Editorial

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Iron supplementation in infants: a reflection on hepcidin and fractional iron absorption

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In 1687 Sydenham used iron filings in cold wine to treat the malady green sickness, a condition of pallor and fatigue in young women that was first described by Lange in the 1500s (1). The presence of microcytic, hypochromic erythrocytes on a peripheral blood smear later confirmed that the disorder was due to iron deficiency. One hundred and fifty years after Sydenham's first successful trial of iron, Blaud renamed the disorder chlorosis and reported his successful utilization of ferrous sulfate to treat it. Oral iron is inexpensive, widely available, and, when taken and tolerated, efficacious. Unfortunately, not only is this combination uncommon, but >70% of adults to whom oral iron is prescribed report significant gastrointestinal perturbation (2). The standard recommendation to consume ferrous sulfate thrice daily, a regimen also initiated by Blaud, is rarely tolerated, associated with constipation and gastric irritation, and alters the gastrointestinal microbiome (3). In infants and young children, poor taste of liquid iron supplements often results in spitting up and vomiting, further complicating adherence efforts (4). Thus, regarding the traditional paradigm, which is often ineffective and poorly tolerated, a need for improvement abounds. In this issue of *The American Journal of Clinical Nutrition*, (5) extend the previous exciting work of their coauthors Stoffel and Zimmermann (6, 7) by assessing iron absorption administered in a variety of methods in a high-risk pediatric population.

Iron supplementation has long been known to elevate the iron regulatory hormone hepcidin (8–10). Yet its clinical effects on iron absorption were best described in a 2015 publication (6) on 54 adult iron-deficient nonanemic women, which reported that a 6-fold increase in iron dose (from 40 to 240 mg) resulted in only a 3-fold increase in absorbed iron (from 6.7 to 18.1 mg). In addition, total iron absorption from 3 doses (2 mornings and 1 afternoon) was not significantly greater than that from 2 morning doses. The duration of hepcidin elevation in response to iron dosing suggested that alternate-day supplementation may be superior to traditional dosing (6). In 2017, these data were corroborated in a subsequent study in 40 adult nonanemic iron-deficient women using radiolabeled iron, which compared daily and twice-daily dosing of ferrous sulfate with a single tablet on alternate days (7). The results were dramatic: in iron-depleted women, providing iron supplements daily as divided doses increased serum hepcidin and reduced fractional iron absorption compared with alternate-day ingestion, again supporting the paradigm of supplementation every other day. These data are also in direct contradiction to the long-held notion that multiple divided doses increase iron absorption and imply that, in fact, the opposite is true: less frequent dosing results in increased fractional absorption (the amount of iron absorbed per dose).

Infants receive an iron "endowment" from their mothers during the third trimester of pregnancy. It is therefore not surprising that infants of iron-deficient mothers, or those born prematurely, are at increased risk of iron deficiency themselves. Decades of research has demonstrated that iron deficiency in infants and children has long-term neurocognitive effects that persist into adulthood (11). In under-resourced countries, iron deficiency may affect ≤90% of pregnant women. Absent the use of intravenous iron in high-risk neonates and young children, which is challenging to study and unrealistic in most pediatric populations, a better-tolerated schedule of oral supplementation which is less toxic, more cost-effective and convenient, and, most importantly, equally efficacious has the potential to formidably improve such outcomes.

In the current study, (5) studied 67 infants receiving 3 different regimens of iron supplementation. The infants were born to families whose major livelihood was subsistence maize farming in Southern Kenya, and 70% were iron deficient. Using stable isotopes of iron, the authors reported that 12-mg doses of ferrous sulfate given in fortified meals as either morning or afternoon doses resulted in comparable absorption. Dosing of the same form of iron on consecutive days increased plasma hepcidin concentrations and concomitantly decreased absorption compared with alternate-day dosing. Finally, dosing of pure ferrous sulfate supplementation on alternate days compared with every third day did not increase plasma hepcidin, and therefore resulted in no change in fractional iron absorption.

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At first glance one could posit that iron deficiency during infancy is largely a problem affecting under-resourced countries. Moreover, in 2015 the US Preventive Services Task Force published a report stating that there was insufficient evidence to recommend routine screening for iron deficiency in pregnant women (12). However, a recent prospective study of 2400 urban Chinese iron-deficient mothers supplemented with oral iron observed that 45% of the infants were iron deficient based on neonatal iron measurements despite improvements in hematologic and iron parameters for the women who adhered to supplementation (13). Additional evidence supporting a more rigorous screening paradigm was reported in another study of 104 consecutive, nonselected, nonanemic, first-trimester pregnant women seen in a suburban Maryland practice in the United States in whom screening iron parameters (serum iron, total iron binding capacity, transferrin saturation, and serum ferritin) were drawn (14). Defining iron deficiency as serum ferritin <30 ng/mL and/or transferrin saturation <19%, which has a 98% sensitivity and 92% specificity for absent marrow hemosiderin, 42% were iron deficient. In 2019, a report on a large population of Swedish infants found poorer neurodevelopment outcomes in infants of mothers who were anemic at any time during pregnancy (15). Infants and young children in the United States and globally across all socioeconomic populations remain at risk of iron deficiency and stand to benefit from the present findings. The exciting results of this study in a cohort of Kenyan infants add to the mounting evidence for a more simplified treatment approach (16) for one of the commonest maladies on the planet. Decreasing the dose and frequency of iron supplements and medications, as with simplifying any medication regimen, is sure to result in improved adherence with resultant improved and critically important infant outcomes.

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