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Original Article

Racial disparity in placental pathology in the collaborative perinatal project

Yan Chen[1,2], Lisu Huang[1,3], Huijuan Zhang[4], Mark Klebanoff[5], Zujing Yang[6], Jun Zhang[1]

[1]MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [2]Department of Neonatology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [3]Department of Pediatrics, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [4]Departments of Pathology and Bio-Bank, The International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [5]Department of Pediatrics, Nationwide Children's Hospital, College of Medicine, The Ohio State University, Columbus, Ohio, U.S; [6]Department of Obstetrics, Xin Hua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

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Abstract: Objective: There is substantial disparity in perinatal outcomes between white and African-American women, but the underlying biological mechanisms are poorly understood. The placenta is the principal metabolic, respiratory, excretory, and endocrine organ of the fetus. We studied the association between maternal race and types and severity of placental pathology. Methods: Using data from the U.S. Collaborative Perinatal Project (1959-1966), we studied 32,295 African-American and white women with singleton births. CPP pathologists conducted detailed placental examinations following a standard protocol with quality control procedures. Logistic regression modeling was used to test the association between race and placental pathology adjusting for potential confounders. Results: Compared to white women, African-American women had a higher risk of fetal neutrophilic infiltration (adjusted odds ratio [aOR], 1.2; 95% confidence interval [CI], 1.0-1.4), and 1.5-fold higher risk of low placental weight (95% CI, 1.3-1.7). However, various placental vascular lesions were significantly less common in African-American women, including infarcts and thrombosis in the cut surface, villous infarcts in the intervillous space, emergence of stromal fibrosis and Langerhans layer in the terminal villi, old hemorrhage in the maternal surface, thrombosis in the intervillous space, and calcification throughout the cut surface (aOR ranging from 0.5 to 0.8). Similar patterns were observed in pregnancies with pregnancy associated hypertension, small-for-gestational-age, and preterm birth. Conclusion: As compared with white women, African-American had higher prevalence of inflammatory lesions but lower prevalence of vascular lesions in placental pathology.

Keywords: Race, placental pathology, pregnancy associated hypertension, small for gestational age, preterm birth

Introduction

As compared with white women, African-American women have higher risks of pregnancy complications including hypertensive disorders of pregnancy, fetal growth restriction, fetal death, preterm birth and other morbidities [1, 2]. For example, African-American women are 2-3 times as likely as white women to experience an intrauterine fetal death or infant death [3, 4], and 1.5-2.5 fold greater risk of delivering a preterm or very preterm infant [5]. Adjustment for sociocultural differences, maternal age, education, prenatal care and obstetric history as well as other perinatal factors does not fully account for the higher incidence of these adverse pregnancies and birth outcomes in African-American women [6]. Despite decades of study, little is known about the biological mechanism of racial disparity in adverse birth outcomes [3].

The placenta is the principal metabolic, respiratory, excretory, and endocrine organ of the fetuses, and several pregnancy complications may originate from the placenta [7]. There are

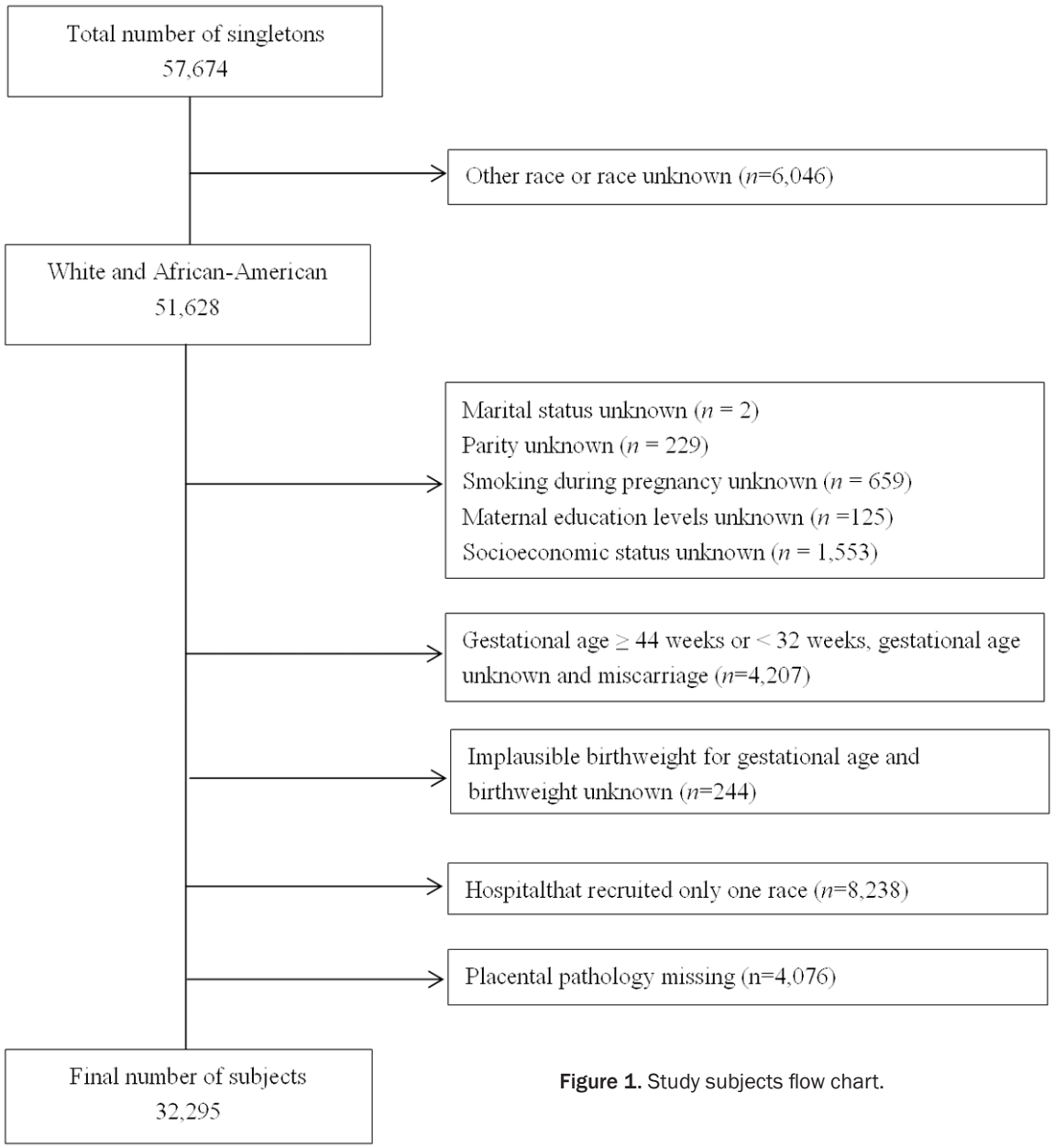

Figure 1. Study subjects flow chart.

substantial molecular variations across the fetal and maternal compartment and may affect birth weight even after adjustment for placental weight [8]. We used data from the Collaborative Perinatal Project (CPP), a large prospective cohort, to explore this issue [9-11].

Materials and methods

Population and study design

The CPP was a prospective cohort study that recruited pregnant women from 1959 to 1966 at 12 university-based academic centers across the US. Study data files, with identifying information removed, are publicly available. The CPP was originally designed to examine perinatal risk factors for neurologic disorders in children. A detailed description of the study has been provided elsewhere [12]. Women were enrolled at their first prenatal visit, at a mean gestation of 21.3 ± 8.4 (SD) weeks by last menstrual period, which formed the basis of gestational age estimation in the CPP. In-depth demographic, socioeconomic and behavioral information was collected by in-person inter-

Table 1. Maternal characteristics by race in the Collaborative Perinatal Project, 1959-1966

Characteristics	White	Black	P
N	17,662	14,633	
Maternal age (year)			< 0.0001
< 20	2,960 (16.8)	4,026 (27.5)	
20-25	6,866 (38.9)	4,848 (33.1)	
25-30	4,152 (23.5)	2,894 (19.8)	
30-35	2,233 (12.6)	1,710 (11.7)	
≥ 35	1,451 (8.2)	1,155 (7.9)	
Married	15,722 (89.0)	9,261 (63.3)	< 0.0001
Maternal education levels (year)			< 0.0001
Less than high school (≤ 9)	4,133 (23.4)	4,076 (27.9)	
High school (10-12)	10,071 (57.0)	9,852 (67.3)	
College and above (> 12)	3,458 (19.6)	705 (4.8)	
Socioeconomic status			< 0.0001
1 (Lowest)	492 (2.8)	1,436 (9.8)	
2	3,351 (19.0)	5,607 (38.3)	
3	5,231 (29.6)	5,089 (34.8)	
4	5,109 (28.9)	2,128 (14.5)	
5 (Highest)	3,479 (19.7)	373 (2.6)	
Parity			< 0.0001
0	5,548 (31.4)	3,968 (27.1)	
1	4,492 (25.4)	3,049 (20.8)	
≥ 2	7,622 (43.2)	7,616 (52.1)	
Smoking during pregnancy	9,551 (54.1)	6,660 (45.5)	< 0.0001
Maternal pre-pregnancy BMI (kg/m^2)			< 0.0001
< 18.5	3,597 (20.4)	1,624 (11.1)	
18.5-25	11,142 (63.1)	9,003 (61.5)	
25-30	1,999 (11.3)	2,600 (17.8)	
≥ 30	924 (5.2)	1,406 (9.6)	
Stillbirth	149 (0.8)	150 (1.0)	< 0.0001
Birth weight (g)			< 0.0001
< 2500	1,183 (6.7)	1,694 (11.6)	
2500-2999	3,563 (20.2)	4,380 (29.9)	
3000-3499	7,096 (40.2)	5,814 (39.7)	
3500-3999	4,534 (25.7)	2,279 (15.6)	
≥ 4000	1,286 (7.3)	466 (3.2)	
Gestational age (week)			< 0.0001
32-36	1,505 (8.5)	2,564 (17.5)	
37-41	13,787 (78.1)	10,538 (72.0)	
42-44	2,370 (13.4)	1,531 (10.5)	
Small for gestational age	1,575 (10.3)	1,381 (10.5)	0.5076
Pregnancy associated hypertension	3,445 (19.6)	3,443 (23.6)	< 0.0001
Chronic hypertension	1,136 (6.4)	1,573 (10.8)	0.0002
Gestational diabetes	221 (1.3)	119 (0.8)	0.0002
Pre-pregnancy diabetes	400 (2.3)	149 (1.0)	< 0.0001

view at entry. Obstetrical factors such as hypertensive disorders and diabetes were determined by the medical staff taking care of the woman, and at the conclusion of the pregnancy, all diagnoses were reviewed and confirmed against pre-specified criteria by a senior study obstetrician at each site. Following delivery, placental gross morphology was examined and samples were collected for histological examination. Gross and microscopic examinations were conducted by trained pathologists according to a standard protocol [13].

There were 57,674 singleton pregnancies, of which 51,628 were to white or African-American women (**Figure 1**). Pregnancies ending in spontaneous abortion and those without information on maternal age, parity, marital status, education, smoking, or socioeconomic status were also excluded (n = 2,568). Because gestational age by menstrual dating is often inaccurate in early preterm and extremely postterm births [14, 15], we excluded pregnancies with nominal gestational age at delivery of < 32 or > 43 completed weeks. Pregnancies with missing birth weight or gestational age, and those with implausible combinations of birth weight and gestational age were also excluded. Three of the 12 CPP centers recruited either few or no white, or few or no African-American women. Since there might be subtle differences in patient demographic char-

Table 2. Placental pathological lesions by race in the Collaborative Perinatal Project, 1959-1966

Placenta pathological lesions	White Race	African-American	Crude OR	Adjusted OR[1]	Adjusted OR[2]
N (%)	17,662 (54.7)	14,633 (45.3)	/	/	/
Placental weight					
Placental weight < 10th	1,388 (7.9)	1,828 (12.5)	**1.7 (1.6, 1.8)**	**1.5 (1.4, 1.7)**	**1.5 (1.3, 1.7)**
PBW ratio > 90th	1,687 (9.6)	1,752 (12.0)	**1.3 (1.2, 1.4)**	**1.2 (1.1, 1.4)**	**1.2 (1.1, 1.4)**
Vascular lesions of maternal origin					
Infarcts in the cut surface					
Occurrence of vascular infarcts	3,049 (17.3)	1,520 (10.4)	**0.6 (0.5, 0.6)**	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Infarct size	795 (4.5)	349 (2.4)	**0.5 (0.4, 0.6)**	**0.7 (0.6, 0.9)**	**0.7 (0.6, 0.9)**
Number of infarcts	1,056 (6.0)	422 (2.9)	**0.5 (0.4, 0.5)**	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Thrombosis in the cut surface	1,427 (8.1)	403 (2.8)	**0.5 (0.4, 0.5)**	**0.8 (0.7, 0.8)**	**0.8 (0.7, 0.9)**
Vessel fibroid in the decidua	368 (2.1)	245 (1.7)	0.9 (0.7, 1.0)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)
Villous lesions of maternal origin					
Villous infarcts in the intervillous space	2,578 (14.6)	2,080 (14.2)	1.0 (0.9, 1.0)	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Syncytium-Nuclear clumping in the decidua	508 (3.2)	203 (1.5)	**0.5 (0.4, 0.6)**	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)
Vascular lesions of fetal origin	160 (0.9)	133 (0.9)	1.0 (0.8, 1.3)	1.3 (0.9, 1.9)	1.2 (0.8, 1.8)
Villous lesions of fetal origin					
Stromal fibrosis in the terminal villi	336 (1.9)	138 (0.9)	**0.5 (0.4, 0.6)**	**0.7 (0.5, 0.9)**	**0.7 (0.5, 0.9)**
Langerhans layer in the terminal villi	142 (0.8)	83 (0.6)	**0.7 (0.5, 1.0)**	**0.5 (0.3, 0.8)**	**0.5 (0.3, 0.8)**
Marginal insertion of cord	874 (5.0)	442 (3.0)	**0.6 (0.5, 0.7)**	**0.7 (0.6, 0.8)**	**0.7 (0.6, 0.8)**
Calcification throughout the cut surface	2,072 (11.7)	1,470 (10.1)	**0.5 (0.5, 0.5)**	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Hemorrhage					
Occurrence of hemorrhage	1,480 (8.4)	858 (5.9)	0.7 (0.6, 0.8)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)
Old hemorrhage in the maternal surface	1,408 (8.0)	562 (3.8)	**0.2 (0.2, 0.3)**	**0.6 (0.4, 0.9)**	**0.6 (0.4, 0.8)**
Thrombosis in the intervillous space	2,404 (13.6)	965 (6.6)	**0.4 (0.4, 0.5)**	**0.7 (0.7, 0.8)**	**0.7 (0.7, 0.9)**
Inflammatory cell infiltration					
Fetal neutrophilic infiltration	878 (5.0)	747 (5.1)	1.0 (0.9, 1.1)	**1.2 (1.0, 1.4)**	**1.1 (1.0, 1.4)**
Maternal neutrophilic infiltration	1,338 (7.6)	1,401 (9.6)	**1.3 (1.2, 1.4)**	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)
Maternal lymphocytic infiltration	142 (0.8)	176 (1.2)	**1.5 (1.2, 1.9)**	1.3 (0.9, 1.9)	**1.7 (1.1, 2.5)**
Meconium	1,059 (6.0)	1,481 (10.1)	**1.8 (1.6, 1.9)**	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)

PBW ratio: Placenta-to-birth weight ratio. Crude OR. Unadjusted logistic model. Reference group: white race. Adjusted OR[1]. Logistic model adjusted for maternal age, educations, marital status, parity, socioeconomic status, gestational age, pre-pregnancy body mass index, and study center. Adjusted OR[2]. Women with pregnancy associated hypertension and diabetes excluded. Bold font: $P < 0.05$.

acteristics, clinical management and diagnoses, and pathological examinations within each site (in spite of the standard protocol), these 3 sites were excluded, as adjustment is not possible when all women in that hospital are of one or the other race. Finally, there were 32,295 women with placental pathology available for analysis, which represents 88.8% of women who were otherwise eligible for this study.

Covariates

Maternal characteristics that may affect the association between race and placental pathology were considered as potential confounders in this study, including maternal age (< 20, 20-25, 25-30, 30-35, and ≥ 35 years); marital status (married/unmarried); education (< 9, 10-12 and > 12 years); number of previous deliveries (0, 1 and ≥ 2); smoking during pregnancy (yes/no); pre-pregnancy diabetes (yes/no); gestational diabetes (yes/no); pre-pregnancy BMI (underweight, normal, overweight, and obesity) [16], and socioeconomic status (1-5 grades from lowest to highest) [17]. Small-for-gestational-age (SGA) was defined as birth weight less than the 10th percentile for gestational week and race [18].

As previously published by us, pregnancy associated hypertension (PAH), including pre-eclampsia and eclampsia, was defined as mild hypertension (diastolic blood pressure ≥ 90 mmHg but < 110 mmHg) on two occasions or severe hypertension (diastolic blood pressure ≥ 110 mmHg) on one occasion from 25 weeks of gestation to 4 weeks postpartum without renal disease or gestational proteinuria, excluding cases where mild hypertension occurred for the first time during labor and delivery or post-

Table 3. Placental pathological lesions by race in women with pregnancy associated hypertension, the Collaborative Perinatal Project, 1959-1966

Placenta pathological lesions	White Race	African-American	Crude OR	Adjusted OR
N (%)	3,445 (50.0)	3,443 (50.0)	/	/
Placental weight				
Placental weight < 10th	276 (8.0)	432 (12.6)	**1.6 (1.4, 1.9)**	**1.5 (1.2, 2.0)**
PBW ratio > 90th	315 (9.2)	403 (11.8)	**1.3 (1.1, 1.5)**	1.2 (0.9, 1.5)
Vascular lesions of maternal origin				
Infarcts in the cut surface				
Occurrence of vascular infarcts	781 (22.7)	430 (12.5)	**0.5 (0.4, 0.6)**	**0.8 (0.7, 1.0)**
Infarct size	203 (5.9)	97 (2.8)	**0.5 (0.4, 0.6)**	0.7 (0.5, 1.0)
Number of infarcts	305 (8.9)	132 (3.9)	**0.4 (0.3, 0.5)**	0.8 (0.6, 1.1)
Thrombosis in the cut surface	351 (10.2)	91 (2.6)	**0.2 (0.2, 0.3)**	**0.6 (0.4, 0.8)**
Vessel fibroid in the decidua	74 (2.2)	51 (1.5)	0.7 (0.5, 1.0)	0.9 (0.5, 1.5)
Villous lesions of maternal origin				
Villous infarcts in the intervillous space	572 (16.6)	463 (13.5)	**0.8 (0.7, 0.9)**	**0.7 (0.6, 0.9)**
Syncytium-Nuclear clumping in the decidua	131 (4.1)	59 (1.8)	**0.4 (0.3, 0.6)**	0.7 (0.4, 1.1)
Vascular lesions of fetal origin	33 (1.0)	35 (1.0)	1.1 (0.7, 1.7)	1.9 (0.9, 3.9)
Villous lesions of fetal origin				
Stromal fibrosis in the terminal villi	78 (2.3)	36 (1.1)	**0.3 (0.1, 0.9)**	0.3 (0.1, 1.3)
Langerhans layer in the terminal villi	28 (0.8)	15 (0.4)	0.7 (0.2, 3.3)	0.8 (0.1, 10.0)
Marginal insertion of cord	177 (5.2)	99 (2.9)	**0.6 (0.3, 0.9)**	0.6 (0.3, 1.2)
Calcification throughout the cut surface	397 (11.5)	356 (10.4)	**0.5 (0.4, 0.7)**	**0.5 (0.3, 0.7)**
Hemorrhage				
Occurrence of hemorrhage	317 (9.2)	184 (5.3)	**0.6 (0.5, 0.7)**	0.8 (0.6, 1.1)
Old hemorrhage in the maternal surface	318 (9.2)	124 (3.6)	**0.4 (0.3, 0.5)**	**0.6 (0.5, 0.8)**
Thrombosis in the intervillous space	541 (15.7)	220 (6.4)	**0.4 (0.3, 0.4)**	**0.6 (0.5, 0.8)**
Inflammatory cell infiltration				
Fetal neutrophilic infiltration	173 (5.0)	188 (5.5)	1.1 (0.9, 1.4)	**1.5 (1.1, 2.1)**
Maternal neutrophilic infiltration	237 (6.9)	326 (9.5)	**1.4 (1.2, 1.7)**	1.1 (0.9, 1.5)
Maternal lymphocytic infiltration	34 (1.0)	36 (1.1)	1.1 (0.7, 1.7)	0.6 (0.3, 1.3)
Meconium	211 (6.1)	412 (12.0)	**2.1 (1.8, 2.5)**	1.2 (0.9, 1.5)

PBW ratio: Placenta-to-birth weight ratio. Crude OR. Unadjusted logistic model. Reference group: white race. Adjusted OR. Logistic model adjusted for maternal age, education, marital status, parity, socioeconomic status, prepregnancy body mass index, gestational age, and study center. Bold font: $P < 0.05$.

partum [19]. The diagnosis was based on the actual blood pressure values as recorded in the data files, rather than on diagnostic summaries completed at the time. While our definition is not identical to the one in current use, it has similar characteristics to the modern definition, as we have previously published [20].

Placental sample collection

Pathologists first conducted a gross examination of the freshly delivered placenta. A full-thickness placental sample was taken from a representative block of the central portion of tissue 3-4 cm from the cord insertion. One umbilical cord sample, one membrane roll sample, and any significant gross abnormalities were also taken for microscopic examination. Pathologists conducting the placental examinations were blinded to the clinical course for 98% of gross and 97% of microscopic examinations. We created dichotomous variables for placental pathological lesions defined by the presence of one or more of 10 pathologies identified on gross and microscopic examinations, including evidence of low placental weight, vascular lesions of maternal origin, villous changes of maternal origin, vascular lesions of fetal origin, villous changes of fetal origin, type of cord insertion, calcification throughout the cut surface, inflammatory cell infiltration, hemorrhage of the maternal sur-

Table 4. Placental pathological lesions by race in women with preterm delivery (32-36 weeks), the Collaborative Perinatal Project, 1959-1966

Placenta pathological lesions	White Race	African-American	Crude OR	Adjusted OR
N (%)	1,505 (37.4)	2,564 (62.6)	/	/
Placental weight				
Placental weight < 10th	250 (16.7)	533 (20.9)	**1.3 (1.1, 1.6)**	**1.3 (1.0, 1.7)**
PBW ratio > 90th	452 (30.2)	554 (21.7)	**0.6 (0.6, 0.7)**	0.8 (0.7, 1.0)
Vascular lesions of maternal origin				
Infarcts in the cut surface				
Occurrence of vascular infarcts	216 (14.4)	230 (9.0)	**0.6 (0.5, 0.7)**	0.8 (0.6, 1.1)
Infarct size	66 (4.4)	69 (2.7)	**0.6 (0.4, 0.8)**	**0.5 (0.3, 0.9)**
Number of infarcts	85 (5.7)	76 (3.0)	**0.5 (0.3, 0.7)**	**0.6 (0.3, 1.0)**
Thrombosis in the cut surface	101 (6.7)	56 (2.2)	**0.4 (0.3, 0.5)**	0.8 (0.6, 1.2)
Vessel fibroid in the decidua	56 (3.7)	47 (1.9)	0.7 (0.4, 1.0)	1.1 (0.6, 2.2)
Villous lesions of maternal origin				
Villous infarcts in the intervillous space	217 (14.4)	337 (13.2)	0.9 (0.8, 1.1)	1.0 (0.7, 1.4)
Syncytium-Nuclear clumping in the decidua	40 (3.5)	30 (1.4)	**0.4 (0.2, 0.6)**	0.6 (0.3, 1.3)
Vascular lesions of fetal origin	23 (1.5)	29 (1.1)	**1.0 (0.5, 1.8)**	1.0 (0.4, 2.6)
Villous lesions of fetal origin				
Stromal fibrosis in the terminal villi	41 (2.7)	31 (1.2)	**0.4 (0.2, 0.8)**	1.0 (0.4, 2.1)
Langerhans layer in the terminal villi	59 (3.9)	24 (0.9)	**0.2 (0.1, 0.4)**	**0.3 (0.1, 0.7)**
Marginal insertion of cord	84 (5.6)	96 (3.8)	**0.6 (0.5, 0.9)**	0.9 (0.5, 1.4)
Calcification throughout the cut surface	128 (8.5)	195 (7.6)	**0.6 (0.5, 0.8)**	0.8 (0.5, 1.2)
Hemorrhage				
Occurrence of hemorrhage	179 (11.9)	163 (6.4)	**0.6 (0.4, 0.7)**	0.9 (0.6, 1.3)
Old hemorrhage in the maternal surface	136 (9.0)	98 (3.8)	**0.2 (0.1, 0.4)**	0.6 (0.2, 1.7)
Thrombosis in the intervillous space	208 (13.8)	147 (5.7)	**0.4 (0.3, 0.5)**	0.7 (0.5, 1.0)
Inflammatory cell infiltration				
Fetal neutrophilic infiltration	91 (6.1)	227 (8.9)	**1.5 (1.2, 1.9)**	**1.7 (1.1, 2.4)**
Maternal neutrophilic infiltration	190 (12.6)	384 (15.0)	**1.2 (1.0, 1.5)**	1.1 (0.8, 1.4)
Maternal lymphocytic infiltration	16 (1.1)	37 (1.4)	1.4 (0.8, 2.5)	1.4 (0.6, 3.5)
Meconium	68 (4.5)	225 (8.8)	**2.2 (1.6, 3.0)**	1.1 (0.8, 1.7)

PBW ratio: Placenta-to-birth weight ratio. Crude OR. Unadjusted logistic model. Reference group: white women. Adjusted OR. Logistic model adjusted for maternal age, education, marital status, parity, socioeconomic status, pre-pregnancy body mass index, gestational age, and study center. Bold font: $P < 0.05$.

face, and meconium staining in the membranes or decidua [21-23] (**Appendix Table 1**). Low placental weight was defined as less than the 10th percentile for CPP placentas delivered at each gestational age. Placenta-to-birth weight ratio (PBW ratio) was defined as the ratio of placental weight to birth weight multiplied by 100%. High PBW ratio was defined as PBW ratio greater than the 90th percentile of CPP placentas at each gestational age.

Statistical analysis

We initially examined the differences in maternal characteristics between white and African-American women using the chi-square test. The association between race and placental pathology was evaluated by logistic regression. Model 1 presents the unadjusted association between race and placental pathology. Model 2 adjusted for maternal age, education, marital status, parity, socioeconomic status, gestational age, prepregnancy body mass index, and study center. Model 3 adjusted for the maternal characteristics mentioned above after excluding women with diabetes and hypertensive disorders. The association was also tested separately in women with PAH, preterm and small-for-gestational-age (SGA) births, respectively, adjusting for potential confounders.

Table 5. Placental pathological lesions by race in women with small-for-gestational-age infants, the Collaborative Perinatal Project, 1959-1966

Placenta pathological lesions	White Race	African-American	Crude OR	Adjusted OR
N	1,575 (53.3)	1,381 (46.7)	/	/
Placental weight				
Placental weight < 10th	559 (35.6)	605 (44.1)	**1.4 (1.2, 1.7)**	**1.5 (1.2, 1.9)**
PBW ratio > 90th	278 (17.7)	330 (24.0)	**1.5 (1.2, 1.8)**	1.1 (0.8, 1.4)
Vascular lesions of maternal origin				
Infarcts in the cut surface				
Occurrence of vascular infarcts	365 (23.2)	208 (15.1)	**0.6 (0.5, 0.7)**	0.8 (0.6, 1.1)
Infarct size	103 (6.6)	66 (4.8)	**0.7 (0.5, 1.0)**	1.1 (0.7, 1.8)
Number of infarcts	187 (10.7)	64 (4.4)	**0.4 (0.3, 0.5)**	0.8 (0.5, 1.3)
Thrombosis in the cut surface	125 (7.9)	37 (2.7)	**0.4 (0.3, 0.5)**	**0.7 (0.5, 0.9)**
Vessel fibroid in the decidua	64 (4.1)	30 (2.3)	**0.5 (0.3, 0.9)**	0.9 (0.4, 1.7)
Villous lesions of maternal origin				
Villous infarcts in the intervillous space	292 (18.5)	213 (15.4)	**0.7 (0.6, 0.9)**	0.8 (0.6, 1.1)
Syncytium-Nuclear clumping in the decidua	83 (6.1)	31 (2.6)	**0.4 (0.3, 0.6)**	1.1 (0.6, 2.0)
Vascular lesions of fetal origin	26 (1.7)	13 (0.9)	0.8 (0.4, 1.8)	1.0 (0.3, 3.2)
Villous lesions of fetal origin				
Stromal fibrosis in the terminal villi	60 (3.8)	30 (2.2)	**0.6 (0.4, 0.9)**	**0.4 (0.2, 0.8)**
Langerhans layer in the terminal villi	37 (2.4)	18 (1.3)	**0.5 (0.3, 1.0)**	**0.3 (0.1, 0.7)**
Marginal insertion of cord	119 (7.6)	64 (4.7)	**0.6 (0.4, 0.8)**	**0.6 (0.4, 0.9)**
Calcification throughout the cut surface	160 (10.2)	123 (8.9)	0.9 (0.7, 1.1)	0.8 (0.5, 1.1)
Hemorrhage				
Occurrence of hemorrhage	179 (11.4)	104 (7.5)	**0.7 (0.5, 0.9)**	1.1 (0.8, 1.7)
Old hemorrhage in the maternal surface	136 (8.6)	57 (4.1)	**0.3 (0.2, 0.6)**	0.9 (0.4, 2.3)
Thrombosis in the intervillous space	183 (11.6)	88 (6.4)	**0.5 (0.4, 0.7)**	0.8 (0.5, 1.2)
Inflammatory cell infiltration				
Fetal neutrophilic infiltration	85 (5.4)	102 (7.4)	1.4 (1.0, 1.9)	**2.0 (1.2, 3.2)**
Maternal neutrophilic infiltration	144 (9.1)	207 (15.0)	**1.8 (1.4, 2.2)**	**1.6 (1.1, 2.2)**
Maternal lymphocytic infiltration	105 (6.7)	152 (11.0)	**2.5 (1.2, 5.2)**	2.4 (0.7, 7.6)
Meconium	83 (6.8)	180 (10.8)	**1.6 (1.3, 2.2)**	0.9 (0.6, 1.3)

PBW ratio: Placenta-to-birth weight ratio. Crude OR. Unadjusted logistic model. Reference group: white women. Adjusted OR. Logistic model adjusted for maternal age, education, marital status, parity, socioeconomic status, prepregnancy body mass index, gestational age, and study center. Bold font: $P < 0.05$.

Results

A total of 14,633 African-American and 17,662 white women were included in this study (**Table 1**). Compared with white women, African-American women were younger and less educated, and had lower socioeconomic status. African-American women accounted for 63% of preterm deliveries, while white women accounted for 61% of post-term deliveries. PAH was also more prevalent in African-American women.

Table 2 shows that African-American women had 1.5-fold higher risk of low placental weight and a higher prevalence of fetal neutrophilic infiltration (aOR, 1.2; 95% CI, 1.0-1.4) after adjustment for potential confounders. On the contrary, the risks of most placental vascular lesions, including infarcts and thrombosis in the cut surface, villous infarcts in the inter-villous space, emergence of stromal fibrosis and Langerhans layer in the terminal villi, and calcification throughout the cut surface, were lower in African-American women. All of the odds ratios, ranging from 0.5 to 0.8, changed very slightly after adjustment for maternal characteristics and exclusion of women with PAH or diabetes.

Table 3 shows that placentas of white women with PAH were more likely to have severe vascular lesions than placentas of African-American women, including 1.5 to 2-fold higher occurrence of infarcts in the cut surface, thrombosis in the cut surface, and villous infarcts in the intervillous space. Although African-American women had higher risk of PAH, African-American women with PAH had lower prevalence of maternal original vascular and villous lesions. Among women with PAH, the occurrence of vascular infarcts in the cut surface was 10% lower in African-American women than among white women (aOR, 0.8; 95% CI, 0.7-1.0). This pattern of a lower risk of vascular lesions and a higher risk of neutrophilic infiltration was similar in the placenta of SGA and preterm births (**Tables 4** and **5**).

Pathologists at each center evaluated placentas separately, which may lead to systematic error in measurements. Although hospitals that enrolled only women of one race were excluded from our analysis, we conducted a sensitivity analyses by excluding all hospitals where < 20% or > 80% of women were African-American. Results were generally unchanged, although the confidence intervals became wider, likely due to reduced sample size (**Appendix Table 2**). Since gestational age in our study was defined by the last menstrual period, which is not as accurate as ultrasound, we also did a sensitivity analysis restricted to term (37-42 week) births, when menstrual dating is usually accurate [24]. The lower risk of vascular lesions and higher risk of neutrophilic infiltration in African-American than in white women was unchanged (**Appendix Table 3**).

Discussion

African-American women tend to have higher risks of pregnancy complications than white women [10, 25]. Differences in socioeconomic status cannot entirely explain the racial disparity [25]. In the present study, we found that fetal and maternal neutrophilic infiltrations were more prevalent in African-American than in white women after adjusting for potential confounders. Surprisingly, African-American women had lower risks of almost all placental vascular pathologies, including vascular and villous lesions of maternal origin, vascular and villous lesions of fetal origin in all subjects. This trend was similar in women with PAH, preterm and SGA births.

In our study, we found that the prevalence of neutrophilic infiltration of both the fetal and maternal compartments was higher in African-American than in white women. This may in part explain the increased risk of preterm birth, SGA and even child's morbidity among African-American [26-28]. The inflammatory process may contribute to dysregulation of metabolic, vascular and inflammatory pathways, all of which change the level of inflammatory mediators and environment of fetal growth. Meanwhile, inflammation may also modulate the developing immune system which contributes to morbidity and mortality in the future [29]. However, in our analysis, although the prevalence of adverse outcomes was higher in African-American women, placental vascular and villous lesions were much less common in African-American than in white women. The disparity cannot be explained by potential confounders that we controlled. Racial differences in plasma hemostatic factors have been reported, suggesting that African-American may have a prothrombotic profile compared with whites [30]. African-American women have a somewhat higher risk of developing venous thromboembolism during pregnancy than white women (OR, 1.4; 95% CI, 1.2-1.6) [31, 32]. This hypercoagulable state may contribute to the lower placental hemorrhage in African-American women. African-American were also shown to be more likely to suffer from bleeding complications after thrombolysis [33], more often hospitalized for hemophilia-related bleeding complications [34], and at increased risk for primary intracerebral hemorrhage than the whites (OR 3.31, 95% CI 1.14-9.57) [35]. In addition, while African-American women with severe preeclampsia manifest more severe hypertension, white women more frequently have HELLP syndrome [36]. All of these conflicting findings imply that racial differences in coagulation, especially during pregnancy, remain poorly understood.

Our study has several strengths. The CPP was the largest prospective birth cohort study in the U.S., and collected standardized information on maternal characteristics and medical and obstetrical events. Placentas from the vast majority of pregnancies (82%) were examined,

blind to clinical events and according to a standardized protocol. This is still among the most comprehensive placenta databases in existence.

On the other hand, our study has limitations. Placental diagnostic criteria have changed since the 1960s, when the CPP was conducted. For example, acute chorioamnionitisis currently diagnosed either according to the number of polymorphonuclear leukocytes per high power field, or by detailed grading systems involving documentation of polymorphonuclear leukocyte location, density, and degeneration to estimate intensity [37]. In our study, the inflammatory cell infiltration in the CPP was typically classified into 3 categories (not seen, slight and marked) without detailed numbers of cells. However, for most other diseases such as infarction, thrombosis and hemorrhage, the diagnostic criteria of pathological lesions remain unchanged. Most importantly, diagnostic criteria were unrelated to race. Therefore, changes in criteria should not affect our findings.

A second limitation is an inherent problem in studying the placenta. Placental examination is cross-sectional, but pregnancy is longitudinal. Although we found fewer placental vascular lesions at delivery in African-American women, we don't know when those lesions were formed. With the progress of gestation, some vascular lesion may increase because of placental 'aging'. African-American women tend to have a shorter gestational duration, which might in part explain why African-American have less vascular lesions. However, when we adjusted for gestational age, the association still existed, and the trend was also similar when we restricted to term births (**Appendix Table 3**).

A related limitation is that due to concerns regarding the accuracy of menstrual estimates of gestational age of < 32 weeks, we excluded pregnancies with these short gestations; therefore, pregnancies had to survive to 32 weeks to be included in our study. In the United States African-American women were at over two-fold increased risk of delivering before 32 weeks as compared to white women [38]. If African-American women who were predisposed to develop severe vascular lesions did so earlier in pregnancy than similar white women and delivered before 32 weeks' gestation, a spurious decrease in vascular lesions might be observed in surviving pregnancies. Similarly, since intrauterine inflammation is involved in the majority of very preterm births [39] the increase in inflammation we observed in the placentas of African-American women might be even greater than our findings would indicate. Nonetheless, it should be pointed out that although theoretically possible, the above scenario is less likely an explanation for our observation because the vast majority of births occurred after 32 weeks of gestation.

In conclusion, fetal and maternal neutrophilic infiltration in the placenta was more prevalent in African-American than in white women after adjusting for potential confounders. Surprisingly, African-American women had lower risks of almost all placental vascular pathology, including vascular and villous lesions of the maternal and fetal origin, as well as among pregnancies complicated by PAH, preterm birth and SGA. Understanding this puzzling phenomenon may shed light on the underlying mechanisms for poorer pregnancy outcomes in African-American than in white women.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun Zhang, MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, 1665 Kong Jiang Road, Shanghai 200092, China. Tel: +86-21-2507 8871; Fax: +86-21-2507 8875; E-mail: junjimzhang@gmail.com

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Appendix Table 1. Definition of placental pathological lesions in the Collaborative Perinatal Project, 1959-1976

Placental characteristic	Content
Placental weight	
Placental weight < 10th	Proportion of placental weight lower than 10th percentile of each gestational age
PBW ratio > 90th	Proportion of placental weight/birthweight ratio higher than 90th percentile of each gestational age
Vascular lesions of maternal origin	
Infarcts in the cut surface	
Occurrence of vascular infarcts	Infarcts in the maternal surface
Infarct size	At least one infarct ≥ 3 cm in the cut surface
Number of infarcts	Total number of infarcts in the maternal surface
Thrombosis in the cur surfaces and deciduas	Vessels thrombosis in the cut surfaces and deciduas
Vessel fibroid in the decidua	Vessels fibroid in the decidua
Villous lesions of maternal origin	
Villous infarcts in intervillous space	Micro infarcts in the terminal villi or intervillious thrombi with adjancent villous infarction
Syncytium-Nuclear clumping in decidua	Excessive Syncytium-Nuclear clumping in the decidua
Vascular lesions of fetal origin	Thrombosed fetal vessels in the fetal surface or cord
Villous lesions of fetal origin	Occurrence of stromal fibrosis in the terminal villous or Langerhans layer in the terminal villous
Marginal insertion of cord	Membranous insertion or marginal insertion
Calcification	Calcification throughout the cut surface
Hemorrhage	
Occurrence of hemorrhage	Hemorrhage in the maternal surface
Old hemorrhage in the maternal surface	Old hemorrhagic lesions
Thrombosis in the intervillous space	Intervillous thrombi
Inflammatory cell infiltration	
Fetal neutrophilic infiltration	Neutrophilic infiltration in umbilical vessels or cord substance
Maternal neutrophilic infiltration	Neutrophilic infiltration in deciduas, in chorion or amnion of membrane roll, or at chorion of placental surface
Maternal Lymphocytic infiltration	Lymphocytic infiltration in capsularis or basalis or at margin
Meconium	Macrophage with meconium pigment in the amnion or chorion in the membranes or decidua

Appendix Table 2. Sensitivity analysis of the racial disparity in placental pathological lesions, including only births in hospitals both African-American and white women each account for at least 20% of the total population at each hospital, the Collaborative Perinatal Project, 1959-1976

Placenta pathological lesions	White	African-American	Crude OR	Adjusted OR[1]	Adjusted OR[2]
2N	5,971 (49.3)	6,132 (50.7)	/	/	/
Placenta weight					
Placental weight < 10th percentile	561 (9.4)	864 (14.2)	**1.6 (1.4, 1.8)**	**1.5 (1.3, 1.8)**	**1.5 (1.3, 1.8)**
PBW ratio > 90th percentile	601 (10.1)	726 (11.9)	**1.2 (1.1, 1.4)**	**1.4 (1.2, 1.6)**	**1.3 (1.1, 1.6)**
Maternal origin vascular lesions					
Infarcts in cut surface					
Occurrence of vascular infarcts	800 (13.4)	780 (12.7)	0.9 (0.8, 1.0)	**0.9 (0.7, 1.0)**	**0.8 (0.7, 0.9)**
Infarct size	166 (2.8)	147 (2.4)	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)
Number of infarcts	185 (3.1)	214 (3.5)	1.1 (0.9, 1.4)	0.8 (0.6, 1.0)	**0.6 (0.5, 0.9)**
Thrombosis in cut surface	277 (4.6)	228 (3.7)	0.9 (0.8, 1.0)	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Vessel fibroid in decidua	163 (2.8)	142 (2.5)	0.9 (0.7, 1.1)	0.9 (0.6, 1.1)	0.9 (0.7, 1.2)
Maternal origin villous lesions					
Villous infarcts in intervillous space	1,276 (21.4)	1,673 (27.3)	**1.4 (1.3, 1.5)**	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)
Syncytium-Nuclear clumping in decidua	144 (2.8)	168 (3.2)	1.2 (0.9, 1.5)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)
Fetal origin vascular lesions	41 (0.7)	90 (1.5)	**2.2 (1.5, 3.1)**	1.3 (0.8, 2.0)	1.3 (0.8, 2.0)
Fetal origin villous lesions					
Stromal fibrosis in terminal villi	174 (2.9)	108 (1.8)	**0.6 (0.5, 0.8)**	**0.6 (0.5, 0.9)**	**0.7 (0.5, 1.0)**
Langerhans layer in terminal villi	47 (0.8)	52 (0.9)	1.1 (0.7, 1.6)	**0.6 (0.4, 1.0)**	**0.6 (0.3, 0.9)**
Marginal insertion of cord	374 (6.3)	244 (4.0)	**0.6 (0.5, 0.7)**	**0.7 (0.5, 0.8)**	**0.7 (0.5, 0.8)**
Calcification throughout cut surface	1,358 (22.8)	671 (11.0)	**0.4 (0.4, 0.5)**	**0.8 (0.7, 0.9)**	**0.8 (0.7, 1.0)**

Hemorrhage					
Occurrence of hemorrhage	446 (7.5)	589 (9.6)	**1.3 (1.2, 1.5)**	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)
Old hemorrhage in maternal surface	349 (5.8)	310 (5.1)	**2.0 (1.6, 2.6)**	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)
Thrombosis in intervillous	630 (10.6)	577 (9.4)	**0.9 (0.8, 1.0)**	**0.7 (0.6, 0.9)**	**0.8 (0.6, 0.9)**
Inflammatory cell infiltration					
Fetal neutrophilic infiltration	172 (2.9)	282 (4.6)	**1.6 (1.3, 2.0)**	**1.3 (1.0, 1.6)**	1.2 (0.9, 1.6)
Maternal neutrophilic infiltration	576 (9.7)	616 (10.1)	1.0 (0.9, 1.2)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)
Maternal lymphocytic infiltration	39 (0.7)	80 (1.3)	**2.0 (1.4, 3.0)**	1.3 (0.8, 2.1)	**1.8 (1.0, 3.1)**
Meconium	598 (10.0)	712 (11.6)	**1.2 (1.0, 1.3)**	1.1 (1.0, 1.3)	1.2 (1.0, 1.3)

PBW ratio: Placenta-to-birthweight ratio. Crude OR. Unadjusted logistic model. Adjusted OR[1]. Logistic model adjusted by maternal age, education levels, marital status, parity, social economic status, gestational age, maternal prepregnancy body mass index, and study center, with reference group of White race. Adjusted OR[2]. Pregnancy associated hypertension and diabetes excluded on the basis of adjusted model above. Bold font: $P < 0.05$.

Appendix Table 3. Sensitivity analysis of the racial disparity in placental pathological lesions, with term (37-42 week) births included only, the Collaborative Perinatal Project, 1959-1966

Placenta pathological lesions	White Race	African-American	Crude OR	Adjusted OR[1]	Adjusted OR[2]
N	16,157 (57.2)	12,069 (42.8)	/	/	/
Placental weight					
Placental weight < 10th	1,138 (7.1)	1,295 (10.8)	**1.6 (1.5, 1.7)**	**1.4 (1.2, 1.5)**	**1.4 (1.2, 1.6)**
PBW ratio > 90th	1,235 (7.7)	1,198 (10.0)	**1.3 (1.2, 1.4)**	**1.2 (1.0, 1.3)**	1.1 (1.0, 1.3)
Vascular lesions of maternal origin					
Infarcts in the cut surface					
Occurrence of vascular infarcts	2,833 (17.5)	1,290 (10.7)	**0.6 (0.5, 0.6)**	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Infarct size	729 (4.5)	280 (2.3)	**0.5 (0.5, 0.6)**	**0.7 (0.6, 0.9)**	**0.7 (0.6, 0.9)**
Number of infarcts	971 (6.0)	346 (2.9)	**0.5 (0.4, 0.5)**	**0.8 (0.7, 1.0)**	**0.8 (0.6, 1.0)**
Thrombosis in the cut surface	1,326 (8.2)	347 (2.9)	**0.3 (0.3, 0.4)**	**0.8 (0.7, 0.9)**	0.9 (0.7, 1.1)
Vessel fibroid in the decidua	312 (2.0)	198 (1.7)	0.9 (0.7, 1.0)	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)
Villous lesions of maternal origin					
Villous infarcts in the intervillous space	2,361 (14.6)	1,743 (14.5)	1.0 (0.9, 1.1)	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**
Syncytium-Nuclear clumping in the decidua	468 (3.2)	173 (1.6)	**0.5 (0.4, 0.6)**	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
Vascular lesions of fetal origin	137 (0.9)	104 (0.9)	1.0 (0.7, 1.3)	1.4 (0.9, 2.1)	1.4 (0.9, 2.2)
Villous lesions of fetal origin					
Stromal fibrosis in the terminal villi	295 (1.8)	107 (0.9)	**0.5 (0.4, 0.6)**	**0.6 (0.5, 0.9)**	**0.7 (0.5, 1.0)**
Langerhans layer in the terminal villi	83 (0.5)	59 (0.5)	1.0 (0.7, 1.3)	0.7 (0.4, 1.1)	**0.6 (0.4, 1.0)**
Marginal insertion of cord	790 (4.9)	346 (2.9)	**0.6 (0.5, 0.7)**	**0.6 (0.5, 0.7)**	**0.6 (0.5, 0.8)**
Calcification throughout the cut surface	1,944 (27.6)	1,275 (16.6)	**0.9 (0.8, 0.9)**	**0.9 (0.8, 1.0)**	**0.9 (0.8, 1.0)**
Hemorrhage					
Occurrence of hemorrhage	1301 (8.1)	695 (5.8)	**0.7 (0.6, 0.8)**	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)
Old hemorrhage in the maternal surface	1272 (7.9)	464 (3.8)	**0.8 (0.7, 0.9)**	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)
Thrombosis in the intervillous space	2,196 (13.6)	818 (6.8)	**0.5 (0.4, 0.5)**	**0.7 (0.7, 0.8)**	**0.7 (0.7, 0.8)**
Inflammatory cell infiltration					
Fetal neutrophilic infiltration	787 (4.9)	520 (4.3)	**0.9 (0.8, 1.0)**	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
Maternal neutrophilic infiltration	1,148 (7.1)	1,017 (8.4)	**1.2 (1.1, 1.3)**	1.1 (1.0, 1.3)	1.1 (0.9, 1.2)
Maternal lymphocytic infiltration	126 (0.8)	139 (1.2)	**1.5 (1.2, 1.9)**	1.3 (0.9, 1.9)	1.4 (0.9, 2.1)
Meconium	991 (6.2)	1,256 (10.5)	**1.8 (1.6, 1.9)**	**1.2 (1.0, 1.3)**	**1.2 (1.0, 1.3)**

PBW ratio: Placenta-to-birthweight ratio. Model 1. Unadjusted logistic model. Model 2. Logistic model adjusted by maternal age, education levels, marital status, parity, social economic status, gestational age, maternal prepregnancy body mass index, and study center, with reference group of White race. Model 3. Pregnancy associated hypertension and diabetes excluded on the basis of adjusted model above. Bold font: $P < 0.05$.