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## ABSTRACT

**BACKGROUND:** Iron is an essential nutrient for normal growth and neurodevelopment of infants. Iron deficiency (ID) remains the most common micronutrient deficiency worldwide. There are convincing data that ID is associated with negative effects on neurological and psychomotor development.

**OBJECTIVES:** In this review, we provide an overview of current knowledge of the importance of iron in normal term breast-fed infants with a focus on recommendations, metabolism, and iron requirements.

**CONCLUSIONS:** Health organizations around the world recommend the introduction of iron-rich foods or iron supplements for growing infants to prevent ID. However, there is no routine screening for ID in infancy. Multicenter trials with long-term follow-up are needed to investigate the association between iron fortification/supplementation and various health outcomes.

**KEY WORDS:** iron deficiency, iron metabolism, iron recommendations, iron requirements, iron in breast-fed infants

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## Introduction

The period of infancy constitutes a critical window of growth and brain development, and thus micronutrient deficiencies, during this vulnerable period may have adverse effects on neurocognitive functions.<sup>1</sup> The most common micronutrient deficiency in the world is iron deficiency (ID) and results in approximately one billion cases of anemia worldwide.<sup>2</sup> At about six months, infants are at risk of developing ID because of the exhaustion of their iron stores needed for rapid growth. In addition, iron concentration in breast milk is relatively low.<sup>3</sup> Therefore, various organizations recommend the introduction of iron-rich foods to infants or medicinal iron supplements in order to meet their iron requirements.<sup>4,5</sup> The aim of the following review is to update health-care professionals on the current state of knowledge of iron in full-term breast-fed infants with particular focus on the recommendations, metabolism, and requirements.

## Full-Term Infant

Full-term infants are those who are born between 37 and 42 weeks of gestation. The normal birth weight of a healthy full-term newborn ranges between 2500 g and 4000 g. Low birth weight describes a weight of less than 2500 g at birth regardless of gestational age.<sup>6</sup> For the first few months of life, the length of a healthy full-term infant would increase about 3–5 cm/month. An infant's head circumference will increase

by 1–2 cm each month until six months of age to account for the increase in brain development. Growth is an important indicator of normal child development. The period of infancy is characterized by rapid progression of growth that is largely dependent on the infant's endogenous stores of nutrients and exogenous sources such as human or formula milk. The breast milk intake in exclusively breast-fed (EBF) infants appears to meet the energy and nutrient requirements of most infants.<sup>7</sup> An extensive body of evidence with improved epidemiological methods substantiates the advantages of breast-feeding for the infants and their mothers. These include developmental, nutritional, immunological, health, psychological, economical, environmental, and social advantages.<sup>5</sup> The data from the Maternity Experiences Survey of the Canadian Perinatal Surveillance System show that the rate of initiation of breast-feeding is 90.3%, while the rate of exclusive breast-feeding at three months is 51.7%. Six months after birth, the proportions of EBF infants further falls to 14.4%.<sup>8</sup> A large data set of 3022 infants and toddlers from the Feeding Infants and Toddler Study (FITS) in the US reported that 76% of infants were exclusively or partially breast-fed at birth, and this percentage declined to 30% at six months.<sup>9</sup> In Europe, data from 14 countries indicated that the rate of initiation of breast-feeding was 90% and 80%–60% in six other countries.<sup>10</sup> At six months, the rate of any breast-feeding was >50% in only six countries.



## Definitions and International Recommendations

In 2001, a joint statement of the World Health Organization (WHO) and the United Nations Children's Fund recommended "exclusive breast-feeding for the first six months of age and introducing nutritionally adequate complementary food along with sustaining breast-feeding up to two years of age or beyond".<sup>11</sup> Exclusive breast-feeding is defined as human breast milk being the only source of food and liquid introduced to the infant. The complementary feeding period (typically 6–12 months of age) begins when food other than human breast milk is introduced to infants in addition to breast-feeding. Weaning is defined as the action of providing non-human milk to the infant regardless of the continuation of breast/bottle feeding.<sup>11</sup>

In 2004, Health Canada, like many other health organizations, revised its statement on the duration of exclusive breast-feeding to support the global strategy of exclusive breast-feeding by WHO.<sup>12</sup> Other organizations that endorsed the WHO recommendations include European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN),<sup>13</sup> United Kingdom Department of Health,<sup>14</sup> Australia National Health and Medical Research Council,<sup>15</sup> and New Zealand Ministry of Health.<sup>16</sup> Although there is universal agreement that breast milk alone is the optimal first food and should be exclusively introduced for the first six months of life, the time of introduction of complementary foods varies between health organizations. For example, in the United States, agencies such as the US Department of Agriculture<sup>17</sup> and the Centers for Disease Control (CDC)<sup>18</sup> recommend complementary food introduction between four and six months of age. Furthermore, the statement on complementary feeding by ESPGHAN also recommends that complementary food should not be introduced before 17 weeks nor later than 26 weeks.<sup>19</sup> In Canada, as with global efforts, increasing the rate and duration of breast-feeding is a main public health target. This has led to less emphasis being given to complementary feeding for the older breast-fed infant.

## Iron

In the human body, iron is the most abundant trace element that acts as a center for a broad spectrum of functions. Its importance is derived from its redox activity because iron exists mainly in ferrous ( $\text{Fe}^{2+}$ ) and ferric ( $\text{Fe}^{3+}$ ) forms, which are interchangeable. This reaction forms part of the electron transport chain, essential in the generation of Adenosine triphosphate (ATP) during metabolism and in the reductions needed for molecule synthesis. About two-thirds of iron are utilized as functional iron, which is found in hemoglobin (Hb) (60%), myoglobin (5%), heme and nonheme enzymes (5%), and transferrin (<0.1%). The rest of the iron is stored in the two main storage proteins, ferritin (20%) and hemosiderin (10%).<sup>20</sup> In Hb, the key function of iron is oxygen transportation, essential for cell respiration. Iron in myoglobin is required to store oxygen in muscles. As a component of tissue

enzymes, iron is important in energy production and immune system functioning.<sup>20</sup> Owing to its high presence in multiple brain regions, iron plays an important role in essential neurologic processes such as neurotransmitter synthesis and myelination.<sup>21</sup> At birth, full-term healthy infants have a notable iron endowment of about 75 mg/kg, high blood volume, and Hb concentration in proportion to their body weight. During the first few months of life, they experience a physiological decline in their blood volume and Hb concentration and an active shift from fetal Hb to adult type Hb.<sup>3,7</sup>

## Iron Metabolism

In the human body, iron is balanced and regulated in order to prevent deficiency and overload. This balance is achieved through three unique mechanisms: iron storage, erythrocyte iron reutilization, and iron absorption regulation. Therefore, when the body is deficient in iron, absorption is maximum, and when the iron level is sufficient, iron absorption is limited.<sup>22,23</sup> The absorption of iron occurs mainly in the duodenum by an active transport process from the intestinal lumen to the enterocytes.<sup>23</sup> If iron is required for metabolic processes, it is released through the enterocytes to the blood and transported by transferrin to the body tissues and the bone marrow. Where there is iron redundancy, it is stored in the enterocytes as ferritin and in the liver, spleen, and bone marrow as hemosiderin. When the enterocytes exfoliate, iron is excreted in the feces.<sup>23</sup> Iron is recycled from senescent red blood cells by macrophages of the reticuloendothelial system. Macrophages export the intracellular iron via ferroportin, and iron is transported bound to transferrin to be available for use or stored in the liver. This is especially true in the first few days of life.<sup>24</sup>

The peptide hepcidin is a major iron absorption regulator.<sup>25</sup> Hepcidin is synthesized in the hepatocytes and secreted in response to high serum iron levels, which further leads to downregulation of ferroportin expression on the basolateral membrane, and thereby resulting in the blocking of iron release through the enterocytes to the bloodstream.<sup>25</sup> Hepcidin levels decline throughout infancy as a response to the physiological change required to mobilize iron stores and absorb dietary iron, thus preventing ID.<sup>26</sup> The exact role of hepcidin in regulating iron absorption and recycling in neonatal period remains unknown.<sup>27</sup> Results from a large study of 191 full-term newborn infants show that hepcidin concentration in cord blood samples correlated with fetal iron stores.<sup>28</sup> Other studies found no association between serum hepcidin concentrations and serum iron parameters in newborn infants.<sup>27,29</sup> Regarding iron absorption at the molecular level, the enzyme duodenal cytochrome b (Dcytb) catalyzes the reduction of  $\text{Fe}^{3+}$  to  $\text{Fe}^{2+}$ , which is further transported to the enterocytes via the divalent metal transporter 1 (DMT1). Available data indicate that the expression of DMT1 transporter is low and remains under developmental regulation. Results from animal studies show that the regulation of DMT1 expression does



not respond to dietary iron supplementation.<sup>30</sup> Excess iron is stored intracellularly as ferritin. When iron is needed in the body, Fe<sup>2+</sup> is further transported by the transporter ferroportin (FPN1/IREG1) located on the basolateral membrane and will be oxidized to Fe<sup>3+</sup> by hephaestin and transported in the blood by transferrin.<sup>20</sup> It has recently been theorized that the lactoferrin receptors that have been found in human infant intestinal cells have a role in iron absorption. This process occurs by receptor-mediated endocytosis of iron bound lactoferrin.<sup>31</sup> However, results from earlier studies on the function of lactoferrin in iron absorption in breast-fed infants who received breast milk or breast milk without lactoferrin do not support the role of lactoferrin in iron absorption.<sup>32</sup>

### Iron Requirements

According to the Institute of Medicine (IOM), the amount of iron in human breast milk was used as the basis to estimate the adequate intake of iron for healthy full-term infants up to six months of age.<sup>33</sup> Thus, an adequate intake of 0.27 mg/L was determined. This was calculated by multiplying the mean iron content of breast milk (0.35 mg/L) by the average daily intake of breast milk in EBF infants (0.78 L/day). For infants aged 7–12 months, according to the IOM the recommended dietary allowance is 11 mg/day.<sup>33</sup> This value was calculated by adding the amount of iron lost from the urinary and intestinal tracts and from the shedding of skin epithelial cells to the amount of iron needed for increasing tissue mass, blood volume, and storage iron during 7–12 months of age. This further reinforces the fact that iron needs increase significantly for six-month-old full-term infants compared with full-term infants aged less than six months.

### Iron Deficiency

ID is a state where the iron stores progressively decline owing to prolonged negative iron balance. Subsequently, the supply of iron to the tissues is diminished leading to ID anemia (IDA). ID is defined as a plasma ferritin concentration of <12 µg/L (for children <five years).<sup>2</sup> IDA is diagnosed clinically with signs and symptoms such as fatigue and pallor. The WHO defines anemia as an Hb level of less than two standard deviations (SDs) of the average Hb level for a normal population of the same gender and age group. IDA is diagnosed when the Hb level is <11.0 g/dL (for children aged six months to 59 months). Other ID and IDA laboratory indicators include serum iron, total iron binding capacity, serum transferrin, and serum transferrin receptors.<sup>2</sup> Available evidence shows that the reference ranges of iron laboratory indicators in neonatal period differ from iron reference ranges established for adults. This is owing to high maternal iron transfer to the fetus and high stimulation of erythropoiesis at the end of gestation.<sup>34</sup>

Untreated ID has detrimental functional outcomes. There is a compelling evidence that early ID during either fetal/neonatal or toddler time periods impairs cognitive

function and retards psychomotor development in childhood and persists to adolescence and adulthood.<sup>35</sup> Neurologic studies in animals have explored the pathophysiology by which ID alters neurodevelopmental function and have found that ID results in an alteration in essential neurologic processes such as dopamine metabolism, myelination, and hippocampal function.<sup>21,36</sup> Evidence from more than 40 human studies has linked the observed neurodevelopmental dysfunctions with these abnormal neurologic processes that occur during the ID period.<sup>37</sup> In these studies, poor behavioral and cognitive test performances were consistent findings in iron-deficient children who were <two years old.<sup>38</sup> Moreover, long-term follow-up studies have reported lower achievement in verbal/quantitative learning, intelligence quotient, memory, and attention scores among formerly iron-deficient children than among children in the control group.<sup>39,40</sup> Although iron fortification of infant formula resulted in dramatic decline in the ID prevalence, ID remains the most common micronutrient deficiency among infants and young children.<sup>2</sup> In developing countries, it is estimated that about 40% of preschool children are iron deficient with the highest prevalence in Africa (67.6%) and South Asia (65.5%).<sup>2</sup> The causes of ID are inadequate iron intake or impaired absorption because of infection or underlying disease.<sup>41</sup> In developed countries, the prevalence of ID is >8% among preschool aged children.<sup>42,43</sup> Breast-fed infants are vulnerable to developing ID because of rapid growth, depletion of their iron endowment, and low iron content in breast milk and in some complementary foods.<sup>44</sup> It has been shown that prolonged exclusive breast-feeding for more than six months is associated with increased risk of IDA.<sup>45</sup> Other nondietary related causes of infantile ID include intrauterine growth restriction, gestational diabetes, small for gestational age, maternal ID, preeclampsia, early clamping of umbilical cord, and prematurity.<sup>46–48</sup> Delayed umbilical cord clamping is of high importance for the extra volume of blood transfused from the placenta to the newborn infant, which therefore alter the risk of developing ID and IDA.<sup>49</sup> A Cochrane meta-analysis supported delayed cord clamping by showing that delayed cord clamping improves the iron status of infants.<sup>50</sup> In Canada, Innis et al found that 34% of breast-fed infants living in Vancouver had ID and 7% had IDA.<sup>51</sup> Similarly, Friel et al showed a 33% prevalence with ID and 14% with IDA among breast-fed infants living in Newfoundland.<sup>52</sup> It was estimated that the prevalence of IDA among Aboriginal children aged 1–5 years was five times higher than among other children living in urban Canada.<sup>53</sup> Similar observations have been documented in other developed countries. For example, it was reported that 4% of Norwegian breast-fed infants had low iron status.<sup>54</sup> In the United States, the National Health and Nutrition Examination Survey (NHANES) has reported an estimated prevalence of ID ± A of 7% in young children.<sup>55</sup> In Australia, Makrides et al found ID in 15% and IDA in 1% of six-month-old breast-fed infants.<sup>56</sup> Thus, it is noticeable that some breast-fed infants are not protected by their iron



endowment. To our knowledge, iron status is not routinely examined in infancy, particularly in EBF infants.

### Sources of Iron for the Growing Infant

Hb iron and storage iron present at birth are the most important iron sources during the first few months of life for full-term infants, particularly breast-fed infants.<sup>3</sup> Another source of iron is breast milk, which contains a low amount (mean iron content = 0.35 mg/L) with a bioavailability of 45%–100%.<sup>57</sup> Ferrous sulfate is the form of iron available in cow's milk-based infant formula. Despite ferrous sulfate being a well absorbable form of iron, the cow's milk proteins available in the formula have an inhibitory effect on iron absorption.<sup>58</sup> Iron-fortified cereals are the most common source of iron during the complementary feeding period.<sup>59</sup> Ferric pyrophosphate and elemental iron are the two types of iron fortificants added to these cereals, which have low bioavailability.<sup>60</sup> Depending on the type of weaning food, the infant may receive a household modified diet with low iron content or a highly absorbable heme iron-rich diet such as meat.

### Iron Supplementation

Iron supplementation can be delivered either by iron-fortified foods or by medicinal iron. Currently, in Canada, there is no recommendation for iron supplementation for the healthy full-term infant. In the United States, the American Academy of Pediatrics recommends iron supplementation of 1 mg/kg/day for EBF infants at four months of age until weaning with iron-rich foods is commenced.<sup>61</sup> The recent ESPGHAN Committee on Nutrition guidelines do not recommend general iron supplementation for breast-fed infants.<sup>62</sup> In developing countries, iron supplementation is an issue in malaria endemic regions and may lead to an increase in *Plasmodium falciparum* complications.<sup>63</sup> Available evidence from developed and developing countries is conflicting regarding whether iron supplementation would suffice and meet the expected beneficial outcomes for the supplemented infants. This may be related to the under development of the iron absorption mechanisms that mature at different postnatal ages.<sup>64</sup> In a randomized controlled trial (RCT) conducted with Honduran and Swedish infants, two different concentrations of iron supplementation were given. It was observed that infants who received the lower iron supplementation had higher head growth and lower rates of infection than infants in the alternate group. Iron supplementation increased the rate of gastrointestinal infections and decreased the linear growth of the infants in the higher iron supplementation group. The prevalence of anemia was also found to be significantly lower among supplemented Honduran infant group.<sup>65</sup> In Canada, Friel et al randomized 77 full-term breast-fed infants to receive either iron supplementation or a placebo.<sup>52</sup> They found improvements in visual acuity and psychomotor functions among infants who received iron supplementation orally. Iron status parameters were also improved among the

iron supplemented group.<sup>52</sup> Iron-fortified infant formula is another important source of iron supplementation for infants. Moffatt et al randomized 283 infants from 2 to 15 months of age to iron-fortified formula vs nonfortified formula. They found improvement of iron status and lower proportion of anemia in infants who received iron-fortified infant formula.<sup>66</sup> In another RCT, young infants who received iron-fortified formula of either 1 or 5 mg/L showed no significant difference in the risk of developing anemia between the two groups.<sup>67</sup> Other iron supplementation trials among 6- to 12-month-old infants showed improvement of serum Hb and ferritin level.<sup>68,69</sup> A meta-analysis of 18 RCTs showed that iron-fortified formula and cereal improve serum Hb levels by 0.87 g/dL (95% CI: 0.57–1.16) and decrease the risk of anemia by 57% (relative risk 0.43, 95% CI: 0.27–0.71).<sup>70</sup> Finally, a recent systematic study of iron supplementation in 6–24-month-old children concluded that the evidence is inconsistent in regard to the efficacy of iron supplementation in the improvement of iron status, the incidence of ID, and growth outcomes.<sup>71</sup>

### Iron Nutrient Interaction

Iron has been found to interact with the following nutrients: lead, zinc, copper, vitamin A, and calcium.<sup>72</sup> These interactions may be caused by the interactions between iron metabolism, especially iron transporter regulation, and these micronutrients. Lead poisoning has been associated with ID in children. The suggested mechanism is that the upregulation of DMT1 during ID leads to increased lead absorption. It was observed that iron supplementation of iron-deficient lead-exposed children resolved high blood lead concentrations.<sup>73</sup> Interaction between zinc and iron appears to be because of the competition between those two nutrients for the same absorptive pathway. However, available evidence is conflicting regarding the negative effects resulting from the interaction between these two nutrients.<sup>74</sup> Iron-deficient status has been linked to negative copper metabolism and vice versa. Iron supplementation showed no effect in improving anemia caused by copper deficiency.<sup>75</sup> A negative effect on copper/zinc superoxide dismutase activity by iron supplementation was observed in breast-fed infants.<sup>76</sup> Vitamin A is another micronutrient that interacts with iron metabolism, thus causing ID.<sup>64</sup> Studies have shown improvement of iron status of lactating women, their breast milk, and their infants who received vitamin A supplementation suggesting an association between improved vitamin A status and iron metabolism.<sup>77</sup>

An interaction between calcium and iron may occur. Therefore, it is recommended to avoid calcium-rich products, ie, milk and calcium supplements, with iron-rich foods.<sup>78</sup>

Another compound that impedes the absorption of iron is phytate. Studies have shown a positive association between the amount of phytate contained in a meal with the inhibitory effect of iron absorption by 82%.<sup>79</sup> Ascorbic acid has been shown to enhance iron absorption when provided as a food





source or as a fortificant.<sup>80</sup> Animal tissues such as beef, pork, and chicken are known to provide a good source of heme iron (30%–70% of the total iron) as well as having an enhancing effect on iron absorption itself.<sup>81</sup>

## Conclusion

There is substantial evidence to support the negative effects of ID on neurodevelopmental outcomes in childhood. Therefore, it is of high importance to ensure adequate iron intake during infancy by either complementary feeding or medicinal supplementation. Currently, there is no routine screening for ID in infants, particularly breast-fed infants. Serum ferritin is the best representative indicator of iron stores. It may be necessary to develop a screening score to identify infants at risk and target them for supplementation. Recent advances in knowledge have led to greater understanding of iron metabolism, which may direct future research of iron fortification strategies. In addition, future research should determine the optimal iron supplementation level by comparing different iron supplementation regimens while avoiding the adverse events of iron toxicity. Multicenter trials with long-term follow-up of infant populations are needed to investigate the association between iron fortification/supplementation and various health outcomes such as growth, iron status, and morbidity.

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## Author Contributions

Wrote the first draft of the manuscript: WAQ. Supervised and guided the preparation of the manuscript: JKF. Agreed with manuscript results and conclusions: WAQ, JKF. Jointly developed the structure and arguments for the paper: WAQ, JKF. Made critical revisions and approved the final version: WAQ, JKF. Both the authors reviewed and approved the final manuscript.

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