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Review Article

Iron Deficiency: A Reflection on Prevention

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Abstract

Iron deficiency is the main nutritional deficiency in the first years of life. In Brazil, studies show a prevalence of 10.1% to 40%, depending on the study. Worldwide, in low-income countries, the statistics are higher, as in India iron deficiency is 53%. The aim of this article is to highlight the importance of breastfeeding and adequate substitution when this is not possible in order to prevent iron deficiency anemia.

Discussion: Adequate nutrition begins at preconception, pregnancy and continues throughout life, especially during the first 1000 days and 2200 days. Exclusive breastfeeding for up to 6 months and supplemented breastfeeding for up to 2 years or more is essential, as is the mother's iron intake. In cases where breastfeeding is not possible, priority should be given to the use of dairy products that contain nutrients as close as possible to breast milk. In lower-income countries, cow's milk is still widely used as a substitute for human milk. However, this can result in nutritional deficiencies and other health implications for infants. Inadequate infant feeding and the risk of nutritional deficiencies should be carefully assessed by health professionals. Thus, the choice of the best food allows for the full growth and development of the child as well as the prevention of iron deficiency.

INTRODUCTION

Nutrition plays a fundamental role in preventing micronutrient deficiencies, such as iron, and chronic non-communicable diseases in adulthood, and should begin during pregnancy and childhood. Childhood nutrition is the basis for metabolic programming and the formation of healthy intestinal microbiota [1,2]. Iron deficiency compromises growth and motor and cognitive development, favors the occurrence of infectious processes and leads to later consequences, including school performance, workforce and quality of life.

The first thousand days are fundamental for the child's "metabolic programming". This period determines early impacts on health or disease, as it induces short- and long-term effects on the child's health, including cognitive impairment, increased infections, the risk of common non-communicable diseases such as obesity, diabetes and cardiovascular diseases. With the advancement of scientific knowledge, research has shown that prevention can start from a woman's childbearing years, in order to promote an adequate nutritional environment to receive the fetus and provide adequate growth and development in utero and after birth with breastfeeding, and extend up to 5 years. The 2200-day period recommended by the Brazilian Association of Nutrology as a window of 2,200 days (100 days of preconception + 270 days of gestation + 1,830 days from the first to the fifth year of life), being the ideal period for professional action to ensure the present and future of children [2,3].

Breastfeeding is one of the newborn's earliest nutritional experiences, continuing the nutrition that began during intrauterine life, with adequate maternal nutrition and iron and folic acid supplementation (and others when necessary), resulting in better physical, psychological and immunological development and the formation of the child's microbiota [4,5].

Exclusive breastfeeding protects against diseases and increases the chance of continued full breastfeeding for at least the 2nd year of life. 4 If exclusive breastfeeding is impossible, infant formula should be used to meet the needs of this age group [2,6,7].

The Codex Alimentarius [8] and ANVISA (National Health Surveillance Agency) [9,10] regulate infant formulas, with strict criteria that the industry must meet. For the production of infant formulas (the first products intended for artificial feeding at the beginning of life), the well-known composition of human milk should be used as a reference.

Iron deficiency, the main nutritional deficiency in the first

years of life, was analyzed by the ENANI study (2019) [11], which found a prevalence of anemia among children aged 6 to 59 months in Brazil of 10.1%, with children aged 6 to 23 months having a prevalence of 19.0%. Ferreira H et al. [12], found a 40% prevalence in children aged 6 to 60 months and Nogueira-de-Almeida et al. [13], found a 33% prevalence of anemia in healthy children under 7 years old.

Iron is essential for the body in the formation of hemoglobin, the transport of oxygen throughout the body, cell oxidation and participation in enzymatic reactions (production of new cells, amino acids, hormonal agents and neurotransmitters), for motor and cognitive development, and acts in the immune system [14]. Children and pregnant women are especially vulnerable to the consequences of iron deficiency. Deficiency must be diagnosed early and intervention must be immediate in order to avoid sequelae Chart 1.

The WHO (2020) assesses iron status in populations with hemoglobin (Hb) and serum ferritin and/or transferrin receptor [16]. The American Academy of Pediatrics (2011) [17] and the Brazilian Society of Pediatrics (2021) [15] recommend laboratory investigation of iron deficiency, with or without anemia, at 12 months of age. However, in the case of suspicion based on the presence of risk factors, investigation should be carried out promptly and early, especially in the absence of adequate iron prophylaxis.

Although iron deficiency affects all socioeconomic classes and cultural groups, certain populations, such as those shown in Chart 2, are at greater risk [14,15].

The most common causes of iron deficiency in infants are dietary errors, such as replacing breast milk with whole cow's milk, lack of heme iron in the diet and lack of drug supplementation.

The prevalence of anemia in pregnancy is approximately 40%, more than 50% of which is due to iron deficiency [18]. Iron requirements during pregnancy are six times higher, requiring the use of maternal reserves and drug supplementation for the proper development of the fetus. Maternal iron deficiency anemia had an influence on the infant's hemoglobin values at six months of age, even in those on exclusive breastfeeding [18,19]. Children of mothers with anemia may be more prone to iron deficiency and anemia in early life [19].

In the period from 4 months to 1 year of age, infants need to incorporate around 200 mg of iron and, in order to do so, they need to absorb 0.8 mg/day. They are most at risk of iron deficiency between 6 and 18 months of age, a period of rapid growth in which the child triples its weight, when iron stores are reduced and intake is often inadequate (the diet should contain 8 mg of iron for efficient absorption of 10%), and chronic gastrointestinal losses can affect the balance between losses and gains (due to

Chart 1: Diagnosis of iron deficiency and iron deficiency anemia.

Laboratory assessment of the different stages of iron deficiency			
	Depletion of iron stores	**Iron deficiency**	**Iron deficiency anemia**
Morphology (VCM, HCM, RDW)	Normal	Normal	↓ VCM* (microcytosis) ↓ HCM* (hypochromia) ↑ RDW
Ferritin	Decreased	Decreased	Decreased
Serum iron	Normal	Decreased	Decreased
TIBC	Normal	Increased	Increased
Transferrin saturation index**	Normal	Decreased	Decreased

Legend: MCH, mean corpuscular hemoglobin; RDW, red cell distribution width (measure of anisocytosis); TIBC, total iron binding capacity; MCV, mean corpuscular volume.

* Varies with age

** Calculation of the transferrin saturation index = (Iron/TIBC) x 100
Source: SBP, 2021 [15]

Chart 2: Risk factors for iron deficiency.

LOW MATERNAL RESERVE
- Short interval between pregnancies
- Multiple pregnancies
- Maternal diet inadequate in iron
- Pregnant women's blood loss
- Lack of iron supplementation during pregnancy and lactation
INCREASED METABOLIC DEMAND
- Prematurity
- Low birth weight (<2,500g)
- Rapidly growing infants (growth velocity p >90)
- Girls with heavy menstrual loss
- Competitive athletes
DECREASED IRON SUPPLY
- Clamping of the umbilical cord before one minute of life
- Lack of iron supplementation
- Prolonged exclusive breastfeeding
- Complementary feeding with foods low in iron or with low bioavailability
- Consumption of cow's milk before one year of age
- Restrictive diets
- Low adherence to prophylactic supplementation
- Consumption of infant formula with low iron content or insufficient quantity
- Vegetarian diets without guidance from a doctor/nutritionist
BLOOD LOSS
- Traumatic or surgical
- Gastrointestinal bleeding (inflammatory bowel disease, colonic polyposis, non-steroidal anti-inflammatory drugs, Helicobacter pylori infection, worms - strongyloides, necatur, hookworm, allergic enteropathies/colitis, schistosomiasis)
- Gynecological bleeding (menorrhagia, intrauterine devices)
- Urological bleeding (schistosomiasis, glomerulonephritis, renal trauma)
- Pulmonary bleeding (tuberculosis, pulmonary malformation, idiopathic pulmonary hemosiderosis, Goodpasture syndrome)
- Blood dyscrasias
- Malaria
- COVID-19
IRON MALABSORPTION
- Malabsorption syndromes (celiac disease, inflammatory bowel disease)
- Atrophic gastritis
- Gastric surgery
- Bariatric surgery
- Reduction of gastric acidity (antacids, H2 blockers, proton pump inhibitors)
- Iron-refractory iron deficiency anemia
- Obesity

Adapted from SBP, 2021[15].

cow's milk allergy, parasitosis, recurrent diarrheal disease and gastroesophageal reflux) [20].

Infant formulas, despite being an ultra-processed food, are the recommended option for feeding children whose mothers are unable or unwilling to breastfeed and are considered nutritionally adequate, as they guarantee the growth of babies, as cited by international researchers such as Koletzko et al, (2009) [21], and Appleton et al, (2018) [22], the ESPGHAN nutrition committee [6,22], and the AAP [20,23]. They emphasize the importance of breast milk in the first 2 years of life and, if this is not possible, the use of low-protein infant formula to prevent obesity and provide the recommended daily amount of micro and macronutrients. The main differences in nutrients between infant formula and whole cow's milk are shown in Chart 3.

The recommendation by the Brazilian Ministry of Health in 2019 [24], and the WHO in 2023 [25], to use whole cow's milk from the age of 4 months will lead to an increase in iron deficiency anemia, malnutrition or obesity. The WHO document points out that "Although breast milk is always preferable, in such situations another milk, such as a milk formula, animal milk or other dairy source, is needed to meet the specific nutritional needs of this age group." Considering that cow's milk doesn't contain the amount of iron recommended for the child's age and that the diet doesn't always meet the daily nutrient recommendations, this child will suffer from iron deficiency anemia and its future consequences.

Iron deficiency anemia in children under two years of age occurs due to the high metabolic need for rapid growth and development, associated with an iron-poor diet [26].

In pediatrics, childcare is mainly focused on prevention and health promotion, working to keep children healthy to ensure their full development, so that they reach adulthood without unfavorable influences and problems brought over from childhood. The paediatrician prioritizes health over disease and considers the promotion of children's health, disease prevention and the education of children and their families. In view of this, they are attentive to the best diet and supplementation whenever necessary [27]. The period between 12 and 60 months of life is fundamental, as it includes the transition from breastfeeding and complementary feeding to the family diet, which is not always adequate [1,2].

The WHO document [25], states that for "the feeding of non-breastfed children from 6 to 24 months of age, feeding with animal milk and appropriate complementary foods is a safe choice, since occult blood losses in children from 6 to 11 months of age are very small and probably do not affect iron levels". In Brazil, the ENANI study [28] showed that the main micronutrient deficiencies in children aged 1 to 3 years were iron, zinc, vitamins A, D and B12. Carvalho et al. [29], in a systematic review showed energy consumption above individual needs. The prevalence of micronutrient inadequacy ranged from 0.4% to 65% for iron.

The reality we find is that the basic guidance given to families is that after 12 months, the child can eat the family's food. And what does the family eat? Data from the latest household budget survey, published in 2020 with data for 2017 and 2018 [30], showed that, among women, inadequate consumption exceeded 50% for calcium, vitamin A, vitamin E, pyridoxine, magnesium and thiamine; and exceeded 30% for vitamin C, riboflavin, folate and iron. The foods with the highest average daily per capita consumption were coffee (163.2 g/day), beans (142.2 g/day), rice (131.4 g/day), juices (124.5 g/day) and soft drinks (67.1 g/day). So this is the family's diet [30].

The WHO document [25] also points out that "iron deficiency can be prevented with the use of iron supplements or complementary foods with adequate iron bioavailability." We observed that many children do not receive routine supplementation due to the side effects of ferrous sulphate. Freitas et al., in EANNI [31] showed that the prevalence of the use of micronutrient supplements was 54.2% among children aged 6 to 23 months; the prevalence of the use of supplements

Chart 3: Nutrients in human milk, whole cow's milk and infant formula.

	Human milk	Whole cow's milk	Infant formulas
Proteins	Adequate quantity, easy digestibility due to casein/whey ratio (40/60), protective against obesity	Increased quantity, difficult to digest due to casein/whey protein ratio (80/20)	Better whey protein/casein ratio (70/30) or 100% whey. Some infant formulas have reduced protein and adequate insulinogenic amino acids (reduces the risk of obesity).
Lipids	Sufficient in essential fatty acids, lipase for digestion	Deficient in essential fatty acids, lacks lipase Too much saturated fat	Addition of essential fatty acids (DHA, ARA), reduction of saturated fat and addition of vegetable oils (AGE). Mandatory addition of linoleic acid and alpha linolenic acid (Codex Alimentarius and Anvisa)
Minerals	Ideal quantity	Excess calcium and phosphorus, sodium, chlorine and potassium	Adequate mineral content (Codex Alimentarius and Anvisa) Adequate calcium/phosphorus ratio, promoting bone mineralization
Iron and zinc	Small quantity, excellent absorption	Small quantity, low absorption	Added. Adequate absorption
Vitamins	Ideal quantity	vitamins D, E and C insufficient	Vitamins added according to Codex Alimentarius and ANVISA
HMO	Ideal quantity	Disabled	Added
Prebiotics	Ideal quantity	Disabled	Added (GOS, FOS, PDX)
Probiotics	Ideal quantity	Disabled	Added
Water	Ideal quantity	Need to supplement between feedings	This may be necessary

Source: SBP [1] Weffort [2].

Chart 4: Recommendation for prophylactic medicinal iron supplementation in infants WITHOUT risk factors for iron deficiency.

infants WITHOUT risk factors for iron deficiency	
Situation	**Recommendation**
Full-term newborns, appropriate weight for gestational age, exclusively breastfed until the 6th month	1 mg of elemental iron/kg/day, starting at 180 days of age until the 24th month of life.

Chart 5: Recommendation for prophylactic medicinal iron supplementation in infants WITH risk factors for iron deficiency.

infants WITH risk factors for iron deficiency	
Situation	**Recommendation**
Full-term newborns, appropriate weight for gestational age, exclusively breastfed	1 mg of elemental iron/kg/day, starting at 90 days of age until the 24th month of life.
Full-term newborns, appropriate weight for gestational age, regardless of the type of feeding	1 mg of elemental iron/kg/day, starting at 90 days of age until the 24th month of life.
Full-term newborns weighing less than 2,500 g.	2 mg of elemental iron/kg/day, starting at 30 days of age, for one year. After that, 1 mg/kg/day for another year
Preterm newborns weighing more than 1,500g	2 mg of elemental iron/kg/day, starting at 30 days of age, for one year. After that, 1 mg/kg/day for another year
Pre-term newborns weighing between 1,500 and 1,000 g	3 mg of elemental iron/kg/day, starting at 30 days of age, for one year. After that, 1 mg/kg/day for another year
Preterm newborns weighing less than 1,000 g	4 mg of elemental iron/kg/day, starting at 30 days of age, for one year. After that, 1 mg/kg/day for another year
Preterm newborns who received more than 100 mL of packed red blood cells during hospitalization	They should be assessed individually as they may not need iron supplementation at 30 days of age, but later on

Source: SBP. Consensus on Iron Deficiency Anemia. Departments of Nutrology and Hematology SBP/2021[15].

containing exclusively iron was 14.6%; and the prevalence of the use of multivitamins with or without minerals in Brazilian children aged 6 to 59 months was 24.3.

In Brazil, the Brazilian Society of Pediatrics recommends prophylactic supplementation according to charts 4 and 5, with no risk factors starting at 180 days and with risk factors (low weight, mother with iron deficiency, newborn in need of support) starting at 90 days [15].

The WHO document [25] quotes "Children who consumed animal milk were more likely to have lower concentrations of vitamin D and to have vitamin D deficiency. Iron level indicators were also generally lower among children who consumed animal milk compared to follow-up formula." Isn't it contradictory to offer a product (unmodified cow's milk) knowing that it's worse?

In 2014, the ESPGHAN Nutrition Committee [32] published a recommendation to reduce iron deficiency, considering that it is the most common micronutrient deficiency worldwide and young children are a special risk group because their rapid growth leads to high iron needs. Risk factors associated with a higher prevalence of iron deficiency anemia include low birth weight, high consumption of cow's milk, low consumption of iron-rich complementary foods and low socioeconomic status [32]. They conclude that unmodified cow's milk should not be provided as the main milk drink for infants before 12 months of age and intake should be limited to <500 mL/day in children over 12 months. It is important to ensure that this dietary advice reaches high-risk groups, such as socioeconomically disadvantaged families [32]. This was also cited by Aksu et al (2023) [33].

Substituting a diet low in micronutrients can lead to a series of damages, such as iron deficiency anemia. Other times, there is an excess supply of macronutrients, predisposing to obesity, hypertension and hypercholesterolemia in the short and long term [2,6,7].

Bortolini et al, (2013) [34], published a review showing dietary inadequacies using data from 4,718 children under 60 months of age. Among the children who received other milks, cow's milk was consumed by 62.4% of children under six months, 74.6% of children aged 6 to 12 months and approximately 80% of children over 12 months. The consumption of infant formulas was 23% in children under six months, 9.8% in those aged between 6 and 12 months and less than 1% in the other ages. Lopes et al, (2018) [35], in a study to assess the frequency of breastfeeding and the introduction of complementary feeding in children aged zero to 24 months, found that when they were 180 days old, 4.0% of the children were exclusively breastfed, 22.4% were predominantly breastfed and 43.4% were complementarily breastfed. The children were already receiving water (56.8%), natural juice/infant formula (15.5%) and cow's milk (10.6%) by the third month of life. By the age of 12 months, 31.1% of the children had been given artificial juice and 50.0% were already eating sweets. And before reaching one year of age, 25.0% of the children had already eaten instant noodles.

The Nutrition Commission of the Portuguese Pediatric Society (2012) [36], reports that cow's milk in nature is deeply unbalanced, with a low iron content and a high saturated fatty acid content. It should not be used for at least the first year of life, and it is even desirable to use "growth milks" beyond 12 months and up to 24 to 36 months of life. In an integrative literature review, Ornelas et al, (2022) [37], found that nutritional practices are at odds with the recommendations of national and international health bodies. There was a high prevalence of the early introduction of other foods to replace breast milk, with cow's milk being the most commonly used food. However, cow's milk is not the most recommended food for children before they are one year old, as not only does it not meet their nutritional needs, but it can also trigger food allergies and intolerances, iron deficiency anemia, chronic diseases such as obesity and diabetes mellitus [37,38].

Siddique, et al, (2021) [39], conducted a study in Pakistan with one hundred and fifty infants with an average age of 7.77 months. They found one hundred and thirteen anemic infants (75.3%). There was a strong association between the type of diet and the frequency of anemia among the infants ($p<0.001$), with children who consumed fortified milk showing higher levels of hemoglobin, MCV and ferritin levels.

Children in the first few years of life may have insufficient

intake, either too much or too little, of various nutrients (vitamins A, D, B12, C and folic acid; iodine; iron and zinc, long-chain fatty acids such as omega-3), which will negatively influence their growth, neuropsychomotor development, immunity, as well as metabolic programming [40-42]. In these situations, it is important to offer foods that meet these needs, such as the Consensus made by ABRAN ((2022) [43]. If we consider that in some situations, after the first year, the child goes through a period of selectivity, picky eating, where they don't consume all the food groups, predisposing them to deficiencies if they don't receive adequate supplementation, the concern for this child's future is greater. In Brazil, ANVISA through Collegiate Board Resolution - RDC 48/2014 - regulated the production and marketing of early childhood formulas, which therefore comply with specific legislation, with adequate macro and micronutrient content to meet the nutritional needs of children aged 1 to 3 years, which differentiates them from other dairy products on the market, which have greater variability in composition [44]. With names such as Infant Toddler Formula (YCF), Growth Milk (GUM), or Early Childhood Formula, already existing and registered in several countries, as regulated by EFSA (European Food Safety Authority) [45], "YCF are one of several means to increase the intake of n-3 PUFA, iron, vitamin D and iodine in infants and young children living in Europe with inadequate or at risk of inadequate status of these nutrients [45]. Researchers such as Koletzko et al., (2013) [46] and Suthutvoravut et al, (2015) [47], emphasize the importance of early childhood formula for children's growth. The ESPGHAN nutrition committee (2018) [48] suggests that, based on the available evidence, there is no need for the routine use of YCF in children aged 1 to 3 years, but they can be used as part of a strategy to increase iron, vitamin D and n-3 PUFA intake and decrease protein intake compared to unfortified cow's milk.

In Brazil, the reality is that there is a high prevalence of hidden hunger in the 1 to 3 age group, which is largely the result of a lack of food, or adequate food. Therefore, as it is a food consumed by practically all children in this age group, milk is an excellent vehicle for fortification, helping to prevent iron deficiency anemia in children aged 1 to 3 [49].

The document drawn up by the WHO/2023 [25], which suggests introducing whole cow's milk in the first year of life, contradicts various studies which prove that cow's milk is not the most recommended food for children before one year of age, because not only does it not meet the child's nutritional needs, leading to a deficiency of various micronutrients, especially iron, but it can also predispose them to chronic diseases such as obesity and diabetes mellitus. And for other ages, knowing how inadequate children's diets are, with various nutritional deficiencies, the child should be carefully assessed to choose the best food, allowing their full development with the prevention of iron deficiency.

FINAL CONSIDERATIONS

Breast milk is irreplaceable! We must fight to increase exclusive and complementary breastfeeding rates. Replacing breast milk with whole cow's milk can cause a number of problems for the child, as many studies have shown: iron deficiency and iron deficiency anemia, delayed myelination, delayed growth and low immunity. If infant formula can be used, iron deficiency anemia and other deficiencies can be prevented. Everyone is fighting to reduce iron deficiency anemia, so proper nutrition should be the first step.

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