

## **Ironing Out the Details of Maternal-Fetal Iron Trafficking: New Tools in the Toolbox**

Pamela J Kling

University of Wisconsin-Madison, Madison, WI, USA

Effective iron trafficking from the mother to fetus in atrisk pregnancies is critical for fetal neurodevelopment. In this month's issue of *The Journal of Nutrition*, Delaney et al. [\(1\)](#page-1-0) leverage innovative tools to better understand maternal-fetal iron trafficking in, "Umbilical cord erythroferrone is inversely associated with hepcidin, but does not capture the most variability in iron status of neonates born to teens carrying singletons and women carrying multiples." Identifying abnormalities of the maternal-fetal iron metabolism is important, as congenital iron deficiency (ID) can no longer be considered a nutritional disorder with cost-effective treatment, but a neurocognitive and behavioral risk factor. Thus, preventing either congenital ID or the development of ID anemia (IDA) in early life is an important arm of an infant neuroprotective strategy [\(2\)](#page-1-1).

Maternal ID in pregnancy is common and impacts the fetal iron status, as the enteral iron supplementation increases fetal iron accretion [\(3\)](#page-1-2). Although women commonly develop ID in the third trimester, current clinical screening for ID utilizes blood hemoglobin concentrations early in pregnancy as the marker, in part because physiological drops in hemoglobin concentrations occur consequent to hemodilution in late pregnancy [\(4\)](#page-1-3). Using hemoglobin as a surrogate screen for ID is inadequate and out of date, being neither specific nor sensitive for diagnosing preanemic ID in most populations. Perhaps because of poor screening tools, the US Preventative Services Task Force concluded there was insufficient current evidence to assess the balance of benefits and harms of IDA screening in pregnancy [\(5\)](#page-1-4). Employing better tools could clarify the utility of screening for ID in pregnancy.

Maternal IDA is a risk factor for congenital ID, despite iron being prioritized for the fetus at the expense of the maternal iron compartment. However, in the setting of placenta dysfunction or certain maternal health issues, this prioritization may be compromised. Intrauterine growth restriction, hypertensive disorders, chronic inflammatory disorder, obesity, or diabetes increase risks for congenital ID even in the face of a normal maternal iron status [\(6–10\)](#page-1-5). Fetal risk factors for congenital ID also include male sex (larger fetus), being large or small for gestational age, multifetal gestation, and/or prematurity [\(7–9,](#page-1-6) [11\)](#page-1-7). In addition, several social determinants of health increase risks for maternal and/or congenital ID, including lower socioeconomic status, maternal youth, maternal ID, maternal childhood lead exposure, and/or maternal ethnic minority status [\(9,](#page-1-8) [12,](#page-1-9) [13\)](#page-1-10).

Clinical tools used to piece together the maternal-fetal ironerythropoiesis puzzle have moved well beyond hemoglobin and are becoming more comprehensive. An assay for erythropoietin (EPO) levels was the first to examine maternal-fetal erythropoiesis in the 1980s [\(14,](#page-1-11) [15\)](#page-1-12). In the 1990s, serum soluble transferrin receptor (sTfR)  $1(16)$  $1(16)$  was applied to assess iron availability for erythropoiesis. With the identification of intestinal iron transporters, divalent metal transporter 1 (DMT1), and ferroportin [\(17\)](#page-1-14) came the recognition in the early 2000s that human placentas express TfR1, DMT1, and ferroportin transporters [\(18–21\)](#page-1-15). The most recent additions to the toolbox examining the maternal-fetal iron metabolism include identification of the iron trafficking regulator, hepcidin [\(22,](#page-1-16) [23\)](#page-1-17), and erythroblast-produced iron regulator, erythroferrone (ERFE) [\(24\)](#page-1-18). The authors of this manuscript previously published on maternal ERFE levels in the same cohorts of at-risk adolescent and multifetal gestation pregnancies used in the current publication  $(25)$ . Their prior study found that maternal ERFE was associated with erythropoietic demand during pregnancy, but not with maternal hepcidin [\(25\)](#page-1-19). Because iron indices, EPO, and hepcidin are known to be also produced by the fetus, the latest piece of the puzzle is to place fetal ERFE levels within this context. Limited data supported an intact fetal EPO-ERFE-hepcidin axis [\(26\)](#page-1-20). Here, Delaney et al. [\(1\)](#page-1-0) examine this axis in the setting of pregnancies at high risk for congenital ID.

These studies both set out to understand the fetal-maternal iron physiology and generate clinically useful biomarkers of congenital ID in this setting. They observed that umbilical cord ERFE levels were found to be inversely related to fetal iron indices and positively related to the fetal erythropoietic drive, supporting fetal regulation of ERFE production [\(1\)](#page-1-0). Cord ERFE levels were higher than maternal ERFE levels, likely due to the relatively higher proportion of immature erythrocytes in fetuses than in pregnant women. Cord ERFE levels were directly related to the cord iron indices, sTfR1, and sTFR index. It is important to note that higher sTfR1 reflects both ID and release from maturing erythrocytes (i.e., erythropoiesis) in early life [\(16\)](#page-1-13). Of the potential biomarkers tested, cord hepcidin and the ratio of cord hepcidin to EPO explain the most variance in fetal iron and hemoglobin levels [\(1\)](#page-1-0). The finding that the hepcidin-EPO ratio was related to the fetal iron status may be related in part to the regulation of EPO production by hypoxiainducible factor 2, which is regulated in turn by iron [\(27,](#page-1-21) [28\)](#page-1-22). Given that ERFE is released from erythroblasts, it would be informative to study pregnancies in which fetal erythropoiesis is increased (e.g., maternal obesity and/or diabetes). In such settings, fetal iron availability for storage is decreased [\(9\)](#page-1-8).

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Another area for further exploration is the observed difference in cord ERFE levels in African American compared with Caucasian infants. It will be informative to determine the relative contributions of genetic and socioeconomic influences. The study by Delaney et al. [\(1\)](#page-1-0) thus provides insights into future directions in understanding the regulation of the maternalfetal iron metabolism and erythropoiesis. Such studies offer the possibility of better identifying those fetuses at risk for ID, as well as approaches to mitigation beyond screening maternal hemoglobin and supplementing iron.

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