Racial Disparities in Delivery Gestational Age among Twin Pregnancies

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Abstract

Objective   This study aims to estimate the association between maternal race and delivery gestational age among women with twin gestations.

Study Design   Secondary analysis of a prospective, randomized control trial of 17-α hydroxyprogesterone caproate versus placebo for preterm birth (PTB) prevention in twin gestations. Non-Hispanic (NH) black and whites were included. Demographic and antenatal characteristics were compared. The primary outcome was delivery gestational age. Secondary outcomes included a composite of major neonatal morbidity. Kaplan–Meier curves estimated survival probabilities for delivery gestational age by race. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI).

Results   A total of 535 women with twin gestations were included; 150 were NH black. NH blacks delivered earlier than NH whites (33.6 ± 4.8 weeks vs. 35.1 ± 3.5 weeks, $p < 0.001$). Differences in delivery gestational age between NH blacks and whites were consistent across gestation. In adjusted analyses, NH black race (HR: 1.24, 95% CI: 1.02–1.51), prior PTB (HR: 1.59, 95% CI: 1.15–2.19), and cerclage (HR: 3.90, 95% CI: 2.00–7.60) were associated with an increased risk of earlier delivery. Major neonatal morbidity was higher for NH blacks compared with NH whites (12.7 vs. 7.0%, $p = 0.036$).

Conclusion   NH blacks with twin gestations have an increased risk of early delivery and neonatal morbidity compared with NH whites.

Keywords
► preterm birth
► health disparities
► twins

Preterm birth (PTB) is the leading cause of infant morbidity and mortality among nonanomalous neonates in the United States[1] and survivors face increased short- and long-term morbidities that may result in a lifetime of medical disability.[2] In adulthood, survivors are at an increased risk for adult-onset chronic metabolic, cardiovascular, and renal diseases compared with their term counterparts.[3–5] The burden of PTB extends well beyond individuals and families. The Institute of Medicine estimated that the annual societal cost of PTB in the United States was at least $26.5 billion in 2005.[6]

After reaching an unacceptably high rate in 2007, the PTB rate met a modest decline from 2007 to 2014, followed by a concerning increase between 2014 and 2015.[7] Though the overall rate of PTB in 2015 was 9.6% in the United States, the rate for non-Hispanic blacks was 50% higher than non-Hispanic whites (13.4%).[8] Unfortunately, the reason for this disparity remains unclear, as the etiologies underlying PTB are numerous and complex and a precise cause of PTB is often difficult to ascertain.[9] Differences in socioeconomic status, risky behaviors during pregnancy, and access to prenatal care may explain some of the disparity in birth

outcomes between black women and those of other races.[10] However, PTB disparities often persist after controlling for these factors.[11–14]

In 2015, the incidence of twin birth was 33.5 per 1,000 total births and PTB was 7.5 times more common in twins than singletons.[8] Though race and plurality are significant independent risk factors for PTB, as well as other adverse perinatal outcomes, little is known about racial differences in delivery gestational age among twin gestations. The objective of this study was to assess the association between maternal black race and gestational age at delivery among a large cohort of women with twin gestations. We also sought to evaluate whether the frequency of adverse pregnancy and neonatal outcomes varies between non-Hispanic black and white women.

Materials and Methods

This is a secondary analysis of women with uncomplicated twin gestations enrolled from April 2004 to February 2006 in a multicenter, prospective double-blind randomized controlled trial of 17-α hydroxyprogesterone caproate (17-OHPC) versus placebo for the prevention of PTB conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.[15] Briefly, the trial enrolled 661 pregnant women with twin gestations and randomized them to receive either weekly 17-OHPC injections or placebo starting at $16^{0/7}$ to $20^{3/7}$ weeks gestation continuing through 35 weeks gestation or delivery, whichever occurred first. Women carrying fetus(es) with major congenital anomalies, those with a spontaneous fetal death after 12 weeks, mono-amniotic twins, suspected twin–twin transfusion syndrome, marked growth discordance, major uterine anomalies, cerclage or planned cerclage, major chronic medical diseases, and twins resulting from intentional fetal reduction were excluded from randomization in the original trial. All patients had a midtrimester ultrasound to confirm or determine gestational age. The trial found no reduction in PTB <37, <35, or <32 weeks gestation or initial neonatal outcomes with 17-OHPC treatment. The original study was approved by each of the 14 clinical sites' institutional review boards (IRB) and the biostatistics coordinating center. A written informed consent was obtained from all subjects before randomization. This secondary analysis used a de-identified dataset and was considered exempt after review by the IRB at the University of North Carolina, Chapel Hill.

For the purpose of this analysis, only self-identified non-Hispanic black and non-Hispanic white women were included. Women of other racial/ethnic groups were excluded due to insufficient sample sizes. Demographic factors (e.g., maternal age, race, educational attainment, marital status), prior pregnancy characteristics (e.g., history of PTB, delivery gestational age of last pregnancy ≥ 14 weeks), and antenatal factors (e.g., tobacco use, baseline cervical length, bacterial vaginosis, chorionicity, conception by assisted reproductive technology) were compared between non-Hispanic black and non-Hispanic white women. The primary outcome

was the gestational age at delivery. Secondary outcomes were selected pregnancy and neonatal outcomes, including a composite of major neonatal morbidity, defined as a diagnosis of at least one of the following complications before initial hospital discharge: fetal or neonatal death, grade III or IV intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, or necrotizing enterocolitis stage II or III. For neonatal outcomes, the unit of analysis was the pregnancy, and if the outcome occurred in the fetus or neonate, then the pregnancy was considered to have the outcome.

Demographic and clinical characteristics and pregnancy and neonatal outcomes were compared by maternal race using student t-test, chi-square, or Fisher's exact test as appropriate. Gestational age at delivery was compared between non-Hispanic black and non-Hispanic white women using Kaplan–Meier survival curves, and the survival distributions were compared using the log-rank test. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between selected characteristics and delivery gestational age. Stepwise regression with backward elimination was used to select an adjusted model. Initial models included variables significant in bivariate analyses. Main effects were retained in the model if p values were < 0.20. Variables were considered statistically significant in the final model only if p values were < 0.05. All statistical analyses were performed with STATA software (version 14.0; Stata Corporation, College Station, TX).

Results

Of the 661 pregnant women with twin gestations enrolled in the original trial, 535 were self-identified as either non-Hispanic black ($n = 150$, 28.0%) or non-Hispanic white ($n = 385$, 72.0%) and met inclusion criteria for this secondary analysis. Demographic and clinical characteristics are compared between non-Hispanic black and non-Hispanic white women in ►Table 1. Non-Hispanic black women were more likely to be younger, nulliparous, report tobacco use during the current pregnancy, have a history of PTB, preexisting hypertension, bacterial vaginosis, and cervical infection resulting from trichomonas and/or chlamydia during pregnancy as compared with non-Hispanic white women. They were less likely to be married, have a high school education, and conceive via assisted reproductive technology. In addition, non-Hispanic black women had higher body mass index and shorter initial cervical lengths than non-Hispanic white women. Other characteristics were similar between the two groups.

Overall, non-Hispanic black women delivered earlier than non-Hispanic white women (mean delivery gestational age: 33.6 ± 4.8 weeks vs. 35.1 ± 3.1 weeks; $p < 0.001$) (data not shown). In addition, a higher proportion of non-Hispanic black women delivered preterm for each of the prespecified gestational age cutoffs: <28 weeks (13.3 vs. 4.9%, $p = 0.001$), <34 weeks (36.0 vs. 24.7%, $p = 0.009$), and <37 weeks (77.3 vs. 66.5%, $p = 0.014$), ►Fig. 1.

**Table 1** Maternal demographics and clinical characteristics by race

Characteristics[a]	Non-Hispanic Black (n = 150)	Non-Hispanic White (n = 385)	p value
Maternal age (y)	26.3 ± 6.3	31.8 ± 6.0	<0.001
Married	52 (34.7)	352 (91.4)	<0.001
Nulliparous	41 (27.3)	199 (51.7)	<0.001
Pre-pregnancy body mass index (kg/m²)	30.8 ± 8.3	25.7 ± 5.8	<0.001
High school education or greater	118 (78.7)	370 (96.1)	<0.001
Prior preterm birth < 37 weeks' gestation	20 (14.7)	23 (7.4)	0.015
Delivery gestational age of last pregnancy[b]	37.6 ± 5.3	37.6 ± 5.0	0.980
Conceived by assisted reproductive technology	8 (5.3)	205 (53.3)	<0.001
Dichorionic placentation	127 (86.4)	333 (86.7)	0.922
Bacterial vaginosis	17 (11.3)	3 (0.8)	<0.001
Trichomonas and/or chlamydia	11 (7.3)	5 (1.3)	0.001
Baseline transvaginal cervical length obtained	50 (33.3)	124 (32.2)	0.803
Initial transvaginal cervical length (mm)	38 ± 7	41 ± 7	0.015
Baseline cervical length <25 mm	3/50 (6.0)	1/124 (0.8)	0.072
Cerclage placed[c]	5 (3.3)	4 (1.0)	0.125

[a]Data presented as n (%) or mean ± standard deviation.
[b]≥ 14 weeks among 227 multiparous women (72 black and 155 white).
[c]After randomization.

Across all gestational ages, the Kaplan–Meier survival analysis demonstrated that non-Hispanic blacks consistently delivered earlier than non-Hispanic whites, log-rank $p = 0.004$, ►**Fig. 2**. In the multivariable Cox model, black race (HR: 1.24, 95% CI: 1.02–1.51), prior PTB (HR: 1.59, 95% CI: 1.15–2.19), and the presence of a cervical cerclage (HR: 3.90, 95% CI: 2.00–7.60) were associated with an increased risk of earlier delivery (►**Table 2**).

Pregnancy and neonatal outcomes are compared by race in ►**Table 3**. Non-Hispanic black women were more likely to have spontaneous deliveries (due to spontaneous onset of contractions or rupture of membranes leading to delivery) compared with non-Hispanic whites (66.7 vs. 50.4%, $p = 0.001$). Among

those delivering due to medical or fetal indications, non-Hispanic black women were more likely to deliver due to fetal complications including oligohydramnios, nonreassuring fetal status, and intrauterine growth restriction. Non-Hispanic blacks were less likely to deliver live births (95.3 vs. 98.7%, $p = 0.018$). Fetal or neonatal death (9.3 vs. 3.1%; $p = 0.006$) and composite major neonatal morbidity (12.7 vs. 7.0%, $p = 0.036$) rates were higher among non-Hispanic blacks compared with non-Hispanic whites. In limited regression models, both gestational age and black race remained significant modifiers of the risk for the major composite neonatal morbidity ($p < 0.20$, data not shown). Additional outcomes are shown in ►**Table 3**.
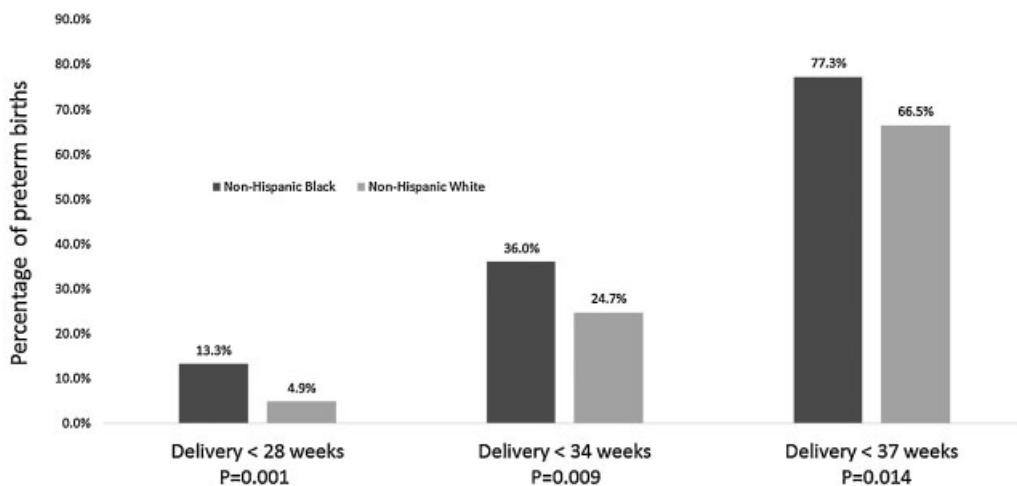
Fig. 1 Percentage of preterm births by maternal race.
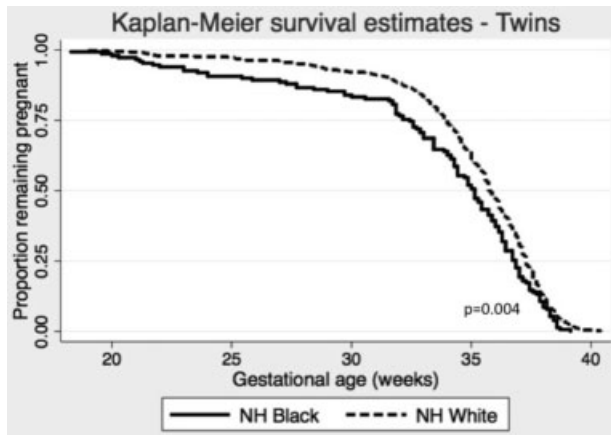
Fig. 2 Kaplan–Meier survival curves of proportions of twin gestations remaining pregnant, by maternal race.

Table 2 Multivariable Cox regression of factors related to gestational age at delivery in twin gestations

Characteristics	Hazard ratio[a]	95% Confidence interval	p Value
Non-Hispanic black	1.24	1.02–1.51	0.031
Prior preterm birth	1.59	1.15–2.19	0.004
Cerclage	3.90	2.00–7.60	<0.001
Tobacco use	1.22	0.93–1.60	0.142

[a]Other factors considered in initial models included education, cervical infection with trichomonas or chlamydia, and history of one or more preterm births.

Table 3 Pregnancy and neonatal outcomes

Outcomes[a]	Non-Hispanic black (n = 150)	Non-Hispanic white (n = 385)	p value
Preeclampsia or gestational hypertension	25 (16.7)	74 (19.2)	0.494
Oligohydramnios	4 (2.7)	12 (3.1)	>0.99
Polyhydramnios	1 (0.7)	4 (1.0)	>0.99
Abruption	5 (3.3)	7 (1.8)	0.332
Chorioamnionitis	3 (2.0)	6 (1.6)	0.716
Preterm premature rupture of membranes	19 (12.9)	46 (12.1)	0.797
Received tocolysis at any time	40 (26.9)	109 (28.3)	0.735
Received antenatal corticosteroids	41 (27.5)	102 (26.5)	0.811
Delivered due to spontaneous labor or rupture of membranes	100 (66.7)	194 (50.4)	0.001
Delivered due to maternal and/or fetal indications:	50 (33.3)	191 (49.6)	0.001
Hypertensive disorders of pregnancy	14/50 (28.0)	64/189 (33.9)[b]	0.432
Nonreassuring fetal status, fetal growth restriction, oligohydramnios	17/50 (34.0)	35/189 (18.5)	0.018
Vaginal delivery	60 (40.5)	161 (42.2)	0.737
Livebirth (both twins)	141/148 (95.3)	377/382 (98.7)	0.018
Birthweight (first-born twin)	2085.8 ± 602.0	2363.9 ± 630.2	0.001
Delivered between enrollment and 23 weeks gestation	9 (6.0)	8 (2.1)	0.028
Neonatal intensive care unit admission	70 (49.7)	177 (47.0)	0.585
Neonatal sepsis	7 (5.0)	12 (3.2)	0.337
Respiratory distress syndrome	22 (15.6)	40 (10.6)	0.119
Composite major neonatal morbidity	19 (12.7)	27 (7.0)	0.036
Necrotizing enterocolitis, stage II or III	1 (0.7)	1 (0.3)	0.471
Intraventricular hemorrhage, grade III or IV	0 (0.0)	3 (0.8)	0.566
Periventricular leukomalacia	3 (0.80)	2 (1.4)	0.617
Bronchopulmonary dysplasia	3 (2.1)	11 (2.9)	0.768
Fetal or neonatal death	14 (9.3)	12 (3.1)	0.006

[a]Data presented as n (%) or mean ± standard deviation.
[b]Two women with delivery for maternal/fetal indications had unknown specific indications for delivery.

Comment

We found that non-Hispanic black women with twin gestations were more likely to deliver at <37, <34, and <28 weeks. They were also more likely to deliver between study enrollment and 23 weeks gestation, though the study design limits our ability to draw conclusions about previable delivery in this population. On average, non-Hispanic blacks delivered 1.5 weeks earlier than non-Hispanic whites. In our adjusted model, black race, history of PTB, and cerclage presence were associated with earlier delivery. We also found that non-Hispanic blacks were less likely to deliver live births. The rates of composite major neonatal morbidity and perinatal death were higher for non-Hispanic blacks compared with non-Hispanic whites.

Previous studies have examined racial disparities in PTB, but most have been limited to study populations of singleton gestations.[11,12,16–20] These studies have consistently demonstrated that non-Hispanic black women deliver earlier than non-Hispanic white women. Our study is one of only a few examining the association between black race and gestational age at delivery in twin gestations. Using U.S. birth records from 1990 to 1995, Rolett and Kiely found that non-Hispanic black women with twin gestations had a 30% higher risk of PTB <35 weeks than non-Hispanic whites.[21] Only black race and age were associated with PTB among twins in their final model. In a retrospective review of over 9,000 live twin births, Cooperstock et al found that socioeconomic factors, including black race, were associated with PTB, with the association limited predominantly to PTB <34 weeks.[22] They reported a relative risk of 1.61 (95% CI: 1.46, 1.76; $p < 0.001$) for PTB <34 weeks comparing blacks with whites. In a large retrospective review of pregnancies resulting from in vitro fertilization (IVF), Xiong et al found that non-Hispanic blacks with twin gestations had higher adjusted odds of delivering preterm at <28 weeks (odds ratio [OR]: 3.3; 95% CI: 2.7, 3.9), <32 weeks (OR: 2.4; 95% CI: 2.1, 2.7), and <37 weeks (OR: 1.4; 95% CI: 1.2, 1.6) as compared with non-Hispanic whites.[23] Their analysis, which also reviewed singleton IVF pregnancies, revealed similar patterns of racial differences among IVF twin and singleton gestations.

The association of race and PTB has been described less consistently in twin gestations. To et al found that only cervical length was predictive of PTB <32 weeks in twin gestations and the addition of maternal characteristics, such as race, did not improve predictability as it had in singleton gestations.[24,25] Likewise, black race was not associated with PTB at <32, <35, and <37 weeks in a prospective study of 150 women with twin gestations.[26] Our sample size was nearly four times larger than their sample size, which had 50 white patients, and was sufficiently powered to demonstrate the association of race and PTB.

The strong association we observed between the history of PTB and gestational age at delivery for recurrent twin gestations was expected. The association between prior PTB and recurrent PTB has been reported in singleton and twin gestations.[27–29] Our findings pertaining to cerclage use in twins

were not unanticipated. Patients with a history of indicated or planned cerclages were excluded before randomization in the original study. Therefore, patients treated with cerclage in our analysis had either examination or ultrasound-indicated cerclages and were inherently at higher risk of preterm delivery. Nonetheless, the utility of cerclage in twins remains questionable.[30]

While many previous studies investigating the relationship between race and twin PTB demonstrated that black women had higher odds of delivering preterm, these studies were retrospective analyses and did not explore the effect of race on PTB throughout gestation or on neonatal outcomes. Historically, black race was thought to confer protection to preterm neonates such that black preterm neonates had reduced risks of death and serious neonatal morbidity.[31] However, this traditional paradigm was recently challenged by findings from a large retrospective review of 19,325 singleton preterm deliveries that demonstrated an increased likelihood of intraventricular hemorrhage, intracranial hemorrhage, and perinatal death among black preterm neonates.[32] Our finding that neonates born to black mothers had increased rates of morbidity is similar to the findings from this prior study. Unfortunately, though both were important in limited regression models, we were underpowered to fully evaluate the contribution of race compared with gestational age to major neonatal morbidity.

Our study has several strengths. It is a secondary analysis of a large multicenter prospective randomized trial. Trained data abstractors utilized a consistent data extraction tool. Gestational age is well-validated, with all patients undergoing a midtrimester ultrasound.

Our study also has limitations. Black and white race was self-identified, and we did not have any data on country of origin or birthplace. However, this is a multicenter study including participants with varied backgrounds. We included all PTBs and made no distinction between spontaneous and indicated PTB for the primary and secondary analysis. However, the presumed effect of indicated PTBs was minimized by excluding monoamniotic twins, those with suspected twin–twin transfusion syndrome, growth discordance, severe fetal anomalies, a spontaneous fetal death after 12 weeks and pregnancies complicated by major maternal chronic diseases. Resultant neonatal outcomes thus were primarily dependent on gestational age at delivery regardless of whether they were indicated or spontaneous. However, the sample size was insufficient to conduct multivariate analyses for pregnancy and neonatal outcomes. Thus there is the potential for residual confounding. Fetal fibronectin and urine drug screens were not conducted for all patients, thus precluding the ability to test the association between PTB and positive fetal fibronectin and urine drug screens.

In summary, our results demonstrate that non-Hispanic black women with twin gestations are at an increased risk of delivering their babies earlier than non-Hispanic white women. Their infants are also more likely to suffer from major morbidity or mortality. These findings parallel

previously reported PTB disparities in singleton gestations. While interventions to decrease PTB in twin gestations have been largely unsuccessful compared with singleton gestations, these findings warrant measures to increase provider awareness for better risk communication. Hypervigilance is also needed to ensure timely evaluation of these patients who are not only at an increased risk of PTB but whose offspring are not protected from the ill effects of prematurity. Providers should educate non-Hispanic black patients with singleton as well as twin gestations on the signs and symptoms of preterm labor early and often. Additionally, these patients should be informed of the value of timely assessments to implement proven time-sensitive interventions associated with improved neonatal outcomes such as neuroprotective magnesium and antenatal steroids. Future studies are needed to determine protective and effective risk-mitigating factors in non-Hispanic blacks with singleton as well as multifetal pregnancies.

Condensation
Non-Hispanic black women with twin gestations deliver earlier than non-Hispanic white women.

Note
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Conflict of Interest
None.

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