



# Iron-deficiency anemia in children

**Kawsari Abdullah, MBBS**, The Hospital for Sick Children, Toronto  
**Stanley Zlotkin, MD, FRCPC**, The Hospital for Sick Children, Toronto  
**Patricia Parkin, MD, FRCPC**, The Hospital for Sick Children, Toronto  
**Danielle Grenier, MD, FRCPC**, Canadian Paediatric Society, Ottawa

## What is iron-deficiency anemia?

Iron deficiency (ID) is a state in which there is insufficient iron to maintain the normal physiological function of blood and tissues, such as the brain and muscles. The more severe stages of ID are associated with anemia. Iron-deficiency anemia (IDA) occurs when the hemoglobin concentration is below two standard deviations ( $-2SD$ ) of the distribution mean for hemoglobin in an otherwise normal population of the same sex and age.<sup>1</sup> IDA is generally characterized by a hemoglobin level of less than 110 g/L, plus a measure of poor iron status.<sup>2</sup>

## Why are children at risk of IDA?

Although the cause of IDA among young children can be multifactorial, the consumption of foods with low bioavailable iron is likely the primary contributing factor. Before 24 months of age, rapid growth coincident with frequently inadequate intake of dietary iron places children at the highest risk of any age group for ID.<sup>3</sup> In full-term infants, the iron stores can meet the iron requirements until ages four to six months, and IDA generally does not occur until approximately nine months of age. Comparatively, preterm and low-birth-weight infants are born with lower iron stores and grow faster during infancy. Consequently, their iron stores are often depleted by two to three months of age and they are at greater risk for ID.<sup>4,5</sup> After 24 months of age, the growth rate of children slows and the diet becomes more diversified, the risk for ID drops.<sup>6,7</sup> After 36 months of age, dietary iron and iron status are usually adequate;<sup>7</sup> however, risks for ID include limited access to food, a low-iron or other specialized diet, and medical conditions that affect iron status (e.g., malaria or parasitic infections).<sup>7</sup>

## What is the epidemiology of IDA?

Around the world, IDA affects approximately 750 million children.<sup>8</sup> Using anemia as an indicator, it has been found that at least 30% to 40% of children and pregnant women in industrialized countries are iron deficient.<sup>9,10</sup> Data from the third National Health and Nutrition Examination Survey (NHANES III) in the United States indicated that 3% of children aged 12–36 months and less than 1% in the 37–60 months age group had IDA.<sup>11</sup>



Although the prevalence of IDA in Canadian children among the general population is low (3.5% to 10.5%), there are certain Canadian Aboriginal populations in whom the prevalence is very high (14% to 50%).<sup>12-14</sup> Factors associated with the increased prevalence of IDA in these populations include high consumption of evaporated milk and cow's milk after six months of age, prolonged exclusive breastfeeding and significant burden of *Helicobacter pylori* infection.<sup>8</sup> Other high-risk groups include children from families of low socioeconomic status, children of Chinese background, infants of low birth weight, and children who consume whole cow's milk before 12 months of age.<sup>4,5,8,15-17</sup>

### **How can IDA and ID be detected?**

The most reliable indicator of ID is the bone marrow histopathology; however, this is an invasive procedure that is not needed. The Committee on Nutrition of the American Academy of Pediatrics (AAP) recommends measurement of hemoglobin concentration (Hb) plus tests of iron status.<sup>18</sup> For infants of 12 months of age, an Hb level less than 110 g/L is considered anemia. Several tests of iron status are available, but each has limitations. A serum ferritin of less than 10 µg/L has been suggested as a cut-off for children indicating depletion of iron stores; however, as it is an acute phase reactant, the Committee on Nutrition recommends simultaneous measurement of C-reactive protein (CRP). Other promising tests include reticulocyte hemoglobin content (CHr) and serum transferrin receptor 1 (TfR1).

### **What are the clinical signs and symptoms of IDA?**

The clinical signs of IDA are those of anemia itself. Children with severe ID are often described as irritable, apathetic with a poor appetite. The physical signs of anemia include pallor of the conjunctivae, the tongue, the palms and the nailbeds.<sup>19</sup> When anemia is severe, children can also have signs of congestive heart failure with fatigue, tachypnea, hepatomegaly, and edema.

### **What are the risk factors of ID and IDA?**

The following have been identified as risk factors for ID and IDA:

- Race/ethnicity
- Low socioeconomic status
- Prematurity and low birth weight
- Excessive milk intake
- Early introduction of whole cow's milk
- Prolonged bottle feeding
- Prolonged exclusive breastfeeding
- Overweight and obesity
- Non-attendance to daycare

### **What long-term problems can IDA cause?**

ID is a systemic condition impairing physical endurance, work capacity, infant growth and development, and depressing immune function.<sup>20</sup> Among these conditions, the association between ID and child development has evoked the most attention among researchers. Decreased brain iron stores may impair the activity of iron-dependent enzymes necessary for the synthesis, function and degradation of neurotransmitters,



### ***Iron-deficiency anemia in children (continued)***

such as dopamine, serotonin and noradrenaline, causing changes in behaviour and lowering of development test scores in children.<sup>21</sup>

Several extensive reviews have been published on the association between IDA and child development.<sup>2,22,23</sup> These reviews have clearly shown that IDA does expose children to concurrent and future risk of poor development. Whether this condition is reversible by treatment of iron has been inconclusive. Of six randomized controlled trials in children less than two years old, only one showed a significant impact. Of eight double-blind, randomized controlled trials of iron therapy in children older than two years, four reported significant outcome.<sup>22</sup> This indicates that either the impact of ID is irreversible or there are other factors associated with this condition. However, the authors have cautioned on the results of these studies, as many suffered from lack of statistical power and also very few trials have followed the children after the treatment stopped.<sup>22</sup>

ID can occur without the presence of anemia, and whether this state is also capable of causing developmental delay in children remains controversial. Only one study has demonstrated a significant effect of iron supplementation in these children.<sup>24</sup> Further studies are needed to fully understand the effectiveness of oral iron treatment for children with only ID.

### **How can IDA be prevented?**

The problem of IDA can be addressed through primary prevention efforts or through the secondary prevention efforts of early detection and subsequent therapy.

Primary prevention has the potential of providing benefit to a whole population and preventing the onset of IDA. The Canadian Task Force on Periodic Health Examination (renamed The Canadian Task Force on Preventive Health Care), last updated in 1994, has recommended primary prevention of IDA in infants and preschool children to be achieved through various dietary interventions, including breastfeeding and fortification of formula (if not breast-fed) or infant cereal. These interventions are only effective when they are available and affordable for all children.<sup>25</sup> The Nutrition and Gastroenterology Committee of the Canadian Paediatric Society recommends that assuming 10% of the iron in a mixed diet is absorbed, the required iron intake is approximately 7 mg/day for term infants aged five to 12 months, 6 mg/day for toddlers aged one to three years, and 8 mg/day for children aged four to 12 years.<sup>26</sup> The AAP Committee on Nutrition recommends that healthy exclusively breast-fed infants be supplemented with 1 mg/kg/day of oral iron beginning at four months of age until iron-containing complementary foods are introduced. Whole milk should not be introduced before 12 months of age. Red meat and vegetables with higher iron content should be introduced early. Preterm infants fed human milk should receive an iron supplement of 2 mg/kg/day by one month of age until weaned to iron-fortified formula or beginning complementary foods.<sup>18</sup>

Secondary prevention includes efforts to identify children with IDA through screening programs. The success of this approach depends on being able to accurately identify individuals with IDA and on subsequent effectiveness of the therapy.<sup>25</sup> Several studies have shown that routine screening for IDA, followed by a therapeutic trial of iron, to be problematic due to low follow-up rates, high spontaneous resolution rate and changing patterns of anemia.<sup>27,28</sup> The effectiveness of screening programs has not been



investigated through controlled trials; hence, the results cannot be considered conclusive. The Canadian Task Force on Preventive Health Care concluded there was insufficient evidence to recommend screening for infants between six and 12 months of age. However, for all infants in high-risk groups, physicians may consider screening between six and 12 months of age, perhaps optimally at nine months.<sup>27</sup> The AAP recommends screening with hemoglobin at 12 months. If the Hb level is less than 110 g/L at 12 months, additional screening tests should include measurement of serum ferritin plus CRP levels, or CHr concentration.<sup>18</sup>

## What is the recommended treatment for IDA in children?

When IDA is identified, the family should be counseled regarding the importance of limiting the total daily milk intake and increasing iron-rich foods, including those with vitamin C that improves iron absorption, and avoiding foods that impair iron absorption such as tea. Children with IDA should also receive iron supplementation. The recommended therapeutic dose of oral iron is 6 mg/kg/day of elemental iron, for three to four months. Adequate follow-up is also important.

## Conclusion

In Canada, IDA in children remains a public health problem, and certain populations of children are at particularly high risk. IDA is associated with poor developmental outcomes in children; the impact of ID is less well understood. Laboratory investigations include hemoglobin and iron tests, such as serum ferritin. Primary prevention of IDA is recommended; the role of secondary prevention through screening programs remains inconclusive but recommended by some professional organizations. Treatment of children identified with IDA includes both dietary counseling and oral iron supplementation.

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RESOURCES



## Quiz

**1. Iron-deficiency anemia (IDA) is characterized by:**

- a) hemoglobin level of  $<110$  g/L plus serum ferritin  $<10$   $\mu$ g/L (provided CRP is normal)
- b) hemoglobin level of  $>110$  g/L plus serum ferritin  $<10$   $\mu$ g/L (provided CRP is normal)
- c) hemoglobin level of  $<110$  g/L
- d) All of above

**2. The iron stores of full-term, normal birth-weight infants can meet an infant's iron requirements:**

- a) until 28 days of age
- b) until ages four to six months
- c) until six years of age
- d) until 12 months of age

**3. The most reliable indicator of iron deficiency:**

- a) serum ferritin
- b) transferrin saturation
- c) bone marrow histopathology
- d) erythrocyte protoporphyrins

**4. Which one of the following is not an evidence-based clinical predictor of IDA?**

- a) Obesity
- b) Bottle use
- c) Daycare attendance
- d) School attendance rate

**5. IDA is treated with:**

- a) iron therapy of 6 mg/kg/day elemental iron for three to four months
- b) iron therapy of 6 mg/kg/day elemental iron for three to four weeks
- c) bone marrow transplant
- d) iron-chelating agent

**5. The American Academy of Pediatrics recommends screening for IDA at:**

- a) one month of age
- b) three months of age
- c) nine months of age
- d) twelve months of age

**Answers: 1-a, 2-b, 3-c, 4-d, 5-a, 6-d**