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IN FOCUS

Iron Metabolism in African American Women in the Second and Third Trimesters of High-Risk Pregnancies

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ABSTRACT

Objective: To examine iron metabolism during the second and third trimesters in African American women with high-risk pregnancies.

Design: Longitudinal pilot study.

Setting: Large, university-based, urban Midwestern U.S. medical center.

Participants: Convenience sample of 32 African American women with high-risk pregnancies seeking care at an urban maternal–fetal medicine clinic.

Methods: Nonfasting venous blood was collected in the second and third trimesters to assess iron status, hepcidin, and systemic inflammation. Anthropometric and survey data were obtained via self-report. Descriptive statistics were calculated from these data, and changes in the clinical parameters between the second and third trimesters were evaluated via paired *t* tests. Associations among demographic, reproductive, anthropometric, inflammatory, and iron-related parameters were also assessed in each trimester.

Results: The mean age of participants was 28.3 (± 6.8) years, and mean prepregnancy body mass index was 31.9 (± 10.7) kg/m^2. In the longitudinal analysis, significant ($p < .05$) declines in serum iron, ferritin, transferrin saturation, and C-reactive protein were observed between the second and third trimesters. There was no statistically significant change in hepcidin between trimesters. When using a ferritin level cut-point of less than 15 ng/ml and soluble transferrin receptor level of greater than 28.1 nmol/L, 48% of the participants (14 of 29) were classified with iron deficiency in the third trimester.

Conclusion: In this pilot study, iron deficiency was prevalent among a small cohort of African American women with high-risk pregnancies. Hepcidin concentrations were greater than previously reported in healthy, pregnant, primarily White women, which suggests decreased iron bioavailability in this high-risk group.

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African American women are more likely to have high-risk pregnancies than women in other racial/ethnic groups (Centers for Disease Control and Prevention, 2013). This disparity may be due in part to greater rates of known risk factors, including preexisting conditions such as obesity (Ogden, Carroll, & Flegal, 2014), hypertension (Go et al., 2013), type 2 diabetes (Chow, Foster, Gonzalez, & McIver, 2012), and adverse pregnancy-related conditions such as gestational diabetes mellitus and gestational hypertension (Ferrara, 2007). Such disorders have also been reported to negatively influence iron metabolism in pregnant women of all racial/ethnic groups (Dao, Sen, Iyer, Klebenov, & Meydani, 2013; Garcia-Valdes et al., 2015; Phillips et al., 2014). Several research teams have linked obesity (Dao et al., 2013; Garcia-Valdes et al., 2015; Jones et al., 2016) and gestational diabetes mellitus (Phillips et al., 2014), conditions that would classify a pregnancy as high-risk, with iron deficiency (ID) and impaired iron metabolism in pregnancy.

ID during pregnancy, defined as a measurable decrease in circulating and body iron stores (Suominen, Punnonen, Rajamäki, & Irjala, 1998), is associated with a multitude of well-documented negative maternal and fetal health events that

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Pregnant women are prone to iron deficiency because additional iron is required to support the mother's expanding blood volume and growth of the placenta and fetus.

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include greater risk for maternal and infant morbidity (Allen, 2000), preterm birth (Siega-Riz et al., 2006), and transient and irreversible neurocognitive defects in infants (Beard, Murray-Kolb, Haas, & Lawrence, 2007). All pregnant women are at risk for ID because a substantial increase in iron is required to support the expansion of the woman's blood volume and the growth of the placenta and fetus (McArdle, Lang, Hayes, & Gambling, 2011). To fulfill this elevated iron demand, pregnant women are advised to increase their dietary iron intake from 16 to 27 mg daily (Institute of Medicine, Food and Nutrition Board, 2001). Further, women's bodies adapt to changing iron needs via compensatory mechanisms that allow for greater dietary iron absorption and enhanced placental iron uptake and flux to the developing fetus (Bothwell, 2000; Gambling, Lang, & McArdle, 2011; Rehu et al., 2010). Recent estimates suggest that approximately 30% to 40% of pregnant women in the United States are classified with ID during the third trimester of pregnancy, and racial/ethnic minorities, specifically African American women, are at even greater risk than their non-Hispanic White counterparts (Mei et al., 2011).

Systemic iron metabolism does not differ during gestation and is maintained by the hepatic-derived peptide hormone hepcidin (Ganz & Nemeth, 2012). Hepcidin promotes degradation of the body's only known iron exporter, ferroportin-1 (Fpn). Degradation of Fpn reduces the transportation of iron into circulation from the diet and body storage sites (Ganz & Nemeth, 2012; Goodnough, Nemeth, & Ganz, 2010; see Figure 1). In the nonpregnant and pregnant states, hepcidin is simultaneously regulated by body iron stores, erythropoiesis, and systemic inflammation (Darshan & Anderson, 2009; see Figure 1). In the presence of systemic inflammation, hepcidin production and secretion from the liver is enhanced, which results in diminished Fpn expression and reduced iron export into circulation from stores and diet—in other words, iron restriction (Goodnough et al., 2010; see Figure 1).

In women who experience uncomplicated pregnancies, serum hepcidin levels have been reported to be very low or undetectable in the third trimester (Rehu et al., 2010; van Santen et al., 2011; Young et al., 2010). It is believed that suppression of hepcidin is a compensatory mechanism that allows for enhanced dietary iron absorption and efflux of iron from a woman's body storage sites in pregnancy (Rehu et al., 2010). However, in conditions with underlying systemic inflammation, the flow of iron from the diet and body iron stores may be restricted because of elevated hepcidin (Dao et al., 2013). In fact, investigators in one study showed that elevated hepcidin in women during the third trimester was associated with reduced dietary iron absorption (Young et al., 2010). Thus, when coupled with a high demand for iron, such a state could exacerbate ID, given that iron from food and supplements may be less readily absorbed because of elevated hepcidin and suppressed Fpn. Therefore, the provision of additional oral iron may not resolve ID or improve iron status in pregnant women with inflammation-driven, hepcidin-mediated iron restriction.

Women with high-risk pregnancies may be a subset of pregnant women who are particularly vulnerable to adverse changes to iron metabolism and ID due to inflammation stemming from conditions of high-risk pregnancy (e.g., obesity, gestational diabetes, preexisting type 2 diabetes). Our goal in this small pilot study was to explore systemic iron metabolism, including hepcidin and systemic inflammation, in African American women during the second and third trimesters of high-risk pregnancies.

Methods

Design and Recruitment

Women who sought care at an urban maternal–fetal medicine clinic affiliated with the University of Illinois Hospital and Health Sciences System were recruited for the pilot study. Eligibility criteria included singleton high-risk pregnancy, African American race, at least 15 years of age, born in the United States, living in the greater Chicago area, and able to read and write English. Exclusion criteria included major fetal anomaly, autoimmune disease (e.g., HIV, type 1 diabetes, rheumatoid arthritis, lupus, and Graves' disease), receipt of steroid treatments (including inhalers for asthma), sickle cell disease, or placement of a cervical cerclage. An obstetrician classified women as having high-risk pregnancies on the basis of their risk for prematurity or other pregnancy-related complications. At our maternal–fetal medicine clinic, *high-risk* was defined as previous preterm

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