

Maternal Subpopulation Variances in Vaginal and Cesarean Section Delivery Method Predicts Excess Infant Mortality of Black/African Americans in the United States: Linked Birth/Infant Death Records, 2007-2016

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ABSTRACT

Objective:

Racial/ethnic disparities in infant mortality (IM) continue to persist in the United States, with Black/African Americans (AA) being disproportionally affected with threefold increase in mortality compared to Whites. Epidemiologic data have identified maternal characteristics as risk IM such as eclampsia, maternal education, smoking, maternal weight, maternal SES, and family structure. Understanding the cause of causes including the method of labor and delivery and the racial heterogeneity may facilitate intervention mapping in narrowing the Black White IM risk differences. We aimed to assess the temporal/racial trends and the methods of delivery, mainly vaginal versus cesarean section (C-section) as exposure function of IM. **Methods:** The United States linked Birth/Infant Death records (2007-2016) were used with a cross-sectional ecologic design. The analysis involved chi squared statistic, incidence rate estimation, and period percent change. **Results:** Of the 40,445,070 births between 2007 and 2016, cumulative mortality incidence was 249,135 (1.16 per 1000). The IM rate was highest among Black/AA (11.41 per 1000), intermediate among Whites (5.19 per 1000), and lowest among Asian /Pacific Islanders (4.24 per 1000). The cumulative incidence rate difference, comparing vaginal to cesarean procedure was 1.73 per 1000 infants, implying excess IM with C-section. Compared to C-section, there was a 31% decreased risk of IM among mothers with vaginal delivery, rate ratio (RR) = 0.69, 95% CI 0.64-0.74. Racial disparities was observed in the method of delivery associated with IM. Black/AA mothers with vaginal delivery had a 6% decreased risk of IM

compared to C-section, RR = 0.94, 95%CI 0.92-0.95, while Whites with vaginal delivery had a 38% decrease risk of IM relative to C-section, RR= 0.68, 95%CI 0.67-0.69, $p<0.001$.

Conclusion: Infant mortality varied by race, with Black/AA disproportionately affected which is explained in part by labor and delivery procedures, suggesting reliable and equitable intrapartum assessment of Black/AA mothers during labor.

Keywords: vaginal; cesarean section; African American women; infant mortality; race/ethnicity

Introduction:

The United States (U.S.) has experienced since the creation of the National Center for Health Statistics (NCHS) racial/ethnic differences, where Black/African American (AA) children experienced excess rates of chronic diseases and untimely deaths compared to their White counterparts, which is explained in part by built environment, institutional racism, crime and segregation [1]. The National Institutes of Health (NIH), has indicted that the inability for United States to achieve its full health potentials is mainly as a result of the health disparities, which reflects subpopulation differences in social economic and environmental conditions related to health [2]. These health disparities are also demonstrated in African American women who are twice as likely to experience life-threatening pregnancy-related complications, also known as severe maternal morbidity (SMM) [3,4]. Because pregnancy-related complications are correlated with infant mortality, African American mothers are twice as likely to have children who experience mortality within the first 12 months of birth. Previous studies have observed the correlation between low socioeconomic status and excess morbidity and mortality in the U.S population, which explains in part the excess infant mortality among Black/AA [5]. The U.S. racial differences in infant mortality continue to persist, with Blacks/AA children being 2 to 3 times as likely to die compared to Whites. The observed disparities may be explained by racial variances in maternal factors, mainly pre-term birth, low birth weight, obesity, diabetes, hypertension, pre-eclampsia, alcohol, tobacco, HIV, rural residence, race, prenatal visits and psychosocial stressors. A study on preterm weight observed increased likelihood of infant mortality with low birth weight and very small for gestational age (VSGA). Children with VSGA (<2th percentile vs. >50th -74th percentile) had increased risk of infant mortality in a large cohort (n=4,525) of infants without congenital anomalies [6].

In the U.S., the Center for Disease Control and Prevention (CDC) provides a comprehensive listing of infant mortality, by clinical conditions and by mother's self-identified race and/or ethnicity, from 1968 to 2015. The predisposing factors or causes of infant mortality remain to be fully understood despite the race differences in risk by clinical disorders. With the multifactorial etiology of infant mortality and stillbirth, the cause of causes, implying the etio-pathogenesis of the racial differences remains unclear and not very well understood. However, an investigation on the clinical conditions such as the method of labor and delivery, resulting in the observed differences in infant mortality remains a viable and pragmatic pathway of an explanatory epidemiologic model.

Cesarean and vaginal delivery are two forms of delivery methods. Even though vaginal deliveries already double the number of cesarean deliveries, vaginal deliveries are declining as rates of cesarean delivery are increasing. More specifically, there are two different types of vaginal deliveries: vacuum assisted and forceps assisted. From 2005 to 2013, rates of both vacuum assisted (from 5.8% to 4.1%) and forceps assisted (from 1.4% to 0.9%) vaginal deliveries decreased [7]. In contrast, the number of cesarean deliveries has increased from 2016 from 31.9% in 2017 to 32% [8]. Even though this difference is marginal, it represents increasing trends in elective cesareans [9]. With such a higher rate of cesarean deliveries, there is an increased risk of maternal and fetal complications, such as maternal death, infant mortality, hemorrhage, infection, incidental surgical injuries and extended hospitalization. The rates of these complications are higher in incidences of cesarean deliveries than vaginal deliveries [10]. Studies have shown that cesarean delivery rates are positively correlated with infant mortality rates among industrialized countries [11]. Available epidemiologic data have indicated disparity in cesarean delivery rates and infant mortality rates between non-Hispanic Black and White women. Non-Hispanic Black women have a higher rate of cesarean delivery (36%) compared to non-Hispanic White women (30.9%) [12]. With the availability of data explaining in part the contributory effects of the methods of delivery in the perpetual and persistent disparities in infant mortality, the current study aims to examine the racial differences in infant mortality comparing cesarean with vaginal delivery. Additionally, we sought to utilize maternal education in explaining the racial variance in the method of delivery as the exposure function of infant mortality.

Methods:

This study aim to assess the implication of method of labor and delivery as well as child factor such as birth weight in infant mortality and maternal education variances by race/ethnicity. The availability of these data allow for the subpopulations specific needs assessment, given the multifactorial etiology in infant mortality. Therefore the understanding of factors especially healthcare delivery system contributory effect (labor and delivery method) associated with the excess infant deaths among Black/AA will facilitate intervention mapping and subsequent risk reduction; thus transforming health equity in this dimension. After an institutional review board (IRB) approval, we conducted a study to assess the relationship between infant mortality and method of delivery, and racial heterogeneity therein.

Data from the National Center for Health Statistics (NCHS, 2007-2016) were used to examine infant death prevalence by race/ethnicity as well as to determine the labor and delivery method associated with Black-White differences in infant mortality. This data set represent the United State Linked Birth/Infant Death Records, 2007-2016. As an aggregate database, the Center for Disease Control provides information on death records by year of death of the infant, the race of the infant as mother's bridge race, maternal education, sex of the child, weight of the child, attending healthcare provider and geography (location / region, urbanization and state). The details of the utilized database is available elsewhere (www.wonder.cdc.gov).

Study Design:

A cross sectional ecologic non-experimental design was used to examine Black - White risk differences in infant mortality, with the method of delivery as the exposure function of the variance. This design involves the utilization of preexisting data in aggregate form and are accurate given the simultaneous gathering of all the variables in the dataset. Additionally, this design allows for the examination of other independent variables as potential exposures or potential confounding variables.

Study Eligibility

This study used a consecutive sample which represents a probability sample given its sampling representativeness ($n = 40,445,070$). To estimate the power, implying the ability of the study to detect a clinically meaningful differences between race in infant mortality, we estimated the power using the following parameters, sample size of American Indian/ Alaska Native (AI/AN), $n = 469,563$, which was the smallest sample size in the subpopulation by race. The effect size (Δ) = 0.20 (20%). The type I error tolerance was 0.05 (5%) implying 95% CI. With these parameters, we estimated the statistical power (type II error tolerance <20%) as a power sufficient to detect a minimum difference of 20% in comparing the mortality experience of Black/AA relative to Whites, with respect to the delivery method. Should such a difference, really exist.

Statistical Analysis

A pre analysis screening was used to examine the dataset for accuracy in terms of data gathering based on the linked birth/infant death records from 2007-2016. The descriptive statistics was performed to examine the distribution of the study variables by the main independent variable, race and methods of delivery frequencies and percentages, while, annual and period percent change was used to examine the temporal trends by rates from 2007-2017. The chi square statistic, incidence rate ratio and tabulation analysis were used to assess the variable's independence as well as the association between independent (race and delivery method) and outcome (infant mortality) variables. The period prevalence was assessed using a standardized formula which determined whether or not method of delivery, with respect to mortality, remained stable or changed over a specified period of time:

$$\text{Period percent change} = \frac{\text{current or final period or year (rate)} - \text{initial or previous period or year (rate)}}{\text{initial or previous period or year (rate)}} * 100$$

The type 1 error tolerance 5% (95 CI) and all test were 2 tailed. The entire analyses were performed using STATA statistical software (Version 15, STATA Cooperation, College Station Texas).

Results:

The data in this study represents the United States Linked Birth/Infant Death Records, from 2007-2016. Of the 40,445,070 births, between 2007 and 2016, there were 249,135 deaths. (6.16 per 1000). Although not in Table 1, the cumulative infant mortality rate during this period was 6.16 per 1,000 infants. This rate varied by race of the infants. The rates were highest among Black/AA (11.41 per 1,000), intermediate among American Indian/Alaskan Natives (8.32 per 1,000) and lowest among Whites (5.19 per 1,000) and Asian/Pacific Islanders (4.24 per 1000). The rates also varied by the method of delivery, and the infant mortality related to cesarean section (8.49 per 1,000) was higher compared to vaginal delivery (6.75 per 1,000), implying a 1.74 per 1,000 infant mortality rate difference.

Table 1 illustrates vaginal and cesarean delivery rates, comparing American Indian/Alaskan Native, Asian/Pacific Islander, Black/AA and White mothers. There was racial differences in the infant mortality rate. The rates were highest among Black/AA (vaginal, 1.1% versus caesarian, 1.2%), intermediate among American Indian/Alaskan Natives (vaginal, 0.7% versus caesarian, 1.1%), and lowest among Whites (vaginal, 0.5% versus caesarian, 0.7%), and Asian/Pacific Islanders (vaginal, 0.4% versus caesarian, 0.5%). The rates of infant mortality by vaginal and cesarean section stratified by race, generally, irrespective of race, vaginal delivery indicated a lower risk of infant mortality relative to C-section, implying the protective effect of vaginal delivery on overall US infant mortality. Among Whites, infant mortality associated with vaginal delivery was 0.5% while among Black/AA it was 1.1%, implying a 0.6% infant mortality risk difference comparing Black/AA and Whites in this method of delivery. Similarly, infant mortality varied by C-section comparing Black to White infants. Among White infants, C-section accounted for 0.7% of overall mortality while among Black/AA was 1.2%, $X^2(4) = 40,000$, $p < 0.001$. There was a statistically significant difference in infant mortality by the method of delivery among American Indians/Alaskan Natives. Vaginal delivery was associated with 0.7% while cesarean section was associated with 1.1% infant mortality $X^2(4) = 40,000$, $p < 0.001$. Among American Indians/Alaskan Natives vaginal delivery was protective against infant mortality. Compared to C-section there was a 31% decreased risk of infant mortality, incidence rate ratio = 0.69, 95% CI, 0.64 - 0.74, $p < 0.001$

Table 2 demonstrates the overall incidence rate ratio in infant mortality risk stratified by race comparing vaginal with C-section. The infant mortality risk associated with C-section was lowest among Whites, as well as American Indians/Alaskan Natives. Compared to C-section in these two races, there were 32% and 31% decreased risk of infant mortality among Whites and American Indians/Alaskan Natives respectively, comparing vaginal to C-section methods of delivery. In contrast, the incidence rate ratio difference was very marginal among Black/AA compared with C-section there was 6% decreased risk of infant mortality with vaginal delivery. A statistically significant difference in mortality was observed by the method of delivery among Asian/Pacific Islanders. The vaginal delivery method in this population was associated with 0.4% while C-section was associated with a 0.5% of infant mortality, $X^2(1) = 90.6$, $p < 0.001$.

Among Asian/Pacific Islanders there was a decreased risk of infant mortality following vaginal delivery relative to cesarean section. Compared with C-section there was a 17% decreased risk of infant mortality, incidence rate ratio (IRR) = 0.83, 95% CI, 0.80 - 0.86, $p < 0.001$. The incidence rate of dying given the method of delivery indicated increased risk among Black/African American mothers who underwent cesarean section. Compared to C-section, there was a 6% decreased risk of infant mortality among mothers with vaginal delivery, IRR = 0.94, 95% CI, 0.92 - 0.95, $p < 0.001$. Similarly, there was a statistically significant difference in infant mortality by the method of delivery for Whites. The infant mortality was higher with C-section compared to vaginal delivery (0.45% vs 0.66%), $X^2(1) = 5600$, $p < 0.001$. Among White mothers' vaginal delivery was protective against infant mortality. White mothers who underwent vaginal delivery had 32% decreased risk infant mortality, IRR = 0.68, 95% CI, 0.67 - 0.69, $p < 0.001$.

Table 3 presents the method of delivery stratified by maternal education and race implying the effects of race and education on infant mortality in the United States. Regardless of race, infant mortality was highest among mothers with less than high school but lowest among mothers with post college degree. Among American Indian/Alaskan Native, mothers with less than high school, vaginal delivery was associated with 9.33 per 1000 while C-section was associated with 14.3 per 1000. Similarly, for Black/African American infant death among mothers who possessed less than high school was 9.8 per 1000 and 13.0 per 1000 for vaginal and cesarean, respectively. A similar pattern was observed among White and Asian/Pacific Islander

mothers. Among White mothers with less than high school, vaginal delivery was associated with 5.5 per 1000 while C-section was associated with 8.85 per 1000. Additionally, White mothers with post college degree experienced the lowest infant mortality associated with vaginal delivery 2.5 per 1000 during this time interval.

Table 4 describes the rate of infant mortality related to the method of delivery, race and the sex of the infants. Regardless of the method of delivery or race, the risk of dying as an infant was higher for males compared to females. Among American Indian/Alaskan Native female delivered through vaginal method were 20% less likely to die relative to male, IRR = 0.80, 95% CI, 0.74-0.87. Similarly with respect to cesarean section, females were 18% less likely to die among American Indian/Alaskan Native, IRR = 0.82, 95% CI, 0.74-0.91. Similarly among Black/AA mothers, their female infants were less likely to die regardless of the method of delivery compared to male infants. Regarding vaginal delivery Black/AA infant females were 21% less likely to die compared to males, IRR = 0.79, 95% CI, 0.78-0.81. In addition, concerning C-section there was an 11% decreased risk of infant mortality among males compared to vaginal method, IRR = 0.89, 95% CI, 0.87-0.90.

Table 5 exhibits the cumulative infant mortality rates by 5 year intervals and the percent change by race and method of labor and delivery. Regardless of race, the cesarean section method of delivery was higher in the first period (2007-2011) of the 5 year intervals relative to the second period (2012-2016). The highest rate in the C-section was observed among Black/AA, 12.63 per 1000, while the lowest rate was observed among Asian/Pacific Islanders, 4.61 per 1000. The infant mortality rate slightly lowered in the second period, with the lowest rate observed among Asian/Pacific Islanders despite the slight increase in this period (2007-2011), 4.97 per 1000. The lowest infant mortality rate in the first period was observed among Asian/Pacific Islanders (3.74 per 1000) while the highest was observed among Black/AA (11.60 per 1000). In these two subpopulations, namely Asian/PI and Black/AA, rates slightly increased in the second period. With respect to percent change, a positive percent change was observed in cesarean delivery (CD) among American Indian/Alaskan Natives, while negative trends were observed in either C-section or vaginal delivery (VD) among other racial groups, indicative of infant mortality overall reduction despite the highest rates among Black/AA and lowest rates

among Whites and Asian/PI. The trends and the period percent change are indicated in figure 1. There is overall increase in infant mortality in the first period relative to the second period. The period percent change indicated reduction in infant mortality with non-substantial effect on the temporal trends on the risk of dying, $R^2 = 2\%$.

Discussion

The current study assessed the exposure function of labor and delivery method in the persistently observed excess mortality of Black/AA infants in the United States. There are a few relevant findings from this study. First, regardless of race, vaginal delivery was associated with decreased risk of infant mortality relative to cesarean section. Secondly, there were racial differences in the association between types of labor and delivery in infant mortality. Thirdly, irrespective of race, infant mortality was highest among mothers with less than high school education and lowest among mothers with post college degree. Fourthly, notwithstanding the method of delivery or race, the risk of dying as an infant was higher for males compared to females. Fifthly, there was a negative trend in period percent change, implying lower rates of infant mortality during the later period of the study (2012-2016).

The current study has demonstrated excess infant mortality of Black/AA relative to Whites. The observed racial differences in infant mortality had been illustrated by several studies to be 3 times as likely relative to White in Wisconsin [13]. Previous studies identified low socioeconomic status, maternal stress, maternal education, and psychosocial stressor as exposure functions in infant mortality [14,15,16]. This disproportionate burden of infant mortality by race implies a survival disadvantage of Black/AA infants, and maybe explained by social gradient in health including though not limited to the social determinates of health. Additionally, domestic violence during pregnancy as well as pre-conception stress associated with family structure and violence have been implicated in infant mortality risk [12,17]. The current study intended to explain the observed racial differences in infant mortality by the method of delivery namely vaginal and C-section. Specifically, the excess mortality of Black/AA infants relative to Whites appears to be explained by the marginalized differences between the vaginal and C-section method of deliveries in Black/AA. There are no studies to our knowledge that have accessed

racial differences in infant mortality utilizing this exposures as explanatory model. Available clinical data have implicated C-section in increased risk of infant mortality [18].

We have also demonstrated that there were racial differences in the association between types of labor and delivery in infant mortality. There are no data to support or negate our findings. In the current study, regardless of the race of infant vaginal delivery was protective compared to C-section, while the differences in vaginal versus C-section rates was higher in Whites, such differences was very marginal among Black/AA. The racial variances in the rate differences comparing C-section to vaginal may very well explain the excess mortality of Black/AA infants relative to Whites. However we are unable to explain the marginal differences between vaginal and C-section rates among Blacks/AA in infant mortality. Notwithstanding, it is plausible to suggest that Black mothers maybe provided with incompetent care at labor and delivery suggestive of intrapartum clinicians' believability, implying that Black mothers are used to pain and therefore ignorability.¹⁹ This racial bias in pain perception results in clinician delay in response to patients' complaint hence poor prognosis [19]. The implicated maternal stress at labor may induce pathologic changes in the neonates resulting in excess infant mortality among Black/AA

Our data have clearly indicated that regardless of race, infant mortality was highest among mothers with less than high school education and lowest among mothers with post college degree. Previous studies have indicated inverse correlation between maternal education and infant mortality implying that the less educated the mother, the higher the infant mortality rate [20]. However, some studies have indicated that among Black/AA regardless of the mothers' education, infant mortality rate does not vary [21]. The observed inconsistency or perceived deviation from the exposure function of education in infant mortality risk reduction maybe explained by work related stress and employment instability among Black mothers [22]. The implication of workplace stress serves as a confounding in the association between higher education and lower infant mortality may be explained by the gene and job environment interaction. The work environment as human social condition defined by low socioeconomic status, psychosocial stressors, isolation and unstable social class may predispose Black/AA mothers to increased elaboration of conserved transcriptional response to adversity gene (CTRA). Such elaboration has been implicated in increased pro-inflammatory cytokine such as

interleukin-6 and decreased synthesis of immunoglobulin G (IgG) such as (antibodies synthesis) as well as decreased interferon gamma production, as an innate response to viral pathogens. The overall molecular level events in this context may result in the constriction of the uterine blood vessels inducing fetal hypo perfusion and the subsequent pathologic outcomes in the neonate increasing infant mortality.

This study has also illustrated that irrespective of the method of delivery or race, the risk of dying as an infant was higher for males compared to females. The observed sex variance in infant mortality has been previously observed [23]. Whereas genetic stability based on the sex chromosome, mainly, XX and XY have been utilized to explain the survival advantage of human female species. The epigenomic stability might provide additional information on such observation. The constantly observed survival advantage of female infant is explained by the interaction between the gene in the sex chromosomes and endogenous environment such as hormones as well as exogenous such as maternal exposure to hypomethylated diet during pregnancy. Epigenomic modulation involves the DNA methylation process as well as histone protein acetylation as a post transcriptional activity. The application of these two mechanistic processes may explain the transcriptional factors deregulation and the subsequent impaired gene expression, while the histone acetylation process may restrict the availability of the DNA and the subsequent gene expression required for cellular, tissue, organ, and system functionality, enhancing infant mortality. Because epigenomic modulation resulting in aberration is transgenerational but reversible especially at gametogenesis and in-utero, the adverse consequence for the fetus, neonate and infant, remains remarkable in influencing survival.

There was a negative trend in period percent change, implying lower rates of infant mortality during the later period of the study (2012-2016). These findings indicate a negative temporal trend in infant mortality rate. Whereas infant mortality has been shown to decrease with time, as confirmed by the current data, there remains racial variances or gaps in infant mortality. Despite the observed infant mortality trend reduction, the United States remains unfavorable in comparison with other industrialized nations in the world with respect to the rankings [24]. The observed low ranking of the U.S. globally with respect to infant mortality is due in major parts by racial differences in the rates, implying health equity transformation, in ranking the U.S. as topmost favorable nation in the world with respect to infant mortality.

Overall the observed racial differences in infant mortality is driven by a structural and organized social system that restricts the opportunity for the Black/AA subpopulation in the U.S. to benefit from social economic and environmental conditions related to human health. Specifically, improving the living conditions, increasing access to care, and care utilization such as prenatal visits and equitable intrapartum care during delivery and labor, as well as minimizing clinician bias may reduce the excess infant mortality of Black/AA infants in the U.S. Further, providing the opportunity in which living conditions are improved among Black mothers will offer the opportunity to improve the health of Black/AA children, thus marginalizing the Black White risk difference in infant mortality. Furthermore, examining the gene and environment interaction, previously observed as epigenomic studies will provide substantial data on intervention mapping in narrowing the gaps between Blacks and Whites in respect to infant mortality. Epigenomic changes which commences at gametogenesis is transgenerational but reversible. The social signal transduction that is evoked from the stress placed on Blacks/AA mothers has a substantial effect on sympathetic nervous system and provokes the beta-adrenergic receptors. This response have been shown to provoke the CTRA gene expression and the consequent elaboration of pro-inflammatory cytokine genes due to the impaired gene expression of the transcription factors and the inhibition of gene expression with respect to anti-inflammatory response. In understanding these pathways of genomic stability and their role in disease causation as well as mortality, epigenomic studies are necessary in determining whether or not Black mothers, relative to White mothers have increased mean demethylation index with respect to the genome-wide analysis. Such initiative will involve the utilization of the bisulfite pyrosequencing that is very specific in differentiating between the methyl group and hydroxyethyl group, as well as the binding of these groups to the CpG region of the gene, inhibiting transcription and the mRNA sequencing leading to impaired gene expression and abnormal cellular functionality. The reference to epigenomics investigation reflects the inability of an infant to respond to treatment modalities due to the drug receptors in-availability resulting from impaired gene expression (impaired mRNA translation). The observed epigenomic lesion clearly illustrates treatment effect heterogeneity in which some subpopulations respond differentially to a given therapeutic agents in the phase of aberrant epigenomic modulation, explaining infant mortality risk racial risk differences.

Despite, the large sample size utilized in this study and the rigorous methodology that is very novel in aggregate data modelling, there are some limitations. First, as a pre-existing data, there remains a potential for information and misclassification biases. Secondly, these findings may be driven by unmeasured confoundings. However, it is highly unlikely that the implication of the method of delivery in explaining the excess infant mortality among Black/AA is driven solely by these unmeasured confoundings. Other limitations of this study include the potential for misclassification of infant race.

Conclusion

In summary, there are racial disparities in infant mortality which were explained in part by the labor and delivery method comparing vaginal to cesarean section. However, due to the aggregate nature of these data, caution is required in the application of these findings, in intervention mapping in reducing the Black, White infant mortality risk differences. Further, these findings recommend effective policies formation implementation and evaluation in understanding the cause of causes mainly, social gradient in addressing the perpetually and persistently observed racial gap in infant mortality.

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