OBSTETRICS

Differences in placental telomere length suggest a link between racial disparities in birth outcomes and cellular aging

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BACKGROUND: Health disparities begin early in life and persist across the life course. Despite current efforts, black women exhibit greater risk for pregnancy complications and negative perinatal outcomes compared with white women. The placenta, which is a complex multi-tissue organ, serves as the primary transducer of bidirectional information between the mother and fetus. Altered placental function is linked to multiple racially disparate pregnancy complications; however, little is known about racial differences in molecular factors within the placenta. Several pregnancy complications, which include preeclampsia and fetal growth restriction, exhibit racial disparities and are associated with shorter placental telomere length, which is an indicator of cellular stress and aging. Cellular senescence and telomere dynamics are linked to the molecular mechanisms that are associated with the onset of labor and parturition. Further, racial differences in telomere length are found in a range of different peripheral tissues. Together these factors suggest that exploration of racial differences in telomere length of the placenta may provide novel mechanistic insight into racial disparities in birth outcomes.

OBJECTIVE: This study examined whether telomere length measured in 4 distinct fetally derived tissues were significantly different between black and white women. The study had 2 hypotheses: (1) that telomere length that is measured in different placental tissue types would be correlated and (2) that across all sampled tissues telomere length would differ by race.

STUDY DESIGN: In a prospective study, placental tissue samples were collected from the amnion, chorion, villus, and umbilical cord from black and white singleton pregnancies (N=46). Telomere length was determined with the use of monochrome multiplex quantitative real-time polymerase chain reaction in each placental tissue. Demographic and pregnancy-related data were also collected. Descriptive statistics characterized the sample overall and among black and white women separately. The overall impact of race was assessed by multilevel mixed-effects linear regression models that included empirically relevant covariates.

RESULTS: Telomere length was correlated significantly across all placental tissues. Pairwise analyses of placental tissue telomere length revealed significantly longer telomere length in the amnion compared with the chorion (t=−2.06; P=.043). Overall telomere length measured in placenta samples from black mothers were significantly shorter than those from white mothers (β=−0.09; P=.04). Controlling for relevant maternal and infant characteristics strengthened the significance of the observed racial differences (β=−0.12; P=.02). Within tissue analyses revealed that the greatest difference by race was found in chorionic telomere length (t=−2.81; P=.007).

CONCLUSION: These findings provide the first evidence of racial differences in placental telomere length. Telomere length was significantly shorter in placental samples from black mothers compared with white mothers. Given previous studies that have reported that telomere length, cellular senescence, and telomere dynamics are molecular factors that contribute to the rupture of the amniotic sac, onset of labor, and parturition, our findings of shorter telomere length in placentas from black mothers suggest that accelerated cellular aging across placental tissues may be relevant to the increased risk of preterm delivery in black pregnancies. Our results suggest that racial differences in cellular aging in the placenta contribute to the earliest roots of health disparities.

Key words: cellular aging, health disparity, placenta, pregnancy complication, race, telomere length

Health disparities are well documented, beginning early in life and persisting over the life course.[1] Non-Hispanic black women have higher rates of preterm delivery, low birthweight infants, and infant mortality relative to non-Hispanic white women.[2-7] In addition, racial differences in pregnancy complications that include preeclampsia, gestational diabetes mellitus (GDM), and fetal growth restriction (FGR) also exist,[5,7,8] which likely contributes to other infant health disparities across the first year of life. Despite substantial efforts and heightened awareness, these disparities persist. Increased understanding of the underlying mechanisms and how they contribute to perinatal outcomes are needed.[9]

The placenta is a critical organ at the interface between the fetus and mother because it coordinates maternal physiology and fetal development. The human placenta is comprised of maternally and fetally derived tissues with interdigitated vascular flow. The fetal portion includes 4 anatomically distinct tissues: amnion, chorion, villus, and umbilical cord, all of which exhibit unique gene expression profiles and different time points of differentiation during fetal development.[10-13] The vascularized villus is the main site of oxygen and nutrient exchange; the umbilical cord enables fetoplacental circulation.[14] The amnion and chorion protect the developing fetus and facilitate nutrient and hormone transfer between the mother and fetus.[10,11,13] Pregnancy complications that exhibit racial

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disparities, which include preeclampsia, GDM, preterm birth, and premature rupture of membranes are all associated with altered placental physiologic condition, metabolism, and function.[15-20] As such, exploration of racial differences in placental function may provide insight into the mechanisms underlying early health disparities.

One biologic marker that is associated with altered placental function and these pregnancy complications is telomere length (TL). Telomeres are nucleoprotein complexes that cap chromosomes in eukaryotic cells, that are essential for cell survival and chromosome stability, and that influence cellular differentiation, senescence, and apoptosis.[21-23] Shortening of TL has been associated with cellular aging; TL is influenced by DNA repair mechanisms, oxidative stress, and inflammation.[24] TL tends to be highly correlated across tissues at birth, but this correlation lessens as an individual ages.[25-27] Shorter placental TL has been associated with racially disparate pregnancy complications such as FGR, GDM, and preeclampsia.[5,8,28-32] Correlations among placental TL and gestational age, socioeconomic status, and parity have also been reported.[30,33,34] To date no previous studies have addressed racial differences in placental TL. Previous studies of placental TL have used DNA that was extracted from an array of sites, with inconsistent attention to confounding maternal tissue, inclusion of multiple cell tissue types, or failure to define the specific sampling site altogether.[28-31,34,35] Given the complexity of placenta, these methodologic variations curtail their generalizability and warrant further investigation.

Racial differences in TL have also been observed, for which black newborn infants and adolescents exhibit longer TL than white infants.[36-38] Longer TL and associated greater TL attrition across the life course has been reported in black adults, although some debate exists.[37,39-41] Longer initial TL is a predictor of increased TL attrition over time and, consistent with this, an aged cohort of black infants displayed shorter TLs than white infants.[42,43] From an aging and health disparities perspective, the placenta represents a unique opportunity to examine racial differences in cellular aging, given its definitive lifespan and the molecular evidence pointing to a role of cellular aging and telomeres in parturition.[44-47]

To better understand how placental factors may contribute to persistent racial disparities in perinatal outcomes, this study examined both the correlation of TL across fetally derived tissues and racial differences.

Materials and Methods

Subjects

Subjects were a subset of mothers (n=46) who were recruited January 2015 from a larger longitudinal study in New Orleans, LA, and who consented to placental collection. Recruitment of pregnant women, aged 18-41 years, took place in prenatal and Women, Infant, and Children clinics and from other ongoing studies that involved pregnant women at Tulane University. The women were at least 18 years of age, English-speaking, and pregnant with a singleton fetus. They provided information via a face-to-face interview-assisted computer survey (Questionnaire Development System; Nova Research, Bethesda, MD) that was conducted by trained interviewers. This study was approved by the Tulane University Institutional Review Board.

Demographic (eg, maternal and infant characteristics) and pregnancy-related data were collected by maternal report and medical record abstraction. Data that were collected by maternal report included maternal age at conception, race, and education level. Data collected from medical records included gestational age, infant birthweight, infant sex, delivery mode, parity, and pregnancy complications. Pregnancy complications included preeclampsia, FGR, GDM, gestational hypertension, and eclampsia/preeclampsia. Given the low prevalence of individual pregnancy complications in the sample, a composite categoric variable (yes/no) was created.[48]

Placental tissue sample collection

Placenta collection and dissection occurred within approximately 1 hour of delivery. The reflected fetal membranes (eg, amnion and chorion) were separated manually, isolated, and excised >4 cm from the fusion to the placental disk. For fetal villus tissue sampling, the chorionic plate was removed, and approximately 2 cm of fetal villus tissue was excised within approximately 4 cm of the umbilical cord insertion site. Fetal villus samples were collected just below the chorionic plate to avoid sampling maternal villi, and visible vasculature was excised. Umbilical cord samples were collected within approximately 4 cm of the insertion site after removal of any fused membranes. Tissues were washed thoroughly in 1 mol/L phosphate-buffered saline solution to minimize contamination from blood or atrophied villi. Samples were flash frozen in liquid nitrogen and stored at −80°C. DNA was extracted from placental tissues with the use of QIAamp DNA mini kit protocol for tissues (Qiagen, Valencia, CA). Samples were evaluated for double-stranded DNA integrity and concentration by Qubit dsDNA BR assay kit (Invitrogen, Carlsbad, CA) and for purity by NanoDrop-2000 (Thermo Fisher Scientific, Waltham, MA). DNA was stored at −35°C.

Telomere length measurement

The average relative TL, as represented by the T/S ratio, was determined by monochrome multiplex quantitative real-time polymerase chain reaction and standard methods in our laboratory.[36,49] All tissue samples from each individual placenta were run on the sample duplicate plates; all samples were run with the same control purchased genomic placental DNA from a single donor (BioChain Institute Inc, Newark, CA). Coefficient of variance (CV) for the whole sample was 2.12% for all plates. Samples (n=4) with unacceptably high CV were repeated.

Statistical analysis

Descriptive statistics characterized the sample overall and among black and white women with chi-square and *t*-tests. One black infant birthweight exceeded 3 standard deviations above the mean and was winsorized for analyses.

The duration between delivery and sample collection was missing for 4 deliveries, and the mean duration by delivery type was imputed. Spearman correlation coefficients compared crude relationships between TL across the 4 placental tissue types. The normality of TL was examined with the use of visual inspection of plots, skewness, and kurtosis. TL was distributed normally.

Multilevel analysis with mixed-effects linear regression models was used to produce intraclass correlation coefficients (ICC) to estimate the degree of within individual correlation of TL across the 4 tissue types. First, we examined an empty model (regressing TL without covariates) to determine the degree of association among TLs within individuals and to allow for decomposition of the variation in TL into between- and within-individual variation (Model 1). Next, we added maternal race and a tissue type indicator variable in a model with randomly distributed individual-specific intercepts (Model 2). We tested for heterogeneity in the relationship between tissue type and TL among individuals by fitting this model with tissue type as a random effect in addition to the random intercept. Because of statistical power considerations, clustering TL at both the level of the individual and tissue type was not feasible. The study hypotheses explored differences between race at the level individual above tissue type and therefore clustered TL within an individual. Model 2 was used to test for an interaction between race and tissue type to determine whether the relationship between TLs across tissues differed between racial groups. Finally, we fit a model that included empirically relevant covariates with a fixed slope value for each predictor variable and random individual-specific intercepts (Model 3). We used this fully adjusted model to test for an interaction between race and tissue type to determine whether the relationship between TL across tissues differed between racial groups.

In a sensitivity analysis, we repeated the modeling after excluding the chorion (the tissue type with the largest racial difference in TL) to assess the degree to which the chorion drove the race effect. All analyses were conducted with the use of SAS software (version 9.4; SAS Institute, Inc, Cary, NC).

Results

Placental tissue TL was available from 46 pregnancies (black, 34; white,12). Mean age at conception was 27 years, and 63% of women attained at least some college education (Table 1). Most deliveries were vaginal (56.5%), and all infants were born at term. Collection of placental

TABLE 1
Demographic characteristics and pregnancy-related outcomes of study participants

Variable	Total (N=46)	Black (n=34)	White (n=12)	*P* value
Descriptive outcome, mean±SD				
Maternal conception age, y	26.94±6.73	26.50±6.94	28.17±6.19	.467
Gestational age, wk	38.94±1.14	38.76±1.23	39.42±0.67	.029
Infant birthweight, kg	3.28±0.56	3.21±0.54	3.49±0.58	.140
Duration to sample collection, min	44.52±29.56	44.78±29.24	43.77±31.76	.920
Parity	1.11±1.35	1.21±1.50	0.83±0.84	.293
Infant sex, % (n)				.883
Male	56.5 (26)	55.9 (19)	58.3 (7)	
Female	43.5 (20)	44.1 (15)	41.7 (5)	
Delivery mode, % (n)				.410
Vaginal	56.5 (26)	52.9 (18)	66.7 (8)	
Cesarean section	43.5 (20)	47.1 (16)	33.3 (4)	
Maternal education level, % (n)				.001
<High school	37.0 (17)	44.1 (15)	16.7 (2)	
<Some college	32.6 (15)	41.2 (14)	8.3 (1)	
≥College degree	30.4 (14)	14.7 (5)	75.0 (9)	
Pregnancy complications, % (n)				.300
No	73.9 (34)	67.7 (23)	83.3 (10)	
Yes	26.1 (12)	32.4 (11)	16.7 (2)	

Groups were compared with the use of *t*-tests, chi-squared tests, or Fisher's exact test, where appropriate. Pregnancy complications included preeclampsia/eclampsia, fetal growth restriction, gestational diabetes mellitus, and gestational hypertension.

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tissue samples occurred on average 45 minutes after delivery.

There were no racial differences in maternal age at conception, delivery mode, duration between delivery and sample collection, infant birthweight, composite maternal pregnancy complications, parity, or infant sex (Table 1). A greater proportion of white women attained a college degree or higher (P=.001); infants born to black women had earlier gestational age (P=.029).

The rank order of placental tissue TLs from longest to shortest was amnion, which exhibited the longest TL with a mean of 0.877±0.15 T/S (black = 0.862±0.16 T/S; white = 0.919±0.09 T/S), cord with a mean of 0.845±0.15 T/S (black = 0.829±0.16 T/S; white = 0.891±0.10 T/S), and villus with a mean of 0.831±0.16 T/S (black = 0.806±0.16 T/S; white = 0.900±0.15 T/S); the shortest was the chorion with a mean of 0.812±0.16 T/S (black = 0.776±0.15 T/S; white = 0.912±0.12 T/S). Chorionic TL was significantly shorter than TL from the amnion (t=−2.06; P=.043); no other pairwise comparisons between tissues were significant (Figure 1). Crude racial differences were observed in chorionic TL (t=−2.81; P=.007); villus TL approached significance (t=−1.80; P=.079), where placentas from black pregnancies exhibited shorter TL relative to white pregnancies (Figure 2).

TL was correlated positively across placental tissues (Table 2). Correlation coefficients between placental tissue types ranged from 0.67−0.53. A high degree of correlation across placental tissue types from within the same individual was evident in the mixed effects empty model (Model 1; ICC, 60.6%), which indicated that most of the variance was accounted for by differences between individuals (Table 3).

Estimates from Model 2 indicated that, independent of the tissue type, placental TL was shorter among black pregnancies (β=−0.09; P=.04). Positive β estimates for amnion, villus, and cord tissues indicated longer TLs relative to chorion, with the difference between amnion and chorion being largest (β=0.07; P=.0011). Allowing the relationship between TL to vary across tissues randomly between individuals did not change the estimate that was associated with race. Race did not significantly interact with placental tissue type, which indicates that the relationship between TL and race was consistent across tissue types.

The main effect of race remained significant when we accounted for empirically relevant covariates: infant sex, maternal education and age at conception, gestational age, and duration to sample collection (Table 3; Model 3). The ICC that was derived from Model 3 (ICC, 61.4%) was higher than Model 1 (ICC, 60.6%), given the addition of covariates that captured a greater proportion of the variance in TL between individuals. None of the empirically relevant covariates in Model 3 were associated with placental TL. Delivery mode, parity, and composite pregnancy complications were not associated with placental TL and not included in final model.

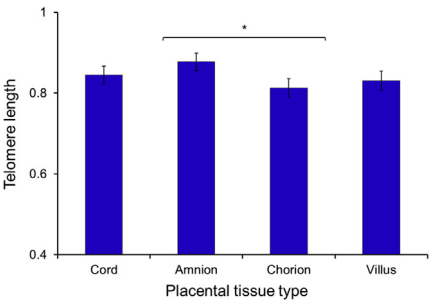
Sensitivity analysis that excluded chorion resulted in an attenuated racial difference in Model 2 (black vs white: β=−0.07; P=.10) but remained significant in Model 3 (black vs white: β=−0.10; P=.045).

Comment

TL from fetally derived placental tissues was significantly shorter in placentas from pregnancies of black, compared with white, mothers. This finding is the inverse of racial differences in TL that has been reported in newborn infants, adolescents, and adults, where black placentas exhibited longer TL than white placentas.[36-38,40,41] However, it is consistent with reports of accelerated TL decline in black women in adulthood.[42] Although racial differences in maternal education and gestational age existed, these were not associated significantly with TL, and their inclusion did not alter results, nor did the inclusion of pregnancy complications or parity. Crude placental TL pairwise comparison revealed the greatest racial difference in TL was in the chorion.

In this study, black mothers had shorter gestational periods relative to white mothers, which was evident only in vaginal deliveries; there was no racial difference in the gestational period for cesarean deliveries. However, along with a shorter gestational period, black mothers also exhibited shorter placental TL. Because earlier gestational age is associated with longer TL, the results indicate that larger studies with matched gestational ages may reveal larger racial differences.[30] Shorter TL is an indicator of accelerated aging and cellular stress. Shorter TL in placentas from black pregnancies may reflect accelerated cellular aging. This is consistent with the "Weathering Hypothesis" proposed by Geronimus[50] whereby health disparities in black women are presumed to be the consequence of cumulative socioeconomic disadvantage across generations that resulted in accelerated aging and earlier health decline. This model is supported by data that found greater allostatic load in black mothers relative to white mothers beyond differences in socioeconomic status.[51] If gestational age is considered to be the "age" of the placenta, the findings of shorter TL with earlier gestational age in black placentas offer novel evidence that the molecular processes that is related to racial

FIGURE 1
Placental tissue telomere length across all tissue types



The bar graph of telomere length by placental tissue type for all subjects shows the mean and the standard error of the mean for each group. *T*-tests examined crude differences of placental telomere length between tissue types. Chorionic telomere length was significantly shorter than amnionic telomere length (t=−2.06; P=.043). The *asterisk* indicates a probablity value of <.05.

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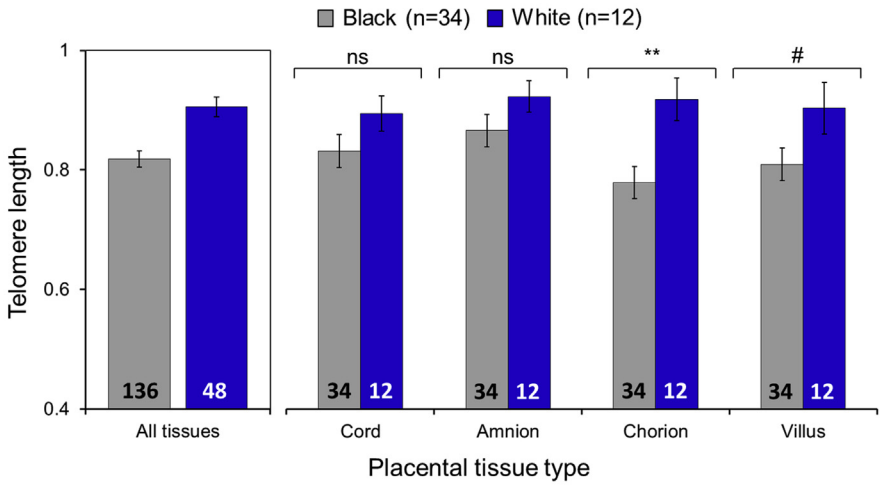
FIGURE 2
Crude racial differences in placental tissue telomere length



The bar graph shows telomere length by all placental tissues and by placental tissue type stratified by race, where placental tissues from black pregnancies are *grey* and tissues from white pregnancies are *blue*. The mean and and the standard error of the mean are presented for each group. *Numbers* represent total number of samples for individual bars. Chorionic telomere length exhibited the greatest difference between racial groups (t=−2.81; *P*=.007); villus telomere length showed a marginal difference between races (t=−1.80; *P*=.079). The *pound sign* indicates a probability value of <.1; the *double asterisks* indicate a probability value of <.01.

ns, not significant.

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differences in TL attrition and cellular aging found in older adults may be programed in utero.

The placenta represents a unique organ system in which the aging process is accelerated and occurs within gestation and ending at delivery. Across a variety of different cell types, TL shortening triggers cellular senescence and the activation of apoptotic pathways. Within placental trophoblasts, decreased TL has been reported to trigger apoptosis, increase proinflammatory cytokines, and result in the release of cell-free fetal DNA.[45,46] Increased inflammation and cell-free fetal DNA contribute to the onset of labor.[45,46] Increases in cellular senescence and inflammatory markers in the chorioamniotic membrane are reported in women who are in active labor at term compared with women who delivered at term but not in active labor.[44-46,52] Preterm premature rupture of membranes has been hypothesized to be linked to increased cellular senescence because of oxidative stress and, consistent with this pathway, exhibited shorter placental membrane TL relative term births.[47,53,54] In term births, telomere fragments from the amniochorion that are shed into the amniotic fluid elicit oxidative stress and contribute to the onset of parturition.[55] The chorion contains the most trophoblast cells of the membranes, and trophoblast dysfunction and senescence are relevant for rupture of the amniotic sac. Our findings that chorionic TL is both the shortest across placental tissues and has the greatest racial difference, when combined with a molecular mechanism linked to parturition and rupture of amniotic membranes provide intriguing initial evidence that accelerated cellular aging and TL decline, specifically in the chorion, may contribute mechanistically to the higher incidence of preterm births in black women.

Placental collection is fraught with methodologic challenges that begin with issues that are related to the time of collection. Placentas for this study were collected approximately 45 minutes after partition (range, 6−128 minutes). Practical issues related to placenta collection underlie inconsistencies in the duration between parturition and sample collection in previous placental TL studies in which durations ranged from 20 minutes to 24 hours.[29,30,33] In this study, the duration between parturition and placenta collection was not associated with TL, which suggests that this window of time (eg, <2 hours) is an acceptable interval for telomere studies; however, caution is warranted before extending this interval to other epigenetic or RNA studies. Controlled time course studies of TL, RNA expression, and other epigenetic markers are needed to determine the optimal collection parameters.

Despite the strengths of this study, limitations exist. The number of individual placentas was small, although similar to previous epigenetic and molecular studies in placentas. Analyses that leveraged samples across 4 tissue types partially mitigates the concern of sample size; however, larger studies are needed. Racial groups were unbalanced as a result of initial study design, and demographic differences existed but did not alter the findings. Despite population data that showed racial differences in pregnancy complications and studies that were associated with shorter placental TL with pregnancy complications, composite pregnancy complications did not predict placental TL significantly (data not shown). Inclusion of composite pregnancy complications in the final model (Model 3) did not alter significant findings and was not an independent predictor of placental TL. This is likely a function of sample size or the low incidence of pregnancy complications. Although placental TL has been associated inversely with gestational age, no association was found in this study.[30] This may be due to the inclusion of only term deliveries (>37 weeks of gestation) or that the previous study was racially homogeneous.[30] Concerns about inter- and intraassay variability for the monochrome multiplex quantitative real-time polymerase chain reaction method also exist. To address this concern, we integrated several protocol adaptations. First, we used commercially available

TABLE 2
Spearman correlation between placental tissue telomere length and relevant covariates

Outcome	Telomere length				Duration to sample collection, min	Gestational age, wk
	Cord	Amnion	Chorion	Villus		
Telomere length						
Cord	1					
Amnion	0.640[a]	1				
Chorion	0.543	0.613[a]	1			
Villus	0.665	0.526[b]	0.540[b]	1		
Duration to sample collection, min	0.343[c]	0.233	0.190	0.094	1	
Gestational age, wk	−0.016	−0.017	−0.011	−0.018	−0.108	1
Maternal conception age, y	−0.011	−0.018	0.067	0.112	0.138	−0.165

Spearman rank correlation coefficient values are given.

[a] $P<.0001$; [b] $P<.001$; [c] $P<0.05$.

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reference genomic DNA from a single placenta. Second, to minimize the potential for plate-to-plate variability that would influence the findings, all samples from the same placenta were run on matched duplicate plates. Third, a stringent quality control algorithm for polymerase chain reaction efficiencies and CVs was used; the resultant CV across all samples was 2.12%. Blood contamination remains a challenge for all molecular studies of the placenta. Although all samples were washed thoroughly to reduce blood contamination, minimal contamination is probable. The chorion contains microscopic maternal vasculature that also may contribute to measurement of TL in the chorion. Future studies that will include maternal TL as a covariate or other histopathologic measurements of TL (ie, quantitative fluorescence in situ hybridization) can address concerns of blood and maternal contamination. However, these techniques are time intensive, and a balance between contamination and feasibility is needed for larger studies.

TABLE 3
Multilevel modeling results for estimates of association with placental tissue telomere length

	Intraclass correlation coefficient				
	Model 1: empty model	Model 2: race and tissue type		Model 3: full model	
	60.6%	60.4%		61.4%	
Variable		β	*P* value	β	*P* value
Race					
White		Reference		Reference	
Black		−0.09	.04	−0.12	.02
Placental tissue type					
Chorion		Reference		Reference	
Amnion		0.07	.001	0.07	.001
Villus		0.02	.35	0.02	.35
Cord		0.03	.10	0.03	.10
Infant sex				−0.008	.86
Maternal education				−0.02	.44
Maternal age				0.0001	.96
Gestational age				−0.02	.52
Duration to sample collection				0.001	.13

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This is the first study to identify racial differences in placental TL that represents the earliest developmental time point when differences have been reported in TL. The low prevalence of pregnancy complications in this cohort limits the ability to make direct inferences in this sample. However, the findings of shorter placental TL in black women suggests that accelerated cellular aging is 1 mechanism that contributes to persistent racial disparities in birth outcomes, particularly preterm birth and preterm rupture of membranes. Future studies that will examine placental TL in larger sample sizes and in preterm deliveries in both races are needed. The findings also highlight that, although correlated, differences between placental tissue types exist. Careful examination of

both similarities and differences in placental tissues is an important area of future placental research that may enhance the understanding of typical and atypical placental function. Larger studies are needed to better define the implications of shorter chorionic TL in placentas from pregnancies of black women and their potential contribution to racial differences in preterm birth. From a clinical perspective, confirmation of accelerated placental aging in black pregnancies may lead to novel approaches to decreasing preterm birth that will be focused on telomere dynamics, oxidative stress, and apoptosis-related inflammation. Decreasing the rate of preterm birth in black pregnancies represents a critical starting point truly to shift the needle on the earliest roots of racial health disparities. ■

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