

## **Editorial**

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### Current Issues for the Prevention and Treatment of Iron Deficiency Anemia

Iron deficiency anemia is a leading cause of morbidity and mortality worldwide(1). Numerous studies have demonstrated that even moderate anemia (hemoglobin <100 g/L) is associated with depressed mental and motor development in children that may not be reversible(2-4). Thus, primary prevention of anemia and iron deficiency should be the goal of nutritional intervention programs. In the United States, approximately 5% of children from 1-5 years of age suffer from iron deficiency anemia(5). In developing countries, however, the prevalence of anemia reaches and in some countries exceeds 50% in one-year old children(5). This communication will address why the prevalence of anemia is so high in the developing world and what can be done about it.

The high prevalence of iron deficiency anemia found in most developing countries is accounted for by the combination of limited iron stores at birth, timing of umbilical cord clamping, timing and type of complementary food introduction, and frequency of infections.

The placenta is a rich source of transferrin receptor that avidly binds and transfers iron from the mother to the fetus(6). The majority of iron is transferred during the last trimester of gestation. In the fetus and newborn, iron is stored mainly in the liver and bone marrow; however, the amount of iron stored depends on the length of the gestational period and the weight of the baby at birth. Since internationally, some 13 million infants are born either prematurely or with a birth weight of less than 2.5 kg, these factors play a large role in increasing the predisposition to anemia. Over the first months of life human milk supplies a minimal amount of iron so stores in the liver and bone marrow are used to meet the iron requirements of the infant(7). Iron stores are generally depleted by six months of age, yet from four to twelve months after birth the infant's blood volume doubles. Thus, at this age, dietary sources of iron become critical in order to keep up with this rapid rate of red blood cell synthesis(8). The timing of the clamping of the umbilical cord at delivery is also a factor in the development of anemia(9). The amount of blood transferred to the infant depends on whether the cord is clamped early (less than a minute), inter-mediate (one to three minutes), or late (after pulsations cease)(9). For example, if the cord is not cut until pulsations cease, the infants will receive a 20-30 ml/kg body weight transfusion, which is the equivalent to approximately 30-35 mg of additional iron. To put this amount of iron into perspective, this is the equivalent to the amount of iron in 100 liters of human milk.

As previously mentioned, human milk contains very little iron (about 0.3 mg/L), thus iron stores in the exclusively breastfed infant will quickly be depleted so that by six months of age most storage iron is used up. If human milk remains the only food source, iron deficiency anemia will ultimately develop. To prevent the development of anemia, the WHO and other organizations recommend

the introduction of iron-containing complementary foods as well as foods containing ascorbic acid which enhance iron absorption at the age of six months(1). The choice of complementary foods at this stage will markedly influence the risk of iron deficiency and anemia. Unfortunately, typical grain-based complementary foods are poor sources of iron and contain phytic acid, which is a potent inhibitor of iron absorption. For example, per 100 g, rice-based complementary foods contain 1 mg of iron and maize and wheat-based complementary foods contain 0.8 mg of iron(10).

Lastly, additional predisposing factors for the development of anemia include childhood infections. During early childhood, the infant may be exposed to parasitic infections, common childhood infectious diseases and malaria. These infections predispose infants to blood loss in the stool, depressed erythropoiesis and erythrocyte hemolysis. Recurrent childhood infections may also lead to anorexia and inadequate dietary iron intake.

The United Nations and their various agencies have recognized that the treatment and prevention of iron deficiency anemia is a priority. However, much to the dismay of policymakers and pediatricians, there has been virtually no progress in the past ten years towards achieving successful intervention programs for infants and children. There are three possible interventions for the prevention of anemia. These include dietary diversification, food fortification and individual supplementation.

Dietary diversification involves promotion of a diet with a wider variety of iron-containing foods, especially meat or fish. This intervention is often not possible among the poor populations of the developing world due to the high cost of foods rich in bioavailable iron.

The fortification of staple foods such as wheat or other grains is likely to increase iron intake for those populations that have access to them. However, infants and children who have a limited capacity to eat large quantities of fortified food are not likely to benefit significantly from this strategy. Targeted fortification (for example, the fortification of foods specifically eaten by infants and children) as is practiced in the developed world, is an excellent way to increase the intake of iron in children. However, fortified commercially prepared infant foods are relatively expensive and may not be affordable for many families with children at highest risk of iron deficiency.

The final approach is through supplementation of individuals or communities at risk. For infants and young children, this approach is the most likely to succeed. For the past 150 years or more, oral ferrous sulphate drops or syrup has been the primary source of iron for the treatment (and prevention) of iron deficiency anemia(11). When a soluble form of iron (such as ferrous sulphate) is ingested in the proper dose, this intervention is effective. However, adherence to long-term ingestion of oral iron drops is often poor because of the unpleasant metallic taste of drops; drops can stain a baby's teeth unless wiped off immediately after use; and if the dose is high, the infant may complain of abdominal discomfort. In fact, there is very little evidence to date of the large-scale effectiveness of iron supplementation with drops in young children.

In 1996, a group of UNICEF consultants suggested the possibility of using a simple and potentially viable new method to provide micronutrient supplements (including iron) to populations at risk(12). The new method was based on two observations from the 'West' where micronutrient deficiencies are rare: (i) fortification of targeted commercially available food provides essential micro-nutrients; and, (ii) if the addition of micro-nutrients imparts no change in the color, texture or taste of the food, compliance is enhanced or even ensured.

Responding to the UNICEF directive, the Metabolic Research Group at the Hospital for Sick Children, University of Toronto, developed a supplement containing microencapsulated ferrous fumarate in powder form (plus ascorbic acid) which can be sprinkled on to any complementary food at the table by a caregiver. The supplement is referred to as 'Supplefer Sprinkles'. The iron is encapsulated in a thin coating of soya-based hydrogenated lipid that prevents oxidation reactions and masks its metallic taste. The encapsulation prevents changes in the color and taste of foods to which the micronutrients are added. To administer the correct amount of iron, the micronutrients are packaged in single-dose sachets (similar to oral rehydration sachets), and the entire contents are then sprinkled onto foods served in the household. One of the advantages of a powder supplement containing micronutrients that are microencapsulated is that other essential micronutrients such as Vitamins A, C and D, folic acid as well as minerals like iodine and zinc can be formulated into the sachet to prevent common deficiencies.

Initially *in vitro* dissolution studies were conducted to demonstrate that the lipid encapsulation would dissolve at the low pH of the stomach, leaving the iron available for absorption (unpublished observations). To test the efficacy of the supplement, we have performed a number of large-scale clinical trials. Recent studies in Ghana have demonstrated that the sprinkles are as efficacious in preventing and treating iron deficiency anemia in infants as the standard iron drops, yet Sprinkles have improved ease of use and is more readily accepted by children(13).

The dose of iron that is appropriate for large population-based interventions for infants and young children is not straight-forward. The dose must take into consideration whether the population is anemic and iron deficient; the age of the population in question (the higher the growth rate the higher the iron requirements); the type of diet consumed and whether the source of iron in the diet is bioavailable; and the form of iron and the vehicle in which the iron is delivered to the population. For a population of infants that is generally non-anemic, the Indian RDA is likely adequate. For an anemic population, however, one must provide enough iron to meet ongoing needs and an additional amount to account for the erythrocyte synthesis necessary to achieve a normal hemoglobin concentration and the replenishment of iron stores. Because microencapsulated iron sprinkles are added to foods which may be high in inhibitors of iron absorption (such as phytic acid and other fibre), the dose must also account for this negative impact on absorption. Although our group is still performing studies to determine the exact dose of iron to include in the Supplefer sachets, the range is likely between 15-45 mg/sachet.

As previously mentioned, adherence to treatment of iron-deficiency anemia is often poor in both developed and developing countries. The current standard therapy is ferrous sulfate drops (or syrup) administered three-times daily. It is possible that adherence would improve with a single-dose daily treatment regimen. We recently compared the use of single versus three-times daily ferrous sulphate drops, at the same total iron dose, on treatment of anemia in more than 550 infants(14). We demonstrated that a single daily dose of drops over two months resulted in a similar rate of successful treatment of anemia, without side effects.

Improving the safety, adherence, sustainability and cost-effectiveness of iron supplementation is a continued goal for researchers around the world. The option of using once daily drops or sprinkles, therefore, may improve adherence to treatment and thus the success rate for the prevention and treatment of anemia.

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*Competing interests:* Dr. Zlotkin is an occasional consultant for Bristol Myers, Squibb, Mead Johnson Ltd. and the Gerber Company, USA. Dr. Zlotkin owns the intellectual property rights to Supplefer Sprinkles. The HJ Heinz Company Ltd. is supporting the technical development of the sprinkles on a not-for-profit-basis

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### Key Messages

- Iron deficiency is a significant problem in infants, especially in developing countries. It is associated with delays in mental and physical development.
- The causes of iron deficiency in infants include low birth weight, early cord clamping, low iron content and poor bioavailability of iron in complementary (weaning) foods and recurrent childhood infections.
- Traditionally, iron deficiency is prevented by increasing the use of iron rich foods, targeted fortification of foods for children and the use of iron drops. None of these interventions have proven to be successful in the developing world. Therefore UNICEF has suggested that alternative strategies are necessary.
- If drops are used, they should be used once daily to improve compliance. In the future, microencapsulated iron sprinkles may be a useful strategy for treating and preventing iron deficiency in infants because they are simple to use, lack side effects and are as efficacious as drops.

### References

1. World Health Organization. Malnutrition: The Global Picture. Geneva World Health Organization, 2000.
2. Lozoff B, Brittenham GM, Wolf AW. Iron deficiency anemia and iron therapy effects on infants developmental test performance. *Pediatrics* 1987; 79: 981-995.
3. Pollitt E. Iron deficiency and cognitive function. *Ann Rev Nutr* 1993; 13: 521-537.
4. Lozoff B, Jimenez MD, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000; 105: e51.
5. Yip R. The challenge of improving iron nutrition: Limitations and potentials of major intervention approaches. *Eur J Clin Nutr* 1997; 51: 516-524.
6. Skikne B, Flowers CH, Cook JD. Serum transferrin receptor: A quantitative measure of tissue iron deficiency. *Blood* 1990; 75: 1870-1876.
7. Dallman P. Iron deficiency in the weanling: A nutritional problem on the way to resolution. *Acta Pediatr Scand* 1986; 323: 59-67.
8. Saarinen UM. Need for iron supplementation in infants on prolonged breastfeeding. *J Pediatr* 1978; 93: 177-180.
9. Mercer J, Nelson C, Skovgaard R. Umbilical cord clamping: Beliefs and practices of American nurse-midwives. *Clin Pract Exch* 2000; 45: 58-66.

10. Gibson RS, Ferguson EL, Lehrfeld J. Complimentary foods for infants feeding in developing countries: Their nutrient adequacy and improvement. *Eur J Clin Nutr* 1998; 52: 764-770.
11. Andres NC. Disorders of iron metabolism. *New Eng J Med* 1999; 341: 1986-1995.
12. Nestel P, Alnwick D. Iron/multi-micronutrient supplements for young children. Summary and Conclusions of a Consultation Held at UNICEF, Copenhagen, Denmark, August 19-20, 1996. INACG Publication, Washington DC, 1997. Pisacane A. Neonatal prevention of iron deficiency. *BMJ* 1996; 312: 136-137.
13. Zlotkin SH, Arthur P, Antwi KY, Yeung G. Treatment of anemia with microencapsulated ferrous fumarate plus ascorbic acid supplied as 'sprinkles' to complementary (weaning) foods. *Am J Clin Nutr* 2001; 74: 791-795.
14. Zlotkin SH, Arthur P, Antwi KY, Yeung G. Randomized controlled trial of single versus three-times daily ferrous sulfate drops for treatment of anemia. *Pediatrics* 2001; 108: 613-616.