Editorial

Iron Deficiency in Pregnancy and Postpartum

It Is Time for a Change

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See related articles on pages 1049 and 1052.

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Financial Disclosure

Michael Auerbach reported the following: Covis Pharma–research funding for data management only; Pharmacosmos–funding for educational, non-promotional programs. Malcolm G. Munro reported the following: Pharmacosmos–grant unrestricted; Pharmacosmos–consulting; AbbVie–consulting; Myovant–consultant; Shield Pharma–consultant; American Regent–consultant; Vifor–consultant; Daiichi-Sankyo–consultant and speaker.

ISSN: 0029-7844/23

In 1687, Syndenham used iron filings in cold wine and initiated the therapy for our planet's most common malady, iron deficiency, and its end stage, iron deficiency anemia. Today, iron is the world's most common micronutrient deficiency, estimated to affect nearly 3 billion people and more than half of pregnancies worldwide, with a higher prevalence in under-resourced countries.[1] A century and a half after Syndenham, Blaud reported the first successful use of ferrous sulfate, ushering in an era of oral iron formulations. Oral iron is ubiquitously available, inexpensive, and, when avoided in those with conditions for which it is known to be ineffective or harmful, safe and effective. Unfortunately, oral iron is associated with a frequency of gastrointestinal side effects that exceeds 70%, hampering adherence and resulting in decreased efficacy.[2] New evidence reporting physiologic elevation of serum hepcidin for more than 24 hours after a single oral dose has led to evidence supporting alternate-day dosing, which is better absorbed and improves the toxicity profile of oral supplementation.[3]

The intravenous (IV) iron formulations introduced in the 1930s were colloidal suspensions of ferric hydroxide that were so toxic, contemporary recommendations proscribed their use. In the 1950s, iron dextran was released and offered the ability to administer a large IV dose. Nonetheless, self-limited infusion reactions were mistakenly believed to be anaphylaxis, which fomented a folklore of danger that persists. Encouragingly, at the turn of the 21st century, formulations of IV iron were introduced that allow safe, rapid, and complete replacement dosing in a single setting. Indeed, a single dose of IV iron accomplishes in an hour or less what oral iron achieves in a year, considering both the iron deficiency and the need to replenish stores. Importantly, for the patient, IV iron avoids oral iron's frequent gastrointestinal side effects. The availability of these new IV formulations has led to an explosion in the use of IV iron in a host of iron-deficient states, most notably in women in their reproductive years.[4]

In this month's issue of *Obstetrics & Gynecology*, two articles (see pages 1049 and 1052) report cautionary and reassuring outcomes associated with the use of IV iron.[5,6] The former is a case report of rhabdomyolysis after a second IV dose of iron sucrose. Iron sucrose, with a small carbohydrate carrier, releases more labile free iron than the newer formulations, which is believed to be responsible for the majority of adverse events reported with IV iron.[7] As a result, lower doses requiring multiple visits must be used, which limits the utility of this treatment in outpatient settings. If a reaction is suspected after the initial administration of iron sucrose, a different formulation should be enlisted. That being said, the authors report a convincing account of rhabdomyolysis after repeat infusion with iron sucrose, informing clinician awareness of its occurrence. Notably, rhabdomyolysis has never been described with newer

formulations with carbohydrate cores binding the elemental iron more tightly, allowing large doses to be administered in 20–60 minutes without the need for additional doses.

In the second article, a randomized controlled trial, the authors demonstrate the feasibility of administering a complete or near-complete replacement dose (1,000 mg) of low-molecular-weight iron dextran. Low-molecular-weight iron dextran was the formulation used in the first prospective U.S. study of IV iron in pregnancy[8] and is considered to be a cost effective and safe choice. The authors cogently elucidate the problems with oral iron and the administrative and clinical advantages of administering iron intravenously. Although the authors used the time-honored method of thrice-daily dosing, one could posit that a better clinical outcome could have been achieved had the oral iron been administered with a once-daily or alternate-day schedule.

Iron deficiency is magnified in pregnancy because the developing fetus demands 50% of the mother's iron endowment. Approximately 50% of first-trimester, nonanemic pregnant patients have iron deficiency based on levels of serum ferritin, transferrin saturation, or both.[8] Prospective neonatology evidence shows that 25% of infants born to mothers with iron deficiency are depleted to a level associated with increased developmental, cognitive, and behavioral deficits.[9] However, although oral replacement improves mothers' hematologic parameters, neonatal ferritin levels remain depleted.[10] A Scandinavian study of 299,768 mothers and their 532,232 offspring reports a statistically significant association between autism spectrum disorders and maternal anemia.[11] Ongoing randomized trials comparing oral and IV iron in pregnant patients with iron deficiency should be designed to examine whether IV iron can improve neonatal outcomes.

The high prevalence of iron deficiency in the first trimester suggests that the frequent finding of iron deficiency anemia during pregnancy may be related to iron deficiency before pregnancy. Although iron deficiency may be in part secondary to deficient nutrition, the more likely culprit is heavy menstrual bleeding draining iron reserves before pregnancy even begins.[12] Regardless, and unlike initiatives for normalization of folate and glucose levels before pregnancy, no U.S. guidance suggests that individuals contemplating pregnancy should have hemoglobin measured, save an evaluation of iron status. Consequently, it would seem prudent, to revisit the current paradigm that ignores iron status in reproductive-aged females outside of pregnancy, not only to reduce the need for oral or IV iron during and after pregnancy but perhaps to ultimately improve fetal development, neonatal iron stores, and outcomes.[13]

Further, excepting the first trimester, for which we do not have safety data, the current policy of oral replacement should be reevaluated as frontline therapy for iron deficiency discovered during pregnancy. Saad et al[6] add to the available literature supporting the use of IV iron in the immediate postpartum period, which could contribute to improved iron status in subsequent pregnancies. The convincing data on the ease of IV replacement, coupled with emerging data on formulations facilitating a full course of therapy in 20–60 minutes, support a change in standard treatment for the most common epiphenomenon observed in the pregnant and postpartum population.

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