory effect has been also explained by means of diverse biases, which are beyond the scope of this study [49–51]. Also, social ties and familiar bonds [52] may be stronger in immigrants, favoring the acquisition of a better prenatal health. To complicate the scenario, a decrease of the effect has been observed in parallel to the length of residence in the hosting country [53].

Our results agree with the first group of researchers because Indo-Pakistan immigrants were smaller. In addition they presented a higher degree of FGR, which is in agreement with the higher levels of leptin and endothelin-1, earlier described in these children [54,55].

Be that as it may, according to our data, the tendency to fetal smallness and FGR unrelated to ethnicity seem to be transmitted at least to the next generation of individuals. Future works will be needed to elucidate the reason for this phenomenon.

Clinical implications

Our approach was retested in first-generation immigrants in whom BW differences persisted. These differences were again explained by placental dysfunction and not by ethnicity. Whatever is the cause, if ethnicity behaves as a risk factor for placental dysfunction this would preclude its inclusion in customization models, as customization should be conducted for physiological factors, not for parameters related to adverse perinatal outcome.

Strengths and limitations

The main strengths of this study include the large number of fetuses and the use of robust statistical analysis. Conversely, the main shortcoming is the retrospective nature, which hinders the collection of some perinatal data such as the smoking habit or the maternal weight gain throughout the pregnancy.

Conclusions

In first-generation immigrants, differences in BW are still explained by CPR and not by ethnicity suggesting the persistence of factors promoting placental dysfunction. The finding that moving to another country does not modify the relative importance of ethnicity and CPR challenges even more the rationale for using ethnicity in customized growth models and opens many questions regarding which factors might be behind a phenomenon that is carried by immigrants to their new residential setting.

Disclosure statement

The authors report no conflicts of interest.

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