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Prematurity and Low Birth Weight as Potential Mediators of Higher Stillbirth Risk in Mixed Black/White Race Couples

Katherine J. Gold, M.D., M.S.W., M.S.,[1,2] Sonya M. DeMonner, M.P.H.,[3,4,5]
Paula M. Lantz, Ph.D.,[6,7] and Rodney A. Hayward, M.D.[3,4,5,6]

Abstract

Objective: Although births of multiracial and multiethnic infants are becoming more common in the United States, little is known about birth outcomes and risks for adverse events. We evaluated risk of fetal death for mixed race couples compared with same race couples and examined the role of prematurity and low birth weight as potential mediating risk factors.

Methods: We performed a retrospective cohort analysis using data from the 1998–2002 California Birth Cohort to evaluate the odds of fetal death, low birth weight, and prematurity for couples with a mother and father who were categorized as either being of same or different racial groups. Risk of prematurity (birth prior to 37 weeks gestation) and low birth weight (<2500 g) were also tested to see if the model could explain variations among groups.

Results: The analysis included approximately 1.6 million live births and 1749 stillbirths. In the unadjusted model, compared with two white parents, black/black and black/white couples had a significantly higher risk of fetal death. When all demographic, social, biological, genetic, congenital, and procedural risk factors except gestational age and birth weight were included, the odds ratios (OR) were all still significant. Black/black couples had the highest level of risk (OR 2.11, CI 1.77-2.51), followed by black mother/white father couples (OR 2.01, CI 1.16-3.48), and white mother/black father couples (OR 1.84, CI 1.33-2.54). Virtually all of the higher risk of fetal death was explainable by higher rates of low birth weight and prematurity.

Conclusions: Mixed race black and white couples face higher odds of prematurity and low birth weight, which appear to contribute to the substantially higher demonstrated risk for stillbirth. There are likely additional unmeasured factors that influence birth outcomes for mixed race couples.

Introduction

Children are increasingly more likely to have parents of different races or ethnicities, and this may have implications for health outcomes. A comparison of births from 1971 to 1974 and from 1991 to 1994 found that the percent of interracial births tripled, and the rate of interracial marriage in the United States tripled from 1970 to 1990.[1–3] A few studies have suggested mixed race/ethnicity couples may face higher risks for premature delivery, low birth weight, and certain congenital anomalies, but little is known about the risk for stillbirth.[4–7] Babies born to African American parents are at substantially higher risk for stillbirth, low birth weight, and prematurity than babies born to white parents, and these differences have not been entirely accounted for by parental, infant, and demographic factors.[8–11] In addition, although infant mortality overall is declining, the drop has been greater for white compared with black infants, and black infants still face twice the risk of mortality.[12]

One study found that compared with white couples, couples with one white and one black parent had a higher relative risk for stillbirth, and couples with two black parents had an even higher risk.[1] However, the analysis controlled for a limited number of parent characteristics and did not examine risks of low birth weight or gestational age. Many maternal, placental, and fetal risk factors for stillbirth affect fetal growth and risk for prematurity. Both prematurity and low birth weight are associated with stillbirths and are major risk factors

[1]Department of Family Medicine, [2]Department of Obstetrics & Gynecology, [3]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.
[4]U.S. Department of Veterans Affairs, HSR&D Center of Excellence, Ann Arbor, Michigan.
[5]Robert Wood Johnson Foundation Clinical Scholars Program, University of Michigan, Ann Arbor, Michigan.
[6]Department of Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor, Michigan.
[7]Institute for Social Research, University of Michigan, Ann Arbor, Michigan.

for infant mortality.[2] Prior studies on fetal death have determined that much of the racial disparity is explained by the distribution of birth weight.[2,3,13] We sought to build upon prior studies of mixed race and risk for fetal death by developing a model with a broader set of potential confounders, including maternal and fetal risk factors, and also sought to identify more precisely which factors mediate the higher risk of fetal death.

Materials and Methods

We performed a retrospective cohort analysis using data from 1998 to 2002 from the California Birth Cohort, which provides birth and death certificate information for all births, fetal deaths, and infant deaths in the state. These 5 years of data contained roughly 2.6 million births. The data are deidentified and publicly available from the State of California; the University of Michigan Institutional Review Board judged the project to be exempt from review.

California requires reporting of fetal deaths that occur between 20 weeks of pregnancy and delivery, which is the generally accepted definition of stillbirth. Because some states further limit reporting to fetal deaths of a minimum weight and we wished to build upon analyses described by other researchers, we limited our analysis to births and fetal deaths in which the fetus was at least at 20 weeks gestation and 500 g. As twins and triplets are known to be at higher risk for fetal mortality, we also limited our sample to singleton pregnancies.

Our outcome of interest (the dependent variable) was pregnancy outcome: live birth or stillbirth. We examined a variety of factors previously reported to be associated with risk of fetal death and grouped them as sociodemographic, biological, and genetic/congenital risk factors. Sociodemographic factors included the mother's age and parity, type of prenatal care insurance (public vs. private), level of education (less than high school, high school, or some college), tobacco use, and the trimester at which the mother initiated prenatal care. Biological risks included maternal medical illness, pregnancy or delivery complications, and health behaviors known to be significant risk factors for pregnancy loss. Specifically, the following biological risks were included in the model: chronic hypertension, diabetes, preeclampsia, eclampsia, Rh sensitivity, uterine bleed prior to labor, polyhydramnios, oligohydramnios, incompetent cervix, seizure during labor, abruption, amnionitis/sepsis, or cord prolapse. Genetic and congenital factors encompassed fetal anomalies that are associated with an increased risk of fetal death. These included anencephaly; microcephaly; anophthalmos; such cardiac malformations as truncus arteriosus, endocardial cushion defects, and hypoplastic left heart; and gastrointenstinal problems, such as choanal atresia, lung abnormalities, tracheal esophageal fistula or esophageal atresia, or atresia/stenosis of the large or small bowel. We also included renal agenesis or congenital ureteral obstruction; musculoskeletal problems, such as diaphragmatic and other anomalies, gastroschisis and omphaoloceoles; visible amniotic bands; all recorded chromosomal abnormalities; and congenital rubella. Finally, we controlled for risks not included in these groupings, such as preterm delivery and procedures (amniocentesis or chorionic villi sampling).

We also evaluated two intermediate outcomes known to be important mediators of risk for stillbirth: gestational age and birth weight. As these two variables could be causal confounders, we added them in stepwise fashion to our multivariable regression model. This approach allows one to observe whether outcomes of the multivariable regression remain relatively unchanged (evidence against their being causal variables) or disappear (evidence that they are causal variables).

Gestational age and birth weight are reported by the delivering hospital. Race and Hispanic origin are voluntarily self-reported by the parents. Starting in 2000, parents were allowed to report up to three race categories for live births; however, California does not currently record multiple race categories for fetal deaths. Given this discrepancy, the fact that multiple races were not recorded for all years in our analysis and to maintain consistency between groups (stillbirths vs. live births), we chose to exclude births in which parents had reported multiple races (1.8% of subjects). We labeled couples as "mixed race" if the race of the mother and father was different, and couples with identical races were labeled as "same race."

In the California dataset, some variables contained outliers that were either biologically implausible or so skewed we feared they would disproportionately bias the results (such as gestations of 2–3 years). Prior to analyzing any associations, we evaluated key variables and excluded data in cases that were biologically extreme or clearly in error. We believe that these entries may represent problems with reporting or data entry, and we did not want these outliers to have a large influence on the other 99% of the population. Specifically, we limited gestational age to births <46 weeks (this affected 1.5% of subjects with reported gestations between 46 and 143 weeks). We excluded birth weights >14 pounds (6372 g), which was 5 standard deviations (SD) from the mean and which removed <0.001% of subjects. We limited age to women ≤50 years (excluding 0.02% of the dataset) and men ≤70 years (excluding <0.01% of the dataset). Similarly, to maintain consistency with published analyses and because of the smaller sample sizes of other ethnic groups, we limited our analyses to the 85% of parents with race reported as black or white (Fig. 1).

Using Stata SE version 10.0 (Stata Corporation, College Station, TX), we performed bivariable and multivariable logistic analyses to evaluate the odds of fetal death for couples with a mother and father who were categorized as being of either same or different racial groups. The level of significance was set at 0.05. We controlled for the variables and sociodemographic, biological, and genetic/congenital confounders previously described. Using the same model, we also calculated the risk of prematurity (birth prior to 37 weeks gestation) and the risk of low birth weight (<2500 g), as these were predicted to be potential intermediate outcomes for stillbirth.

To check the robustness of our model, we tested several permutations. First, because not all experts agree on medical risks for stillbirth, we ran an alternative analysis using all possible genetic and congenital disorders as potential risk factors rather than restricting the analysis to a limited sample. Second, we tested the model without limiting parental age. To test the impact of very small fetuses, we ran another analysis including fetuses ≥302 g (5 SD from the mean). Infants born prior to 24 weeks gestation may be incorrectly classified as stillborn when the baby was alive but died very shortly

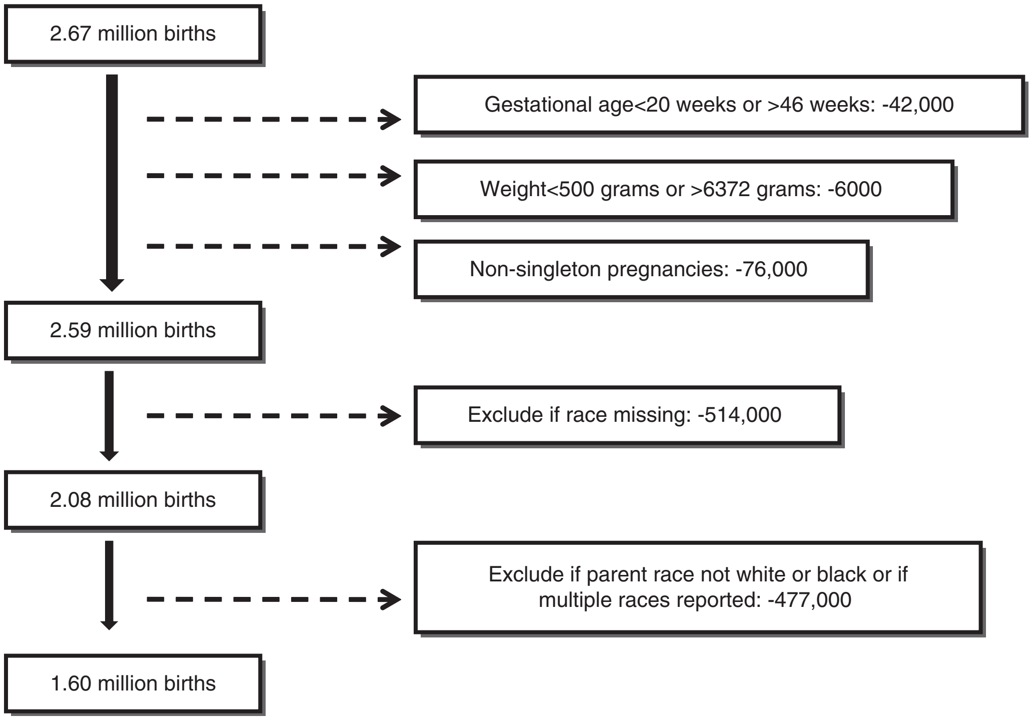

FIG. 1. Data exclusion criteria.

after birth, so we tested for this through an analysis limiting gestational age to ≥24 weeks. Although it was limited in statistical power, we conducted a supplemental analysis limited to white parents and stratified by Hispanic ethnicity.

Results

The main analysis included approximately 1.6 million live births and 1749 stillbirths. These two groups differed significantly by most demographics and risks for fetal death (Table 1). The full model that we developed to control for risk factors for fetal death was highly predictive, with an area under the receiver operating characteristic (AUROC) curve of 0.89. A high AUROC suggests a model is reasonably good at stratifying the population for risk of the outcome. The full California dataset had a stillbirth rate of 5.7/1000 live births; after we limited the data as described, we had a stillbirth rate of 1.1/1000 live births, primarily because 80% of stillbirths had missing data on mother or father's race and were, therefore, excluded from our analysis. Our full multivariable regression model excluded subjects missing data for any variable, leaving 1.42 million cases.

In the unadjusted model, results showed differences among race categories that did not appreciably change once all of the demographic, social, biological, genetic/congenital, and procedural risk factors were included (the partially adjusted model) (Table 2). In the partially adjusted model, compared with two white parents, couples with two black parents (odds ratio [OR] 2.11, CI 1.77-2.51) and couples with a black mother/white father (OR 2.01, CI 1.16-3.48) had roughly twice the odds of fetal death. The white mother/black father couple had a slightly lower OR for fetal death of 1.84 (CI 1.33-2.54).

The stepwise analyses introducing potential mediating factors of birth weight and gestational age demonstrated that once these variables were introduced, there was no longer a significantly increased risk of stillbirth for any of the racial pairings. Sequential addition of birth weight and gestational age suggested gestational age and birth weight were of comparable importance in explaining the higher stillbirth risk. Although gestational age and birth weight are clearly related factors, they were not colinear and were strong independent predictors in the final model for mixed race couples; it was difficult to separate the precise contribution of each variable. There was no evidence of multicolinearity among any other predictor variables used in the full model.

Given the importance of birth weight and gestational age in perinatal outcomes, we performed additional analyses using each of these as outcomes of interest to evaluate outcomes by race. We first used the model to evaluate risks for prematurity (Table 3). The model predicted low birth weight well (AUROC = 0.87). Unadjusted and partially adjusted results with all the demographic, social, biological, genetic/congenital, and procedural risk factors added in showed a similar pattern to the fetal death results, with all comparison groups having a significantly higher risk for prematurity than had the white couple. In the partially adjusted model, couples with two black parents had the highest odds (1.57, CI 1.53-1.60), followed by couples with black mother/white father (OR 1.40, CI 1.30-1.50) and white mother/black father (OR 1.14, CI 1.09-1.19). Controlling for gestational age explained most of the higher prematurity risk for couples with two black parents and couples with black mother/white father but had minimal impact on white mother/black father couples. In the full model, whereas all three groups continued to have statistically higher odds of prematurity compared with white couples, the difference in risk was small, and the confidence interval for black mother/white father couples was 1.00-1.14, suggesting it was not significant. The model was generally

Table 1. Demographics and Pregnancy Risk Factors by Mother/Father Race

	White mother/white father	*Black mother/black father*	*White mother/black father*	*Black mother/white father*
Number ($n = 1,597,156$)	1.47 million	0.09 million	0.03 million	0.01 million
Stillborn (%)	0.10	0.21	0.17	0.22
Maternal factors				
Median maternal age,* years	28	26	26	27
Primiparous (%)*	37	35	39	42
Prenatal care initiation (%)*				
First trimester	87	84	84	86
Second trimester	11	13	13	12
Third trimester or no care	2	3	3	3
Maternal education (%)*				
Less than high school	33	15	15	12
High school/GED	28	41	40	34
Any college	38	44	45	55
Insurance (%)*				
Public	47	50	43	41
Private	53	50	57	59
Pregnancy complications (%)				
Tobacco use in pregnancy*	1	2	2.5	2.2
Preeclampsia-pregnancy*	1.3	2.1	1.5	2.2
Eclampsia-pregnancy	0.03	0.04	0.02	0.04
Chronic hypertension*	0.26	0.68	0.34	0.59
Diabetes*	2.3	2.4	2.5	2.2
Rh sensitive*	0.37	0.22	0.56	0.24
Uterine bleed before labor*	0.3	0.46	0.47	0.46
Poly/oligohydramnios*	0.54	0.7	0.54	0.74
Incompetant cervix*	0.07	0.26	0.12	0.29
Delivery complications (%)				
Preeclampsia*	1.4	2.3	1.5	2.4
Eclampsia*	0.04	0.06	0.05	0.02
Seizure*	0.03	0.05	0.03	0
Abruption*	0.25	0.39	0.29	0.37
Amnionitis/sepsis*	0.24	0.35	0.36	0.4
Cord prolapse*	0.13	0.08	0.09	0.06
Delivery				
Vaginal delivery*	76	72	74	72
Male infant*	51	51	50	51
Mean (SD) birth weight in grams*	3415 (+/−543)	3208 (+/−617)	3409 (+/−578)	3285 (+/−604)
Mean (SD) gestational age in days*	276 (+/−15)	273 (+/−19)	275 (+/−17)	274 (+/−19)

Data limited to 1.60 million births to black or white parents that met multiple inclusion criteria, including singleton pregnancies, birthweight >500 g, and gestational age >20 weeks, among other restrictions. Numbers may not equal 100% because of rounding.

*$p < 0.05$.

Table 2. Risk of Stillbirth for White or Black Parents

	Unadjusted or stillbirth	*Partially adjusted Model A*[a]	*Adjusted Model B*[b]
Same race			
White mother/white father	1	1	1
Black mother/black father	2.10* (1.81-2.44)	2.11* (1.77-2.51)	1.04 (0.86-1.27)
Mixed race			
White mother/black father	1.65* (1.23-2.21)	1.84* (1.33-2.54)	1.35 (0.92-1.98)
Black mother/white father	2.13* (1.34-3.39)	2.01* (1.16-3.48)	1.38 (0.76-2.50)

[a]Model A, adjusted for demographic factors, social, biological, and genetic/congenital risk factors, and procedures.

[b]Model B, adjusted for all the above plus birth weight and gestational age.

*$p < 0.05$; area under the receiver operating characteristic (AUROC) = 0.89.

Table 3. Risk of Prematurity for White or Black Parents

	Unadjusted OR LBW	*Adjusted Model A*[a]	*Adjusted Model B*[b]
Same race			
White mother/white father	1	1	1
Black mother/black father	1.60* (1.57-1.63)	1.57* (1.53-1.60)	1.07* (1.05-1.10)
Mixed race			
White mother/black father	1.12* (1.07-1.16)	1.14* (1.09-1.19)	1.08* (1.04-1.13)
Black mother/white father	1.41* (1.32-1.51)	1.40* (1.30-1.50)	1.07* (1.00-1.14)

[a]Model A, adjusted for demographic factors, social, biological, and genetic/congenital risk factors, and procedures.
[b]Model B, adjusted for all the above plus birth weight.
*$p < 0.05$; area under the receiver operating characteristic (AUROC) = 0.78.
OR, odds ratio; LBW, low birth weight.

not as good at predicting prematurity and had a lower AUROC of 0.78.

We then used the model to evaluate for low birth weight (AUROC = 0.87). Once again, in both the unadjusted model and the partially adjusted model with demographic, social, biological, genetic, congenital, and procedural risks included, all results were significant (Table 4). In the partially adjusted model, black mother/black father couples had the highest odds of low birth weight (OR 2.31, CI 2.25-2.37), followed by black mother/white father (OR 1.78, CI 1.63-1.95) and white mother/black father (OR 1.24, CI 1.17-1.32). The full model included gestational age, which explained some of the variance for black mother/black father and black mother/white father couples and a very small amount of the variance for white mother/black father couples. All the full model results, including the prematurity variable, were significant: black mother/black father had OR 1.99 (CI 1.93-2.06), black mother/white father had OR 1.58 (CI 1.42-1.77), and white mother/black father had OR 1.16 (CI 1.08-1.24).

Alternative analyses that did not limit the type of genetic and congenital abnormalities, did not restrict maternal or paternal age, lowered the minimum birth weight to 302 g, or excluded fetuses at <24 weeks gestation all caused no significant changes in our results for stillbirth, prematurity, and low birth weight. We tested a permutation limited to white parents who were Hispanic vs. non-Hispanic and also found no significant differences in stillbirth outcomes. There was a slightly higher risk for low birth weight when the father was white Hispanic and for prematurity when the mother was white Hispanic. Owing to a very low subgroup sample size in the stillbirth groups, we were not able to test the black/white race categories subdivided for Hispanic/non-Hispanic ethnicity.

We noted that 28% of stillbirths were small for gestational age (SGA) compared with just 9% of live births, and we considered whether being SGA might be a more accurate mediator of stillbirth than birth weight. To test this, we identified whether birth weights were SGA based on previously published fetal growth data and then ran the model using SGA instead of birth weight.[14] In contrast to adding the birth weight variable, the differences seen among different race groups in the partially controlled model did not change significantly when SGA was added, suggesting it was not a causal variable.

Discussion

Although racial disparities in birth outcomes have received much attention, little research has considered outcomes for multirace infants. Previous studies on stillbirth have not controlled for important factors, such as birth weight and gestational age. This is striking, given the strong associations between these variables and fetal death, with the highest rates of mortality seen among the youngest and smallest fetuses.[14] Prior studies have also suggested that these factors may explain many of the racial disparities in fetal mortality, which makes them essential variables to incorporate into analyses evaluating risk for mixed race couples.[15] Our finding that differences in fetal mortality disappeared once birth weight and gestational age were included in the analysis supports our hypothesis that they are important in the causal pathway; had their addition not changed the results, this would have been strong evidence against our hypothesis. The discovery that gestational age and birth weight outcomes showed similar patterns of risk by race is also

Table 4. Risk of Low Birth Weight for White or Black Parents

	Unadjusted OR LBW	*Adjusted Model A*[a]	*Adjusted Model B*[b]
Same race			
White mother/white father	1	1	1
Black mother/black father	2.35* (2.30-2.41)	2.31* (2.25-2.37)	1.99* (1.93-2.06)
Mixed race			
White mother/black father	1.26* (1.19-1.33)	1.24* (1.17-1.32)	1.16* (1.08-1.24)
Black mother/white father	1.87* (1.73-2.03)	1.78* (1.63-1.95)	1.58* (1.42-1.77)

[a]Model A, adjusted for demographic factors, social, biological, and genetic/congenital risk factors, and procedures.
[b]Model B, adjusted for all the above plus gestational age.
*$p < 0.05$; area under the receiver operating characteristic (AUROC) = 0.87.

consistent with the idea that such variables might account for racial variations among stillbirths.

Other studies on low birth weight are consistent with our findings, demonstrating that couples with one or two black parents are more likely to have a low birth weight infant than are two white parents.[3–5,16,17] An analysis of gestational age for twin births reports similar trends for mixed black/white couples.[5] A review of congenital malformations found only slight differences among infants of white, black, and white/black mixed parents.[7] Although it seemed plausible that being SGA might be a more important factor in stillbirths than simply low birth weight, this was not borne out by the results. It may be that stillborns in this analysis were more likely to be severely SGA than liveborn infants, such that birth weights reflected much more pronounced weight differences than presence or absence of SGA designation. It is not uncommon to have a delay of days or weeks before recognition and formal diagnosis of an *in utero* fetal demise. Although fetal size may have been appropriate for gestational age when death occurred, the delay often renders it SGA by the time of delivery.

In evaluating our results, we considered whether California data were representative of national birth data. With the restriction to fetuses $\geq$500 g, our dataset had an overall fetal death rate of 4.2/1000 live births. Without this restriction, we calculated overall fetal death rate at 5.7/1000 live births, which is consistent with official State of California fetal death statistics during 1998–2002 and just slightly lower than the national rate of 6.4–6.7 fetal deaths per 1000 live births.[18–20]

In 1997, the federal government changed vital statistics data collection to allow more than one race or ethnicity for an individual, and multirace reporting has risen gradually since that time.[17] Starting in 2000, the rules in California changed to allow parents to self-report up to three distinct races on birth certificates, although the state does not currently record multiple races for fetal deaths.[19]

Although stratifying risk based on racial classification allows an estimate of group risk, understanding why these disparities exist is complex. In this analysis, we have hypothesized that race potentially could be a proxy for some other unmeasured or unidentified risk factor. It is not known if women in different types of mixed race pairings receive different levels of social or family support or face more or less stigma or if race impacts the level of paternal involvement in a pregnancy. In our analysis, maternal race appeared to be more predictive than paternal race of fetal outcome, although this may be the result of more underreporting of paternal race data, particularly for nonwhite parents.

The perinatal mortality rate among black women has been consistently higher than that of white women over time. Despite an encouraging drop in fetal deaths over the last few decades for all races, there has been more improvement in birth outcomes for whites than for blacks. In 1981, black infants had approximately twice the risk of fetal and infant death as white infants; by 2003, the risk for non-Hispanic black mothers was 2.34 that of non-Hispanic whites.[20,21] Although some of this difference appears to be related to differences in maternal health, infection, use of prenatal care, and socioeconomic factors, the etiologies are not entirely understood.[20,22] Stress in the maternal environment, including that caused by racism, may play a role in the increased morbidity and mortality in birth outcomes for black mothers.[23,24]

As with any retrospective study, we were able to identify correlations but not causation. Validity of the data is, or course, dependent on statistics reported on the state birth or fetal death certificate. Other confounders not available in this dataset might help better explain differences in birth outcomes, for example, income, marital status, social support, obesity, sickle cell disease/trait, risky behaviors, or exposure to life stressors. However, we attempted to include as many factors as possible, such as variables that could serve as proxies for information not provided in the dataset. Although we were interested in the effect of Hispanic ethnicity, the small stillbirth sample sizes created when we stratified by both race and ethnicity precluded our ability to measure the magnitude of Hispanic influence in the analysis of black and white couples. In addition, although it is possible that other unmeasured variables affect birth weight, prematurity, and fetal mortality, we could not further clarify this and recognize this as a limitation of the analysis.

Approximately 20% of live births and 80% of stillbirths were missing data on the race of either the mother or the father, which presents a significant possibility for bias and explains why the stillbirth rates in our dataset were so low. (California live birth and fetal death certificates request, but do not require, race reporting.) A study evaluating the validity of maternal race on California birth certificates compared with medical records reported excellent and similar correlation between the two documents for both white and black mothers.[25] Fetal deaths are generally underreported, however, and specific data points on the fetal death certificate may be incomplete or inaccurate, which may have contributed to the low reporting rate of race on the death certificates studied.[26–28] In addition, fewer fetal deaths are recorded at the lower ends of gestational age, and these reports are clearly more likely to contain missing data.[15] Some investigators have noted that birth certificates frequently are missing paternal data, and this is far more common among black women, women with sociodemographic and medical characteristics that have been associated with stillbirth, and women with adverse pregnancy outcomes, including fetal death, prematurity, and low birth weight.[29] Our results must be interpreted in light of these data limitations. Because missing partner data is so much more common for black parents, by eliminating cases with missing race data, our analysis likely underestimates the risk of stillbirth to black and mixed race parents. Similarly, we could not independently verify the accuracy of reporting for maternal and fetal risk factors and congenital outcomes, and these variables are also likely to be substantially underreported. Data reporting is slowly improving, but this is a pervasive issue in stillbirth reporting, and such limitations are likely to be present in most large existing datasets.

This analysis builds on our understanding of stillbirth in mixed race couples by demonstrating birth weight and gestational age as potential mediators related to the risk of stillbirth. The risks did not dissipate even when we controlled for multiple social and biological risk factors, raising questions about how these variables impact mixed race partnerships and adverse birth outcomes. Our findings reframe concerns about stillbirth for prospective mixed race/ethnicity parents by underscoring that the risk factor is not skin color *per se* but is related to risks for low birth weight and prematurity, particularly among black women. This information will be increasingly important in clinical discussions as the prevalence of mixed race couples and multiracial and multiethnic infants continues to rise in the United States.

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Disclosure Statement

The authors have no conflicts of interest to report.

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Address correspondence to:
Katherine J. Gold, M.D., M.S.W., M.S.
Department of Family Medicine
Department of Obstetrics & Gynecology
University of Michigan
1018 Fuller Street
Ann Arbor, MI 48104-1213

E-mail: ktgold@umich.edu