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Racial difference in preterm birth and low birthweight: Towards a new hypothesis involving the interaction of 25-hydroxyvitamin D with maternal fat mass

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ABSTRACT

Preterm birth (PB) and low birthweight (LBW) remain a leading cause of infant mortality worldwide. Persistent racial disparities in prevalence rates have been reported, with the highest values observed in Subsaharan Africa and South Asia. In United States, non-Hispanic Black women are more likely to have a premature or low-birthweight baby. Beyond the speculative debate on factors explaining such racial disparity, the key-question remains about the path from race to birth outcomes. Several hypotheses emerged from the published literature to explain the racial difference in likelihood for PB and LBW. However, the 'Hispanic paradox' remains unexplained. We relied here on published data to hypothesize that the racial disparity in PB/LBW is a consequence to the joint influence of 25-hydroxyvitamin D and fat mass. Beyond its role as a source of 1,25-dihydroxyvitamin D, the 25-hydroxyvitamin D is directly implicated in the fetal growth and the normal completion of pregnancy. Because of its lipophilic property, a large part of 25-hydroxyvitamin D is swiftly trapped into fat mass and the circulating fraction impact the body development during fetal period. We postulate that the positive effect of vitamin D to prevent PB/LBW is less beneficial for women with high fat mass, independent of race. The core problem may be related to bioavailable 25-hydroxyvitamin D, not directly to race.

Introduction

Preterm birth (PB) is defined as a birth of an infant before 37 completed weeks of gestation. Low birthweight (LBW) is rather defined as birth weight less than 2500 g. Globally, prematurity is the leading cause of death in children under the age of 5 years. Approximately 1 million children die each year due to complications of PB [1]. The overall proportion of LBW infants was reported to be 15.5% in 2000. The highest rates were reported in Africa (14.3%) and Asia (18.3%) [2]. PB and LBW remain a leading cause of infant mortality worldwide [3], and have been linked to both short- and long-term adverse events, including cerebral palsy, mental retardation [4], chronic lung disease, hypertension and diabetes mellitus in adulthood [5–8]. From the published data, it is evident that the probability of experiencing a PB or having an LBW infant varies across races. The risk of adverse birth outcomes has remained about twice as high among African Americans as among Caucasians [9], and this disparity persist across studies and over decades. It has been reported that non-Hispanic Black women had 1.67 times the odds of being delivered preterm compared with non-Hispanic white, and the PB rate among Black women was significantly high compared with Caucasian women (14.3% and 9.0%, respectively) [10]. From a large-scale data sets, Fresbie and associates found that the odds of PB was 2.2 times in Black women (95%CI: 1.1–4.2), with White women as the reference group, after adjusting for prenatal care quality, biomedical variables, socioeconomic and sociodemographic factors [11]. These recent data are similar to those published in early 1990s [12,13] and to data from 1978 to 1988 [14]. Despite progressive decline observed in US birthweight-specific infant mortality, the declines were larger for White than Black children by about 5–15% among LBW children [15]. The increase in black-white infant mortality ratio

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confirms that the overall decline as observed was mostly benefit to White children. Reports on Hispanic women are of great interest for epidemiologists. The lowest rate of LBW among Hispanic US women (compared with African-American) has long been published in the medical literature. The likelihood for preterm and LBW in Mexican-American is similar to the one observed in White US women, regardless of socioeconomic status [12,16–18]. Given the strong relation of socioeconomic disadvantage with birth outcomes, readers would expect to observe a high similarity between individuals sharing the same socioeconomic conditions, independent of race. Surprisingly, Hispanic women are characterized by low prevalence rates of LBW, regardless of socioeconomic status. Beyond the speculative debate on public health implications of such racial disparity, the key-question remains about the path through with birth outcomes are affected by race-related factors.

Existing hypotheses to explain racial disparities in birth outcomes

There are several risk factors identified for PB and LBW in the literature. These include neighborhood disadvantages, low socioeconomic status, exposure to stressful events, short interpregnancy intervals, tobacco exposure, use of illicit drugs, vaginal infections, previous PB, hypertension and diabetes, etc. [19–24]. The complex interaction between some of them makes it difficult to estimate the net contribution of each factor to birth outcomes. Some hypotheses emerged from the published literature to explain the persistent difference observed from race to race in prevalence rates of PB and LBW.

Most of PB and LBW were observed in African-Americans women, and this observation has been reported in several other countries since early 1950s. The role of poor socioeconomic conditions as determinants of racial difference had been previously suspected and reported [25]. However, the racial disparity in LBW persists in wealthiest population [26]. Furthermore, the “Hispanic paradox” suggests that either socioeconomic status does not play a dominant role or there is an effect modification by a third factor. A second hypothesis is related to prenatal care quality/frequency of use. The study report from the U.S. Bureau of Economic Research pointed to this direction [27], suggesting that high rates of adverse birth outcomes observed in Black US women are due to poor/insufficient prenatal cares. From 1981 to 1995, an increasing trend toward more prenatal care use has been observed among women at low-risk of adverse pregnancy outcomes (compared with those at high-risk) [28]. In the early 1990s, Balkazar and co-workers reported that Mexican-Americans were less likely to use prenatal care than African-Americans women [29]. Moreover, study from Fresbie and co-investigators suggested that the odds of inadequate prenatal care was 1.93 times in Mexican-Americans (with White woman as a reference group), while the odds was closest to the null value for African-Americans (1.46) [30]. A third hypothesis is linked to psychosocial factors and culture. Indeed, some authors argued that the high prevalence rate of adverse birth outcomes in Black women may be explained by the discrimination or stressful experiences more prevalent in this group. It should be noted that significant disparities in stressful life events across different racial groups was confirmed by Lu & Chen based on large datasets of US federal-State cooperative survey [10]. Authors did not find significant effect of stressful factors on disparities in PB. The possible implication of protective cultural orientation and social support in Hispanic communities has been evoked by Sherman James [31]. This avenue remains unexplored and underreported in the literature. Sherman James cited the Beccera’s study showed that Mexican-American women born in Mexico were less likely to give birth to LBW babies than their counterparts born in the United States [12]. In addition, there was a nearly two-and-a-half-fold excess risk of LBW infants for black mothers as compared to white mothers, but no comparable excess risk for Mexican American women. A study from Singh and co-workers [17] pointed in the same direction. They observed that US-born Mexicans, Chinese, and Blacks had 38–61% higher risks of LBW than their immigrant counterparts, supporting the potential role of ‘culture’. From a randomized trial, Norbeck et al. (1996) reported the significant protective effect of social support during pregnancy [32]. Although these result suggest the ‘culture’ and social support as a possible mediating pathway between ethnicity and birth outcomes, the substantial question remain about its importance. The rate of LBW is at least as elevated in the native countries of Hispanic Americans as the one observed in Sub-Saharan Africa, questioning the role of culture [2]. Furthermore, in the study from Singh and Stella (1996), Hispanics immigrants were more likely than their US-born counterpart to live alone during pregnancy [17], decreasing beliefs about the marked influence of household support. Finally, some authors speculated about the ‘vitamin D hypothesis’. This hypothesis stipulates that racial disparity in health outcomes may be due to differences in vitamin D synthesis. In the other words, the low rate of adverse health outcomes in the Caucasians is due to their ease of produce vitamin D after sunlight exposure. In the context of birth outcomes, we might then expect to observe low rates of PB and LBW in low latitudes, where people experience a high sunlight exposure for a longer period of time. Surprisingly, very low rates of LBW (< 5%) are reported in Northern countries. In United States, Thayer reported that women living in the North had better birth outcomes than those living in the South [33]. At first glance, this opposite result argues against the potential implication of vitamin D in the racial differences in the probability of PB and LBW. In the present paper, we relied on previous studies to formulate a new hypothesis involving the inactive form of vitamin D.

Towards a new hypothesis

Vitamin D synthesis

The skin is the major site where the vitamin D synthesis is initiated. Up to 90% of vitamin D is produced by sunshine exposure of skin [34]. Darker skin is less efficient than lighter skin for the sunlight-induced synthesis of vitamin D [35,36]. This is due to the fact that melanin absorbs UVB radiations that enters the epidermis and then limits the production of previtamin D3. In spite of the difference between Black and White individuals, a prolonged sunlight exposure is enough to acquire an adequate vitamin D status. However, the poor vitamin D status has been consistently reported in Black women [37,38]. The role of vitamin D is to ensure calcium homeostasis which is required for several physiological functions. The seasonal changes in vitamin D status have been previously reported [39,40], with the high levels observed during warm months. During exposure to sunlight, the solar UVB radiations induce the conversion of 7-dehydrocholesterol (which is mainly present in the Malpighii epidermal cutaneous layer) to previtamin D3. This product is then isomerized to form vitamin D3, which is removed from the skin to the blood circulation. In the hepatocytes, vitamin D3 is hydroxylated at the C-25 position (by 25-hydroxylase) to form 25-hydroxyvitamin D3 (25-OH-D) [41]. The latter is then removed from the liver to the blood circulation and is further hydroxylated in the proximal tubules (kidney). This hydroxylation occurred at the C-1 (by 1α-hydroxylase) or C-24 position (by 24-hydroxylase) to form 1,25-dihydroxyvitamin-D (1,25-(OH)2-D) and 24,25-dihydroxyvitamin-D (24,25-(OH)2-D), respectively [42].

The hypothesis

Previous studies reported that vitamin D intake during pregnancy was associated with increase in birth weight [43,44], and other studies found no association [45,46]. More recently, a prospective study concluded that vitamin D deficiency in late pregnancy was associated with higher odds of small for gestational age and LBW [47]. Despite of inconsistency among previous findings, pooled analyses suggested a protective effect of vitamin D supplementation on LBW [48]. The synthesis of 1,25-(OH)2-D is strongly regulated. Inversely, the