Racial and ethnic differences in preterm birth: A complex, multifactorial problem

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ABSTRACT

Preterm birth remains the leading cause of morbidity and mortality among nonanomalous neonates, and is a major public health problem. Non-Hispanic black women have a 2-fold greater risk for preterm birth compared with non-Hispanic white race. The reasons for this disparity are poorly understood and cannot be explained solely by sociodemographic factors. Underlying factors including a complex interaction between maternal, paternal, and fetal genetics, epigenetics, the microbiome, and these sociodemographic risk factors likely underlies the differences between racial groups, but these relationships are currently poorly understood. This article reviews the epidemiology of disparities in preterm birth rates and adverse pregnancy outcomes and discuss possible explanations for the racial and ethnic differences, while examining potential solutions to this major public health problem.

Introduction

Preterm birth remains a major public health problem. Babies born prior to 37 weeks' gestation are at increased risk for neonatal morbidity and mortality; preterm birth is the direct cause of 35% of all neonatal deaths worldwide.[1] Survivors remain at high risk for complications in early childhood,[2–4] adolescence,[5–7] and into adulthood[5,8–11]; the full extent of the societal burden is likely not yet realized because until recently, long-term survivors of extreme prematurity were uncommon.[5] Mothers who deliver preterm are at elevated risk for serious morbidities\later in life, including cardiovascular disease and stroke.[12–14] Although the preterm birth rate fell from 2007 to 2014 in the United States, the rate recently increased between 2014 and 2015.[15] Even more alarmingly, the gap in the rate of preterm birth between non-Hispanic white and non-Hispanic black women increased during this time.[15] Non-Hispanic black race (compared with non-Hispanic white race) is a consistent risk factor for preterm birth and adverse pregnancy outcomes in the United States. The risk associated with race is significant; in a large systematic review of 30 studies, black women were found to have a 2-fold increased risk (95% CI: 1.8–2.2; pooled odds ratio) compared with whites.[16] Studies of the association between women of other races and ethnicities and preterm birth have been less consistent and results are more heterogeneous. In this same review, 12 studies of Asian ethnicity were examined and mixed results were found; 5 studies showed no significant increase in preterm birth risk whereas 7 studies showed an increased risk (compared to non-Hispanic white women). Further, there was significant variance in the rate of preterm birth across studies ranging from 2.3% to 16.3%, and a wide range of odds ratios for the association between Asian race and preterm birth was found (0.65–1.78).[16] Similarly, Hispanic ethnicity has also produced less consistent results, with Hispanic ethnicity inconsistently

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associating with preterm birth relative to non-Hispanic white women, with odds ratios ranging from 0.1 to 1.5.[16]

The etiologies underlying the disparities in preterm birth rates are poorly understood. Disparities persist even after accounting for known preterm birth risk factors such as smoking, maternal education level, and socioeconomic status. The aim of this article is to review the epidemiology of disparities in preterm birth rates and adverse pregnancy outcomes, discuss possible explanations for the racial and ethnic differences, and examine potential solutions to this major public health problem. This article will focus on the disparities in preterm birth outcomes between non-Hispanic black and non-Hispanic white women in the United States, because these are the best studied and most consistent risks with regard to disparities in birth outcomes in the United States. Since the best described risks are associated with non-Hispanic black women and findings among women of other races are less consistent, review of women of other races are acknowledged but are beyond the scope of the current review.

Epidemiology of disparities

Defining race and ethnicity

Defining the problem of preterm birth is challenging, because many studies of racial disparity in preterm birth use inconsistent definitions and interchange the terms 'race' and 'ethnicity.' For example, some studies examine only 'white' and 'black' populations within the United States, but do so without further classifying individuals with regard to Hispanic ethnicity. Others studies use the terminology 'European-American' and 'African-American,' whereas still others use 'Caucasian' and 'African-American,' or 'non-Hispanic white' and 'non-Hispanic black.' Both the designations of Caucasian and African-American may include some women who are Hispanic. The inconsistency in defining populations can limit the ability to compare results across studies. For the purposes of this article, when reporting results from previous studies, we will use designations reported in the source paper(s). However, for clarity, we prefer to use definitions that incorporate both race and ethnicity, that is, terminology such as non-Hispanic white, non-Hispanic black, and Hispanic. Finally, the vast majority of studies utilize self-reported race and ethnicity to define groups. Previous studies have shown that self-reported ancestry has a high degree of correlation with ancestry proportions estimated by genotype,[17–19] though self-report is imperfect. Modern studies, in particular, may be fraught with more heterogeneity due to increasing admixture across populations.[20]

Trends in preterm birth rates in the United States

The rate of preterm birth in the United States rose to an all-time high in 2007 (10.44%). Due to multiple initiatives aimed primarily at reducing iatrogenic late preterm birth in the late 2000s, prematurity rates fell between 2007 (10.44%) and 2014 (9.57%) before rising again to 9.63% in 2015.[15] This increase was primarily driven by a rise in the percentage of preterm births in non-Hispanic black and Hispanic women. Furthermore, rates of very preterm birth (prior to 34 weeks' gestation) remained largely unchanged over the last 8 years (2.93% in 2007 compared with 2.81% in 2011 and 2.76% in 2015). Rates of preterm birth prior to 34 weeks' gestation are significantly higher among African-American women[21,22] (3.09% in 2015 compared with 1.27% in 2015 in non-Hispanic white women), Figure 1.[15,21,22] Notably, these rates reflect the new standard (as of 2014) for reporting of gestational age (obstetric estimate) compared with the traditional last menstrual period dating. Data using obstetric estimates are available only for 2007 onward, and rates using these calculations generally are lower than last menstrual period estimates. For example, in 2015, the obstetric estimate preterm birth rate was 9.63%, but the last menstrual period based rate was 11.29%.

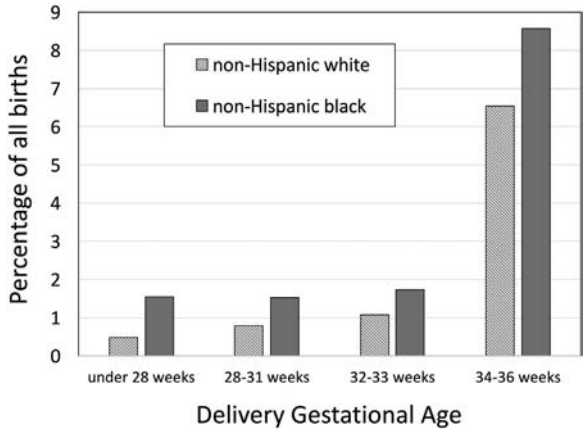

Fig. 1 – Proportion of preterm births, stratified by gestational age at delivery and maternal race, 2015. *Sources*: Martin et al. Final birth data 2015.

Rates of recurrent preterm birth are also higher among non-Hispanic black women. In a population-based study of 644,462 Missouri birth records, black mothers were at higher risk for recurrent preterm birth (aOR = 4.11, 95% CI: 3.78–4.47)[22] and preterm prelabor rupture of membranes (PROM) compared to white mothers (aOR = 6.4, 95% CI: 3.7–11.0).[23]

Preterm birth phenotype

Recently, investigators and clinicians have focused on refining subtypes of preterm birth. Rather than merely designating a birth as spontaneous or medically indicated (e.g., due to pre-eclampsia or fetal growth restriction), additional investigation into the circumstances surrounding delivery can provide information regarding the possible underlying etiology of the preterm birth.[24–26] Phenotype definitions vary between studies, and some studies include variables traditionally considered to be "risk factors" (e.g., maternal stress) with the goal of grouping women who are most likely to have similar underlying preterm birth etiologies.[24] It has been hypothesized that non-Hispanic black women have distinct preterm birth phenotypes compared to non-Hispanic white women. For example, several authors have found that the incidence cervical insufficiency is significantly higher among non-Hispanic black women.[24,27] In one study more broadly evaluating preterm birth phenotypes, African-American

women had distinctly different phenotypes compared with white women, as they were more likely to have pregnancies complicated by maternal stress and cervical insufficiency, but less likely to have a pregnancy complicated by decidual hemorrhage.[24]

Peri-viable deliveries and perinatal mortality

Racial disparities are also present during the pre-viable time period (16–22 weeks' gestation). In a large population-based cohort from Ohio from 2006 to 2012, the incidence of pre-viable delivery for white mothers was 1.8 per 1000; for black mothers, it was 6.9 per 1000; the majority of deliveries during the pre-viable period were spontaneous in nature, and they were found to account for 28% of total infant mortalities in Ohio. It is unclear whether these observed differences can be partly or primarily attributed to the observed differences in cervical insufficiency as described above.

In turn, preterm birth and complications related to prematurity also account for a higher percentage of infant deaths among non-Hispanic black women (42.5%) compared to non-Hispanic white women (30.8%). These figures also translate into higher overall infant mortality rates among non-Hispanic black women compared with non-Hispanic white women (11.5 per 1000, vs. 6.1 per 1000). Though overall infant mortality rates in the United States have decreased since 1960, the racial gaps in infant mortality rates have widened since that time.[28] The disparity in neonatal death has followed a similar pattern[29,30]; one study found non-Hispanic black very low birthweight infants have a 34% higher odds of neonatal mortality (aOR = 1.34, 95% CI: 1.14–1.56) compared to very low birthweight non-Hispanic white neonates.[29]

Differences in response to prophylactic treatment

The Society for Maternal-Fetal Medicine and American Congress of Obstetricians and Gynecologists currently recommend that weekly injections of 17-alpha hydroxyprogesterone caproate (17-OHPC) should be offered to all women in subsequent pregnancies to reduce the risk of recurrent PTB[31,32]; this therapy has been proven to reduce the risk of recurrence by approximately one-third.[33] In a large meta-analysis including 11 trials (n = 1899 women) of women at increased risk for preterm birth due to a prior spontaneous preterm birth, progesterone supplementation (with either 17-OHPC or vaginal formulation) was proven to reduce several risks related to prematurity, including the risk of birth <37 weeks [relative risk (RR) = 0.55, 95% CI: 0.42–0.74], <34 weeks (RR = 0.31, 95% CI: 0.14–0.69), neonatal death (RR = 0.45, 95% CI: 0.27–0.76), use of assisted ventilation (RR = 0.40, 95% CI: 0.18–0.90), necrotizing enterocolitis (RR = 0.30, 95% CI: 0.10–0.89), and neonatal intensive care unit admission (RR = 0.24, 95% CI: 0.14–0.40).[34]

Unfortunately, disparities are also seen in response to treatment for the prevention of recurrent preterm birth. Multiple studies have shown disparities in both 17-OHPC use and in recurrent PTB rates among women administered 17-OHPC. One study of 472 women eligible for 17-OHPC found that non-Hispanic black women had increased rates of non-adherence to 17-OHPC (70% vs. 91% for non-Hispanic white women), defined as missing more than one dose, initiation of therapy >20 weeks' gestation, or discontinuation of therapy prior to 37 weeks' gestation.[35] These findings were similar to those of Timofeev et al.,[36] who found that African-American women initiated 17-OHPC later and discontinued them earlier compared with Caucasian women. Timofeev also found that African-American women receiving 17-OHPC carried a more than 2-fold greater risk of recurrent PTB compared to Caucasian women receiving 17-OHPC.[36] Similar findings were also observed in a large secondary analysis of 754 women receiving 17P, where black race conferred additional risk for nonresponse to 17-OHPC treatment.[37]

Possible explanations for racial and ethnic differences

Multiple investigators have attempted to determine the underlying etiologies behind the observed racial and ethnic disparities in prematurity in the United States. Several contributing factors have been proposed.

Socioeconomic factors

Investigators have attempted to evaluate the impact of socioeconomic status on preterm birth disparities by evaluating women from similar backgrounds or living in similar settings in order to evaluate the influence of race. The overarching conclusions of these studies are that sociodemographic factors may account for some risk, but are unable to account for the majority of the observed differences in birth outcomes. Schempf et al. evaluated the contribution of neighborhood of residence to racial disparity in two counties in North Carolina, and concluded that while individual sociodemographic characteristics and neighborhood differences partly explained some of the observed racial disparity in later preterm birth rates (32–36 weeks' gestation), these factors could not explain the disparities in prematurity <32 weeks' gestation.[38] In contrast, other studies have observed that neighborhood deprivation is associated with preterm birth among *both* non-Hispanic white and non-Hispanic black women.[39] A large systematic review and meta-analysis concluded that women living in the most disadvantaged neighborhoods have a significantly higher risk for PTB (RR = 1.27; 95% CI: 1.16–1.39) compared to those in the least disadvantaged neighborhoods, and that these effects are most significant for black mothers.[40]

McGrady and colleagues investigated the influence of maternal education by evaluating the rates of preterm birth and low-birth weight among first-born infants of black and white college graduates. They found relative risks of 1.28–1.67 for preterm birth and 1.75–2.48 for low-birth weight among black women.[41] Disparity in preterm birth rates, however, has been found in populations where women of different races are afforded the same access to healthcare, such as the military. It is therefore clear that while some of the disparity in the rates of prematurity may be attributed to differences in risk factors, many other preterm deliveries are unexplained merely by sociodemographic differences.

Table 1 – Summary of factors associated with higher risk of preterm birth among non-Hispanic black women.

Characteristic	Summary of findings and/or magnitude of association	Comment
Short interpregnancy interval (less than 6 months between delivery and conception)	• 2-fold more common among non-Hispanic blacks • Associated with 40% risk of preterm birth	Estimated to account for 4% of the disparity in the rates of prematurity[47]
Neighborhood deprivation	• Associated with elevated risk of preterm birth (RR = 1.27), effects largest in non-Hispanic blacks[40] • Other studies suggest risk is present among both non-Hispanic blacks and whites[39]	
Maternal education	• Lower education: RR for preterm birth 1.3–1.7	• Studies inconsistent with regard to disparity
Differences in biomarkers	• Race-dependent biomarker models predict preterm birth[49,50]	• Biomarkers differ across maternal, fetal, and intra-amniotic compartments
Genetic variation	• Numerous differences in genomic DNA[58] and methylation[59–61]	
Microbiome	• African-American women may have a more diverse vaginal microbiome, associated with preterm birth[64,69–71]	
Telomere length	• Preliminary data suggest telomeres are shorter among black mothers compared to white mothers[72]	• Novel marker of cellular senescence and aging

RR, relative risk.

Differences in risk factors

Risk factors associated with preterm birth are difficult to quantify and study because many are interrelated. For example, psychosocial stress is likely related to education level and the ability to hold a job and maintain an income; the relative importance of each of these factors with regard to the outcome of preterm birth may be difficult to quantify. Selected factors associated with preterm birth among non-Hispanic black women are summarized in Table 1. Goldenberg et al.[42] prospectively studied a cohort of 1491 multiparous women (69% black and 31% white) and comprehensively assessed life stress and psychosocial parameters. Some risk factors traditionally associated with an elevated risk for preterm birth, including smoking, illicit drug use, and elements of psychosocial stress (e.g., reports of electricity disconnection during pregnancy) were more common among white women compared to black women. Despite this, 16.7% of black women delivered preterm and 11.3% of white women delivered preterm ($p < 0.007$). After statistical modeling incorporating various sociodemographic factors, the authors concluded that race could explain only 4% of the variance in gestational age, and the majority of the disparity remained unexplained.[42]

The interpregnancy interval, defined as the duration between birth of one pregnancy and conception of the subsequent pregnancy, has been evaluated as a potential risk factor for preterm birth and adverse perinatal outcomes. A short interpregnancy interval, less than 6 months (irrespective of underlying preterm birth risk) is an established risk factor for spontaneous preterm birth; women with short interpregnancy intervals have up to a 40% risk of preterm birth.[43–45] Several researchers have investigated whether variation in the interpregnancy interval can explain some of the racial disparity in birth outcome, as many have observed shorter interpregnancy intervals among non-Hispanic black women.[46,47] One group concluded that a short interpregnancy interval may explain 4% of the disparity in the preterm birth rate between African-Americans and Caucasians due to the increased frequency of short interpregnancy intervals in African-American women.[47]

Others have evaluated whether the influence of certain risk factors differs by race. Limited evidence suggests some interaction between maternal race, specific risk factors, and preterm birth. For example, Torloni et al. evaluated 447 preterm cases ($n = 145$ African-Americans, $n = 302$ Caucasians) and 1315 term controls ($n = 522$ African-Americans, $n = 793$ Caucasians) to determine whether the influence of body mass index varied by race and ethnicity. The authors found that the odds for early preterm birth (<32 weeks) were decreased in obese African-American women (compared to normal weight African-American women, OR = 0.23, 95% CI: 0.08–0.70); in contrast, risks of early preterm birth were increased in obese Caucasian women (compared to normal weight Caucasian women, OR = 2.30, 95% CI: 1.32–4.00).[48]

Differences in biological response

In a large study evaluating the ability of multiple inflammatory biomarkers to predict preterm birth in multiple compartments (amniotic fluid, fetal plasma, and maternal plasma), overlap between biomarkers in the combined analysis, Caucasian-only analysis, and African-American only analysis was uncommon across the measured compartments. The

authors concluded that optimal biomarker models to predict preterm birth are race-dependent.[49] Another study evaluating 36 biomarkers in 105 preterm cases (59 African-American and 46 European-American) and 86 term controls (40 African-American and 46 European-American) reported similar results.[50] Again, biomarker concentrations were noted to significantly differ between cases and controls, and racial disparity in these levels was noted across maternal, fetal, and intra-amniotic compartments. In this study, though dysregulated fetal plasma biomarkers were the largest contributor to prematurity in European-Americans, maternal plasma biomarkers were most significant in African-Americans.[50] Combined, these studies suggest distinct differences in pathophysiology underlying preterm birth.

Genetics and epigenetics

Multiple studies have found genetic variation influences risk for preterm birth. There is a clear familial predisposition to preterm delivery; women with a first degree relative with a preterm birth and those women who themselves were delivered preterm carry an increased risk for preterm birth.[51] Women with a sibling with a pregnancy complicated by preterm birth, preterm PROM, placental abruption, and preeclampsia are at increased risk for these complications in orders of magnitude ranging from 3.8 to 9.6.[52] These findings are confirmed in twin studies,[53] and the overall heritability of preterm birth has been estimated to range between 25% and 40%.

Unfortunately, candidate gene studies of preterm birth have been largely difficult to reproduce and some results are inconsistent across populations. Racial and ethnic differences in allele frequencies across the genome may influence racial disparities in preterm birth. Studies of couples of mixed race have found increasing odds of preterm birth as the proportion of black genes increases, with the maternal genetic contribution most influential (risks lowest for white mother–white father; intermediate-low for white mother–black father, intermediate-high for black mother–white father, highest for black mother–black father).[54–56] Specific differences in maternal genotypes have been found in association with preterm birth. Some smaller studies have been difficult to reproduce, but have been fraught with heterogeneity and small sample size. Most consistently, studies have found differences in genes related to infection and inflammation. One effort illustrating these principles evaluated the effect of the maternal interleukin-6 genotype at rs1800795, and examined 1165 women with preterm birth compared to 3830 term controls. In a stratified analysis, the 'CC' genotype was protective against preterm birth among European-Americans (OR = 0.68, 95% CI: 0.51–0.91), but there was no apparent effect in African-Americans (OR = 1.01, 95% CI: 0.72–1.33).[57] In another large study of 1536 single-nucleotide polymorphisms (SNPs), researchers found 7 genes involved with inflammation, extracellular remodeling, and cell signaling to be associated with prematurity in African-American women; the strongest relationship was found with the protein kinase C-alpha (PRKCA) gene.[58]

Recently, researchers have broadened investigations past evaluation of genotype to compare epigenetic changes between women delivering preterm compared to at term. Epigenetics describes genetic changes that impact gene activity and gene expression, and are both potentially heritable and modifiable in response to environmental stimuli. Epigenetics may provide the key to understanding some of the heritability of preterm birth. Cruickshank et al.[59] evaluated genome-wide CpG methylation from 12 surviving very early preterm birth cases (delivered at a median 26 weeks' gestation) compared with 12 matched term controls (delivered at a median 39 weeks' gestation). In this study, CpG methylation changes were evaluated from birth blood spots and again from peripheral blood obtained at 18 years of age. Though many changes seen in birth samples resolved at age 18, ten probes were found to have >5% methylation discordance at birth *and* at 18 years of age, suggesting longer-term epigenetic changes may contribute to the heritability of preterm birth.[59] Parets et al. studied DNA methylation from maternal leukocytes and cord blood, comparing African-American women and neonates delivering preterm (24–34 weeks' gestation, $n = 16$) to those delivering at term (39–41 weeks' gestation, $n = 24$) and found 5171 CpG sites where methylation in fetal samples was correlated with methylation in maternal samples (false discovery rate $p < 0.05$). These CpG sites were in genes involved in metabolic, cardiovascular, and immune pathways.[60] Parets et al.[61] also reported an association between methylation of 29 specific CpG sites in African-American fetal samples and preterm birth, and found 9637 specific methylation sites associated with delivery gestational age; most (62%) had decreasing methylation with decreasing gestational age.

Microbiome

The diagnosis of bacterial vaginosis during early pregnancy is an established risk factor for preterm birth; non-Hispanic black women are more likely to be diagnosed with bacterial vaginosis during pregnancy. Modern investigations have evaluated with more precision the genomes corresponding to the community of organisms harbored by humans and have termed this the "microbiome." In pregnancy, the microbiome of multiple sites has been studied—including the mouth, gut, placenta, and vagina.[62] Emerging evidence suggests that composition of the microbiome in the mid-trimester differs among women destined to deliver preterm,[63,64] among those with preterm premature rupture of membranes,[65] and among those with and without chorioamnionitis.[66] Further, though some studies have found the majority of women—regardless of maternal race—have a Lactobacillus-dominant vaginal microbiome,[67,68] some report that African-American women are more likely to have a diverse vaginal microbiome (e.g., non-Lactobacillus dominant).[64,69,70] Lactobacillus is generally thought to offer anti-bacterial defense; the absence of a lactobacillus-dominated vaginal microbiome is associated with intra-amniotic infection and preterm birth.[71]

Telomere length

Recently, Jones et al.[72] evaluated telomere length (a potential marker of cellular senescence and aging) from placental

tissue and found telomere length was significantly shorter in placental samples from black mothers compared to white mothers. Unfortunately, however, these authors were unable to correlate telomere length with pregnancy outcome given a very low rate of preterm birth in their cohort.[72]

Conclusions and future directions potential solutions

Preterm birth is a complex phenotype, and there will not be a single etiology nor single "one size fits all" solution. In the vast majority of cases, neither a single candidate gene, nor a single environmental exposure will be sufficient to cause preterm birth. Likewise, a single etiology is unlikely to explain the observed disparities between race and ethnicities. Though maternal risk factors and genetic characteristics have been evaluated in depth in many studies, fewer studies have incorporated paternal and fetal components. Future studies should consider these critical data in assessing the "complete picture" with regard to prematurity risk. As bioinformatics techniques become more sophisticated and can incorporate newer ways to evaluate key clinical variables, social factors, exposures, the microbiome, and genetic factors (now understood not as a static code of DNA but rather a dynamic reflection of the environment), this will provide the ability to comprehensively determine risk for prematurity and develop new solutions for prevention and treatment.

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