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Race and risk of maternal vascular malperfusion lesions in the placenta

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ABSTRACT

Introduction: The biological mechanisms that underlie racial disparities in placenta-mediated pregnancy complications remain unknown. Placental evidence of maternal vascular malperfusion (MVM), a common pathologic feature of these outcomes, represents hypoxic-ischemic damage to the placenta. We sought to separately estimate the risk of MVM and individual lesions associated with maternal race.

Methods: This was a retrospective cohort study of black and white women with singleton live births and placental pathology data at Magee-Womens Hospital during 2008–2012 (n = 15,581). MVM consisted of ≥1 individual lesions: low placental weight, decidual vasculopathy, accelerated villous maturation, infarcts, and fibrinoid deposition. We separately compared the incidence of MVM and individual lesions in black and white women using logistic regression with generalized estimating equations.

Results: After adjusting for covariates, black women had increased risks of MVM (aOR 1.14, 95% CI 1.05–1.23), low placental weight (aOR 1.41, 95% CI 1.28–1.55), and decidual vasculopathy (aOR 1.58, 95% CI 1.36–1.83), also observed in uncomplicated, preterm, and term births. Conversely, black women had decreased risk of infarcts (aOR 0.84, 95% CI 0.75–0.95) compared with white women, also observed in uncomplicated and full-term births. Race was not associated with accelerated villous maturation or fibrinoid deposition. Inverse probability weighting to account for potential selection bias generated similar results.

Discussion: Our findings suggest that excess risks of MVM, specifically low placental weight and decidual vasculopathy in black women may be due to a pathological susceptibility to an underlying high-risk vascular phenotype. The clinical significance of race differences in the occurrence of infarcts warrants further investigation.

1. Introduction

Black women in the United Sates have an increased risk of placenta-mediated pregnancy complications such as fetal growth restriction [1], placental abruption [2,3], and preeclampsia [1,3,4] as compared with white women. These racial differences contribute to disparities in obstetric outcomes such as preterm birth. For example, the percentage of infants born preterm is nearly 50% higher in black as compared with white mothers (13.4% vs. 8.9%) [5]. Despite substantial public health efforts, the black-white gap persists [6]. This disparity continues to exist even after accounting for social, obstetric, behavioral, and psychosocial factors [6]. Increased understanding of the underlying biological mechanisms that contribute to race differences in adverse perinatal outcomes is urgently needed.

The placenta is a metabolic and endocrine organ that serves as the interface between the mother and fetus. One clinical feature that is notably associated with altered placental function is maternal vascular malperfusion (MVM) [7]. MVM lesions develop as a consequence of defective trophoblast invasion and remodeling of maternal spiral arteries during early pregnancy [8–10]. The poorly perfused placenta fails to provide adequate oxygen and nutrients to the growing fetus and can lead to adverse pregnancy and neonatal outcomes [11–15]. MVM lesions may represent placental hypoxia-ischemia and contribute to features of preeclampsia, fetal growth restriction, and preterm birth [7]. However, the relationship between race and susceptibility to vascular impairments in the placenta has been understudied. To date, the only clinical registry that compared the risk of placental lesions in black and white women utilized data from the Collaborative Perinatal Project

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(CPP), a prospective cohort that recruited pregnant women from 1959 to 1966, and did not use current standardized criteria to define types of placental lesions [16].

We utilized a contemporary perinatal hospital registry linked to placental pathology data to explore the role of race on the development of evidence of MVM (≥1 lesion and specific lesion type) in black and white women that delivered between 24 and 42 completed weeks of gestation during 2008–2012. We hypothesized that black women would have an increased risk of MVM lesions. We further considered whether this increased risk would persist among black women after excluding women with adverse pregnancy outcomes (APO), and we examined whether race differences were associated with increased risk in MVM in preterm, early-term, full-term, or late-term births.

2. Materials and methods

This was a retrospective cohort study of women with singleton live births and placental pathology data at Magee-Womens Hospital during 2008–2012 (n = 20,165). Placental pathology data were linked to the Magee Obstetric Medical and Infant database, which collects information from admitting services, International Classification of Diseases, Ninth Revision codes, electronic medical record abstraction, and ultrasound for all women who have delivered at Magee-Womens Hospital in Pittsburgh, PA. Births during 2008–2012 were selected because during that time two placental pathologists used a standardized protocol, uniform reporting, and identical diagnostic criteria to prepare placental pathology reports. Indications for submission of placenta for pathologic examination and our placental matching and extraction process have been previously described [12,17]. Briefly, some of the indications for submission of the placenta by the obstetricians consisted of some of the following: multiple gestation, preterm delivery, post-term delivery, placental abruption, amniotic fluid abnormalities, hypertensive disorders of pregnancy, history of substance abuse, or meconium fluid or staining. These indications for submission were in accordance with the Practice Guideline for the Examination of the Placenta [18]. The broad criteria that was followed resulted in approximately 45% of placentas being sent for pathologic examination. Placental sampling included the submission of two full thickness sections of the placental parenchyma. One full thickness section of central placenta was submitted in one cassette, and a second full thickness section from the placental periphery was submitted in a second cassette. The third cassette included a membrane roll (extending from the site of membrane rupture to the placental periphery) and two sections of the umbilical cord. One section of the umbilical cord was taken near to the site of cord insertion into the placenta, with the other taken from near to the site of cord insertion into the fetus. MVM lesions were sampled liberally, with generally up to the first four included. Lesions were submitted in additional cassettes. Central sections were taken to avoid macroscopically identifiable lesions. If significant microscopic lesions were identified on the central section (e.g. an infarct), an additional central section was taken. The University of Pittsburgh Institutional Review Board approved the project, which did not require informed consent as all data were de-identified.

We restricted the study population to black and white women due to the evidence supporting disparities in pregnancy outcomes between these two groups and because maternal race reported as other (i.e., Hispanic, Asian, American Indian, Biracial/Multiracial) was too small to evaluate (n = 784). We excluded those with unknown or missing race (n = 852), missing education, or parity (n = 2,287), and infants with congenital anomalies (n = 661). After the above exclusions, our population included 15,581 births with placental data (Fig. 1).

Maternal race was self-reported as white or black. The primary outcome was evidence of MVM (0 vs. ≥1 individual lesions), a combined outcome consisting of the presence of one or more of the following types of lesions: low placental weight (placental weight < 10th percentile), decidual vasculopathy, increased accelerated villous maturation, infarcts, and fibrinoid deposition (Table 1). Individual MVM lesions were evaluated as secondary outcomes. MVM lesions were grouped by a placental pathologist (WTP) in accordance with recent efforts to standardize these evaluations [10]. The study placental pathologist was not blinded to clinical information or gestational age, as these were clinical specimens. We assessed the validity of our method in a convenience sample (n = 88) by comparing the diagnosis of MVM on clinical pathology reports to a review of the slides by a single pathologist blinded to all clinical information except gestational age (WTP). There was excellent agreement between the clinical pathology reports and the review by the pathologist for vasculopathy (86%) and infarcts (95%). There was good agreement for evidence of MVM (73%) and accelerated villous maturation (76%), and moderate agreement for fibrinoid deposition (63%).

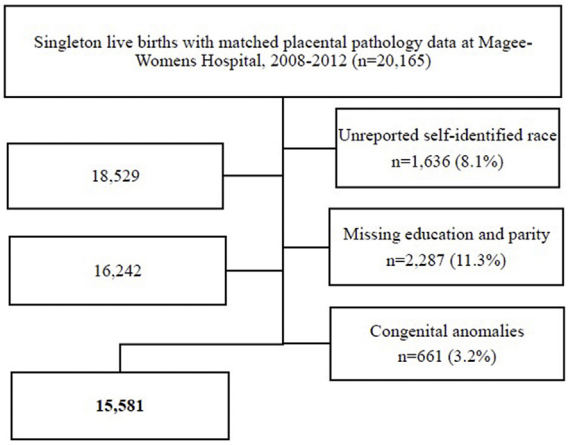

Fig. 1. Flowchat of exclusions for analysis of race and maternal vascular malperfusion lesions.

3. Statistical methods

Maternal characteristics between black and white women were compared using Chi-square tests. Covariates included: maternal age at delivery, maternal education, primiparity, pre-pregnancy body mass index (BMI), smoking during pregnancy, and fetal sex. Those covariates that were associated ($P < 0.10$) with both race and MVM lesions, or only the outcomes were included in all multivariable analyses.

We used logistic regression with generalized estimating equations [19] to account for correlated repeated placental measures within women who contributed more than one birth to the analysis (n = 1,030) and to compare race-specific incidence of MVM and individual lesions, after adjusting for age, education, and primiparity. White women without MVM were the referent. We further adjusted for smoking and pre-pregnancy BMI, potential confounders. For those missing pre-pregnancy BMI (n = 1,727), Markov Chain Monte Carlo method of multiple imputation [20] was used to average estimates across three datasets. We further restricted our analyses to three groups: healthy women or those without APO and pre-existing conditions, women with APO, and women with pre-existing conditions. APO included: preterm birth (delivery at < 37 gestational weeks), small-for-gestational age (birthweight < 10th percentile at each completed week of gestation) [21], gestational hypertension, preeclampsia/eclampsia, superimposed preeclampsia, and gestational diabetes. Pre-existing conditions included chronic hypertension and diabetes mellitus. APO and pre-existing conditions may confer a greater risk of MVM so excluding this subgroup would enable us to determine the association between race and risk of these lesions in women with otherwise normal placentas. Given evidence that black women have excess risk of preterm birth and that preterm births are associated with placental pathology, we considered gestational age at delivery to be on the causal pathway