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PERINATAL EPIDEMIOLOGY

Is the fetoplacental ratio a differential marker of fetal growth restriction in small for gestational age infants?

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Abstract Higher placental weight relative to birthweight has been described as an adaptive mechanism to fetal hypoxia in small for gestational age (SGA) infants. However, placental weight alone may not be a good marker reflecting intrauterine growth restriction. We hypothesized that fetoplacental ratio (FPR)—the ratio between birthweight and placental weight—may serve as a good marker of SGA after adjustment for surrogates of fetal hypoxemia (maternal iron deficiency anemia, smoking and choriodecidual necrosis). We conducted a within-sibling analysis using data from the US National Collaborative Perinatal Project (1959–1966) of 1,803 women who delivered their first two (or more) consecutive infants at term (n = 3,494). We used variance-component fixed-effect linear regression models to explore the effect of observed time-varying factors on placental weight and conditional logistic regression to estimate the effects of the tertiles of FPRs (1st small, 2nd normal and 3rd large) on the odds of SGA infants. We found placental weights to be 15 g [95 % confidence interval (CI) 8, 23] higher and −7 g (95 % CI −13, −2) lower among women that had anemia and choriodecidual necrosis, respectively. After multivariable adjustment, newborns with a small FPR (1st-tertile ≤7) had twofold higher odds of being SGA (OR 2.0, 95 % CI 1.2, 3.5) than their siblings with a large FPR (3nd-tertile ≥9). A small FPR was associated with higher odds of SGA, suggesting that small FPR may serve as an

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indicator suggestive of adverse intrauterine environment. This observation may help to distinguish pathological from constitutional SGA.

Keywords Placenta · Fetal growth retardation · Birth weight · Siblings · Epidemiology · Regression analysis

Background

Placental weight has been associated with neonatal and infant morbidity and mortality [1] as well as the development of chronic diseases during adulthood [2–4]. In the absence of congenital malformations or chromosomal anomalies, intrauterine growth restriction (IUGR) refers to a fetus that has not met its growth potential because of genetics or environmental factors or their combination [5]. Small for gestational age (SGA) infants are internationally accepted to be the consequence of IUGR [6]. However, infants classified as SGA may represent at least two groups: infants, that are constitutionally small and those that are pathologically growth restricted due to fetal hypoxemia and ischemic placental disorders [7].

The adequate transfer of oxygen to the fetus depends on the placenta's potential to adapt to hypoxemia due to reduced uteroplacental perfusion [1, 8–11]. Placental weight is correlated with birthweight and maternal anthropometric measures, and thus placental weight may serve as a proxy measure of placental function [8, 12]. However, fetoplacental weight ratio (FPR), defined as the ratio of birthweight and placental weight, is known to change across gestation as the placenta matures [8]. Therefore, the FPR may be a better marker of uteroplacental efficiency, defined as the placental potential of adaption to hypoxemia [8, 13].

To facilitate the interpretation of the association between fetal hypoxemia and placental weight, efforts must be made to reduce or eliminate potential confounding due to maternal genetic and environmental factors associated with the enlargement or the reduction of the placenta. In addition to these time-invariant genetic and environmental factors, other time-varying (i.e., across successive pregnancies) exposures have been associated with placental weight, such as birth order, infant sex, maternal anthropometric measurements and maternal smoking [1, 13–17].

Consequently, we argue that controlling for both time-invariant genetic and environmental factors and time-varying (i.e., across pregnancies) characteristics associated with the placental weight will permit FPR at delivery to better differentiation SGA into groups representing those that are constitutionally small and those are small secondary to IUGR. This more precise stratification of individual's SGA status at birth may potentially refine estimations of chronic disease risk trajectories across the life course. We, therefore, explored the effect of fetal hypoxemia on placental weight at delivery and analyzed the extent to which a low or high placental weight relative to birthweight is associated with risk of delivering term SGA infants after controlling for potential time-invariant and varying confounders.

Methods

We conducted a within-sibling study using data from the US National Collaborative Perinatal Project (NCPP). This study was a multicenter, prospective cohort study of pregnancy and child health that enrolled 58,391 pregnancies between 1959 and 1966. The NCPP was specifically designed to identify determinants of cerebral palsy and other neurological defects [18]. A detailed description of the methods is published elsewhere [18]. In order to address censoring as birth order is associated with both placental and birthweight [19], we restricted the analyses to women who delivered their first two (and up to four) consecutive singleton non-malformed, live-births at term (37–42 weeks) (Fig. 1) [20].

Covariates

We selected time varying covariates (i.e., change in covariate values across successive pregnancies) potentially associated with changes in placental weight based on previous evidence [8–12]. We considered three sets of covariates: placental-level, infant-level and maternal-level. Placental-level covariates included choriodecidual necrosis and FPR; infant-level covariates included infant sex, and birth order; maternal-level covariates included pre-pregnancy body-mass index (BMI), weight gain, smoking status and iron deficiency anemia (IDA). IDA, maternal smoking and choriodecidual necrosis were used as surrogates of fetal hypoxemia, due to reduced oxygen, vascularization problems and reduced uteroplacental perfusion [9–11]. These factors represent chronic placental injury and may generally reflect long-standing processes [22].

Maternal education, marital status and race were ascertained by self-report during a personal interview. Maternal education was based on the number of years of education attained and categorized as having <8, 8–11, 12–15 and ≥ 16 years of education. Choriodecidual necrosis was defined as the presence of necrosis caused by hemorrhage, atrophy or infarct after macro and microscopic evaluation of the decidua capsularis and basalis [23]. IDA was defined as serum hemoglobin concentrations <10.0 g/dL or hematocrit <30 %. These were ascertained at the first or consecutives prenatal visits during pregnancy. Maternal weight and height were measured upon enrollment in the study. 78 % of

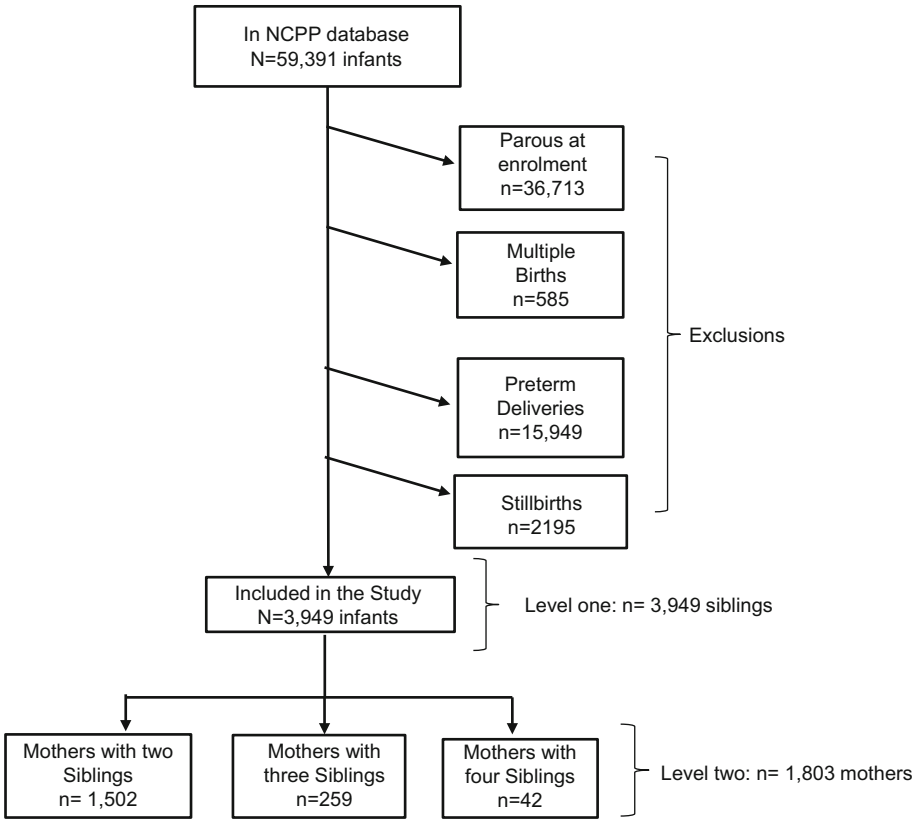

Fig. 1 Flowchart of the sample selection inclusion and exclusion criteria, National Collaborative Perinatal Project (NCPP) (N = 1,803 mothers and, n = 3,949 infants)

women were enrolled during the first and second pregnancy trimesters. Mother's weight was measured to determine gestational weight gain at the last prenatal visit within 3 weeks of delivery and mother's weight prior to pregnancy was based on self-report. Pre-pregnancy BMI was calculated as self-reported pre-pregnancy weight (kg) divided by height (m) squared. Placentas were weighed and examined at delivery according to a standard protocol after the removal of the membranes and umbilical cord by trained technicians, who examined micro and macroscopically the placentas of those infants whose crown-rump length was 16.5 cm or more (corresponding approximately to a gestational age of 20 weeks or more) [22, 23].

We defined SGA as sex-specific birthweight <10th percentile of birthweight by gestational age [24]. We computed the FPR as the power ratio index between birthweight and placental weight [25] (Appendix). Based on the tertiles of the FPR, we categorized FPR as being small (1st tertile), normal (2nd tertile) and large (3rd tertile). Compared with the second and third tertiles, a small FPR (1st tertile) is interpreted as a higher placenta weight in relation to the birthweight.

Statistical analysis

First, we compared maternal and infant characteristics for the entire NCCP cohort against those selected for the present analysis. Then we used line plots to explore between mothers and within-sibling profiles of variation of placental weight based on birth order for the entire study sample and a randomly selected subsample of the study population. In addition, we plotted mean placental and infant birthweight, and the mean FPR according to birth order.

To better characterize the association between placental weight and maternal and fetal characteristics including smoking, fetal hypoxemia, infant sex and birth order, we estimated univariate and multivariable linear fixed-effects models with robust standard errors [26, 27]. We implemented a mean deviation algorithm to treat mothers' specific intercepts as fixed unknown parameters; that was accomplished by the mean centering for both the outcome and predictors (i.e., in this case the mean over time of measurements for each individual is subtracted from all the individual's measurements) (Appendix). The time-invariant terms were eliminated in the mean-centering equation (maternal education, marital status and race), and only parameters associated with time-varying covariates were estimated by the model [26, 27]. Therefore, the estimated model coefficients represented the within-siblings effects of modeled covariates. The advantage of these estimates is that they are not susceptible to bias due to unmeasured mother-specific covariates (endogeneity or time-invariant residual

confounding) as each mother serves as her own control [26, 27].

We explored the effect of fetal hypoxemia on placental weight. We first fitted a multivariable linear fixed-effects model, with placental weight as dependent variable and maternal IDA, choriodecidual necrosis and tertiles of the FPR as independent variables. We then computed a fully adjusted linear fixed-effect model, which included maternal age, pre-pregnancy BMI, gestational weight gain, infant sex, birth order, fetal hypoxemia (i.e., smoking, anemia and choriodecidual necrosis) and the FPR as independent variables (supplementary Figure S1A). We used the Durbin-Wu-Hausman test [28] in order to test the pertinence of the use of a fixed-effect modeling approach.

We then used a conditional logistic regression with robust standard errors to assess the extent to which a small or large FPR was associated with the delivery of a SGA infant. We adjusted for all time-varying factors previously found in fixed-effects linear models to be associated with the placental weight including maternal age and smoking. We derived univariable and multivariable adjusted odds ratios (OR) with their associated 95 % confidence intervals (CI). In the fully adjusted model we analyzed the effect of the tertiles of the FPR on the odds of delivering a SGA infant adjusted for the potential confounding effects of maternal age, IDA, pre-pregnancy BMI, gestational weight gain, birth order, choriodecidual necrosis, and smoking status (supplementary Figure S1B). We also explored the effect of the percentiles of the FPR on the odds of delivering a SGA infant and assessed the best FPR cutoff based on the Youden index [29].

We used multiple imputation to account for missing covariate data. We assumed that the missing data were "missing at random", and created 10 imputed data sets by means of the expectation maximization bootstrap algorithm [30]. Regression models were fit for each of the 10 imputed data sets and the results combined subsequently [31, 32]. In order to improve estimates of the multiple imputed model, in addition to all time-varying variables, we included in the model maternal education, marital status and race as time-invariant covariates associated with the process of missingness.

Finally, we developed a sensitivity analysis by means of different models specifications, testing for non-linearity of the predictors, different versions of the FPR, and the interactions of maternal gestational weight gain and pre-pregnancy BMI with the infant order. We also compared unadjusted and adjusted models with and without imputation.

For the statistical analysis we used the Amelia II package [33] implemented in R.2.7 (R Foundation for Statistical Computing, Vienna, Austria) and Stata v.13.1 (Statacorp, College Station, Texas, US) [34].

Results

Figure 1 shows the selection of subjects based on the exclusion criteria (previously described) in the NCPP. In contrast to the complete cohort, the selected study population showed slightly higher proportions of younger white women with higher education (Table 1). Nearly a half of the study sample were smokers (46.2 %), 18.6 % presented with IDA, and more than a half of the placentas showed macro or microscopic signs of choriodecidual necrosis (56.3 %) in any of their first four pregnancies. Women who reported ever smoking during a pregnancy did so in 87 % of their successive pregnancies. Furthermore, within-siblings recurrence in any successive pregnancy of IDA was 66 and 69 % for choriodecidual necrosis. Overall, statistically significant trend was noted (p value of trend <0.001) with 7 % of increase of placental weights by birth order, ranging from 432 g for the first infant to 463 g for the fourth infant, although there was considerable variability between mothers. The FPR decreased not significantly by infant order (p value $= 0.532$) (Fig. 2).

Figure 3 shows maternal profiles of placental weight according to infant birth order and sex. The within-siblings placental weight correlation was 52 %. Male infants had higher placental weight than females up to the third sibling as for the fourth females had higher placental weight than males. The placental weight of male infants was, on average, 5 g higher (440 g, 95 % CI 436, 444) compared to female infants (435 g, 95 % CI 431, 439).

Table 2 shows that conditioned on birth order, infant sex, maternal pre-pregnancy BMI, smoking, IDA and choriodecidual necrosis were independently associated with the placental weight at delivery. Nevertheless, IDA and choriodecidual necrosis, revealed opposite effects; higher placental weight for IDA and lower weight for choriodecidual necrosis. The placenta with evidence of choriodecidual necrosis weighed -7 g less (95 % CI -13, -2) than those of their siblings that did not show evidence of necrosis. The placenta in the setting of maternal IDA weighted, on average, 15 g (95 % CI 8, 23) more compared with the placenta in the absence of IDA. Compared with the second tertile, those infants in the first tertile of the FPR, showed an increase of 69 g on the placental weight.

The prevalence of SGA was 10 % (n = 415), and compared with appropriate for gestational age (AGA) infants, SGA infants had a smaller FPR (7.2 vs. 7.6) (Table 1 and supplementary Table S1). In the multivariable conditional logistic regression model, both maternal IDA and choriodecidual necrosis were independently associated with SGA. After multivariable adjustment for IDA, choriodecidual necrosis, smoking status and other maternal characteristics, infants with a FPR ≤ 7 (1st tertile), had a twofold higher odds (adjusted OR 2.0, 95 % CI 1.2, 3.5) of

Table 1 Maternal and infant characteristics original National Collaborative Perinatal Project (NCPP) (N = 59,391) and NCCP within-siblings sample (n = 1,803 mothers and 3,949 infants)

	NCPP complete cohort			NCPP selected sample*		
	N	%	Mean (SD)	N	%	Mean (SD)
Within-sibling time-varying covariates						
Maternal age (years)	59,389		24.3 (6.1)	3,949		21.4 (4.0)
Gestation age (weeks)	59,044		37.0 (9.0)	3,949		39.8 (1.4)
Pre-pregnancy BMI (kg/m^2)	52,697		22.8 (4.3)	3,517		22.1 (3.5)
Gestational weight gain (kg)	55,165		10.0 (5.0)	3,846		10.5 (4.2)
Female infant sex	28,444	50.9		2,017	51.1	
Smoking (yes)	26,901	46.7		1,817	46.2	
Iron deficiency anemia (yes)	13,356	24.1		692	18.6	
Choriodecidual necrosis (yes)	27,168	57.2		2,022	56.3	
Small for gestational age (yes)	5,558	10.0		415	10.5	
Placental weight (g)	47,072		432 (104)	3,576		438 (88)
Birth weight (g)	55,266		3,121 (608)			3,241 (443)
Fetoplacental ratio	46,888		7.4 (1.4)			7.5 (1.3)
Between mother time-invariant covariates						
Maternal education (years)						
<8	5,576	9.9		172	4.5	
8–11	27,007	47.8		1,511	39.0	
12–15	21,250	37.6		1,939	50.2	
≥16	2,627	4.7		245	6.3	
Race						
White	27,753	46.7		2,547	64.5	
Black	27,241	45.9		1,254	31.7	
Others	4,397	7.4		148	3.8	
Single marital status	14,482	24.4		799	20.2	

SD Standard Deviation

* Percentage of missing information in the selected sample: placental weight (n = 373, 9.5 %); maternal smoking (n = 16, 0.4 %); maternal iron deficiency anemia (n = 220, 5.6 %); choriodecidual necrosis (n = 357, 9.0 %); maternal education (n = 82, 2.1 %); maternal pre-pregnancy BMI (n = 432, 10.9 %)

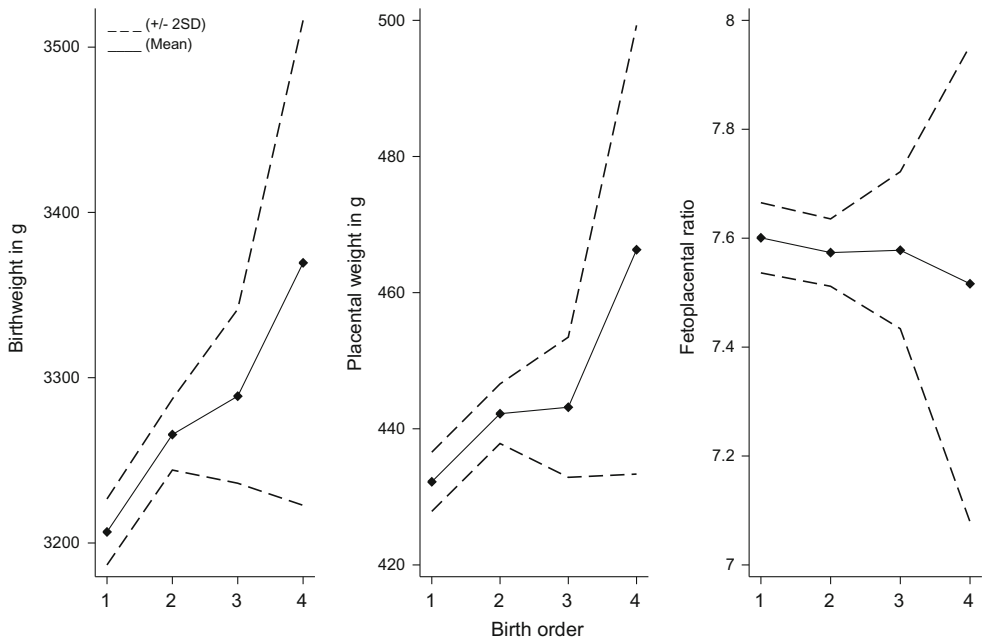

Fig. 2 Mean (*solid lines*) and ±2 SD (*broken lines*) birthweight, placental weight and fetoplacental ratio by infant birth order, (N = 1,803 mothers and n = 3,949 infants)

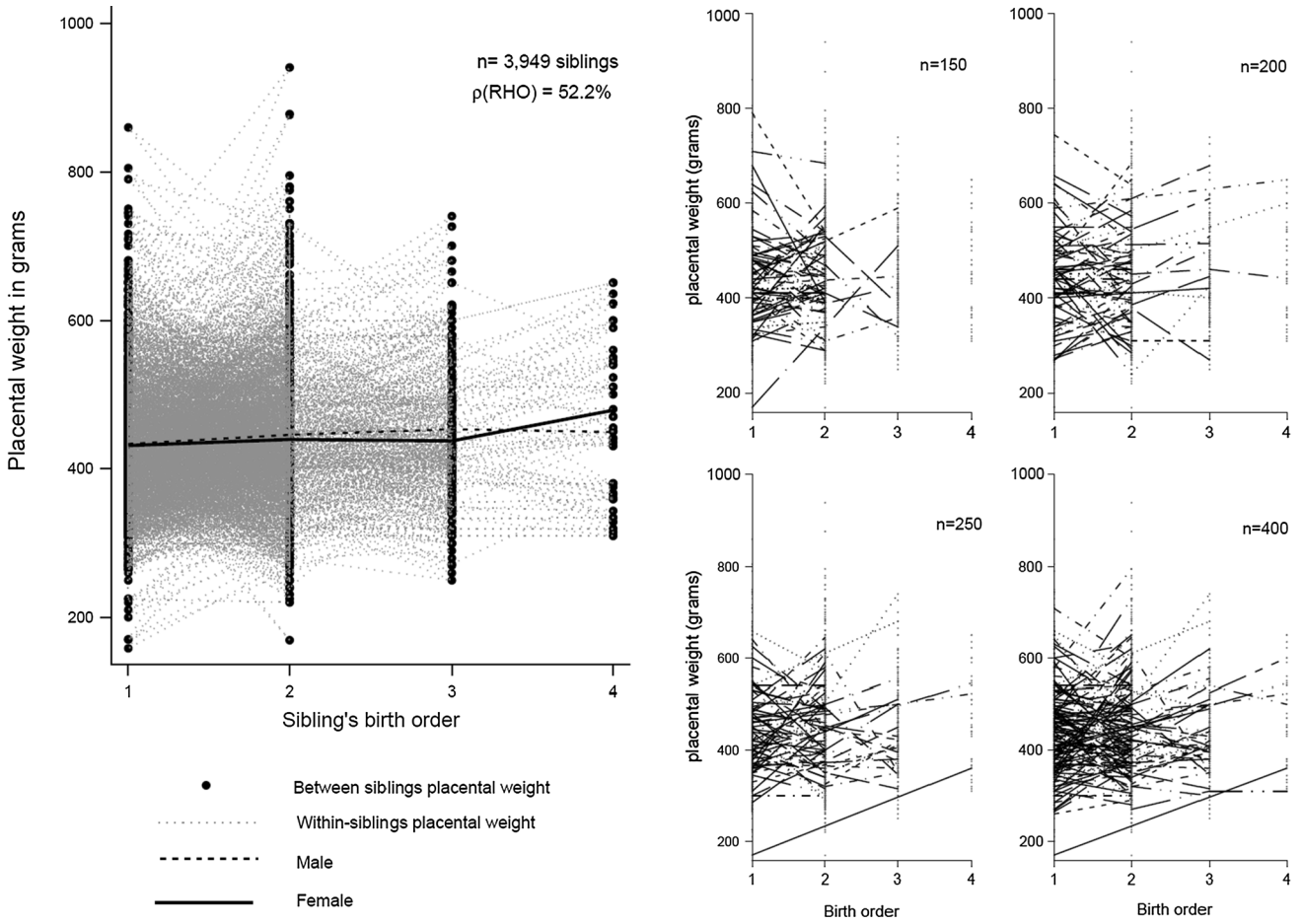

Fig. 3 Between and within-siblings placental weights profiles and mean placental weight trajectory by infant sex (N = 1,803 mothers and n = 3,949y infants)

Table 2 Within-siblings placental weight differences in grams by maternal and infant characteristics (N = 1,803 mothers, 3,949 infants)

Within-siblings time varying covariates	Unadjusted coefficients β (95 % CI)	Adjusted coefficients β (95 % CI)
Birth order		
2nd versus 1st	8 (5, 15)	11 (5, 18)
3rd versus 1st	12 (2, 22)	16 (3, 29)
4th versus 1st	38 (13, 63)	35 (11, 58)
Maternal age (1 year increment)	5 (3, 7)	0 (0, 3)
Iron deficiency anemia (yes vs. no)	20 (10, 29)	15 (8, 23)
Choriodecidual necrosis (yes vs. no)	−11 (−18, −4)	−7 (−13, −2)
Smoking (yes vs. no)	1 (−13, 14)	−2 (−11, 7)
Infant sex (male vs. female)	5 (−2, 11)	20 (7, 17)
Pre-pregnancy BMI (kg/m^2, for 10 units increment)	20 (4, 36)	12 (4, 34)
Gestational weight gain (kg, for 5 kg increment)	8 (3, 14)	14 (10, 18)
Tertiles of the fetoplacental ratio		
1st (≤7) versus 2nd (>7–<9)	67 (60, 74)	67 (60, 74)
3rd (≥9) versus 2nd (>7–<9)	−58 (−65, −51)	−57 (−64, −51)

being a SGA than their siblings with a large FPR (3nd tertile) (Table 3).

In a sensitivity analysis, lower percentiles of the FPR compared with the largest percentile ($p \geq 95$) showed consistently higher risk of SGA. Based on the estimated Youden index, a FPR ≤ 7 was the best cutoff for this specific study population (supplementary Table S2).

Discussion

We found that a small FPR at birth was associated with higher risk of delivering a term SGA infant. To the best of our knowledge, our study is the first to document that term SGA infants have larger placentas in relation to birth weight than term AGA infants after controlling for maternal genetic and environmental time-invariant characteristics and time-varying factors associated with placental weight. Our finding may help to differentiate those SGA constitutionally small from those growth restricted term infants based on the FPR at birth.

Interpretation of the results

Our results are consistent with previous studies that show that SGA infants have larger placentas in relation to birth weight than AGA infants [17, 35]. A small FPR or higher placental weight relative to infant birthweight may represent a potential failed compensation of the placenta function due to an adverse intrauterine environment in SGA infants [8, 36]. Small infants are known to have small placentas [37]. However, investigators have also noted that SGA infants, as compared with AGA infants, have relatively larger placentas which leads to a smaller FPR [8]. Thus the calculation of the FPR allows for interpretation of infant size relative to placental size and consequently may provide information that enable differentiation of constitutionally versus pathologically small infant at birth.

Previous evidence support our findings about two possible distinct types of fetal hypoxemia, the first due to a reduced maternal blood oxygen content and the second when normally oxygenated maternal blood has restricted entry into the uteroplacental tissues as result of ischemia and infarction [21, 38]. Choriodecidual necrosis is a lesion suggestive of decreased uteroplacental perfusion [39]. However, ischemic placental disease including preeclampsia and placental abruption are known to be associated with placental hypoxemia [40].

It has been found that low placental weight relative to the birthweight is strongly associated with preterm preeclampsia and evidence of macroscopic and microscopic choriodecidual necrosis which decreases uteroplancental perfusion [38, 39, 41]. On the other hand, maternal IDA may stimulate blood vessels formation in the growing placenta by increasing the expression of angiogenic growth factors [42, 43]. For example, investigators have reported increased depth of invasion and hypercapillarized villi in the extravillous trophoblast of placentas under hypoxemic conditions [44].

However, there is a third mechanism that reduces levels of maternal circulating oxygen, carbon monoxide hypoxia due to maternal smoking. Cigarette smoking has been identified as responsible for higher placental weight [45, 46]. Although, cigarette smoking suppresses both placental

Table 3 Odds ratios of delivering a small for gestational age infant by maternal and infant characteristics and the tertiles of the fetoplacental ratio (N = 1,803 mothers and 3,949 infants)

Variables	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
Birth order (for one more infant)	1.0 (0.8, 1.1)	0.7 (0.4, 1.2)
Maternal age (1 year increment)	1.0 (0.9, 1.1)	1.1 (0.9, 1.4)
Iron deficiency anemia (yes vs. no)	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)
Choriodecidual necrosis (yes vs. no)	1.4 (0.8, 1.9)	1.4 (0.9, 2.0)
Smoking (yes vs. no)	1.1 (0.4, 1.8)	1.1 (0.5, 2.0)
Pre-pregnancy BMI in Kg/m^2 (for 10 units increment)	0.5 (0.1, 1.6)	0.7 (0.3, 2.1)
Gestational weight gain in kg (for 5 kg increment)	0.6 (0.5, 0.8)	0.6 (0.4, 0.8)
Tertiles of the fetoplacental ratio		
1st (≤7) versus 3rd (≥9)	2.0 (1.1, 2.9)	2.0 (1.2, 3.5)
2nd (>7–<9) versus 3rd (≥9)	1.7 (1.0, 2.5)	1.6 (1.0, 2.7)

OR Odds ratio

Results from univariable and multivariable conditional logistic models with robust error standards estimation: in the fully adjusted model we analyzed the effect of the tertiles of the FPR on the odds of delivering a SGA infant adjusted for maternal age, IDA, gestational weight gain, pre-pregnancy BMI, birth order, choriodecidual necrosis, and smoking status

and fetal growth, the placenta appears to be less impacted by this exposure than the developing fetus [47]. Given this differential response to cigarette smoke-related hypoxemia, one would expect small FPR among mother who smoke during pregnancy as compared with non-smokers. Other factors also have been described to be associated positively with placental weight at birth, such as a maternal anthropometric measures (higher pre-pregnancy BMI and gestational weight gain) [15, 16, 48], higher birth order [49, 50], male infant sex [17] and gestational diabetes mellitus (GDM) [51]. It has been shown that placental weight was higher in African Americans and lower in those infants of Asian ethnicity when compared with other ethnic groups [16, 52]. Differences in birthweight and placental weight have been reported to be associated with birth order. Birthweight typically increases in each successive pregnancy up to five [49, 50].

Similarly, we have found that placentas of first-born infants are smaller and placental weight increased in each successive pregnancy. Previous evidence support the hypothesis that smaller placenta and lower birth weight of first-born infants may be due to maternal sensitization to paternal antigens [53] and maternal age [54]. Maternal age is positively correlated with higher pre-pregnancy weight, and higher maternal weight has been associated with a relative plethora of blood vessels and supporting tissues [55–57]. Other factors have been raised, including the diabetogenic effect of increasing parity and the enlargement of the uterine blood supply improving fetal growth [55].

Strengths and limitations

Given the complex and sometimes divergent biological adaptive responses that the placenta appears to have in response to hypoxemia, we hypothesized that the association between SGA and the FPR as a proxy of placental efficiency, might be affected by confounding due to genetic (i.e., propensity to deliver small or large infants) and environmental factors such as maternal diet, exercise, education, ethnicity, etc. Thus, the inclusion in our study of siblings who share similar genetic and environmental backgrounds made it possible to examine the effects of FPR on SGA, controlling for genetic and environmental factors that may have confounded previous studies [58]. In addition, our analytic approach allowed for controlling within-siblings differences in birthweight and placental weight independently of birth order [58, 59].

Furthermore, our study provides a more precise classification of individual's SGA based on the FPR at birth. Therefore, in low and middle resource settings, where ultrasound during pregnancy is not routinely used to identify IUGR, the FPR could be used as an indicator suggestive of adverse intrauterine environment and help to differentiate constitutionally versus pathologically small infants at birth (SGA). Large placentas due to IUGR have been associated with cardiovascular mortality in adulthood [3]. Thus, it is important not only to develop methods of diagnosing IUGR, such as recognizing at-risk infants through the FPR, but to develop follow-up and adequate treatment programs for the control of disorders which may follow IUGR and SGA. Proper postnatal feeding, for example, may be needed to assure adequate infant growth, which may be essential for long-term outcome [60].

Even if some time-invariant maternal characteristics were recorded in the NCPP study, the fixed-effect approach did not allow us to estimate such effects (i.e., ethnicity effect on placental weight). However, we were not interested in estimating the effect of time-invariant maternal characteristics but rather controlling for them.

Choriodecidual necrosis is an important pathologic feature of placental ischemia [11, 21, 61, 62], suggestive of decreased uteroplacental perfusion, and increased risks of preeclampsia, preterm birth and IUGR [39, 62, 63]. In our study, within and between mothers placental weight differences for choriodecidual necrosis were -7 and -33 g respectively, which is similar to previous published evidence ranging between -11 and -44 g based in preterm infants [61, 64]. In the presence of placental choriodecidual necrosis, oxygen is decreased in the intervillous space due to decreased uteroplacental perfusion, all of which result in hypoxemia in fetal blood and increased risk of preterm birth and IUGR [61, 64]. Placentas of term infants with choriodecidual necrosis could have undergone compensatory or adaptive processes such as hypercapillarized villi [44], thus reducing the observed within-siblings placental weight differences [8]. More precise information regarding the degree or extension of choriodecidual necrosis, would have improved our understanding regarding placental weight differences. The lack of this information should be considered as a limitation.

Regarding maternal IDA, we were not able to ascertain whether IDA was diagnosed first during the first, second or third trimester. Nor did we have information available on possible iron supplementation. Finally, placenta examiners were trained to do not have knowledge of the course or outcome of the pregnancy until placenta's questionnaires were filled out. However, we were not completely able to determine if the technicians were in fact blinded to the clinical scenarios. Consequently, these limitations hinder our capacity to generalize our findings to modern pregnancy cohorts. Furthermore, the external validity of the suggested FPR cutoff is limited to only this specific study population.

Replications of our analysis in more recent cohorts will address these limitations. However after adjusting for

important time-varying factors associated with fetal hypoxemia and placental weight, we found a consistent association between FPR and SGA. Furthermore, our results were robust to different models specifications in sensitivity analysis.

To conclude, in contrast to term SGA with a normal FPR, a small FPR may serve as an indicator suggestive of adverse intrauterine environment. This finding may have important implications toward understanding IUGR and should help to differentiate term SGA infants that are constitutionally small from those that have not met their optimal growth and thus, are intrauterine growth restricted.

This implies a linear relation of ln(numerator) on ln(denominator) and regression analysis can be used to find the power term (p). If $p = 1$, it implies that the numerator and denominator increase proportionally. If $p > 1$, it implies that the numerator increases disproportionately more than the denominator does and it has to be taken into account as a power term in the denominator of the power ratio index.

Using ordinary least squares we derived the value of the constant (intercept) and the slope (p) in (2). The calculated value of (p) in our study population was 0.956 and we rounded it to 1.

```
 reg  lnpwt lnbwt
*lnpwt = ln placental weight
*lnbwt = ln birthweight

      Source |       SS       df       MS              Number of obs =    3574
-------------+------------------------------           F(  1,  3572) = 1897.73
       Model |  49.6513478     1  49.6513478           Prob > F      =  0.0000
    Residual |  93.4561165  3572  .026163526           R-squared     =  0.3470
-------------+------------------------------           Adj R-squared =  0.3468
       Total |  143.107464  3573  .040052467           Root MSE      =  .16175
------------------------------------------------------------------------------
       lnpwt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       lnbwt |   .9560777   .0196515    43.56   0.000     .9175484     .994607
       _cons |  -.8505605   .1587229    -5.36   0.000    -1.161757   -.5393639
------------------------------------------------------------------------------
```

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Appendix

The fetoplacental ratio as power ratio index to quantify fetal growth

A power ratio index is defined by the division of (a function of) one variable x by (a function of) another variable y. For the fetoplacental ratio we use birthweight as x, placental weight as y and power (p) = 1 (1).

$$\text{Power Ratio Index:} \frac{x}{y^p} \tag{1}$$

In studies of growth, ratio indices are usually used to represent body shape (e.g., body mass index) or proportionality (fetoplacental ratio). To compute the power term (p) we used the following equation:

$$\ln(\text{birthweight}) = \ln(\text{constant}) + p \times \ln(\text{placental weight}) \tag{2}$$

Fixed effects estimation: mean deviation algorithm

In the fixed-effect approach, the model where siblings share certain characteristics (e.g., genetic, or environment) can be represented as:

$$Y_{ij} = \alpha_i + \beta x_{ij} + e_{ij}, \tag{3}$$

where the subscript 'i' indexes the mother, while the subscript 'j' indexes the birth order infants (j = 1, 2, 3, …, n). Y_{ij} is the outcome of interest (i.e., placenta weight), and α_i represents the maternal characteristics shared by all siblings that affect the mean estimated result of Y_{ij}.

X_{ij} are relevant covariates, and e_{ij} is a random error term with mean zero. To deal with the α_i we first take the mean of Eq. (3) for each woman. If we denote the mean of y as y*, etc. then we have:

$$Y_i^* = \alpha_i + \beta x_i^* + e_i^* \tag{4}$$

If we now subtract Eq. (4) from Eq. (3) we have:

$$(Y_{ij} - Y_i^*) = \beta(x_{ij} - x_i^*) + (e_{ij} - e_i^*) \tag{5}$$

Thus, we eliminate maternal specific component α_i. If there are more than two births per mother, we can take ($y_{i1}-y_i$*), ($y_{i2}-y_i$*), ($y_{i3}-y_i$*), etc. The fixed-intercept treats maternal specific intercepts as fixed unknown

parameter α_i and the estimated model coefficients represent the within-siblings effects of the covariates.

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