

Physiological iron deficiency in children: The critical balance of growth and nutrition

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Summary

Iron deficiency (ID) remains the most prevalent nutritional deficiency worldwide and a major cause of morbidity in childhood. This review outlines the physiological basis, risk factors, consequences, and prevention strategies for ID and iron deficiency anemia (IDA) in infants, young children, and adolescents. Childhood includes two critical periods of heightened vulnerability—infancy/early childhood and adolescence—when rapid growth markedly increases iron requirements. Preterm birth, low birth weight, exclusive breastfeeding beyond 4–6 months without supplementation, early introduction of cow's milk, poor dietary habits, menstrual blood loss in adolescent girls, and rapid pubertal growth in boys are identified as key contributors to negative iron balance. Beyond hematologic changes, ID can impair neurodevelopment, cognitive performance, immune function, and behavior, with some deficits persisting long-term even after treatment. Early recognition is essential, and serum ferritin combined with inflammatory markers (CRP) and transferrin saturation represent the most reliable diagnostic indicators. Preventive measures—including delayed cord clamping, timely introduction of iron-rich complementary foods, iron supplementation for at-risk groups, and limiting cow's milk intake—are crucial to reducing the global burden of ID. Despite advances in understanding its physiology and management, iron deficiency in childhood remains a significant public health challenge requiring targeted screening and effective preventive strategies.

Key words: Iron deficiency, children, anemia, prevention

Introduction

Iron has several vital functions in the body. It serves as a carrier of oxygen to tissues from the lungs via haemoglobin in red blood cells, as a transport medium for electrons in cells, and as an integral part of important enzyme systems in various tissues (Gupta 2014).

Iron deficiency (ID) is recognised as the most common nutritional deficiency worldwide and remains a significant public health issue globally, particularly in developing countries (Özdemir 2015). Although the terms “iron deficiency” (ID) and “iron deficiency anemia” (IDA) are frequently used interchangeably, it is important to acknowledge that iron deficiency can occur independently of anemia. It may still exert adverse effects on body tissues. Iron deficiency anemia rep-



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resents the most advanced stage of iron deficiency, reflecting a progression from depleted iron stores to impaired erythropoiesis (Animasahun and Itiola 2021).

The fundamental cause of physiological ID in children is a state of long-term negative iron balance, characterised by a disproportion between the maximal amount of iron that can be absorbed from the diet and the increased physiological requirements during periods of rapid growth (Lozoff et al. 2006).

Stages of iron deficiency

The reduction of body iron stores is a progressive process marked by three main stages.

The first stage is the prelatent stage (iron depletion). Iron stores are lowered or absent, typically reflected by a reduction in serum ferritin (SF) level. Haemoglobin (HGB) and hematocrit (HCT) are in the normal range (Özdemir 2015).

The second and more severe stage is the latent stage (Iron-Deficient Erythropoiesis). Beyond depleted stores, serum iron and transferrin saturation (TfSat) are lower than normal, but HGB and HCT levels remain normal. At this stage, tissues may already be affected (Baker et al. 2010; Gupta 2014).

The most severe is IDA, characterised by reduced Hb and hematocrit, depleted stores, and reduced iron transport (Gupta 2014; Animasahun and Itiola 2021). The different stages of ID are presented in Table 1.

Epidemiology and risk factors

IDA is the most common haematological disease in children and adolescents and the most common form of anemia, with a prevalence of 20.1% in children aged 0 to 4 years and 5.9% in children aged 5 to 14 years in developed countries (39% and 48.1% in developing countries, respectively) (WHO 2017). Table 2 summarizes the main risk factors for ID in low-income and developed countries.

Critical periods of risk

During childhood, there are some critical periods of high physiological risk for ID. IDA is particularly prevalent during two major periods of accelerated physiological demand in childhood: infancy/early childhood and adolescence (Gupta et al. 2016; Aksu and Ünal 2023).

Table 1. Stages of Iron Deficiency.

Stage	Laboratory findings	Clinical signs
Iron Depletion	• Low Ferritin	No anemia
	• Normal HGB, HCT and MCV	
Iron-Deficient Erythropoiesis	• Low Ferritin	No anemia or mild anemia
	• Low TfSat	
	• High TIBC	
Iron Deficiency Anemia	• Low HGB and HCT	Anemia
	• Microcytic, Hypochromic RBCs	

Table 2. Main risk factors for the development of IDA in both developing and developed countries, adapted from Mantadakis et al. (2020).

Low-income countries	Developed countries
Prolonged breastfeeding without iron supplementation beyond the 4 th month of life	Gastrointestinal bleeding of any aetiology
Limited consumption of meat and fish	Genitourinary bleeding of any aetiology
Diets rich in cereal – or legume-based flours, and an excess of dietary fibre	Iron malabsorption of any aetiology
Inadequate vitamin C intake, frequent consumption of coffee and tea	
Multiparity	
Parasitosis	
Chronic or repeated infections	

Iron deficiency in infancy and early childhood may arise from multiple interacting factors, including physiological demands and environmental influences. Iron deficiency, even without anemia, can produce measurable neurodevelopmental consequences. Cohort studies confirm long-lasting deficits in cognition and myelination (McCann 2020; Georgieff 2023). This period is associated with the highest risk of ID.

Approximately 80% of the iron content in a term newborn infant accumulates during the third trimester of pregnancy. A healthy term infant typically has sufficient stores to sustain erythropoiesis for the first 6 months of life. (Lozoff et al. 2006; Baker et al. 2010). Maternal anemia during pregnancy that is left untreated can cause earlier depletion of these stores.

Another risk group with a higher risk of ID are babies with low birth weight (less than 2,5kg) or preterm babies (born before 37 weeks of pregnancy). They have smaller stores that deplete earlier, sometimes as soon as 2–3 months after birth, due to a shortened third trimester and a faster rate of catch-up growth. Low birth weight is a highly significant risk factor for severe anaemia (Odds Ratio [OR] 6.49). (Baker et al. 2010; Joo et al. 2016).

Modern insights into iron physiology clarify how developmental stages uniquely alter iron metabolism. Studies reveal that infancy and adolescence remain the two periods of highest risk due to rapid growth (Lönnerdal 2017).

The rapid growth rate, combined with inadequate intake, most often as a result of an inadequate diet, is a primary cause of deficiency. The peak incidence of IDA is commonly observed among infants aged 9–12 months (Joo et al. 2016), making screening tests extremely important at this age (Girelli et al. 2018).

A variety of dietary mistakes can cause iron deficiency. One of them is exclusive breastfeeding for more than six months. Although the iron in breast milk is highly bioavailable (up to 50% absorption), the overall amount is low (around 0.3–0.4 mg/L). This quantity is insufficient to cover the demands of growth after the sixth month. Prolonged exclusive breastfeeding without supplementation is a significant risk factor for IDA. After 6 months, complementary foods must supply almost all of the iron required, specifically 98% of the iron requirement for infants aged 6–23 months (Gupta et al. 2016; Joo et al. 2016).

A more frequent cause of iron deficiency, especially among families with low social status, is feeding cow's milk before the first year of age.

Exclusive intake of cow's milk at an early age (before one year, or >500–700 mL/day later) is a leading cause of ID/IDA. Cow's milk is poor in bioavailable iron (absorption around 10%). Furthermore, it replaces iron-rich foods, and the proteins in this milk may cause chronic gastrointestinal blood loss in infants (Gupta et al. 2016; Mantadakis et al. 2020).

The fundamental cause of physiological ID in children is a state of long-term negative iron balance, characterised by a disproportion between the maximal amount of iron that can be absorbed from the diet and the increased physiological requirements during periods of rapid growth.

Adolescence presents a second critical period due to the pubertal growth spurt. At this age, girls are more often affected. The most common cause of ID/IDA in adolescent girls is menstrual blood loss (averaging 20 to 58 mg per month). Menarche was identified as a significant risk factor for ID in the medical literature. Therefore, recommended iron intake remains high for pubertal girls (15–22 mg/day) (Animasahun and Itiola 2021; Aabdien et al. 2023).

Among adolescent boys, the causes of ID are more likely to be related to rapid growth and development during puberty. Iron needs are highest during peak pubertal development due to increases in blood volume, muscle mass, and myoglobin (Animasahun and Itiola 2021).

Within this age group, adequate dietary composition is a fundamental determinant in preventing the onset of iron deficiency. Poor dietary habits, including low intake of meat/fish, restrictive diets, and high intake of inhibitors such as tea and coffee, also contribute to the risk of ID during puberty (Mantadakis et al. 2020).

Clinical effects and consequences

Iron deficiency has been associated with a spectrum of neurocognitive impairments and extra-hematologic effects, reflecting its role in both neuronal development and systemic metabolism. Iron is vital for numerous body functions, including oxygen activation, detoxification of oxygen species, and brain development (cell proliferation, differentiation, myelination, and dopamine neurotransmission) (Ennis et al. 2018; Animasahun and Itiola 2021). Even an ID without anemia can have serious consequences. Iron deficiency in children is associated with motor and cognitive retardation, mood disorders, reduced learning capacity, and decreased perception functions. Many studies underline the adverse neurocognitive and behavioural effects of ID during infancy that may persist for more than 10 years after treatment (Baker et al. 2010; Gupta et al. 2016).

Iron plays a crucial role in immune system development and function. Its deficiency can impair both innate and adaptive immune responses, increasing susceptibility to infections. It is also linked to impaired immune function, potentially reducing resistance to infection by affecting T-lymphocytes and polymorphonuclear leukocytes (Aabdien et al. 2023)

General symptoms can include fatigue, irritability, pallor, pica (ingestion of non-food materials), and restlessness (Aksu and Ünal 2023).

Prevention strategies

Given the global importance and the risk of irreversible neurocognitive changes, preventing ID in early childhood is a public health priority. Prevention strategies

target high-risk groups and address the critical balance between iron supply and demand (Baker et al. 2010; Gupta et al. 2016).

Perinatal factors significantly influence the iron status of the newborn. Delayed umbilical cord clamping (1–3 minutes) is recommended, especially for preterm babies, as it improves iron status and reduces the risk of ID (Gupta et al. 2016).

Breastfeeding and appropriate iron supplementation are fundamental strategies for preventing iron deficiency during infancy and early childhood. (Burke et al. 2021; Miniello et al. 2021).

Consequently, exclusively breastfed infants may become at risk of iron deficiency after four to six months of age, particularly if complementary foods rich in iron are not introduced on time. To mitigate this risk, iron supplementation or iron-fortified complementary feeding is recommended for populations with a high prevalence of iron deficiency anaemia. (Burke et al. 2021; Miniello et al. 2021). The combined promotion of exclusive breastfeeding during the first six months of life and the implementation of appropriate supplementation or fortification strategies thereafter are key components of effective prevention programs targeting iron deficiency in early childhood. (Gupta et al. 2016). Term, exclusively breastfed infants should receive an elemental iron supplement of 1 mg/kg/day starting at 4 months of age and continuing until iron-rich complementary foods are introduced (Baker et al. 2010; Mantadakis et al. 2020). To prevent IDA, the American Academy of Paediatrics advises that infants born before 37 weeks of gestation and breastfed should receive elemental iron supplementation at a dose of 2 mg/kg/day. Optimal intake may be provided as medicinal iron, iron-fortified milk, or complementary foods, beginning after the first month of life and continuing until 12 months of age. For exclusively breastfed term infants, a daily iron supplement of 1 mg/kg is recommended, starting at four months of age and maintained until the introduction of iron-rich complementary foods. Infants fed with iron-fortified formula generally do not require additional iron supplementation unless they have other risk factors for IDA (Baker et al. 2010). Dietary practices during the weaning period and early toddlerhood play a pivotal role in maintaining adequate iron status and preventing the onset of iron deficiency.

Introduction of complementary foods rich in iron, particularly heme iron (meat, fish, eggs), should be delayed until after 6 months. Foods rich in vitamin C (ascorbic acid), e.g., citrus fruits/juice) should be included as they enhance iron absorption. Cow's milk should be avoided before one year of age: intake in toddlers should not exceed 500 mL/day. Consuming iron absorption inhibitors such as tea, coffee, milk, and yoghurt should be avoided during meals (Gupta et al. 2016; Aksu and Ünal 2023).

Screening and diagnosis

Early diagnosis and screening are essential components of strategies to reduce the burden of iron deficiency and prevent its hematologic and neurodevelopmental consequences. Screening for ID/IDA is critical. Relying solely on Hb concentration is insufficient because it lacks sensitivity and specificity; many iron-deficient toddlers are not anaemic.

Clues for diagnosing ID (with or without anaemia) include serum ferritin (SF) and C-reactive protein (CRP). Serum ferritin reflects iron stores. Labo-

ratory assessment remains the cornerstone of diagnosis, with serum ferritin recognised as the most sensitive indicator of depleted iron stores. However, ferritin levels may be elevated in the context of inflammation; therefore, concurrent measurement of inflammatory markers, such as C-reactive protein (CRP), is recommended for accurate interpretation. Recent pediatric guidelines recommend risk-based screening and a combination of ferritin and CRP at 12 months to improve early detection (AAP 2021; Mei et al. 2021; Broekaert et al. 2025). The plasma ferritin concentration correlates strongly with the total body iron stores, with approximately 1 µg/L of serum ferritin corresponding to about 120 mg of stored iron per kilogram of body weight. Reference values for serum ferritin vary with age – in children aged 1–6 years, they range from 4 to 67 µg/L, while in infants, values range from 12 to 327 µg/L. A low SF (<10–12 µg/L depending on age/criteria) indicates ID (Baker et al. 2010; Animasahun and Itiola 2021). Large-scale epidemiological analyses demonstrate a persistent global burden, and updated ferritin thresholds have been proposed to improve diagnostic precision. Additional indices, including transferrin saturation, mean corpuscular volume (MCV), haemoglobin concentration and reticulocyte haemoglobin content (CHr). The CHr measures the functional iron available for erythropoiesis in recently released cells (life span 24–48 hours). It is a sensitive indicator, not affected by inflammation, and a low concentration is a strong predictor of ID in children (Baker et al. 2010).

Transferrin Saturation (TfSat) reflects iron transport. A reduction below 16% is considered a reliable indicator of iron under-supply in developing red cells (Animasahun and Itiola 2021).

Alterations in blood count parameters typically appear later, once iron deficiency anemia has already developed. Characteristic findings include reductions in haemoglobin concentration, mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH). However, these haematological changes are not only delayed indicators of iron deficiency but also lack specificity, as similar alterations may occur in other microcytic anaemias. Consequently, reliance on complete blood count (CBC) alone is insufficient for the early detection or screening of iron deficiency, underscoring the need for more sensitive biochemical markers such as serum ferritin and transferrin saturation.

The American Academy of Paediatrics recommends universal screening for IDA in infants at around 12 months of age, using a combination of Hb and SF/CRP or CHr. However, the US Preventive Services Task Force found insufficient evidence for routine screening in asymptomatic children aged 6–12 months, suggesting targeted screening for high-risk infants instead. (Baker et al. 2010; Mantadakis et al. 2020).

Conclusions

Overall, the accumulated data confirm that iron deficiency and its consequences continue to pose substantial challenges in pediatric practice. Iron deficiency and iron deficiency anemia remain major nutritional and haematological problems throughout childhood, particularly in infants, young children, and adolescents who experience rapid growth and increased physiological demands. Significantly, iron deficiency, even in the absence of anemia, is associated with significant neurodevelopmental, cognitive, and

immunological impairments, some of which may persist despite later treatment. Effective prevention requires a comprehensive approach that begins in the perinatal period and extends through all critical stages of growth. Optimising screening strategies according to population risk profiles may further improve early recognition.

In summary, reducing the burden of iron deficiency in childhood requires coordinated efforts in prevention, early diagnosis, and tailored therapy. Strengthening these components is essential to protect growth, cognitive development, and overall health outcomes in pediatric populations.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

The author solely conceived the study, collected and analyzed the data, and wrote and approved the final manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.

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