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Racial differences in placental pathology among very preterm births

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ABSTRACT

Introduction: African American women are at higher risk for preterm birth compared to white women, but no placental pathology has characterized this disparity. The objective of this study was to examine the association of race with placental pathology among very preterm births.

Methods: We conducted an eight-year retrospective cohort study of very preterm infants born at ≤32 weeks at Northwestern Prentice Women's Hospital in Chicago, Illinois. Archived placental slides underwent standardized masked histopathologic review. Logistic regression was performed for placental pathology, adjusting for available relevant covariates and stratified by infant sex and gestational age.

Results: Placentas were available for 296 white and 224 African American mother-infant pairs among births at ≤32 weeks gestation. Compared to placentas from white births, the adjusted OR (aOR) for acute inflammation in placentas from African American births was 1.95 (95% CI 0.87–4.37), the aOR for chronic inflammation was 3.35 (1.49–7.54), the aOR for fetal vascular pathology was 0.82 (0.29–2.32), and the aOR for maternal vascular pathology was 1.01 (0.51–1.99). Stratified analysis showed associations between all placental pathologies and race among male births. Across gestational age groups (< 28 and ≥ 28 weeks), the association between race and placental pathology was present for chronic inflammation and fetal vascular pathology.

Discussion.: Race is associated with placental pathology, and in particular, with chronic inflammation among very preterm births. The effect is modified by infant sex and gestational age. Placental histopathology may be useful markers for understanding the biological processes that shape disparities in pregnancy outcomes.

1. Introduction

Despite advances in perinatal medicine, racial differences in birth outcomes remain major public health issues in the United States. In 2016, 13.8% of all non-Hispanic black births were preterm at < 37 weeks gestation, compared to 9.0% of non-Hispanic white births [1]. Moreover, African American infants are twice as likely to die in the first year of life compared to non-Hispanic white infants, with a mortality rate of 11.7 versus 4.8 per 1000 live births, respectively, in 2016 [2]. The underlying mechanisms for this long-standing racial disparity in infant health outcomes are incompletely understood, and likely include a complex array of prenatal and postnatal environmental factors interacting at social, individual, and molecular levels [3].

The placenta is the principal metabolic, respiratory, and endocrine organ of the fetus, and several pregnancy complications, including preterm birth, originate from its dysfunction. As a key route by which exposures are transmitted from mother to offspring, it may serve as a marker of differences in prenatal exposures, and may manifest differently by race. To date, limited studies have suggested variable racial differences in placental pathology across various gestational ages. Using an archived cohort of placentas from 1959 to 1966, Chen et al. [4] found that, at 33–42 weeks gestation, African American women had a higher prevalence of inflammatory lesions and lower prevalence of vascular lesions compared to white women. Recently, Assibey-Mensah et al. reported higher risks of placental maternal vascular malperfusion among African American women, in a large sample of births ranging from 24 to 42 weeks [5]. To our knowledge, no study among very preterm births has examined the relationship between maternal race

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and placental pathology with comprehensive histopathological categories.

We therefore designed a retrospective study to examine differences in placental pathology between African American and white women who gave birth to very preterm births. Given the widely established evidence supporting disparities in preterm birth rates, we hypothesized that the prevalence of placental pathologies differ between races among very preterm births.

2. Methods

We conducted an eight-year retrospective cohort study at Northwestern Prentice Women's Hospital, in which all preterm infants born ≤32 completed weeks (gestational age, GA, range $23^{0/7}$ to $32^{6/7}$ weeks) between January 2005 and December 2012 were identified. Standardized chart reviews were performed. Available archived placental pathology slides were retrieved and reviewed by a single perinatal pathologist using a standardized algorithm. The pathologist was blinded to all patient demographics including race/ethnicity and neonatal outcomes, but not blinded to gestational age, as placental examinations are part of the clinical practice. Included were all infants who were inborn at Prentice Women's Hospital and for whom placental tissues were retrievable. Excluded were births in which reliable GA dating criteria, as defined by the American Congress of Obstetricians and Gynecologists (ACOG), could not be determined, and subjects with unavailable placental tissue, and those with missing race variables. We restricted the study population to African American and white women due to established literature on black-white racial disparities in maternal and infant health outcomes, and because other reported races/ethnicities (Asian, Hispanic) was too small to analyze (n = 44, n = 66, respectively). The study was approved by the institutional review boards at Northwestern University and Ann & Robert H. Lurie Children's Hospital of Chicago.

Clinical information was collected from electronic medical records, using standardized abstraction forms that included data on intrapartum management, pregnancy complications and birth outcomes. Available variables that have been previously reported in the literature and observed in the clinical setting to be associated with preterm birth, placental dysfunction and race/ethnicity were selected for analysis. GA was determined based on last normal menstrual period, confirmed by ultrasounds obtained prior to 20 weeks gestation [6]. Preeclampsia and other hypertensive disorders of pregnancy, such as eclampsia and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, were defined according to ACOG criteria [7]. Intrauterine growth restriction (IUGR) was defined as birth weight (BW) < 10th percentile for GA based upon Fenton growth curves for premature infants [8].

The primary exposure of interest was African American or white maternal race as entered in medical records from self-report. Those whose reported race/ethnicity were missing or coded as “unknown/other” were excluded from analysis. The primary outcomes were placental pathologies including acute inflammation, chronic inflammation, fetal vascular pathology and maternal vascular pathology. Each of these four pathologies represent a combination of pathological findings described in detail below.

At Northwestern Prentice Women's Hospital, placenta tissue from all women who deliver at ≤32 weeks gestation are routinely reviewed and archived by the Department of Pathology. Both gross pathology and histologic pathology were performed and collected for each placenta using standardized protocols. Information on trimmed placental weight was obtained from the pathology reports. Archived samples included sections of membranes, umbilical cord, and at least two sections of the placental parenchyma. A comprehensive, standardized histopathology review was performed on the slides by a single perinatal pathologist, who was masked to maternal race or infant health outcomes. The histologic data were recorded and divided into the following four major pathologic categories [9]: 1) Acute inflammation was defined by evidence of amniotic fluid infection/acute inflammatory pathology [10]. Maternal acute inflammation was identified as: a) acute subchorionitis or chorionitis by neutrophil infiltration in subchorion and/or membrane trophoblast (stage 1), b) as acute chorioamnionitis by neutrophils in fibrous subchorion and/or amnion (stage 2), and c) neutrophil karyorrhexis, amniocyte necrosis, and/or amnion basement membrane thickening/hypereosinophilia, or necrotizing chorioamnionitis (stage 3). Fetal acute inflammation was identified by neutrophil diapedesis through the wall of the chorionic vessels or umbilical vein (stage 1), umbilical artery (stage 2), and necrotizing funisitis (stage 3) defined by neutrophil karyorrhexis in a band-like configuration within the Wharton's jelly. High stage inflammation was defined as those with stage 2 and stage 3 acute inflammation. 2) Chronic inflammation was defined as presence of significant chronic (lymphocytic or histiocytic) infiltrates in the membranes (chorion and/or amnion), chorionic villi, intervillous space or basal plate. Chronic villitis was defined as lymphocytes or histiocytes infiltrating the chorionic villi and was graded as low (few, small foci) or high (multiple, large foci). Chronic intervillositis was identified when a lymphohistiocytic infiltrate was present in the intervillous space without a villous infiltrate. Basal chronic inflammation was considered diagnostic for chronic deciduitis when plasma cells were identified within the chronic inflammatory infiltrate.3) Fetal vascular pathology was defined according to the criteria published by Redline et al. [11]. These lesions included the presence of thrombi within chorionic, stem villous, or umbilical vessels. Avascular villi were identified as two or more terminal villi showing total loss of villous capillaries and uniform fibrosis of the villous stroma. A diagnosis of fetal thrombotic vasculopathy was made when multifocal avascular villi were present (> 15 villi involved/slide). 4) Maternal vascular pathology was defined according to criteria described by Redline et al. [12] to pathologic findings in the maternal vasculature of the parietal and basal decidua (vessel changes), which included mural fibrinoid necrosis/acute atherosis, muscularized basal plate arteries, and mural hypertrophy of membrane arteries. In addition, villous hypoxic lesions (villous changes) including infarcts, increased syncytial knots, villous agglutination, increased perivillous fibrin, distal villous hypoplasia/small terminal villi were recorded.

2.1. Statistical analysis

Maternal and infant characteristics were compared using Chi-square tests for categorical variables and student's t-test for continuous variables. Infant characteristics included birth weight, gestational age, sex, and small for gestational age status (birth weight less than 10th percentile.) Maternal characteristics included age, preterm labor, premature rupture of membranes, prolonged rupture of membranes, mode of delivery, antenatal steroids, preeclampsia, eclampsia, HELLP syndrome, reasons for delivery, gestational and chronic hypertension, chorioamnionitis, gestational diabetes, oligohydramnios, intrauterine growth restriction, and placental abruption. Prevalence in specific placental pathologies were compared between races using Chi-square tests.

Multivariate logistic regression models were used to determine the odds ratio (OR) and 95% confidence intervals (CI) for each placental pathology using white women as the reference. First, bivariate analyses were performed to examine the association between race and placental pathology. Adjustments for confounders were made when the crude OR differed from the adjusted OR for each confounder by 10% or more [13]. To consider potential effect modification, for all variables, stratum-specific measures of association (OR) to pathology type were assessed and tested with Breslow-Day test, testing for homogeneity of the stratum-specific effect measures on multiplicative scale. When the stratum-specific OR were meaningfully different in magnitude and Breslow-Day Test showed heterogeneity with $p < 0.10$, these variables were considered potential effect modifiers. Subsequently, we performed stratified analyses of the sample according to infant sex and gestational

Table 1
Infant and maternal characteristic by race.

	White (n = 296)	African American (n = 224)	p[a]
Birth weight, mean ± SD, g	1084.4 ± 351.2	924.8 ± 307.3	< 0.01
Gestational age, mean ± SD, wk	27.8 ± 2.4	26.8 ± 2.1	< 0.01
Male sex, n(%)	154 (52.0)	132 (58.9)	0.11
Birth weight < 10th percentile, n(%)	12 (4.1)	30 (13.4)	< 0.01
Maternal age, mean ± SD, y	33.2 ± 5.7	26.5 ± 5.9	< 0.01
Preterm labor, n(%)	237 (80.1)	170 (75.9)	0.25
Premature rupture of membranes, n(%)	127 (43.2)	105 (46.9)	0.40
Prolonged rupture of membranes, n(%)	51 (17.2)	54 (24.6)	0.04
Cesarean section delivery, n (%)	177 (59.8)	114 (50.9)	0.04
Antenatal steroids, n(%)	242 (82.3)	161 (73.9)	0.02
Preeclampsia, n(%)	42 (14.2)	40 (17.9)	0.26
Eclampsia, n(%)	1 (0.3)	2 (0.9)	0.41
HELLP syndrome, n(%)	12 (4.1)	8 (3.6)	0.78
Reason for delivery, n(%)			
Preterm labor	233 (78.7)	158 (70.5)	0.01
Intrauterine growth restriction	4 (1.4)	4 (1.8)	
Non-reassuring fetal heart tones	13 (4.4)	22 (9.8)	
Chorioamnionitis	6 (2.0)	12 (5.4)	
Preeclampsia	31 (10.5)	28 (12.5)	
Other	2 (0.7)	0	
Gestational hypertension, n (%)	1 (0.3)	7 (3.1)	0.01
Chronic hypertension, n(%)	4 (1.4)	10 (4.5)	0.03
Chorioamnionitis, n(%)	28 (9.5)	44 (19.6)	< 0.01
Gestational diabetes, n(%)	8 (2.7)	16 (7.1)	0.02
Oligohydramnios, n(%)	10 (3.4)	20 (8.9)	< 0.01
Intrauterine growth restriction, n(%)	23 (7.8)	38 (17.0)	< 0.01
Placental abruption, n(%)	24 (8.1)	28 (12.5)	0.1

HELLP indicates hemolysis, elevated liver enzyme levels, and low platelet count.

[a] p values were based on the Chi-square test for categorical variables and the student's t-test for continuous variables.

age categories (< 28 and ≥ 28 weeks) All analyses were performed using SAS version 9.4 (Cary, NC).

3. Results

There were placentas available for 296 white and 224 African American mother-infant pairs among births at ≤32 weeks gestation, inborn and admitted at Prentice between January 1, 2005 and December 31, 2012. The sample flow was as follows: there were 1697 subjects in the database from 2005 to 2012. Placental reports based on the most recent protocol were unavailable in n = 891. Race/ethnicity variables were missing in n = 304, with n = 128 missing both placental reports and race/ethnicity variables. Excluded were Hispanic (n = 66) and Asian (n = 44) births, due to their small sample sizes.

The infant and maternal clinical characteristics by race are shown in Table 1. There were significant differences in birth weight and gestational age between races. Compared to white infants, African American infants were lower in mean birth weight and delivered at earlier mean gestational age (925 g, 26.8 weeks), compared to white infants (1084 g, 27.8 weeks.) African American mothers were younger (mean 26.5 years vs. 33.2 years), and had higher rates of chorioamnionitis, compared to white mothers. Rates of antenatal steroid use and cesarean delivery were lower in African American mothers.

The prevalence of specific placental pathologies by race are shown in Table 2. Compared to white mothers, placentas of African American mothers had higher percentages of acute and chronic inflammation (67.9% vs 52.7%, 37.5% vs 14.9%, respectively), lower percentages of fetal vascular pathology (7.6% vs 15.5%), and no difference in percentages of maternal vascular pathology.

Table 3 shows the results of the multivariable logistic regression models and stratified analyses. Using white mothers' placentas as reference, adjusted OR (aOR) for each placental histopathology are shown. Among placentas from African American births, the aOR (controlling for maternal age, preterm labor, antenatal steroids, gestational age and infant sex) of acute inflammation equaled 1.95 (0.87–4.37), the aOR for chronic inflammation equaled 3.35 (1.49–7.54), the aOR for fetal vascular pathology equaled 0.82 (0.29–2.32) and the aOR for maternal vascular pathology equaled 1.01 (0.51–1.99).

To study the effect modification of infant sex and gestational age on the race-placental pathology association, we stratified the sample into placentas from male and female infant births, as well as < 28 and ≥ 28 weeks gestational age groups (Table 3). While the overall non-stratified association between acute inflammation and race was not significant (1.95, 0.87–4.37), stratification by sex showed that among African American male births, the aOR was 2.95 (1.55–5.61) compared to white male births. Similarly, among African American male infant births, the association with fetal vascular pathology was significant with the aOR 0.08 (0.02–0.38), and 0.44 (0.25–0.77) for maternal vascular pathology, while the overall, non-stratified associations were not significant (0.82, 0.29–2.32). The pattern of association between placental pathology and race persisted for chronic inflammation with the aOR of 3.03 (1.65–5.54). Among female infant births, significant association with race was present only for chronic inflammation, with the aOR of 4.85 (2.35–10.02).

With stratification by gestational age categories (< 28 and ≥ 28 weeks), the association between race and placental pathology was modified in both groups for acute inflammation with high and similar aORs (2.48 and 2.29 for < 28 and ≥ 28 weeks groups, respectively). For chronic inflammation, the ≥28 weeks group had a markedly higher aOR at 6.94 (3.24–14.87) compared to the < 28 week group at 2.59 (1.44–4.66). For fetal vascular pathology, both gestational groups had similar and statistically significant aOR (0.23, 0.25) that were modified from overall, non-stratified aOR (0.82, 0.29–2.32).

4. Discussion

Among very preterm births, African American race was associated with higher odds of placental chronic inflammation compared to white race, but not with other pathologies. This association was significant even after adjustment for clinical and demographic covariates of preterm birth that were available. Gestational age and infant sex modified this relationship for chronic inflammation, acute inflammation and fetal vascular pathology.

These findings suggest that increased prevalence of placental inflammation among African American women, across a range of gestational age, may be a marker for adverse pregnancy outcomes. Racial differences in pregnancy complications – preeclampsia, preterm birth, preterm premature rupture of membranes - are associated with altered placental physiologic condition, metabolism, and function [14–19]. As such, exploration of racial differences in placental pathology may provide insight into the mechanisms underlying racial disparities in maternal and infant health, such as exposure to acute and chronic stress.

Stress is a social and biological risk factor that has been speculated as a possible explanation for disparities in pregnancy outcomes [3,20,21]. Theoretical models of the mechanism by which stress modifies pregnancy outcomes include the developmental origins of health and disease [22], the weathering hypothesis [23], and psychological responses to stress, or coping behaviors, such as smoking, that result in preterm births [24]. Biologically, it is known that the placental enzyme 11 beta-hydroxysteroid dehydrogenase-2 transforms maternal cortisol to inactive cortisone, protecting the fetus from elevated

Table 2
Distribution of placental pathology by race.

	White (n = 296)	African American (n = 224)	p
Placenta weight, mean ± SD, g	315.3 ± 153.4	269.8 ± 112.9	< 0.01
ACUTE INFLAMMATION, n(%)	156 (52.7)	152 (67.9)	< 0.01
Maternal inflammation	156 (52.7)	152 (67.9)	< 0.01
Maternal high stage inflammation	93 (31.4)	111 (50.0)	< 0.01
Fetal inflammation	89 (30.1)	115 (51.3)	< 0.01
Fetal high stage inflammation	55 (18.6)	92 (41.1)	< 0.01
Funisitis	52 (17.6)	95 (42.4)	< 0.01
CHRONIC INFLAMMATION	44 (14.9)	84 (37.5)	< 0.01
Chronic villitis	5 (1.7)	7 (3.1)	0.28
Chronic deciduitis with plasma cells	38 (12.8)	76 (33.9)	< 0.01
FETAL VASCULAR PATHOLOGY	46 (15.5)	17 (7.6)	< 0.01
Fetal vascular thrombi	24 (8.1)	12 (5.4)	0.22
Avascular villi	30 (10.1)	5 (2.2)	< 0.01
MATERNAL VASCULAR PATHOLOGY	145 (49.0)	95 (42.4)	0.14
Maternal vessel pathology	29 (9.8)	62 (27.7)	< 0.01
Villous changes	137 (46.3)	86 (38.4)	0.07
Infarct	17 (5.7)	32 (14.3)	< 0.01
Multiple infarcts	8 (2.7)	6 (2.7)	0.99

maternal cortisol exposure [25]. Significant differences in self-reported and serum markers of chronic stress have been identified between non-Hispanic black and non-Hispanic white pregnant women between 14 and 22 weeks gestation, with similar economic characteristics [21]. Two of these serum markers – C-reactive protein (CRP), Epstein-Barr virus (EBV) antibody – have also been associated with chronic placental inflammation among women who delivered at 32–41 weeks gestation [26].

There are several pathways that support a link between maternal stress and pregnancy [21]. First, stress activates the hypothalamic-pituitary-adrenal axis stress response, leading to increased corticotropin-releasing hormone (CRH) and an increase in placental CRH. The CRH increase results in increased cytokine release from the decidua and amnion, which can stimulate myometrial contractions [27–29]. Second, chronic stress is linked to increased glucocorticoid production and inhibition of immune function [30], possibly leading to susceptibility to infection and preterm birth [31]. Finally, chronic stress may upregulate the inflammatory response to stimuli, leading to a chronic inflammatory state [32]. As such, elevated C-reactive protein (CRP), a marker of inflammatory response, has been associated with chronic stress and preterm birth [33–35].

Our findings are consistent with those described by Chen et al. [4], who also found higher prevalence of inflammatory lesions, and lower prevalence of vascular lesions in African American women's placentas compared to those of white women, using data from the U.S Collaborative Project (1959–1966) with 32,295 placentas. Similar to our findings, placental vascular lesions such as thrombosis and villous infarcts were less common in African American than in white women. In contrast, a recent study reported high risks of maternal vascular malperfusion, a specific pathological finding which represents hypoxic-ischemic injury to the placenta, in black women compared to white women [5]. The findings were similar even when restricted to uncomplicated preterm and term births, suggesting racial differences in pathological susceptibility to an underlying high-risk vascular phenotype. The discrepancies in prevalence of vascular pathologies across these three studies may be due to differences in inclusion criteria or variations in classification of placental lesions. Nevertheless, efforts to understand the underlying biological mechanisms that contribute to racial differences in birth outcomes is urgently warranted.

Sex-specific differences in fetal and neonatal morbidity and mortality are known [36,37]. Male sex has been shown to significantly increase the risk of several adverse perinatal outcomes, including placental abruption [38] and extreme preterm delivery [37,39]. Similarly, differences in placental pathology by infant sex have been reported [37,40,41]. Our results showed significant association with African American male sex in vascular and inflammatory lesions. With regard to chronic inflammation, while we report association with both sexes among African American infants, Ghidini et al. found that male sex was associated with significantly higher rates of placental chronic inflammatory lesions [42]. Their sample (n = 437) of preterm infants under 32 weeks gestation consisted of a mix of Caucasian, African American, and races classified as other. Because significantly more severe chronic inflammatory lesions were noted in male than in female fetuses at the implantation site, the authors speculated whether this reflects a more aggressive maternal immune response against the invading interstitial trophoblast in male compared with female fetuses [42].

We also found different degrees of race-pathology association by gestational age categories. Literature on placental pathology differences by gestational age are few, and variable in gestational age cut-offs. Nonetheless, in comparing placental pathology between extreme ($23^{0/7}$-$27^{6/7}$ weeks), moderate ($28^{0/7}$-$33^{6/7}$ weeks) and late ($34^{0/7}$-$36^{6/7}$ weeks) preterm categories, Dogan et al. [43] have reported that inflammatory lesions were the predominant pathology in < 28 weeks gestational age groups, and chorioamnionitis has been reported as the most frequent pathological finding [44]. In contrast, we found that with regards to chronic inflammation, among African American births at ≥28 weeks gestation, the association was particularly striking with the aOR of 6.94 compared to 2.59 for < 23 weeks, possibly suggesting the effects of chronicity of inflammation with increasing gestational length.

Other placental differences by race and ethnicity have been described. For example, in a large northern California cohort from Kaiser Permanente, placenta previa was found to be most prevalent in Asian women (0.64%), followed by Native Americans (0.60%), AfricanAmericans (0.44%), Caucasian (0.36%) and Hispanic (0.34%) women [45]. In a cohort of very low birth weight (VLBW)infants, histological chorioamnionitis was present in 43% of the placentas from African American women, compared to 27% of those from Whites (OR 2.1, 1.5–2.8) [46]. Also described are racial differences in placental telomere length [47]: Jones et al. found shorter telomere length in placental samples from African American mothers compared with white mothers, suggesting possibly accelerated cellular aging across placental tissues. This is consistent with the “weathering hypothesis” proposed by Geronimus [48], whereby health disparities in African American women are presumed to be the consequence of cumulative socioeconomic disadvantage across generations that result in accelerated aging and earlier health decline.

Despite these speculations, our data lacked relevant demographic information that are known to correlate with stress, such as poverty, homelessness, residence in dangerous neighborhoods, domestic

Table 3
Associations between race and placental pathology.

	n	Unadjusted OR	Adjusted OR[a]
ACUTE INFLAMMATION			
White	296	Ref.	Ref.
African American (AA)	224	1,90 (1.32-2.72)	1.95 (0.87-4.37)
Female			
White	142	Ref.	Ref.
AA	92	1.47 (0.86–2.52)	1.89 (0.94–3.81)
Male			
White	154	Ref.	Ref.
AA	132	2.32 (1.42–3.79)	2.95 (1.55–5.61)
< 28 weeks			
White	123	Ref.	Ref.
AA	77	1.78 (1.00–3.17)	2.48 (1.33–4.63)
≥28 weeks			
White	173	Ref.	Ref.
AA	147	1.20 (1.13–3.04)	2.29 (1.09–4.79)
CHRONIC INFLAMMATION			
White	296	Ref.	Ref.
African American	224	3.44 (2.26–5.23)	3.35 (1.49–7.54)
Female			
White	142	Ref.	Ref.
AA	92	5.06 (2.60–9.87)	4.85 (2.35–10.02)
Male			
White	154	Ref.	Ref.
AA	132	2.57 (1.50–4.42)	3.03 (1.65–5.54)
< 28 weeks			
White	123	Ref.	Ref.
AA	77	2.51 (1.48–4.27)	2.59 (1.44–4.66)
≥28 weeks			
White	173	Ref.	Ref.
AA	147	5.87 (2.94–11.71)	6.94 (3.24–14.87)
FETAL VASCULAR PATHOLOGY			
White	296	Ref.	Ref.
African American	224	0.45 (0.25–0.80)	0.82 (0.29–2.32)
Female			
White	142	Ref.	Ref.
AA	92	0.98 (0.47–2.03)	0.84 (0.36–1.97)
Male			
White	154	Ref.	Ref.
AA	132	0.13 (0.04–0.43)	0.08 (0.02–0.38)
< 28 weeks			
White	123	Ref.	Ref.
AA	77	0.52 (0.23–1.18)	0.23 (0.08–0.70)
≥28 weeks			
White	173	Ref.	Ref.
AA	147	0.42 (0.18–0.97)	0.25 (0.08–0.81)
MATERNAL VASCULAR PATHOLOGYr PAt			
White	296	Ref.	Ref.
African American	224	0.77 (0.54–1.09)	1.01 (0.51–1.99)
Female			
White	142	Ref.	Ref.
AA	92	1.31 (0.78–2.22)	0.99 (0.54–1.82)
Male			
White	154	Ref.	Ref.
AA	132	0.51 (0.32–0.82)	0.44 (0.25–0.77)
< 28 weeks			
White	123	Ref.	Ref.
AA	77	0.52 (0.23–1.18)	0.64 (0.38–1.09)
≥28 weeks			
White	173	Ref.	Ref.
AA	147	0.42 (0.18–0.97)	0.62 (0.31–1.24)

[a] Adjusted for maternal age, preterm labor, steroids, gestational age, infant sex.

violence, and racial discrimination. Future studies should include measures of individual and neighborhood-level stressors to correlate with placental histopathology. For example, Miller et al. [49] accounted for measures of maternal socioeconomic disadvantage, in examining its association with transcriptional indications of immune activation and tissue maturation in placental biopsies. Their results of mRNA transcriptional patterns in economically disadvantaged mothers suggest the possibility that some of the biological substrates of life-course disparities may originate in utero.

Our study has several other limitations. One is the retrospective nature of this study and potential for bias due to unavailable placental records, although review of placental slides by a single perinatal pathologist masked to maternal race should have minimized such bias. In addition, because of the study's retrospective design, it is unclear whether these associations reflect a causal influence of stress. Second, variables of maternal race for this study relied on self-report, and exclusion of those who were either coded as “other” or “unknown”, may have resulted in some degree of bias or misclassification. Another major limitation is the lack of other social and biological variables known to be associated with both the exposure and outcome of interest for this study, namely race and preterm birth, such as maternal body mass index (BMI), parity, prenatal care utilization, educational attainment, and marital status. While some of these variables exist in the medical records, they were not abstracted into the study database, and it is possible that inclusion of these variables may have attenuated the findings. Finally, as a single-center study, our results will need to be confirmed in multi-center investigations for generalizability.

5. Conclusion

This study supports emerging evidence that race is associated with placental pathology in preterm births. Placental histopathology, in combination with established clinical and demographic variables, may be useful in understanding racial disparities in pregnancy outcomes.

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Contributors’ statement

Drs. Matoba and Mestan conceptualized and designed the study, carried out the analyses, drafted the initial manuscript, reviewed and revised the manuscript.

Dr. Ernst conducted the placental pathology examinations and Dr. Yallapragada designed the data collection.

Drs. Collins and Davis critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2019.06.385.

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