Paucity of Clinical Trials in Iron Deficiency: Lessons Learned From Study of VLBW Infants

Pediatricians and hematologists alike should take keen interest in the report by Taylor and Kennedy1 in this issue of Pediatrics of a randomized, placebo-controlled study of daily oral iron supplementation in very low birth weight (VLBW) infants <36 weeks’ postgestational age. Study subjects, managed according to relatively liberal transfusion guidelines, derived no benefit from the additional iron supplement of 2 mg/kg with regard to hematocrit (the primary outcome), reticulocyte count, or transfusion requirements. This result supports the concept that the need for 2 mg/kg per day of iron for low birth weight infants can be met by using iron-fortified formula or breast milk alone without medicinal iron supplementation. Two previous studies in this field2,3 were noted by Taylor and Kennedy to be inconclusive, whereas another investigation suggesting the need for iron supplementation was limited to infants whose birth weights were between 2000 and 2500 g.4

Taylor and Kennedy’s study,1 although well designed and well executed, does not provide the final word regarding the optimal method and timing of iron delivery to VLBW infants. The report failed to describe the specific types of iron used in the multivitamin with iron supplement and in the iron-fortified mother’s milk used in the study. Different forms of iron (Table 1) have different absorption profiles and toxicities. Moreover, both the benefits and potential adverse effects of medicinal iron supplements require additional study in VLBW infants, especially in settings in which transfusions are used less frequently and where outcomes other than hematocrit at 36 weeks’ postgestational age are assessed.

The implications of this well-designed clinical trial involving VLBW infants1 are relevant to all infants and young children facing the risks of iron deficiency. Iron is required for all living cells, and a deficiency of this vital element therefore interferes appreciably with their function,5,6 regardless of whether they are erythroid progenitors, neurons, or cardiomyocytes. Thus, all pediatricians should be knowledgeable about optimal means to prevent iron deficiency by using effective feeding strategies in normal and VLBW neonates as well as later in infancy when iron requirements remain high due to continued rapid growth.

Emphasis on prevention and early diagnosis of iron deficiency is critically important in older infants and toddlers just as it was in the VLBW infants studied by Taylor and Kennedy.1 Yet despite the many reports and recommendations from the American Academy of Pediatrics and others,7–9 prevention of iron deficiency is often not achieved.10 Too many exclusively breastfed infants fail to receive adequate supplemental iron after 5 or 6 months of age, and excessive quantities of whole cow’s milk constitute a large part of the diet of...
TABLE 1 Uncertainties Regarding Treatment of Iron-Deficiency Anemia and Opportunities for Future Research

<table>
<thead>
<tr>
<th>Steps Involved in Delivering Successful Iron Treatment</th>
<th>Specific Examples and/or Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis and management of the primary form of iron therapy*</td>
<td>Dietary deficiencies, bleeding, malabsorption</td>
</tr>
<tr>
<td>Preferred form of iron therapy</td>
<td>Iron salt (sulfate, gluconate, fumarate), polysaccharide, or powder (carbonyl iron)</td>
</tr>
<tr>
<td>Type of preparation</td>
<td>Tablet, capsule, solution, suspension, syrup</td>
</tr>
<tr>
<td>Recommended total daily iron dose</td>
<td>3 to 6 mg/kg per day often recommended (but probably excessive for adolescents)</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>1, 2, or 3 doses daily</td>
</tr>
<tr>
<td>Anticipated adverse effects</td>
<td>Bad taste, constipation, diarrhea, abdominal pain, stained teeth</td>
</tr>
<tr>
<td>Preferred monitoring strategy</td>
<td>Laboratory testing and physician assessment before, during, and after therapy</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>To correct anemia and reconstitute iron stores</td>
</tr>
</tbody>
</table>

*The nonspecific term “supplement,” appearing on the label of many iron medications, implies that it is not a treatment of a specific disorder but something that is optional and not necessarily a therapeutic agent.

many older infants.9,11 Screening at age 9 to 12 months may not identify the marginal iron status that evolves into frank iron deficiency during the second year of life.12 The unfortunate result has been a virtual epidemic of iron-deficiency anemia. Recent data summarized by Eden and Sandoval18 indicate that up to 20% of preschool-aged children have depleted iron stores and as many as 8% have iron-deficiency anemia resulting primarily from the “milkaholic” epidemic affecting many toddlers.9,11 These authors9,12 and others13 have recommended additional iron-deficiency screening of high-risk toddlers or even all toddlers at 15 to 18 months of age.

Despite adherence to breastfeeding and use of iron-fortified formula during the first 9 to 12 months of life, many infants subsequently receive excessive amounts of cow’s milk as a major component of their diet because parents often believe that this practice is healthy and nutritious. The result of this misconception is most prevalent among Hispanic14,15 and Asian16 toddlers and is associated with prolonged bottle-feeding and obesity.17 Cow’s milk indeed has many nutritional benefits when consumed in moderation,17 yet the limited iron in cow’s milk is poorly absorbed, and milk also inhibits absorption of the iron in other foods taken concurrently. Moreover, pasteurized cow’s milk may result in occult gastrointestinal bleeding in some infants,12 and the satiety resulting from prodigious milk intake (often ≥48 ounces daily) limits the desire for more nutritious iron-rich foods. This excess consumption of cow’s milk11 creates the “perfect storm” for the multiple sequelae of iron deficiency, including developmental delay, pica (with its attendant risk of increased environmental lead absorption18), and the myriad other manifestations of severe iron-deficiency anemia in young children16 such as pallor, lethargy, irritability, breath-holding spells, and (occasionally) stroke.19

Clearly, nutritional iron deficiency is a major problem in infants and toddlers. Given that prevention is often ineffective, where are the therapeutic studies designed to define how to best diagnose and treat it? With rare exception, they do not exist. Many pediatricians and other primary care providers fail to consider iron deficiency as a real “problem” and overlook offering preventive nutritional guidance. Even when screening is conducted and iron deficiency is identified, appropriate and effective treatment is often overlooked, delayed, or inadequate.18 Management guidelines and treatment recommendations for iron-deficient children offered in textbooks and review articles are not evidence based and are often vague and inconsistent. Few granting agencies (federal or industry) have supported therapeutic research involving infants and children with iron deficiency, and most reference sources and commentaries overlook acknowledging the paucity of high-quality investigations in this area. Instead, they offer nonspecific generalities regarding the many important decisions that are involved in treatment (Table 1). All of the desirable steps to be taken regarding management assume, of course, that the primary cause of iron deficiency is identified and controlled or eliminated, which is often not the case. It is gratifying that at least a few pediatricians and hematologists have taken notice of this serious problem and have recommended action steps to fix it.9,12 However, far more attention to this problem is required.

The excellent study of Taylor and Kennedy in this issue of Pediatrics1 assessing the role of iron supplementation in VLBW infants should be a stimulus for partnerships among general pediatricians and hematologists interested in iron deficiency, with the goal of planning and undertaking randomized trials in premature and term infants during the second 6 months of life and the subsequent preschool years. Their aims should be to scientifically validate the most effective methods for iron-deficiency screening and to conduct rigorous clinical studies to define how this common and potentially serious disorder can best be treated.

Several decades ago, a few prominent hematologists, including Drs Frank Oski, Peter Dallman, and Jerry Reeves, were deeply engaged in iron-deficiency research involving infants and young
children. Although iron deficiency remains the world’s most common hematologic disorder, it is disheartening that the US pediatric hematology community has not more recently taken notice of current insufficiencies in its management. It is time for that to change. An initial step would be to leverage the recently established alliance between the American Academy of Pediatrics and the American Society of Pediatric Hematology/Oncology. A collaboration between these 2 professional organizations could potentially foster involvement of the American Academy of Pediatrics’ Pediatric Research in Office Settings network and other investigative groups of general pediatricians and hematologists to design prospective studies that address the many management uncertainties described in Table 1 to provide high-quality evidence necessary to inform improved management of this condition. When prevention of iron deficiency fails, we must be prepared to offer effective treatment. With such firm commitments and partnerships, the “tragedy” of iron deficiency affecting our nation’s infants and young children can be overcome.

REFERENCES

1. Taylor T, Kennedy K. Randomized trial comparing iron supplementation versus routine intake in very low birth weight infants. Pediatr Res. 2015;131(2)
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George R. Buchanan
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