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Role of Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency and Altered Redox Status in Racial Disparities of Neonatal Outcomes: An Innocent Bystander or Unaccused Accomplice?

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"Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent inherited enzymopathy worldwide, with the highest population prevalence in sub-Saharan Africa and Southeast Asia and the lowest in the Americas (1)."

Introduction:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent inherited enzymopathy worldwide, with the highest population prevalence in sub-Saharan Africa and Southeast Asia and the lowest in the Americas (1). G6PD is a crucial rate-limiting regulatory enzyme in the hexose monophosphate shunt pathway, which clears free radicals and safeguards cellular structures against oxidant-induced damage, thereby maintaining a balanced redox status (2). It is essential for the equilibrium of the glutathione system, NADP oxidase system, and nitric oxide synthase (3) (Figure 1). This X-linked genetic disorder is mapped to the chromosome Xq28 region and encompasses over 140 described mutations, primarily point mutations (4). With more than 400 biochemical variants, this enzyme deficiency can manifest as neonatal jaundice, the hemolytic crisis resulting from medication exposure and infections, and chronic hemolytic anemia (5). The diverse biochemical variants and point mutations predispose affected individuals to exhibit various clinical manifestations.

Recent gene network analysis has revealed that G6PD-associated genes are involved in various cellular signaling mechanisms, and impaired regulation of these genes has been implicated in cancers, autoimmune diseases, and disorders associated with oxidative stress (6). In order to mitigate the clinical consequences of G6PD deficiency, some countries with higher prevalence rates have implemented universal newborn screening along with provider and parental education about this disorder. The primary objective of this commentary is to emphasize the connection between G6PD deficiency, prematurity, and racial disparities in perinatal outcomes.

"Absent or reduced G6PD enzyme activity can accelerate oxidant-induced hemolysis in term and preterm newborns, thereby increasing the risk of hazardous levels of hyperbilirubinemia and neurotoxicity."

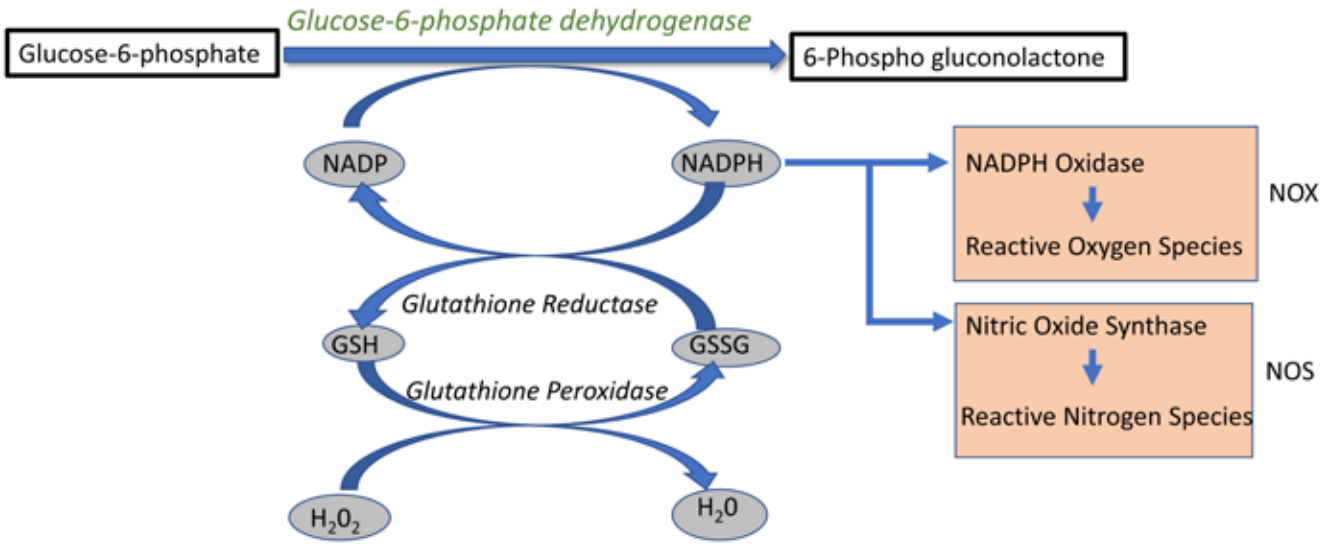
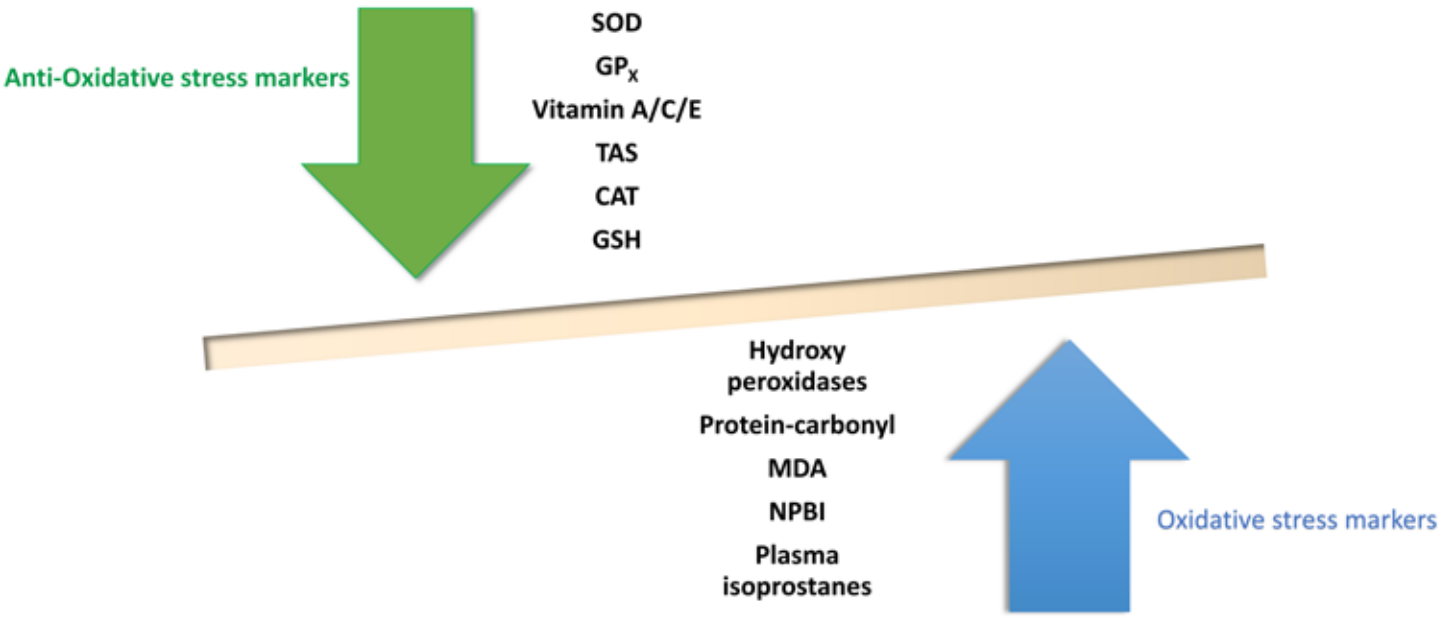


Figure 1: Interaction of G6PD with Glutathione, NOX, and NOS systems.



SOD-Super oxide dismutase; GP_X-Glutathione peroxidase; TAS-Total antioxidant status; CAT-catalase

Figure 2: Oxidative and Antioxidantstress markers in preterm infants at birth.

G6PD Deficiency and Hyperbilirubinemia:

Absent or reduced G6PD enzyme activity can accelerate oxidant-induced hemolysis in term and preterm newborns, thereby increasing the risk of hazardous levels of hyperbilirubinemia and neurotoxicity. Two large population studies conducted in the United States military revealed an overall G6PD deficiency prevalence of 2.2% (7). Disproportionately higher prevalence was observed among African Americans in both studies (overall prevalence: 9.5%; 11.2% in males and 5.6% in females). Based on 2018 US census data (8), out of 3.8 million annual births, 552,029 were non-Hispanic black infants, and 1.9 million were White Americans. Considering the population prevalence data from the aforementioned studies, approximately 52,445 non-Hispanic black infants are born with G6PD deficiency annually.

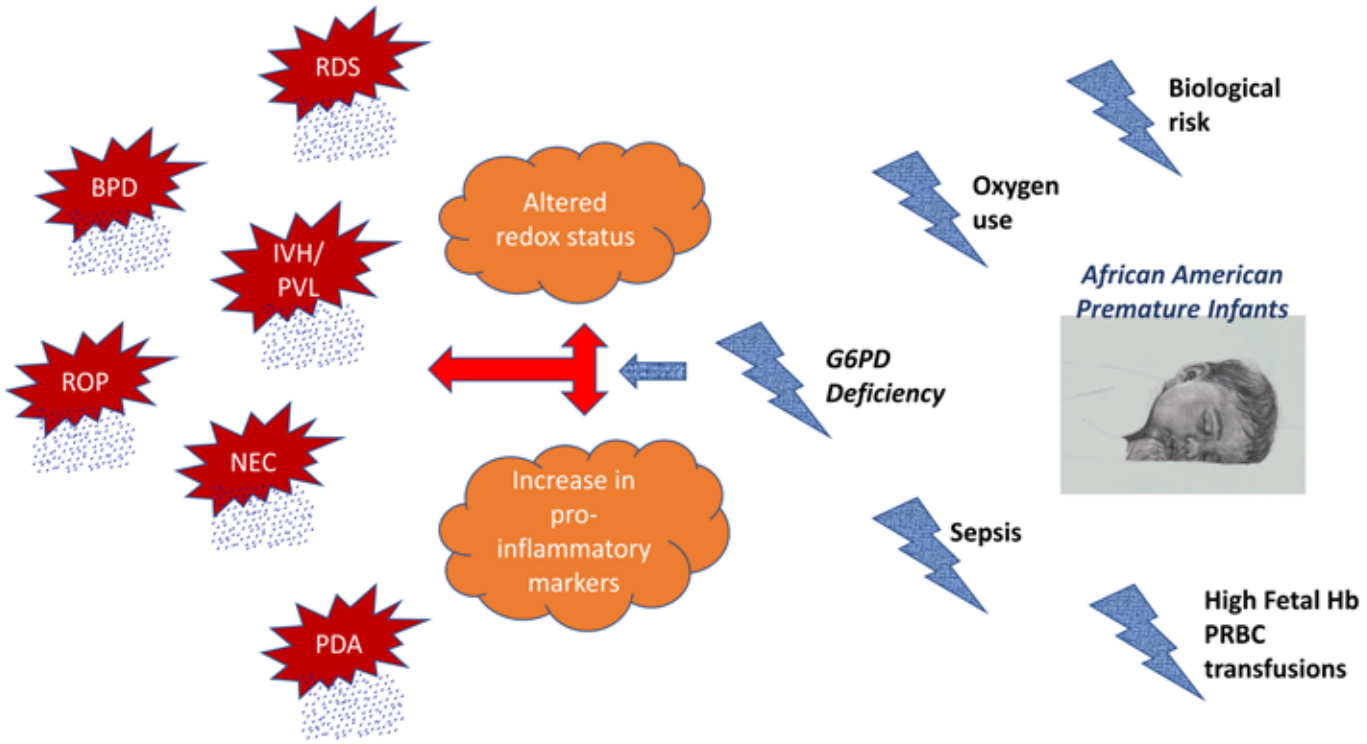
"Mounting evidence (17,30) suggests that small preterm infants have significantly lower catalase and GSH:NADPH ratios than late preterm and term infants. The compounding effect of G6PD deficiency on already weakened antioxidant defense mechanisms can theoretically cause cumulative end-organ damage in preterm infants. Future in vitro and in vivo research could shed light on this area."

Data from the Kernicterus Registry indicate that 1 in 5 cases of kernicterus involved G6PD deficiency, which was believed to contribute to at least 2/3 of these cases among African American infants (9). Another population study conducted in California confirmed a four-fold increase (0.013% vs. 0.003%) in the rate of hazardous hyperbilirubinemia (bilirubin > 30mg/dl) among African American infants compared to White infants (10). Applying these rates to 2018-linked US birth population data (11), at least 72 African American and 58 White infants are expected to develop bilirubin levels > 30mg/dl. While studies conducted in Cleveland and Chicago (12,13) confirmed the prevalence and short-term outcomes of G6PD deficiency among the newborn population, there is a lack of data elucidating prematurity-related perinatal outcomes comparing normal and G6PD-deficient preterm newborns.

G6PD Deficiency, Prematurity, and Oxidative Injury:

G6PD enzyme is present in vital organs throughout the body, with the highest concentrations found in red blood cells, lungs, heart, and smooth muscles. It plays a key role in clearing and recycling free radicals, thereby maintaining cell redox equilibrium. Free radicals are highly reactive and unstable molecules that can cause extensive damage to cellular components. The generation of free radicals is a well-regulated process during cellular respiration, aided by three main intracellular antioxidant defenses: glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) systems. Nicotinamide adenine dinucleotide phosphate (NADPH) is critical for the detoxification of reactive free radicals by maintaining GSH in its reduced form, and G6PD plays a vital role in the regeneration cycle of NADPH (14). The allosteric binding site for NADPH is offered by catalase (CAT), and CAT activity is dependent on the amount of NADPH (15). Thus, NADPH is key in strengthening all organs' G6PD-related cellular antioxidant systems.

Despite significant technological advances and care practice improvements, preterm birth remains a major contributor to infant



BPD-Bronchopulmonary dysplasia; RDS-Respiratory distress syndrome; NEC-Necrotizing enterocolitis; PDA-Patent ductus arteriosus; ROP-Retinopathy of prematurity; PVL- Periventricular leukomalacia; IVH-Intraventricular hemorrhage

Figure 3: G6PD deficiency and perinatal morbidities.

mortality and morbidity. Multiple human studies have demonstrated that premature infants have higher oxidative stress markers and lower antioxidant defenses at birth (16,17) (Figure 2). Many of these markers are directly associated with the NADPH system. However, there is a lack of data regarding the detrimental effects of reduced enzyme activity in asymptomatic extremely preterm infants.

"Given the multitude of etiological factors influencing retinopathy of prematurity (ROP), the impact of G6PD deficiency on immature retinal vasculature remains unknown."

G6PD Deficiency, Race, and Perinatal Outcomes:

Numerous studies have shown significant racial differences in prematurity-related perinatal outcomes, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP), even after controlling for care practices, maternal risk factors, and quality of care (18-23). Recent population studies conducted in Wisconsin and California revealed that prematurity and race pose a significant risk to gestational age-adjusted infant mortality and morbidity in black infants compared to white infants, even when receiving advanced equitable neonatal care in the United States, after accounting for potential confounders such as birth weight, sex, maternal characteristics, and social factors (24,25).

to all these morbidities, a few case reports have associated it with neonatal sepsis and necrotizing enterocolitis (26,27). Two human studies demonstrated a negative correlation between G6PD activity and gestational age in G6PD-normal infants with similar GSH levels at baseline, and G6PD activity did not interfere with diagnosing G6PD deficiency (28,29). Given the heterogeneity of effects generated by pentose pathway byproducts in G6PD deficiency, predicting the ultimate effects on specific organs and tissues is challenging. Mounting evidence (17,30) suggests that small preterm infants have significantly lower catalase and GSH:NADPH ratios than late preterm and term infants. The compounding effect of G6PD deficiency on already weakened antioxidant defense mechanisms can theoretically cause cumulative end-organ damage in preterm infants. Future in vitro and in vivo research could shed light on this area.

Another prospective study in adult diabetic patients revealed a six-fold higher incidence of proliferative diabetic retinopathy in G6PD-deficient diabetic adults than those without this deficiency (18). Given the multitude of etiological factors influencing retinopathy of prematurity (ROP), the impact of G6PD deficiency on immature retinal vasculature remains unknown. Similarly, new bronchopulmonary dysplasia (BPD) is characterized by arrested alveolar and vascular development due to altered cytokine exposure and signaling pathways (30). Interestingly, similar cytokine and gene profiles have been implicated in the pathophysiology of G6PD deficiency (6). A community population study confirmed significantly lower plasma glutathione levels in African Americans, even after adjusting for traditional cardiovascular disease risk factors and inflammation (31). However, further studies are needed to understand the relative contribution and attributable risk of G6PD deficiency to higher oxidative stress in the black population. After adjusting for relevant covariates, another recent perinatal study in placentas from preterm births confirmed significantly greater chronic inflammatory changes in African American mothers. Whether these chronic inflammatory markers and underlying

biological mechanisms influence postnatal transition through oxidative stress and impact preterm morbidities remains unknown.

"Given the interconnected pathways associated with higher oxidative stress in premature infants, studying the relative contribution of quantitative G6PD enzyme activity and its correlation with perinatal morbidities is prudent (29-35) (Figure 3). Specifically, understanding the influence of altered redox status and unregulated free radical activity, with different phenotypes and genotypes, on the outcomes among vulnerable African American preterm infants should be a priority in future neonatal research."

Although various intrinsic and extrinsic factors can influence prematurity-related morbidities, questions remain regarding the plausible biological contribution of suboptimal G6PD enzyme activity to these outcomes. Given the interconnected pathways associated with higher oxidative stress in premature infants, studying the relative contribution of quantitative G6PD enzyme activity and its correlation with perinatal morbidities is prudent (29-35) (Figure 3). Specifically, understanding the influence of altered redox status and unregulated free radical activity, with different phenotypes and genotypes, on the outcomes among vulnerable African American preterm infants should be a priority in future neonatal research.

Conclusion:

Approximately 10% of births nationwide are preterm, and G6PD deficiency affects at least 50,000-60,000 newborns annually in the United States. The influence of altered redox status from G6PD deficiency on immature respiratory, digestive, immune, and cardiovascular systems in preterm infants is unknown. The combination of a high prevalence of G6PD deficiency in African Americans, poor social determinants of health, higher morbidities, and oxidative injury may create a perfect storm leading to underestimated poor outcomes. Postnatal adaptation resulting from altered oxidative stress in these infants may further influence the onset of chronic diseases such as hypertension and metabolic syndrome in adulthood. Therefore, understanding G6PD deficiency, prematurity, and their interrelationships with underlying immature cellular and organ systems can provide critical insights.

References:

1. Howes RE, Piel FB, Patil AP, Nyangiri OA, Gething PW, Dewi M, et al. G6pd deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. von Seidlein L, editor. PLoS Med. 2012 Nov 13;9(11):e1001339.
2. Desforges JF, Beutler E. Glucose-6-phosphate dehydrogenase deficiency. N Engl J Med. 1991 Jan 17;324(3):169–74.
3. Yang H-C, Wu Y-H, Liu H-Y, Stern A, Chiu DT-Y. What has passed is prolog: new cellular and physiological roles of G6PD. Free Radical Research. 2016 Oct 2;50(10):1047–64.
4. Luzzatto L, Nannelli C, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Hematology/Oncology Clinics of North America. 2016 Apr;30(2):373–93.
5. Cappellini M, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. The Lancet. 2008 Jan;371(9606):64–74.
6. Chen L, Zhang C, Wang Y, Li Y, Han Q, Yang H, et al. Data mining and pathway analysis of glucose-6-phosphate dehydrogenase with natural language processing. Molecular Medicine Reports. 2017 Feb;16(2):1900–10.
7. Lee J, Poitras BT. Prevalence of glucose-6-phosphate dehydrogenase deficiency, US Armed Forces, May 2004-September 2018. MSMR. 2019 Dec;26(12):14–7.
8. Nvss - national vital statistics system homepage [Internet]. 2021 [cited 2021 Apr 29]. Available from: https://www.cdc.gov/nchs/nvss/index.htm
9. Johnson L, Bhutani VK, Karp K, Sivieri EM, Shapiro SM. Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). Journal of Perinatology. 2009 Feb;29(1):S25–45.
10. Wickremasinghe AC, Kuzniewicz MW, Newman TB. Black race is not protective against hazardous bilirubin levels. J Pediatr. 2013 May;162(5):1068–9.
11. Ely DM, Driscoll AK. Infant mortality in the united states, 2018: data from the period linked birth/infant death file. Natl Vital Stat Rep. 2020 Jul;69(7):1–18.
12. Nock ML, Johnson EM, Krugman RR, Di Fiore JM, Fitzgerald S, Sandhaus LM, et al. Implementation and analysis of a pilot in-hospital newborn screening program for glucose-6-phosphate dehydrogenase deficiency in the United States. J Perinatol. 2011 Feb;31(2):112–7.
13. Kaplan M, Herschel M, Hammerman C, Hoyer JD, Heller GZ, Stevenson DK. Neonatal hyperbilirubinemia in African American males: The importance of glucose-6-phosphate dehydrogenase deficiency. The Journal of Pediatrics. 2006 Jul;149(1):83–8.
14. Kehrer JP, Lund LG. Cellular reducing equivalents and oxidative stress. Free Radical Biology and Medicine. 1994 Jul;17(1):65–75.
15. Kirkman HN, Gaetani GF. Catalase: a tetrameric enzyme with four tightly bound molecules of NADPH. Proceedings of the National Academy of Sciences. 1984 Jul 1;81(14):4343–7.
16. Weber D, Stuetz W, Bernhard W, Franz A, Raith M, Grune T, et al. Oxidative stress markers and micronutrients in maternal and cord blood in relation to neonatal outcome. Eur J Clin Nutr. 2014 Feb;68(2):215–22.
17. Lee Y-S, Chou Y-H. Antioxidant profiles in full term and preterm neonates. Chang Gung Med J. 2005 Dec;28(12):846–51.
18. Cappai G, Songini M, Doria A, Cavallerano JD, Lorenzi M.

Increased prevalence of proliferative retinopathy in patients with type 1 diabetes who are deficient in glucose-6-phosphate dehydrogenase. Diabetologia. 2011 Jun;54(6):1539–42.

19. Jammeh ML, Adibe OO, Tracy ET, Rice HE, Clark RH, Smith PB, et al. Racial/ethnic differences in necrotizing enterocolitis incidence and outcomes in premature very low birth weight infants. J Perinatol. 2018 Oct;38(10):1386–90.

20. Janevic T, Zeitlin J, Auger N, Egorova NN, Hebert P, Balbierz A, et al. Association of race/ethnicity with very preterm neonatal morbidities. JAMA Pediatr. 2018 Nov 1;172(11):1061.

21. Townsel C, Keller R, Kuo C-L, Campbell WA, Hussain N. Racial/ethnic disparities in morbidity and mortality for preterm neonates admitted to a tertiary neonatal intensive care unit. J Racial and Ethnic Health Disparities. 2018 Aug;5(4):867–74.

22. Howell EA, Janevic T, Hebert PL, Egorova NN, Balbierz A, Zeitlin J. Differences in morbidity and mortality rates in black, white, and hispanic very preterm infants among new york city hospitals. JAMA Pediatr. 2018 Mar 1;172(3):269.

23. Anderson JG, Rogers EE, Baer RJ, Oltman SP, Paynter R, Partridge JC, et al. Racial and ethnic disparities in preterm infant mortality and severe morbidity: a population-based study. Neonatology. 2018;113(1):44–54.

24. Tomlin BD, McAdams RM, Zapata JY, Kaluarachchi DC. High Black infant mortality in Wisconsin: factors associated with the ongoing racial inequity. J Perinatol. 2021 Feb;41(2):212–9.

25. Karvonen KL, Baer RJ, Rogers EE, Steurer MA, Ryckman KK, Feuer SK, et al. Racial and ethnic disparities in outcomes through 1 year of life in infants born prematurely: a population based study in California. J Perinatol. 2021 Feb;41(2):220–31.

26. Schutzman DL, Porat R. Glucose-6-phosphate dehydrogenase deficiency: another risk factor for necrotizing enterocolitis? The Journal of Pediatrics. 2007 Oct;151(4):435–7.

27. Rostami-Far Z, Ghadiri K, Rostami-Far M, Shaveisi-Zadeh F, Amiri A, Rahimian Zarif B. Glucose-6-phosphate dehydrogenase deficiency (G6pd) as a risk factor of male neonatal sepsis. J Med Life. 2016 Mar;9(1):34–8.

28. Ko CH, Wong RP-O, Ng PC, Li K, Chui KM, Yuen PM-P, et al. Oxidative challenge and glucose-6-phosphate dehydrogenase activity of preterm and term neonatal red blood cells. Neonatology. 2009;96(2):96–101.

29. Mesner O. Glucose-6-phosphate dehydrogenase activity in male premature and term neonates. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2004 Nov 1;89(6):F555–7.

30. Jobe AJ. The new bpd: an arrest of lung development. Pediatric Research. 1999 Dec;46(6):641–641.

31. Morris AA, Zhao L, Patel RS, Jones DP, Ahmed Y, Stoyanova N, et al. Differences in systemic oxidative stress based on race and the metabolic syndrome: the morehouse and emory team up to eliminate health disparities (Meta-health) study. Metabolic Syndrome and Related Disorders. 2012 Aug;10(4):252–9.

32. Matoba N, Yallapragada S, Davis MM, Ernst LM, Collins JW, Mestan KK. Racial differences in placental pathology among very preterm births. Placenta. 2019 Aug;83:37–42.

33. Saugstad OD. Update on oxygen radical disease in neonatology: Current Opinion in Obstetrics and Gynecology. 2001 Apr;13(2):147–53.

34. Gveric-Ahmetasevic S, Sunjic SB, Skala H, Andrisic L, Stroser M, Zarkovic K, et al. Oxidative stress in small-for-gestational age (Sga) term newborns and their mothers. Free Radical Research. 2009 Jan;43(4):376–84.

35. O'Donovan DJ, Fernandes CJ. Free radicals and diseases in premature infants. Antioxidants & Redox Signaling. 2004 Feb;6(1):169–76.

Conflict of Interest: The author has no conflicts of interest relevant to this article to disclose.

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