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Associations Between the Features of Gross Placental Morphology and Birthweight

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Abstract

The placenta plays a critical role in regulating fetal growth. Recent studies suggest that there may be sex-specific differences in placental development. The purpose of our study was to evaluate the associations between birthweight and placental morphology in models adjusted for covariates and to assess sex-specific differences in these associations. We analyzed data from the Stillbirth Collaborative Research Network's population-based case-control study conducted between 2006 and 2008, which recruited cases of stillbirth and population-based controls in 5 states. Our analysis was restricted to singleton live births with a placental examination (n = 1229). Characteristics of placental morphology evaluated include thickness, surface area, difference in diameters, shape, and umbilical cord insertion site. We used linear regression to model birthweight as a function of placental morphology and covariates. Surface area had the greatest association

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Declaration of Conflicting Interests

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with birthweight; a reduction in surface area of 83 cm², which reflects the interquartile range, is associated with a 260.2-g reduction in birthweight (95% confidence interval, – 299.9 to – 220.6), after adjustment for other features of placental morphology and covariates. Reduced placental thickness was also associated with lower birthweight. These associations did not differ between males and females. Our results suggest that reduced placental thickness and surface area are independently associated with lower birthweight and that these relationships are not related to sex.

Keywords

placental size; placental shape; birthweight; placenta; neonatal; fetal

Introduction

The placenta plays a critical role in regulating fetal growth and development. In particular, the placenta acts as a mediator of oxygen, nutrient, and waste exchange; is immunologically active; and produces hormones and growth factors necessary for fetal development and maintenance of pregnancy.¹ Reduced placental function can prevent the placenta from meeting the oxygen and nutrient needs of the fetus.² This may result in suboptimal fetal growth, which has both short-and long-term health consequences and is a strong risk factor for perinatal morbidity and mortality.^{3,4}

Gross features of placental morphology reflect its function and efficiency.^{5,6} Placental thickness may reflect the vascularization and branching of the chorionic villi and is the main dimension of placental growth during the third trimester.^{7,8} Surface area of the chorionic plate is mostly established prior to the third trimester and may reflect the number of spiral arteries supplying the placenta.^{7–10} Placentas are typically round or oval, but abnormal shapes may result from uterine abnormalities or as an adaptive response to stress during early placental development.^{11,12} Similarly, the difference in the diameters of the placenta reflects how circular or oval the placenta is, which may indicate adaptive growth.^{8,13} Noncentral umbilical cord insertion may reflect poor placental development in early pregnancy or adaptive growth of the placenta and has been associated with reduced placental efficiency.^{12,14,15}

Several studies have identified sex-specific differences in placental development and morphology. One group found that male placentas tend to be thicker while female placentas tend to have a larger surface area.¹⁶ Another group reported that male placentas are smaller than female placentas when controlling for birthweight, which indicates that male placentas may be more efficient than female placentas.¹⁷ However, as a trade-off for efficiency, male placentas are hypothesized to have less reserve capacity, which may result in a higher risk of the fetus becoming undernourished.¹⁷ Although studies have reported differences in placental development, few have evaluated the functional impact of these differences in relation to fetal development.

Previous studies of placental morphology and fetal size have limitations that warrant additional investigation. Most studies report correlations or statistical tests for differences and do not quantify the magnitude of the relationship between placental morphology and

fetal size.^{18–24} In addition, many studies have not adjusted for covariates such as gestational age, parity, maternal body size, and fetal sex.^{7,18–26} These maternal and pregnancy characteristics may influence both birthweight and placental size and may confound reported associations.^{27,28} Two studies have estimated associations in models adjusted for some covariates; however, they report inconsistent results.^{29,30} Furthermore, only 1 study has evaluated sex-specific differences in placental development in relation to birthweight, and this study did not adjust for many important covariates.²⁵

The purpose of our study was to evaluate the associations between placental morphology and birthweight while adjusting for key confounders, including evaluating interaction by sex. We hypothesized that the features of placental morphology would be associated with birth-weight, and that these associations would differ by sex.

Methods

Study Sample

The Stillbirth Collaborative Research Network (SCRN) conducted a population-based case-control study of stillbirth. Participants were enrolled around the time of delivery between March 2006 and September 2008 at 59 hospitals representing 5 catchment areas of the United States: the state of Rhode Island and counties in Massachusetts, Georgia, Texas, and Utah. Cases included stillbirths in the catchment areas and controls were sampled from all live births in the same catchment areas. The SCRN study enrolled 663 women with a stillbirth and 1932 women with a live birth. Details on the study design, including sampling methods, have been published earlier.³¹ The study was approved by the Institutional Review Board at each study site, and all participants gave written informed consent.

We restricted our analysis to the 1760 singleton live births with complete chart abstraction and maternal interview. Of these, 93.8% consented to a placental examination, and the examination was conducted in 1229 (Figure 1). Some women were enrolled postpartum, and the most common reason for an incomplete examination was that the placenta was discarded and could not be examined.³² Characteristics related to the completion of a placental examination included clinic site, induction, mode of delivery, year of study, time of day of delivery, and weekend delivery. Data weights were calculated and used in the analysis to account for differences in characteristics related to completion of the placental examination, differential consent for enrollment, and sampling methods.³¹

Information on maternal, pregnancy, and neonatal characteristics, including birthweight, were obtained from medical chart abstraction and maternal interview. The features of placental morphology of interest were determined from the placental examination, which was performed by perinatal pathologists using a standardized, published protocol.³²

Thickness—measured at the thickest point and rounded to the nearest 0.5 cm.

Surface area—determined based on the formula for the area of an ellipse using the recorded maximum (a) and minimum (b) diameters ($\text{area} = ab\pi/4$).

Difference in diameters—measured by subtracting minimum diameter from maximum diameter. Differences of zero indicate circular placentas while larger differences indicate increasingly oval placentas.

Shape—determined based on pathologist classification. Options included round, ellipse, bilobed, membranacea, or other. We dichotomized shape by grouping round and ellipse to indicate normal shapes and grouping bilobed, membranacea, and other to indicate abnormal shapes.¹¹

Umbilical cord insertion—pathologists measured the distance from the insertion site to the nearest placental edge and recorded if the insertion was velamentous. We divided the distance from the insertion site to the nearest edge by the average radius of the placenta (velamentous insertions were coded as a negative distance). Ratios of 0 indicate marginal insertions, ratios close to 0 indicate peripheral insertions, and ratios close to 1 indicate central insertions.^{33,34}

Statistical Analysis

We conducted linear regression to evaluate the relationship between birthweight and the placental characteristics. Linear regression allows for quantifying the association between birthweight and placental characteristics while controlling for other variables that may affect the observed association.³⁵ We incorporated the data weights in the analysis to account for study design, characteristics related to consent, and characteristics related to the availability of the placental examination. We controlled for maternal age, maternal education, maternal race/ethnicity, smoking, maternal height, maternal weight, gestational hypertension, gestational diabetes, parity (primiparae vs multiparae), gestational age, and sex, as these characteristics may influence both placental morphology and birthweight and confound the association. We also evaluated potential interaction between the features of placental morphology and sex. In addition to modeling the total sample of live births, we evaluated models restricted to term births, defined as ≥ 37 weeks' gestation.

In supplemental models, we further adjusted for the presence of 1 or more indicators of placental developmental disorders (umbilical cord: single umbilical artery, velamentous insertion, furcate insertion; placental membranes: circummarginate insertion, circumvallate insertion; fetal villous capillaries: terminal villous immaturity [diffuse], terminal villous hypoplasia [diffuse]), inflammatory disorders (maternal inflammatory response: acute chorioamnionitis—placental membranes, acute chorioamnionitis—chorionic plate; fetal inflammatory response: acute funisitis, acute umbilical cord arteritis, acute umbilical cord phlebitis, chorionic plate acute vasculitis, chorionic plate vascular degenerative changes), maternal vascular malperfusion (retroplacental hematoma, parenchymal infarction, intraparenchymal thrombus, perivillous/intervillous fibrin/fibrinoid deposition [diffuse]), and fetal vascular malperfusion (fetal vascular thrombi in the chorionic plate, avascular villi, placental edema) in order to evaluate the independence of the features of gross morphology from these characteristics.³⁶ Contributions of the specific placental diameters were also evaluated by modeling birthweight as a function of maximum diameter, minimum diameter, and thickness.²⁶

We conducted a secondary analysis using polytomous logistic regression to evaluate the placental variables associated with small for gestational age (SGA; birthweight <10th percentile for gestational age) or large for gestational age (LGA; > 90th percentile) as compared to appropriate for gestational age (AGA; 10th–90th percentile). Categories of birthweight for gestational age were determined from adapting individualized norms using estimated fetal weight developed by Bukowski et al., which adjust for pregnancy characteristics.³⁷ Details on the modifications made to the individualized norms in this study have been published.³⁸ As this birthweight percentile is adjusted for many of the potential confounders, only maternal age, gestational hypertension, and gestational diabetes were included as confounders in the logistic models.

To facilitate comparison of the magnitude of the association across placental measures, reported measures of association for the continuous variables reflect a comparison of the 25th and 75th percentiles of the characteristic of interest within the specified sample (total or term). Estimates reflect a comparison of 25th versus 75th for thickness (thin vs thick), surface area (small vs large), and umbilical cord insertion (eccentric insertion vs more central insertion). For difference in diameters, estimates reflect a comparison of 75th to 25th (oval vs circular). The values used for each comparison are reported in Table S1. Shape was analyzed as a dichotomous variable, and measures of association reflect the comparison of abnormal to normal.

A *P* value of < .05 was used to determine statistical significance. Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) and SUDAAN version 11.0 (Research Triangle Institute, Research Triangle Park, North Carolina).³⁹

Results

Descriptive Characteristics

The majority of our sample (71.1%) had a birthweight that was considered to be between the 10th and 90th percentiles for gestational age, and 50.0% of the neonates were male (Table 1). In addition, 43.9% of the women were non-Hispanic white, 12.1% were non-Hispanic black, and 36.8% were Hispanic. A majority of the women did not smoke (87.1%) or report consuming alcohol (58.0%) in the 3 months prior to pregnancy.

In the total sample, males had a mean birthweight of 3309 g and females had a mean birthweight of 3224 g (Table 2). On average, males had larger minimum placental diameters (males: 16.63, standard error [SE]: 0.12; females: 16.29, SE: 0.11; *P* < .05), while females had larger differences in diameters (males: 3.14, SE: 0.13; females: 3.61, SE: 0.13; *P* < .01). There were no differences in the placentas of males and females with respect to the other features of placental morphology. When differences by birthweight for gestational age category were evaluated, at least 1 group (SGA, AGA, and LGA) was statistically significantly different from the other groups for placental weight, maximum diameter, minimum diameter, and surface area. These characteristics generally increased with increasing birthweight for gestational age category. Results stratified by both sex and fetal size for gestational age category were similar when restricted to term births (Table S2).

Birthweight Analysis

In a model including all placental variables of interest (model 2), reduced thickness and smaller surface area were associated with reduced birthweight in the total (Figure 2) and term (Figure 3) samples (Table S3). After adjustment for covariates (model 3), reduced thickness and smaller surface area remained associated with lower birthweight, although estimates of association were attenuated. Among term births, abnormal shape was additionally associated with lower birthweight (Figure 3 and Table S3). Difference in diameters and umbilical cord insertion site were not associated with birthweight. Surface area had the largest impact on birthweight. In the total sample, a neonate with a placenta in the 25th percentile for surface area is expected to have a birth-weight 260.2 g lower than a neonate with a placenta in the 75th percentile (95% confidence interval [CI], -299.9 to -220.6). In comparison, a neonate with a placenta in the 25th percentile for thickness is expected to have a birthweight 82.8 g lower than a neonate with a placenta in the 75th percentile (95% CI, -117.9 to -47.7). There was no statistically significant interaction between sex and any of the features of placental morphology. When placental thickness and surface area were evaluated in a model additionally containing placental findings indicative of developmental disorders, inflammatory disorders, maternal vascular malperfusion, and fetal vascular malperfusion, estimates of association for thickness and surface area were consistent with estimates obtained in models not taking these abnormalities into account (Table S4).

In a model containing maximum diameter, minimum diameter, and thickness, all 3 placental characteristics were significantly associated with birthweight (Figure S1 and Table S5). In the total sample, a thin placenta (25th vs 75th) is associated with a birthweight 90.0 g lower than a thick placenta (95% CI, -123.6 to -56.3). Similarly, a smaller maximum diameter is associated with a reduction in birthweight (-103.4 g; 95% CI, -136.5 to -70.2). Minimum diameter exhibited a larger magnitude of association; a smaller minimum diameter was associated with a reduction in birthweight of 174.5 g (95% CI, -217.2, -131.9). These associations were not significantly different for males and females.

SGA Analysis

The observed associations in the linear models of birth-weight were mirrored by changes in the risk of SGA (Figure 4 and Table S6). In the total sample, reduced surface area (25th vs 75th) was associated with increased risk of SGA as compared to AGA in a model adjusted for covariates (odds ratio [OR]: 3.1; 95% CI, 2.2 to 4.5). In addition, reduced surface area was associated with lower risk of LGA as compared to AGA (OR: 0.5; 95% CI, 0.4 to 0.7). A similar relationship was observed with placental thickness for SGA and LGA compared to AGA; however, the magnitude of the association was smaller. The other placental variables were not associated with risk of SGA or LGA as compared to AGA.

Discussion

We found that gross placental features, particularly thickness and surface area, were associated with birthweight. Our results indicate that these features of placental morphology may independently contribute to birthweight. Adjustment for confounders, including

gestational age and maternal body size, reduced observed associations by nearly half. In addition, adjustment for characteristics indicative of placental developmental disorders, inflammatory disorders, maternal vascular malperfusion, and fetal vascular malperfusion did not affect the observed associations for placental thickness and surface area. Moreover, we did not observe evidence of interaction between placental morphology and sex. The results of the linear and logistic models were similar, which supports the robustness of the observed relationships.

Only 1 other study explored sex-specific differences in the relationships between the features of placental morphology and birthweight. These authors used multivariate adaptive regression splines and reported that the relationships of surface area and thickness with birth-weight are different for males and females and that the differences depend on the size of the placental characteristic.²⁵ Specifically, the authors reported that the relationships differed for higher *z* scores of thickness and surface area. Higher *z* scores may reflect greater gestational ages, which is inconsistent with our null findings of interaction among term births. Our null findings may be due the use of linear models, which do not allow the interaction between males and females to differ based on the size of the placental characteristic. However, our null results may also be explained by adjustment for additional confounders, including gestational age.

Our results for the overall associations between placental morphology and birthweight were consistent with available data, although differences in samples studied and analytic methods used make direct comparisons challenging. To our knowledge, only 2 studies have evaluated the independent contributions of the features of gross placental morphology in relation to birthweight in models adjusted for covariates.^{29,30} Grandi et al. found no association between a 1-cm increase in thickness and birthweight (β : 17.1; 95% CI, -30.7 to 65.1).²⁹ However, the data from Grandi et al. were based on a study conducted in Argentina, and the placentas in this sample appear to be thicker (mean: 3.0 cm) with a smaller surface area (mean: 164.8 cm²), which may explain the conflicting results. In contrast, Salafia et al. reported that for every 1 cm increase in thickness, birthweight increases by 213.7 g (95% CI, 202.5 to 224.8) in a model adjusted for gestational age, parity, and sex, which is double the magnitude of our findings (equivalent comparison in our study: 97.4 g; 95% CI, 56.1 to 138.7).³⁰ Salafia et al. also reported that for every 10 cm² increase in surface area, birthweight increases by 41.9 g (95% CI, 40.8 to 42.9; equivalent comparison in our study: 31.3 g; 95% CI, 26.5 to 36.0).³⁰ The smaller associations that we observed may be due to our ability to adjust for additional confounders, including maternal body size and gestational diabetes, which are related to both birthweight and placental size.^{27,28} Several groups have reported no correlation between umbilical cord insertion and birthweight, which is consistent with our results.^{18,19,21} To our knowledge, no studies have evaluated difference in diameters and abnormal shape in relation to birthweight in models adjusted for confounders. However, in evaluating placental shape as the ratio of longest and shortest diameters, Salafia et al. reported no association with birthweight, which is consistent with our results.³⁰

Our findings that surface area and thickness have the largest association with birthweight are consistent with other studies reporting a positive relationship between placental weight and

birthweight.²⁰ In addition, in a supplemental analysis of trimmed placental weight, we found that the estimated association between placental weight and birth weight was comparable to the sum of the associations for surface area and thickness (Table S7). Furthermore, placental weight was positively correlated ($r = .64$; $P < .01$) with estimated placental volume (thickness $\times$ surface area). Surface area and thickness both contribute to placental weight, which is commonly evaluated because it is easy to measure and readily available in existing data sets. However, a limitation of using placental weight is that it is dependent on several factors, including if the cord and membranes are trimmed, timing of cord clamping, time between delivery and weighing, and how the placenta is stored prior to weighing.^{40,41} Evaluating specific components of size, such as surface area and thickness, may be more informative, as these components develop during different periods of gestation and may reflect different mechanisms that have independent effects on birthweight.^{12,29}

One concern with modeling multiple measures from the same placenta is interdependence of the measures. Although the correlation coefficients between some placental variables, such as thickness and surface area, were statistically significant ($P < .05$), the magnitudes of the correlations were small, with none exceeding 0.2, suggesting that collinearity is not a concern. Weak correlations between placental characteristics are consistent with available data.⁹

Another concern with this analysis is how the placental variables were defined. Dichotomization of placental shape may not adequately reflect the variation in this measure and is subject to pathologist classification. Abnormally shaped placentas likely represent a heterogeneous group with different etiologies. Furthermore, our measures of surface area, difference in diameters, and umbilical cord insertion site assume an elliptical shape and may not be appropriate for use in abnormal shapes. However, excluding placentas with abnormal shapes did not modify the results or our conclusions (results not shown). Similarly, we modeled thickness as a continuous variable, which may not capture the adverse associations that have been reported with both thick and thin placentas, or with placentas of variable thickness. In modeling and graphical evaluations, thickness did not demonstrate a gross violation of the linearity assumption, and modeling nonlinear relationships did not meaningfully improve model fit (Figure S2). Furthermore, our adjusted models control for factors that may influence the potential nonlinear relationship, such as preeclampsia.

Another limitation is that the placental measures were obtained at delivery. The placenta is a dynamic organ, and studies have shown that it has the ability to adapt and compensate in the presence of stressors.⁸ Thus, we cannot determine whether the placental measures reflect an adaptive response to a poor intrauterine environment, whether they influence the development of a poor intrauterine environment, or a combination of these. Ongoing longitudinal studies as part of the Human Placenta Project should further inform the relationship between placental function and fetal growth.

Strengths of this analysis include the use of a large data set with detailed information on maternal and pregnancy characteristics. This facilitated control for covariates affecting both placental and fetal development and allowed us to investigate sex-specific differences in the associations. Gestational age was also determined from ultrasound measures, which allows

for improved control of this important confounder in comparison to studies using last menstrual period.⁴² In addition, placental examinations were conducted by trained pathologists using a standard protocol to ensure consistent data collection. We also accounted for selection bias related to differences in those who did not consent to a placental examination and for whom the placental examination was incomplete. A focus on gross placental morphology is also a strength, as these features can be ascertained during routine ultrasound scans.⁴³

Although our results do not suggest sex-specific differences in the associations between birthweight and placental measures at delivery, we found that reduced thickness and surface area were associated with lower birthweight. Furthermore, these results were independent of placental characteristics indicative of developmental and inflammatory disorders and of maternal and fetal vascular malperfusion. Specifically, surface area had the strongest association with birthweight. This suggests that the number of spiral arteries supplying the placenta may be a key contributor to fetal growth and development.¹⁰ Future studies should adjust for potential confounders when evaluating relationships between placental size and fetal size, as adjustment for confounding related to maternal and pregnancy characteristics reduced the magnitudes of the reported associations. Future studies should also consider the adaptability of the placenta and focus on determining the directionality of these associations. This includes evaluating serial placental images throughout pregnancy to track placental development and adaptation, which may allow for improved detection of sex-specific differences in these processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study enrollment and inclusion.

Figure 2.

Estimated changes in birthweight associated with changes in the features of placental morphology of interest using weighted linear regression in the total sample. ^aModel 1 contains each placental variable modeled individually (4 separate models). ^bModel 2 contains all placental variables modeled together. ^cModel 3 contains placental variables and covariates (maternal age, education, maternal race/ethnicity, smoking, prepregnancy weight, height, gestational hypertension, gestational diabetes, parity, gestational age, and sex). ^dModel 4 contains placental variables, covariates (maternal age, education, maternal race/ethnicity, smoking, prepregnancy weight, height, gestational hypertension, gestational diabetes, parity, gestational age, and sex), and interaction between placental variables and sex.

Figure 3.

Estimated changes in birthweight associated with changes in the features of placental morphology of interest using weighted linear regression, restricted to term births. ^aModel 1 contains each placental variable modeled individually (4 separate models). ^bModel 2 contains all placental variables modeled together. ^cModel 3 contains placental variables and covariates (maternal age, education, maternal race/ethnicity, smoking, prepregnancy weight, height, gestational hypertension, gestational diabetes, parity, gestational age, and sex). ^dModel 4 contains placental variables, covariates (maternal age, education, maternal race/ethnicity, smoking, prepregnancy weight, height, gestational hypertension, gestational diabetes, parity, gestational age, and sex), and interaction between placental variables and sex.

Figure 4.

Estimated odds ratios for small for gestational age (<10th percentile) and large for gestational age (>90th percentile) as compared to AGA (10th–90th percentile) for the features of placental morphology of interest using weighted logistic regression in the total sample. AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age. ^aModel 1 contains each placental variable modeled individually (5 separate models). ^bModel 2 contains all placental variables modeled together. ^cModel 3 contains placental variables and covariates (maternal age, gestational hypertension, and gestational diabetes).

Table 1.

Descriptive Characteristics of Singleton Live Births With a Completed Placental Examination for the Total Sample and Term Births.

Characteristic	Total	Term
	N _w (% _w) N = 1229 N _w = 955	N _w (% _w) N = 953 N _w = 864
Adjusted birthweight percentile ^a		
<5th percentile	91 (9.6)	75 (8.7)
5th-10th percentile	61 (6.4)	54 (6.3)
10th-90th percentile	676 (71.1)	627 (72.9)
90th-95th percentile	50 (5.2)	44(5.1)
95th-100th percentile	73 (7.7)	61 (7.1)
Gestational age		
20—23 completed weeks	3 (0.4)	0 (0.0)
24—27 completed weeks	6 (0.6)	0 (0.0)
28–31 completed weeks	9 (0.9)	0 (0.0)
32–36 completed weeks	73 (7.7)	0 (0.0)
37 completed weeks	864 (90.4)	864 (100.0)
Neonate sex, male	478 (50.0)	422 (48.9)
Primiparae	332 (34.8)	303 (35.1)
Maternal age		
<20	100 (10.5)	89 (10.3)
20–34	720 (75.4)	652 (75.5)
35–39	110 (11.6)	101 (11.7)
40+	24 (2.5)	21 (2.5)
Maternal race/ethnicity		
Non-Hispanic white	419 (43.9)	396 (45.8)
Non-Hispanic black	116 (12.1)	98 (11.3)
Hispanic	351 (36.8)	306 (35.5)
Other	69 (7.2)	64 (7.4)
Maternal education		
0—11 (none/primary/some secondary)	172 (18.1)	154 (17.9)
12 (completed secondary)	257 (27.0)	224 (26.0)
13 +(college)	521 (54.8)	483 (56.1)
Marital status		
Not married or cohabitating	146 (15.4)	127 (14.7)
Cohabitating	223 (23.4)	202 (23.4)
Married	584(61.2)	535 (61.9)
Maternal BMI, kg/m ²		
< 18.5	26 (2.7)	25 (2.9)
18.5–24.9	479 (50.5)	439 (50.8)

Characteristic	Total	Term
	N _w (% _w) N = 1229 N _w = 955	N _w (% _w) N = 953 N _w = 864
25–29.9	218 (23.0)	199 (23.0)
30–34.9	117 (12.4)	101 (11.7)
35	108 (11.4)	100 (11.6)
Pregestational hypertension	58 (6.1)	47 (5.5)
Preeclampsia/hypertension	88 (9.4)	68 (7.9)
Diabetes (type 1 or 2)	16 (1.7)	12 (1.4)
Gestational diabetes	79 (8.3)	73 (8.4)
Insurance		
No insurance	41 (4.3)	38 (4.4)
Any public/private insurance	475 (49.8)	410 (47.5)
VA/commercial health insurance/HMO	439 (45.9)	416 (48.1)
Periconceptional maternal smoking ^b		
Did not smoke	830 (87.1)	752 (87.2)
< 10 cigarettes/day	61 (6.4)	54 (6.2)
10 cigarettes/day	61 (6.5)	57 (6.6)
Periconceptional alcohol use ^c		
Did not drink	551 (58.0)	497 (57.8)
Drank, no bingeing	224 (23.6)	202 (23.5)
Binged	174 (18.3)	160 (18.6)
Illicit drug use ^d		
Never used drugs	670 (71.5)	615 (72.0)
Ever used drugs without addiction	247 (26.3)	221 (25.9)
Ever used drugs with addiction	20 (2.1)	18 (2.1)

Abbreviations: BMI, body mass index; HMO, Health Maintenance Organization; N_w, sample size weighted to reflect differential consent, enrollment, and placental examination (rounded to the nearest whole number); VA, Veterans Affairs.

^aBased on Bukowski et al.^{37,38}

^bAverage number of cigarettes per day during 3 months prior to pregnancy.

^cAlcohol consumption during 3 months prior to pregnancy (drank, no bingeing defined as 0–6 drinks in a typical week and no binge [4 or more drinks consumed in a single time period]; binged defined as at least 1 binge and/or 7 or more drinks in a typical week).

^dLifetime drug use.

Table 2.

Descriptive Characteristics for Birthweight and Placental Morphology Stratified by Neonate Sex and Birthweight for Gestational Age Category for the Total Sample.

Characteristic	Sex		Birthweight for Gestational Age Category			
	Male N = 619 N _w = 481	Female N = 610 N _w = 478	SGA N = 217 N _w = 152	AGA N = 841 N _w = 676	LGA N = 161 N _w = 123	
Mean (SE) or %w						
Birthweight, g ^{†††}	3308.55 (27.13)	3224.02 (22.80)	2634.13 (37.67)	3304.82 (15.25)	3834.78 (43.55)	
Placental weight, g ^{†††}	442.51 (4.83)	443.71 (4.74)	367.02 (7.93)	445.42 (3.57)	525.85 (9.08)	
Fetal-placental weight ratio	7.63 (0.07)	7.48 (0.07)	7.45 (0.14)	7.59 (0.05)	7.48 (0.12)	
Maximum diameter, cm ^{†††}	19.77 (0.15)	19.90 (0.14)	18.48 (0.29)	19.87 (0.12)	21.21 (0.24)	
Minimum diameter, cm ^{*,†††}	16.63 (0.12)	16.29 (0.11)	14.97 (0.18)	16.55 (0.09)	17.68 (0.20)	
Thickness, cm	2.38 (0.03)	2.43 (0.03)	2.35 (0.06)	2.40 (0.02)	2.52 (0.06)	
Surface area, cm ² ^{†††}	261.10 (3.40)	257.26 (3.06)	219.42 (5.08)	260.58 (2.60)	296.79 (5.58)	
Difference in diameters, cm ^{**}	3.14 (0.13)	3.61 (0.13)	3.51 (0.28)	3.32 (0.11)	3.54 (0.24)	
Shape, abnormal	44 (9.4%)	51 (10.7%)	18 (12.1%)	61 (9.1%)	16 (12.7%)	
Cord insertion, abnormal	0.54 (0.01)	0.52 (0.01)	0.54 (0.02)	0.53 (0.01)	0.51 (0.02)	

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; N_w, weighted sample size; SE, standard error; SGA, small for gestational age.

^{*} Statistically significant difference ($P < 0.05$) in the characteristic between males and females (P value from t test or Wald χ^2).

^{**} Statistically significant difference ($P < 0.01$) in the characteristic between males and females (P value from t test or Wald χ^2).

^{†††} At least 1 group (SGA, AGA, and LGA) is statistically significantly different ($P < 0.001$; P values from 1-way ANOVA or Wald χ^2).